

JOHN MCMURRY



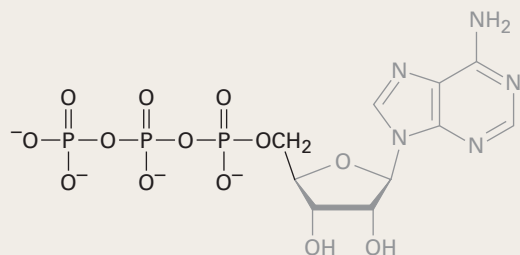
THIRD EDITION

Organic Chemistry
with Biological Applications

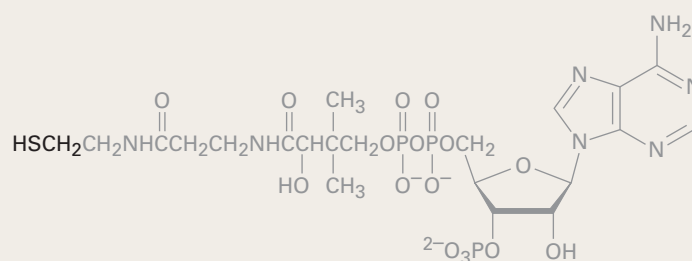
Structures of Common Coenzymes

The reactive parts of the molecules are darkened, while nonreactive parts are ghosted.

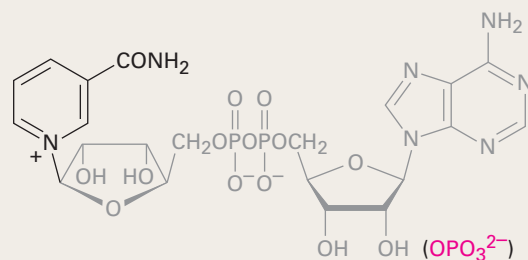
Adenosine triphosphate—ATP (phosphorylation)



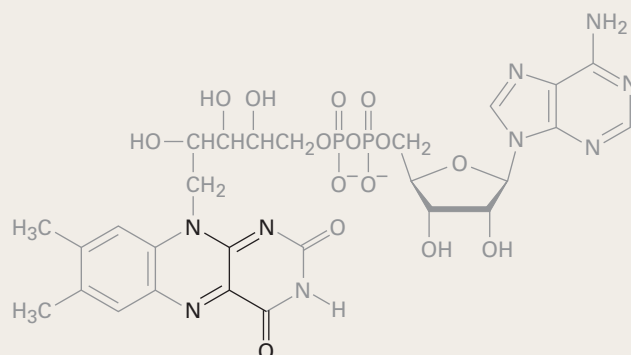
Coenzyme A (acyl transfer)



Nicotinamide adenine dinucleotide—NAD⁺ (oxidation/reduction) (NADP⁺)

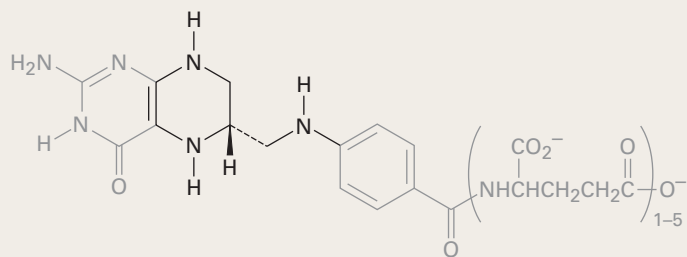


Flavin adenine dinucleotide—FAD (oxidation/reduction)

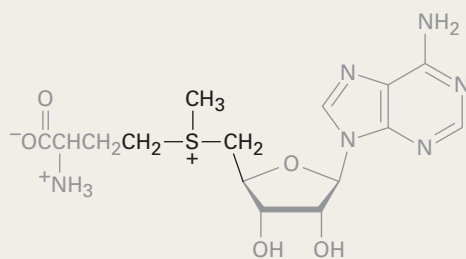


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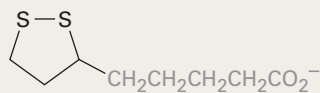
Tetrahydrofolate (transfer of C₁ units)



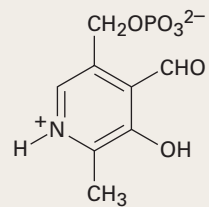
S-Adenosylmethionine (methyl transfer)



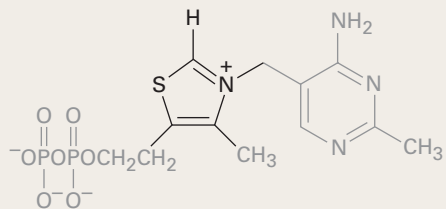
Lipoic acid (acyl transfer)



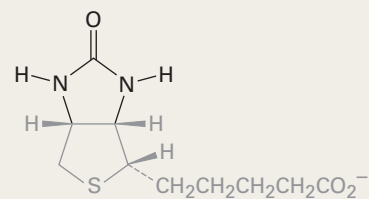
Pyridoxal phosphate (amino acid metabolism)



Thiamin diphosphate (decarboxylation)



Biotin (carboxylation)





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and Chemical Biology

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Dear Colleague:

All of us who teach organic chemistry know that most of the students in our courses, even the chemistry majors, are interested primarily in the life sciences rather than in pure chemistry. Because we are teaching so many future biologists, biochemists, and doctors rather than younger versions of ourselves, more and more of us are questioning why we continue to teach the way we do. Why do we spend so much time discussing the details of reactions that are of interest to research chemists but have little connection to biology? Why don't we instead spend more time discussing the organic chemistry of living organisms?

There is still much to be said for teaching organic chemistry in the traditional way, but it is also true that until now there has been no real alternative for those instructors who want to teach somewhat differently. And that is why I wrote **Organic Chemistry with Biological Applications 3e**. As chemical biology continues to gain in prominence, I suspect that more and more faculty will be changing their teaching accordingly.

Make no mistake: this is still a textbook on organic chemistry. But my guiding principle in deciding what to include and what to leave out has been to focus almost exclusively on those reactions that have a direct counterpart in biological chemistry. The space saved by leaving out nonbiological reactions has been put to good use, for almost every reaction discussed is followed by a biological example and approximately 25% of the book is devoted entirely to biomolecules and the organic chemistry of their biotransformations. In addition, **Organic Chemistry with Biological Applications 3e** is nearly 200 pages shorter than standard texts, making it possible for faculty to cover the entire book in a typical two-semester course.

Organic Chemistry with Biological Applications 3e is different from any other text; I believe that it is ideal for today's students.

Sincerely,

John McMurry

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All royalties from *Organic Chemistry with Biological Applications* will be donated to the Cystic Fibrosis (CF) Foundation. This book and donation are dedicated to the author's eldest son and to the thousands of others who daily fight this disease. To learn more about CF and the programs and services provided by the CF Foundation, please visit <http://www.cff.org>.

Organic Chemistry

WITH BIOLOGICAL APPLICATIONS



3rd Edition

Organic Chemistry

WITH BIOLOGICAL APPLICATIONS

John McMurry

CORNELL UNIVERSITY



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John McMurry

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BRIEF CONTENTS

1	Structure and Bonding	1
2	Polar Covalent Bonds; Acids and Bases	28
3	Organic Compounds: Alkanes and Their Stereochemistry	59
4	Organic Compounds: Cycloalkanes and Their Stereochemistry	87
5	Stereochemistry at Tetrahedral Centers	113
6	An Overview of Organic Reactions	146
7	Alkenes and Alkynes	179
8	Reactions of Alkenes and Alkynes	212
9	Aromatic Compounds	265
10	Structure Determination: Mass Spectrometry, Infrared Spectroscopy, and Ultraviolet Spectroscopy	319
11	Structure Determination: Nuclear Magnetic Resonance Spectroscopy	350
12	Organohalides: Nucleophilic Substitutions and Eliminations	382
13	Alcohols, Phenols, and Thiols; Ethers and Sulfides	435
**	A Preview of Carbonyl Chemistry	483
14	Aldehydes and Ketones: Nucleophilic Addition Reactions	492
15	Carboxylic Acids and Nitriles	530
16	Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions	555
17	Carbonyl Alpha-Substitution and Condensation Reactions	599
18	Amines and Heterocycles	644
19	Biomolecules: Amino Acids, Peptides, and Proteins	678
20	Amino Acid Metabolism	714
21	Biomolecules: Carbohydrates	738
22	Carbohydrate Metabolism	773
23	Biomolecules: Lipids and Their Metabolism	805
24	Biomolecules: Nucleic Acids and Their Metabolism	852
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DETAILED CONTENTS

1

Structure and Bonding | 1

1-1	Atomic Structure: The Nucleus	3
1-2	Atomic Structure: Orbitals	4
1-3	Atomic Structure: Electron Configurations	6
1-4	Development of Chemical Bonding Theory	7
1-5	Describing Chemical Bonds: Valence Bond Theory	10
1-6	sp^3 Hybrid Orbitals and the Structure of Methane	12
1-7	sp^3 Hybrid Orbitals and the Structure of Ethane	13
1-8	sp^2 Hybrid Orbitals and the Structure of Ethylene	14
1-9	sp Hybrid Orbitals and the Structure of Acetylene	16
1-10	Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur	18
1-11	Describing Chemical Bonds: Molecular Orbital Theory	20
1-12	Drawing Chemical Structures	21
	SOMETHING EXTRA Organic Foods: Risk versus Benefit	24

2

Polar Covalent Bonds; Acids and Bases | 28

2-1	Polar Covalent Bonds: Electronegativity	28
2-2	Polar Covalent Bonds: Dipole Moments	31
2-3	Formal Charges	33
2-4	Resonance	36
2-5	Rules for Resonance Forms	37
2-6	Drawing Resonance Forms	39
2-7	Acids and Bases: The Brønsted–Lowry Definition	42
2-8	Acid and Base Strength	44
2-9	Predicting Acid–Base Reactions from pK_a Values	46
2-10	Organic Acids and Organic Bases	47
2-11	Acids and Bases: The Lewis Definition	50
2-12	Noncovalent Interactions between Molecules	54
	SOMETHING EXTRA Alkaloids: From Cocaine to Dental Anesthetics	56

3 Organic Compounds: Alkanes and Their Stereochemistry | 59

3-1	Functional Groups	59
3-2	Alkanes and Alkane Isomers	66
3-3	Alkyl Groups	69
3-4	Naming Alkanes	72
3-5	Properties of Alkanes	78
3-6	Conformations of Ethane	79
3-7	Conformations of Other Alkanes	81
	SOMETHING EXTRA Gasoline	85

4 Organic Compounds: Cycloalkanes and Their Stereochemistry | 87

4-1	Naming Cycloalkanes	88
4-2	Cis–Trans Isomerism in Cycloalkanes	91
4-3	Stability of Cycloalkanes: Ring Strain	93
4-4	Conformations of Cycloalkanes	95
4-5	Conformations of Cyclohexane	97
4-6	Axial and Equatorial Bonds in Cyclohexane	99
4-7	Conformations of Monosubstituted Cyclohexanes	102
4-8	Conformations of Disubstituted Cyclohexanes	105
4-9	Conformations of Polycyclic Molecules	108
	SOMETHING EXTRA Molecular Mechanics	111

5 Stereochemistry at Tetrahedral Centers | 113

5-1	Enantiomers and the Tetrahedral Carbon	114
5-2	The Reason for Handedness in Molecules: Chirality	115
5-3	Optical Activity	119
5-4	Pasteur's Discovery of Enantiomers	121
5-5	Sequence Rules for Specifying Configuration	122

5-6	Diastereomers	127
5-7	Meso Compounds	130
5-8	Racemic Mixtures and the Resolution of Enantiomers	132
5-9	A Review of Isomerism	135
5-10	Chirality at Nitrogen, Phosphorus, and Sulfur	137
5-11	Prochirality	138
5-12	Chirality in Nature and Chiral Environments	141
	SOMETHING EXTRA Chiral Drugs	143

6 An Overview of Organic Reactions | 146

6-1	Kinds of Organic Reactions	146
6-2	How Organic Reactions Occur: Mechanisms	148
6-3	Radical Reactions	149
6-4	Polar Reactions	152
6-5	An Example of a Polar Reaction: Addition of H ₂ O to Ethylene	156
6-6	Using Curved Arrows in Polar Reaction Mechanisms	159
6-7	Describing a Reaction: Equilibria, Rates, and Energy Changes	162
6-8	Describing a Reaction: Bond Dissociation Energies	166
6-9	Describing a Reaction: Energy Diagrams and Transition States	168
6-10	Describing a Reaction: Intermediates	170
6-11	A Comparison between Biological Reactions and Laboratory Reactions	173
	SOMETHING EXTRA Where Do Drugs Come From?	176

7 Alkenes and Alkynes | 179

7-1	Calculating the Degree of Unsaturation	180
7-2	Naming Alkenes and Alkynes	183
7-3	Cis–Trans Isomerism in Alkenes	186
7-4	Alkene Stereochemistry and the <i>E,Z</i> Designation	188
7-5	Stability of Alkenes	191
7-6	Electrophilic Addition Reactions of Alkenes	195
	<u>Writing Organic Reactions</u>	196
7-7	Orientation of Electrophilic Addition: Markovnikov's Rule	197
7-8	Carbocation Structure and Stability	201
7-9	The Hammond Postulate	203

7-10	Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements	206
	SOMETHING EXTRA Terpenes: Naturally Occurring Alkenes	209

8 Reactions of Alkenes and Alkynes | 212

8-1	Preparing Alkenes: A Preview of Elimination Reactions	213
8-2	Halogenation of Alkenes	214
8-3	Halohydrins from Alkenes	217
8-4	Hydration of Alkenes	218
8-5	Reduction of Alkenes: Hydrogenation	223
8-6	Oxidation of Alkenes: Epoxidation	227
8-7	Oxidation of Alkenes: Hydroxylation	229
8-8	Oxidation of Alkenes: Cleavage to Carbonyl Compounds	231
8-9	Addition of Carbenes to Alkenes: Cyclopropane Synthesis	233
8-10	Radical Additions to Alkenes: Chain-Growth Polymers	235
8-11	Biological Additions of Radicals to Alkenes	240
8-12	Conjugated Dienes	241
8-13	Reactions of Conjugated Dienes	245
8-14	The Diels–Alder Cycloaddition Reaction	247
8-15	Reactions of Alkynes	253
	SOMETHING EXTRA Natural Rubber	258
	<u>Learning Reactions</u>	261

9 Aromatic Compounds | 265

9-1	Naming Aromatic Compounds	266
9-2	Structure and Stability of Benzene	268
9-3	Aromaticity and the Hückel $4n + 2$ Rule	272
9-4	Aromatic Ions and Aromatic Heterocycles	274
9-5	Polycyclic Aromatic Compounds	279
9-6	Reactions of Aromatic Compounds: Electrophilic Substitution	281
9-7	Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction	289
9-8	Substituent Effects in Electrophilic Substitutions	295

9-9	Nucleophilic Aromatic Substitution	303
9-10	Oxidation and Reduction of Aromatic Compounds	306
9-11	An Introduction to Organic Synthesis: Polysubstituted Benzenes	308
	SOMETHING EXTRA Aspirin, NSAIDs, and COX-2 Inhibitors	314

10 Structure Determination: Mass Spectrometry, Infrared Spectroscopy, and Ultraviolet Spectroscopy | 319

10-1	Mass Spectrometry of Small Molecules: Magnetic-Sector Instruments	320
10-2	Interpreting Mass Spectra	321
10-3	Mass Spectrometry of Some Common Functional Groups	326
10-4	Mass Spectrometry in Biological Chemistry: Time-of-Flight (TOF) Instruments	328
10-5	Spectroscopy and the Electromagnetic Spectrum	329
10-6	Infrared Spectroscopy	332
10-7	Interpreting Infrared Spectra	334
10-8	Infrared Spectra of Some Common Functional Groups	337
10-9	Ultraviolet Spectroscopy	342
10-10	Interpreting Ultraviolet Spectra: The Effect of Conjugation	345
10-11	Conjugation, Color, and the Chemistry of Vision	346
	SOMETHING EXTRA X-Ray Crystallography	348

11 Structure Determination: Nuclear Magnetic Resonance Spectroscopy | 350

11-1	Nuclear Magnetic Resonance Spectroscopy	350
11-2	The Nature of NMR Absorptions	352
11-3	Chemical Shifts	355
11-4	^{13}C NMR Spectroscopy: Signal Averaging and FT-NMR	357
11-5	Characteristics of ^{13}C NMR Spectroscopy	358
11-6	DEPT ^{13}C NMR Spectroscopy	361
11-7	Uses of ^{13}C NMR Spectroscopy	364
11-8	^1H NMR Spectroscopy and Proton Equivalence	365
11-9	Chemical Shifts in ^1H NMR Spectroscopy	368

11-10	Integration of ^1H NMR Absorptions: Proton Counting	370
11-11	Spin–Spin Splitting in ^1H NMR Spectra	371
11-12	More Complex Spin–Spin Splitting Patterns	376
11-13	Uses of ^1H NMR Spectroscopy	379
	SOMETHING EXTRA Magnetic Resonance Imaging (MRI)	380

12 Organohalides: Nucleophilic Substitutions and Eliminations | 382

12-1	Names and Structures of Alkyl Halides	383
12-2	Preparing Alkyl Halides from Alkenes: Allylic Bromination	385
12-3	Preparing Alkyl Halides from Alcohols	390
12-4	Reactions of Alkyl Halides: Grignard Reagents	391
12-5	Organometallic Coupling Reactions	393
12-6	Discovery of the Nucleophilic Substitution Reaction	395
12-7	The $\text{S}_{\text{N}}2$ Reaction	398
12-8	Characteristics of the $\text{S}_{\text{N}}2$ Reaction	401
12-9	The $\text{S}_{\text{N}}1$ Reaction	408
12-10	Characteristics of the $\text{S}_{\text{N}}1$ Reaction	412
12-11	Biological Substitution Reactions	418
12-12	Elimination Reactions: Zaitsev's Rule	420
12-13	The E2 Reaction and the Deuterium Isotope Effect	422
12-14	The E1 and E1cB Reactions	427
12-15	Biological Elimination Reactions	428
12-16	A Summary of Reactivity: $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, E1, E1cB, and E2	429
	SOMETHING EXTRA Naturally Occurring Organohalides	430

13 Alcohols, Phenols, and Thiols; Ethers and Sulfides | 435

13-1	Naming Alcohols, Phenols, and Thiols	437
13-2	Properties of Alcohols, Phenols, and Thiols	439
13-3	Preparing Alcohols from Carbonyl Compounds	443
13-4	Reactions of Alcohols	452
13-5	Oxidation of Alcohols and Phenols	456

13-6	Protection of Alcohols	460
13-7	Preparation and Reactions of Thiols	463
13-8	Ethers and Sulfides	464
13-9	Preparing Ethers	466
13-10	Reactions of Ethers	467
13-11	Crown Ethers and Ionophores	472
13-12	Preparation and Reactions of Sulfides	474
13-13	Spectroscopy of Alcohols, Phenols, and Ethers	475
	SOMETHING EXTRA Ethanol: Chemical, Drug, Poison	478

A Preview of Carbonyl Chemistry | 483

I	Kinds of Carbonyl Compounds	483
II	Nature of the Carbonyl Group	485
III	General Reactions of Carbonyl Compounds	485
IV	Summary	491

14 Aldehydes and Ketones: Nucleophilic Addition Reactions | 492

14-1	Naming Aldehydes and Ketones	493
14-2	Preparing Aldehydes and Ketones	495
14-3	Oxidation of Aldehydes	497
14-4	Nucleophilic Addition Reactions of Aldehydes and Ketones	497
14-5	Nucleophilic Addition of H ₂ O: Hydration	501
14-6	Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation	503
14-7	Nucleophilic Addition of Amines: Imine and Enamine Formation	505
14-8	Nucleophilic Addition of Alcohols: Acetal Formation	509
14-9	Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction	513
14-10	Biological Reductions	516
14-11	Conjugate Nucleophilic Addition to α,β -Unsaturated Aldehydes and Ketones	518
14-12	Spectroscopy of Aldehydes and Ketones	522
	SOMETHING EXTRA Enantioselective Synthesis	526

15	Carboxylic Acids and Nitriles	530
15-1	Naming Carboxylic Acids and Nitriles	531
15-2	Structure and Properties of Carboxylic Acids	533
15-3	Biological Acids and the Henderson–Hasselbalch Equation	537
15-4	Substituent Effects on Acidity	538
15-5	Preparing Carboxylic Acids	540
15-6	Reactions of Carboxylic Acids: An Overview	543
15-7	Chemistry of Nitriles	543
15-8	Spectroscopy of Carboxylic Acids and Nitriles	548
	SOMETHING EXTRA Vitamin C	550

16	Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions	555
16-1	Naming Carboxylic Acid Derivatives	556
16-2	Nucleophilic Acyl Substitution Reactions	559
16-3	Reactions of Carboxylic Acids	564
16-4	Reactions of Acid Halides	570
16-5	Reactions of Acid Anhydrides	576
16-6	Reactions of Esters	578
16-7	Reactions of Amides	584
16-8	Reactions of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives	587
16-9	Polyamides and Polyesters: Step-Growth Polymers	589
16-10	Spectroscopy of Carboxylic Acid Derivatives	592
	SOMETHING EXTRA β -Lactam Antibiotics	594

17	Carbonyl Alpha-Substitution and Condensation Reactions	599
17-1	Keto–Enol Tautomerism	600
17-2	Reactivity of Enols: α -Substitution Reactions	603
17-3	Alpha Bromination of Carboxylic Acids	606
17-4	Acidity of α Hydrogen Atoms: Enolate Ion Formation	607

17-5	Alkylation of Enolate Ions	610
17-6	Carbonyl Condensations: The Aldol Reaction	620
17-7	Dehydration of Aldol Products	623
17-8	Intramolecular Aldol Reactions	626
17-9	The Claisen Condensation Reaction	627
17-10	Intramolecular Claisen Condensations: The Dieckmann Cyclization	629
17-11	Conjugate Carbonyl Additions: The Michael Reaction	632
17-12	Carbonyl Condensations with Enamines: The Stork Reaction	634
17-13	Biological Carbonyl Condensation Reactions	637
	SOMETHING EXTRA Barbiturates	639

18 Amines and Heterocycles | 644

18-1	Naming Amines	645
18-2	Properties of Amines	647
18-3	Basicity of Amines	649
18-4	Basicity of Arylamines	652
18-5	Biological Amines and the Henderson–Hasselbalch Equation	653
18-6	Synthesis of Amines	654
18-7	Reactions of Amines	659
18-8	Heterocyclic Amines	665
18-9	Fused-Ring Heterocycles	669
18-10	Spectroscopy of Amines	672
	SOMETHING EXTRA Green Chemistry	674

19 Biomolecules: Amino Acids, Peptides, and Proteins | 678

19-1	Structures of Amino Acids	679
19-2	Amino Acids and the Henderson–Hasselbalch Equation: Isoelectric Points	684
19-3	Synthesis of Amino Acids	687
19-4	Peptides and Proteins	689
19-5	Amino Acid Analysis of Peptides	691
19-6	Peptide Sequencing: The Edman Degradation	693
19-7	Peptide Synthesis	696

19-8	Protein Structure	700
19-9	Enzymes and Coenzymes	703
19-10	How Do Enzymes Work? Citrate Synthase	707
	SOMETHING EXTRA The Protein Data Bank	710

20 Amino Acid Metabolism | 714

20-1	An Overview of Metabolism and Biochemical Energy	715
20-2	Catabolism of Amino Acids: Deamination	719
20-3	The Urea Cycle	723
20-4	Catabolism of Amino Acids: The Carbon Chains	728
20-5	Biosynthesis of Amino Acids	731
	SOMETHING EXTRA Visualizing Enzyme Structures	735

21 Biomolecules: Carbohydrates | 738

21-1	Classifying Carbohydrates	739
21-2	Representing Carbohydrate Stereochemistry: Fischer Projections	740
21-3	D,L Sugars	745
21-4	Configurations of the Aldoses	746
21-5	Cyclic Structures of Monosaccharides: Anomers	750
21-6	Reactions of Monosaccharides	753
21-7	The Eight Essential Monosaccharides	761
21-8	Disaccharides	762
21-9	Polysaccharides and Their Synthesis	765
21-10	Some Other Important Carbohydrates	768
	SOMETHING EXTRA Sweetness	770

22 Carbohydrate Metabolism | 773

22-1	Hydrolysis of Complex Carbohydrates	774
22-2	Catabolism of Glucose: Glycolysis	776
22-3	Conversion of Pyruvate to Acetyl CoA	783

22-4	The Citric Acid Cycle	787
22-5	Biosynthesis of Glucose: Gluconeogenesis	794
	SOMETHING EXTRA Influenza Pandemics	802

23 Biomolecules: Lipids and Their Metabolism | 805

23-1	Waxes, Fats, and Oils	806
23-2	Soap	809
23-3	Phospholipids	811
23-4	Catabolism of Triacylglycerols: The Fate of Glycerol	813
23-5	Catabolism of Triacylglycerols: β -Oxidation	816
23-6	Biosynthesis of Fatty Acids	820
23-7	Prostaglandins and Other Eicosanoids	826
23-8	Terpenoids	829
23-9	Steroids	837
23-10	Biosynthesis of Steroids	842
23-11	Some Final Comments on Metabolism	848
	SOMETHING EXTRA Statin Drugs	849

24 Biomolecules: Nucleic Acids and Their Metabolism | 852

24-1	Nucleotides and Nucleic Acids	852
24-2	Base Pairing in DNA: The Watson–Crick Model	855
24-3	Replication of DNA	858
24-4	Transcription of DNA	859
24-5	Translation of RNA: Protein Biosynthesis	861
24-6	DNA Sequencing	864
24-7	DNA Synthesis	866
24-8	The Polymerase Chain Reaction	869
24-9	Catabolism of Nucleotides	871
24-10	Biosynthesis of Nucleotides	873
	SOMETHING EXTRA DNA Fingerprinting	875

To access the following online-only chapters, enter ISBN: 978-1-285-84291-2 at www.cengagebrain.com and visit this book's companion website.

e25 Secondary Metabolites: An Introduction to Natural Products Chemistry | 877

25-1	Classifying Natural Products	878
25-2	Biosynthesis of Pyridoxal Phosphate	879
25-3	Biosynthesis of Morphine	884
25-4	Biosynthesis of Erythromycin	894
	SOMETHING EXTRA Bioprospecting: Hunting for Natural Products	903

e26 Orbitals and Organic Chemistry: Pericyclic Reactions | 905

26-1	Molecular Orbitals of Conjugated Pi Systems	905
26-2	Electrocyclic Reactions	908
26-3	Stereochemistry of Thermal Electrocyclic Reactions	910
26-4	Photochemical Electrocyclic Reactions	912
26-5	Cycloaddition Reactions	913
26-6	Stereochemistry of Cycloadditions	914
26-7	Sigmatropic Rearrangements	917
26-8	Some Examples of Sigmatropic Rearrangements	919
26-9	A Summary of Rules for Pericyclic Reactions	921
	SOMETHING EXTRA Vitamin D, the Sunshine Vitamin	922

e27 Synthetic Polymers | 925

27-1	Chain-Growth Polymers	926
27-2	Stereochemistry of Polymerization: Ziegler–Natta Catalysts	928
27-3	Copolymers	930
27-4	Step-Growth Polymers	932

27-5	Olefin Metathesis Polymerization	934
27-6	Polymer Structure and Physical Properties	936
	SOMETHING EXTRA Biodegradable Polymers	940

Appendices

A	Nomenclature of Polyfunctional Organic Compounds	A-1
B	Acidity Constants for Some Organic Compounds	A-7
C	Glossary	A-9
D	Answers to In-Text Problems	A-31

Index | I-1

I've taught organic chemistry many times for many years. Like most faculty, I began by trying to show 19-year-old students the logic and beauty of the subject, thinking that they would find it as fascinating as I did. It didn't take long, though, before I realized what a disconnect there was between my own interests and expectations and those of my students. Some students did develop a real appreciation for the subject, but most seemed to worry primarily about getting into medical school. And why not? If a student has a clear career goal, why shouldn't that person focus his or her efforts toward meeting that goal?

All of us who teach organic chemistry know that the large majority of our students—90% or more, and including many chemistry majors—are interested primarily in medicine, biology, and other life sciences rather than in pure chemistry. But if we are primarily teaching future physicians, biologists, biochemists, and others in the life sciences (not to mention the occasional lawyer, politician, or business person), why do we continue to teach the way we do? Why do our textbooks and lectures spend so much time discussing details of topics that interest professional chemists but have no connection to biology? Wouldn't the limited amount of time we have be better spent paying more attention to the organic chemistry of living organisms and less to the organic chemistry of the research laboratory? Wouldn't it better serve our students if we helped them reach *their* goals rather than reach goals we set for them? I believe so, and I have written this book, *Organic Chemistry with Biological Applications*, third edition, to encourage others who might also be thinking that the time has come to do things a bit differently.

This is, first and foremost, a textbook on organic chemistry. Look through it and you'll find that almost all the standard topics are here, although the treatment of some has been attenuated to save space. Nevertheless, my guiding principle in writing this text has been to put a greater emphasis on those organic reactions and topics that are relevant to biological chemistry than on those that are not.

Organic chemistry, which began historically as the chemistry of living organisms, is now shifting back in that direction, judging from the increasing amount of biologically oriented research done in many chemistry departments and from the renaming of many departments to include chemical biology. Shouldn't our teaching reflect that shift?



Organization of the Text

Four distinct groups of chapters are apparent in this text. The first group (Chapters 1–6 and 10–11) covers the traditional principles of organic chemistry and spectroscopy that are essential for building further understanding.

The second group (Chapters 7–9 and 12–18) covers the common organic reactions found in all texts. As each laboratory reaction is discussed, however, a biological example is also shown to make the material more interesting and meaningful to students. For instance, trans fatty acids are described at the same time that catalytic hydrogenation is discussed (Section 8-5); biological methylations with *S*-adenosylmethionine are covered with S_N2 reactions (Section 12-11); and biological reductions with NADH are introduced along with laboratory NaBH_4 reductions (Section 13-3).

The third group of chapters (19–24) is unique to this text in its depth of coverage. These chapters deal exclusively with the main classes of biomolecules—amino acids and proteins, carbohydrates, lipids, and nucleic acids—and show how thoroughly organic chemistry permeates biological chemistry. Following an introduction to each class, major metabolic pathways for that class are discussed from the perspective of mechanistic organic chemistry.

And finally, for those faculty who want additional coverage of natural products, polymers, and pericyclic reactions, the book ends with a fourth group of chapters (25–27) devoted to those topics. This final group is available in both electronic and hard-copy formats at the request of the adopter.



What's New

Text content has been revised substantially for this 3rd edition as a result of user feedback. Most noticeably, two new chapters have been made available for those who want them: Chapter 26 on Pericyclic Reactions and Chapter 27 on Synthetic Polymers. Other changes include:

- Every chapter ends with a brief *Something Extra* essay that has been repositioned to follow immediately after the last text section where it is more likely to be noticed and read.
- The problems at the ends of chapters are now organized by topic to make it easier for students to find questions on specific subjects.
- New problems have been added in every chapter, 164 in all.
- Text references to all numbered **FIGURES** and **TABLES** are called out in color to help students move more easily between text and art.
- All figure captions have a boldfaced title, and the captions themselves use colored text to make it easier to focus on specific features in the figure art.

New topics in this 3rd edition include:

- A new *Something Extra*, “Organic Foods: Risk versus Benefit,” in Chapter 1
- A new *Something Extra*, “Alkaloids: From Cocaine to Dental Anesthetics,” in Chapter 2
- New coverage of bridged bicyclic molecules in Section 4-9
- New coverage of mercury-catalyzed alkyne hydration in Section 8-15
- New coverage of aromatic fluorination and fluorinated drugs in Section 9-6
- New coverage of alcohol to alkyl fluoride conversions in Section 12-3
- A new Section 12-5, “Organometallic Coupling Reactions,” covering both organocopper reactions and the palladium-catalyzed Suzuki–Miyaura reaction

- A new *Something Extra*, “Naturally Occurring Organohalides,” in Chapter 12
- New coverage of epoxide cleavage by nucleophiles in Section 13-10
- A new Section 13-11, “Crown Ethers and Ionophores”
- New coverage of hydrates of α -keto acids in Section 14-5
- A new *Something Extra*, “Barbiturates,” in Chapter 17
- Threonine catabolism deleted from Section 20-4
- New coverage of Kiliani–Fischer carbohydrate chain extension and Wohl degradation in Section 21-6
- A new Section 23-7, “Prostaglandins and Other Eicosanoids”
- A new *Something Extra*, “Statin Drugs,” in Chapter 23
- A new electronic Chapter 26, “Orbitals and Organic Chemistry: Pericyclic Reactions”
- A new electronic Chapter 27, “Synthetic Polymers”

I believe that there is more than enough standard organic chemistry in this book, and that the coverage of biological chemistry far surpasses that found in any other text. My hope is that all the students we teach, including those who worry about medical school, will come to agree that there is also logic and beauty here.



Features

Reaction Mechanisms

The innovative vertical presentation of reaction mechanisms that has become a hallmark of all my texts is retained in *Organic Chemistry with Biological Applications*, third edition. Mechanisms in this format have the reaction steps printed vertically, while the changes taking place in each step are explained next to the reaction arrows. With this format, students can see what is occurring at each step in a reaction without having to jump back and forth between structures and text. See Figure 14.4 for a chemical example and Figure 22.8 for a biological example.

Visualization of Biological Reactions

One of the most important goals of this book is to demystify biological chemistry—to show students how the mechanisms of biological reactions are the same as those of laboratory organic reactions. Toward this end, and to let students visualize more easily the changes that occur during reactions of large biomolecules, I use an innovative method for focusing attention on the reacting parts in large molecules by “ghosting” the nonreacting parts. See Figure 13.4 for an example.

Other Features

- “Why do we have to learn this?” I’ve been asked this question by students so many times that I thought I should answer it in writing. Thus, every chapter begins with a short introduction called “Why This Chapter?” that provides an up-front answer to the question, explaining why the material about to be covered is important and how the organic chemistry in each chapter relates to biological chemistry.

- Worked Examples in each chapter are titled to give students a frame of reference. Each Worked Example includes a Strategy and worked-out Solution, followed by Problems for students to try on their own.
- A *Something Extra* is provided in each chapter following the final text section to relate real-world concepts to students' lives. New topics in this edition include Organic Foods: Risk versus Benefit (Chapter 1), Alkaloids: From Cocaine to Dental Anesthetics (Chapter 2), Naturally Occurring Organohalides (Chapter 12), Barbiturates (Chapter 17), and Statin Drugs (Chapter 23).
- Visualizing Chemistry problems at the end of each chapter offer students an opportunity to see chemistry in a different way by visualizing whole molecules rather than simply interpreting structural formulas.
- The Summary and Key Word list at the end of each chapter helps students focus on the key concepts in that chapter.
- The Summary of Reactions at the end of specific chapters brings together the key reactions from those chapters into a single complete list.
- An overview entitled "A Preview of Carbonyl Chemistry" following Chapter 13 highlights the idea that studying organic chemistry involves both summarizing past ideas and looking ahead to new ones.
- Current IUPAC nomenclature rules are used in this text. Recognizing that these rules have not been universally adopted in the United States, the small differences between new and old rules are also discussed.



Alternate Edition

Hybrid version with access (24 months) to OWLv2 with MindTap Reader ISBN: 978-1-285-86784-7

A briefer, paperbound version of *Organic Chemistry with Biological Applications*, third edition, does not contain the end-of-chapter problems, which can be assigned in OWL, the online homework and learning system for this book. Access to OWLv2 and MindTap Reader eBook is included with the Hybrid version. MindTap Reader is the full version of the text, with all end-of-chapter questions and problem sets.



Supporting Materials for Students and Instructors

Please visit www.cengage.com/chemistry/mcmurry/ocba3e for information about student and instructor resources for this text.



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I am grateful to the following colleagues who reviewed the manuscript for this book.

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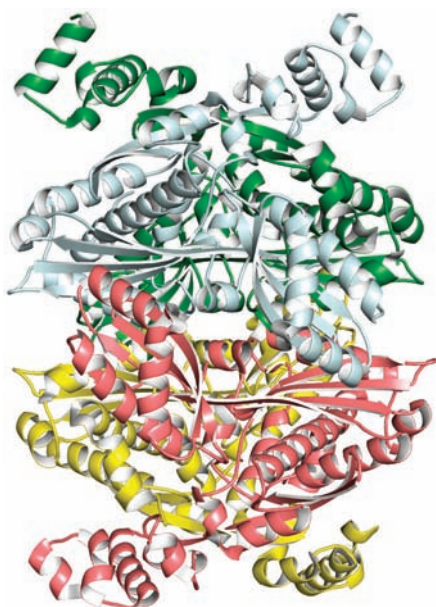
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Structure and Bonding



A model of the enzyme HMG-CoA reductase, which catalyzes a crucial step in the body's synthesis of cholesterol.

WHY THIS CHAPTER?

We'll ease into the study of organic chemistry by first reviewing some ideas about atoms, bonds, and molecular geometry that you may recall from your general chemistry course. Much of the material in this chapter and the next is likely to be familiar to you, but it's nevertheless a good idea to make sure you understand it before going on.

A scientific revolution is now taking place—a revolution that will give us safer and more effective medicines, cure our genetic diseases, increase our life spans, and improve the quality of our lives. The revolution is based in understanding the structure, regulation, and function of the approximately 21,000 genes in the human body, and it relies on organic chemistry as the enabling science. It is our fundamental chemical understanding of biological processes at the molecular level that has made the revolution possible and that continues to drive it. Anyone who wants to understand or be a part of the remarkable advances now occurring in medicine and the biological sciences must first understand organic chemistry.

As an example of how organic and biological chemistry together are affecting modern medicine, look at coronary heart disease—the buildup of cholesterol-containing plaques on the walls of arteries, leading to restricted blood flow and eventual heart attack. Coronary heart disease is the leading cause of death for both men and women older than age 20, and it's estimated that up to one-third of women and one-half of men will develop the disease at some point in their lives.

The onset of coronary heart disease is directly correlated with blood cholesterol levels, and the first step in disease prevention is to lower those levels. It turns out that only about 25% of our blood cholesterol comes from what we eat; the remaining 75% (about 1000 mg each day) is made, or *biosynthesized*, by our bodies from dietary fats and carbohydrates. Thus, any effective plan for

CONTENTS

- 1-1 Atomic Structure: The Nucleus
- 1-2 Atomic Structure: Orbitals
- 1-3 Atomic Structure: Electron Configurations
- 1-4 Development of Chemical Bonding Theory
- 1-5 Describing Chemical Bonds: Valence Bond Theory
- 1-6 sp^3 Hybrid Orbitals and the Structure of Methane
- 1-7 sp^3 Hybrid Orbitals and the Structure of Ethane
- 1-8 sp^2 Hybrid Orbitals and the Structure of Ethylene
- 1-9 sp Hybrid Orbitals and the Structure of Acetylene
- 1-10 Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur
- 1-11 Describing Chemical Bonds: Molecular Orbital Theory
- 1-12 Drawing Chemical Structures

SOMETHING EXTRA

Organic Foods: Risk versus Benefit

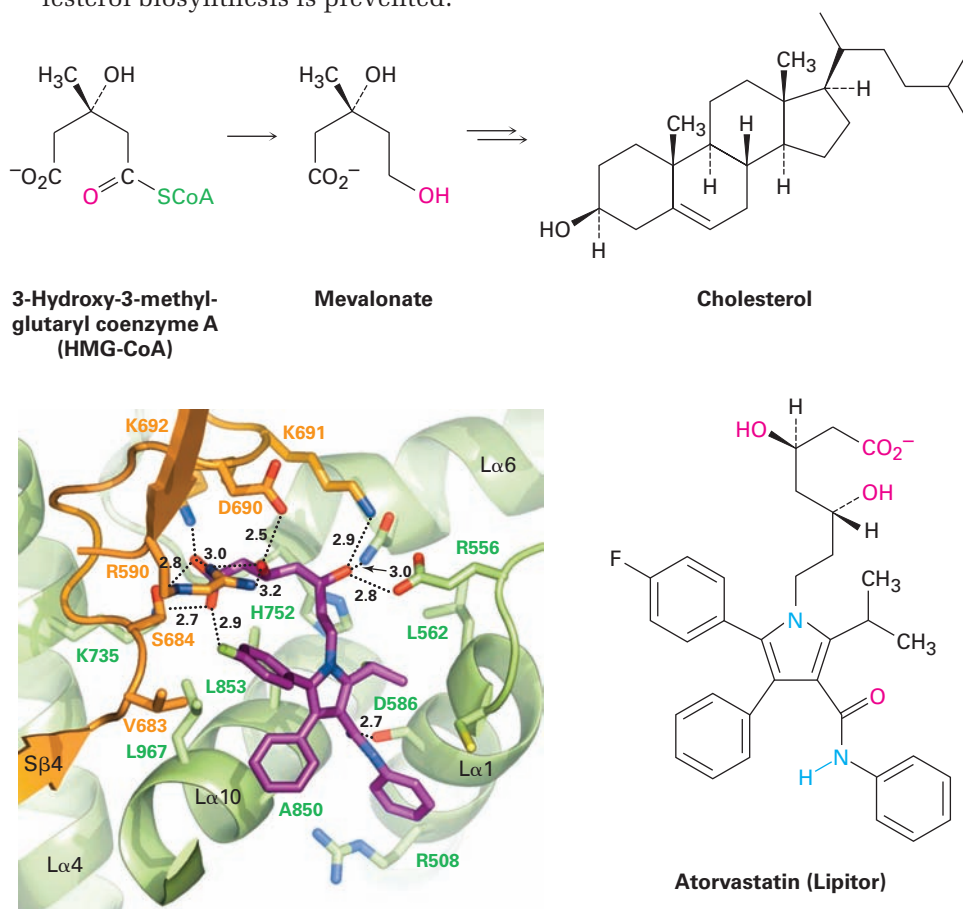


lowering our cholesterol level means limiting the amount that our bodies biosynthesize, which in turn means understanding and controlling the chemical reactions that make up the metabolic pathway for cholesterol biosynthesis.

Now look at **FIGURE 1.1**. Although the figure probably looks unintelligible at this point, don't worry; before long it will make perfectly good sense. What's shown in Figure 1.1 is the biological conversion of a compound called 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate, a crucial step in the pathway by which our bodies synthesize cholesterol. Also shown in the figure is an X-ray crystal structure of the active site in the HMG-CoA reductase enzyme that catalyzes the reaction, along with a molecule of the drug atorvastatin (sold under the trade name Lipitor), which binds to the enzyme and stops it from functioning. With the enzyme thus inactivated, cholesterol biosynthesis is prevented.

FIGURE 1.1 How does atorvastatin control cholesterol biosynthesis?

The metabolic conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate is a crucial step in the body's pathway for biosynthesizing cholesterol. An X-ray crystal structure of the active site in the HMG-CoA reductase enzyme that catalyzes the reaction is shown, along with a molecule of atorvastatin (Lipitor) that is bound in the active site and stops the enzyme from functioning. With the enzyme thus inactivated, cholesterol biosynthesis is prevented.



Atorvastatin is one of a widely prescribed class of drugs called *statins*, which reduce a person's risk of coronary heart disease by lowering the level of cholesterol in his or her blood. Taken together, the statins—atorvastatin (Lipitor), simvastatin (Zocor), rosuvastatin (Crestor), pravastatin (Pravachol), lovastatin (Mevacor), and several others—are the most widely prescribed drugs in the world, with global sales of \$29 billion annually.

The statins function by blocking the HMG-CoA reductase enzyme and preventing it from converting HMG-CoA to mevalonate, thereby limiting the body's biosynthesis of cholesterol. As a result, blood cholesterol levels drop and coronary heart disease becomes less likely. It sounds simple, but it would

be impossible without detailed knowledge of the steps in the pathway for cholesterol biosynthesis, the enzymes that catalyze those steps, and how precisely shaped organic molecules can be designed to block those steps. Organic chemistry is what makes it all happen.

Historically, the term **organic chemistry** dates to the late 1700s, when it was used to mean the chemistry of compounds found in living organisms. Little was known about chemistry at that time, and the behavior of the “organic” substances isolated from plants and animals seemed different from that of the “inorganic” substances found in minerals. Organic compounds were generally low-melting solids and were usually more difficult to isolate, purify, and work with than high-melting inorganic compounds. By the mid-1800s, however, it was clear that there was no fundamental difference between organic and inorganic compounds: the same principles explain the behaviors of all substances, regardless of origin or complexity. The only distinguishing characteristic of organic chemicals is that *all contain the element carbon*.

But why is carbon special? Why, of the more than 70 million presently known chemical compounds, do more than 99% of them contain carbon? The answers to these questions come from carbon’s electronic structure and its consequent position in the periodic table (**FIGURE 1.2**). As a group 4A element, carbon can share four valence electrons and form four strong covalent bonds. Furthermore, carbon atoms can bond to one another, forming long chains and rings. Carbon, alone of all elements, is able to form an immense diversity of compounds, from the simple to the staggeringly complex—from methane, with one carbon atom, to DNA, which can have more than *100 million* carbons.

Group 1A																	8A
H	2A											3A	4A	5A	6A	7A	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac															

FIGURE 1.2 Elements commonly found in organic compounds. Carbon, hydrogen, and other elements commonly found in organic compounds are shown in the colors typically used to represent them.

Not all carbon compounds are derived from living organisms of course. Modern chemists have developed a remarkably sophisticated ability to design and synthesize new organic compounds in the laboratory—medicines, dyes, polymers, and a host of other substances. Organic chemistry touches the lives of everyone; its study can be a fascinating undertaking.

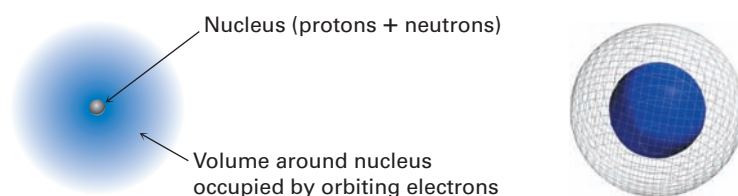
1-1 Atomic Structure: The Nucleus

As you might remember from your general chemistry course, an atom consists of a dense, positively charged *nucleus* surrounded at a relatively large distance by negatively charged *electrons* (**FIGURE 1.3**). The nucleus consists

of subatomic particles called *neutrons*, which are electrically neutral, and *protons*, which are positively charged. Because an atom is neutral overall, the number of positive protons in the nucleus and the number of negative electrons surrounding the nucleus are the same.

Although extremely small—about 10^{-14} to 10^{-15} meter (m) in diameter—the nucleus nevertheless contains essentially all the mass of the atom. Electrons have negligible mass and circulate around the nucleus at a distance of approximately 10^{-10} m. Thus, the diameter of a typical atom is about 2×10^{-10} m, or 200 picometers (pm), where $1 \text{ pm} = 10^{-12} \text{ m}$. To give you an idea of how small this is, a thin pencil line is about 3 million carbon atoms wide. (Many organic chemists and biochemists, particularly those in the United States, still use the unit *angstrom* (\AA) to express atomic distances, where $1 \text{ \AA} = 100 \text{ pm} = 10^{-10} \text{ m}$, but we'll stay with the SI unit picometer in this book.)

FIGURE 1.3 Schematic view of an atom. The dense, positively charged nucleus contains most of the atom's mass and is surrounded by negatively charged electrons. The three-dimensional view on the right shows calculated electron-density surfaces. Electron density increases steadily toward the nucleus and is 40 times greater at the **blue solid surface** than at the **gray mesh surface**.



A specific atom is described by its *atomic number* (Z), which gives the number of protons (or electrons) it contains, and its *mass number* (A), which gives the total number of protons plus neutrons in its nucleus. All the atoms of a given element have the same atomic number—1 for hydrogen, 6 for carbon, 15 for phosphorus, and so on—but they can have different mass numbers depending on how many neutrons they contain. Atoms with the same atomic number but different mass numbers are called **isotopes**. The weighted average mass in unified atomic mass units (u) of an element's naturally occurring isotopes is called the element's *atomic weight*—1.008 u for hydrogen, 12.011 u for carbon, 30.974 u for phosphorus, and so on.

1-2 Atomic Structure: Orbitals

How are the electrons distributed in an atom? According to the quantum mechanical model, the behavior of a specific electron in an atom can be described by a mathematical expression called a *wave equation*—the same sort of expression used to describe the motion of waves in a fluid. The solution to a wave equation is called a *wave function*, or **orbital**, and is denoted by the Greek letter psi, ψ .

When the square of the wave function, ψ^2 , is plotted in three-dimensional space, an orbital describes the volume of space around a nucleus that an electron is most likely to occupy. You might therefore think of an orbital as looking like a photograph of the electron taken at a slow shutter speed. In such a photo, the orbital would appear as a blurry cloud, indicating the region of space around the nucleus where the electron has been. This electron cloud doesn't have a sharp boundary, but for practical purposes we can set the limits

by saying that an orbital represents the space where an electron spends 90% to 95% of its time.

What do orbitals look like? There are four different kinds of orbitals, denoted s , p , d , and f , each with a different shape. Of the four, we'll be concerned primarily with s and p orbitals because these are the most common in organic and biological chemistry. An s orbital is spherical, with the nucleus at its center; a p orbital is dumbbell-shaped; and four of the five d orbitals are cloverleaf-shaped, as shown in **FIGURE 1.4**. The fifth d orbital is shaped like an elongated dumbbell with a doughnut around its middle.

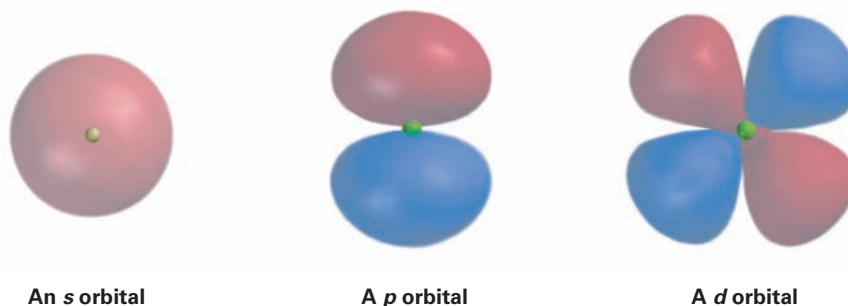


FIGURE 1.4 Representations of s , p , and d orbitals. An s orbital is spherical, a p orbital is dumbbell-shaped, and four of the five d orbitals are cloverleaf-shaped. Different lobes of p orbitals are often drawn for convenience as teardrops, but their true shape is more like that of a doorknob, as indicated.

The orbitals in an atom are organized into different layers around the nucleus, or **electron shells**, of successively larger size and energy. Different shells contain different numbers and kinds of orbitals, and each orbital within a shell can be occupied by a maximum of two electrons. The first shell contains only a single s orbital, denoted $1s$, and thus holds only 2 electrons. The second shell contains one $2s$ orbital and three $2p$ orbitals and thus holds a total of 8 electrons. The third shell contains a $3s$ orbital, three $3p$ orbitals, and five $3d$ orbitals, for a total capacity of 18 electrons. These orbital groupings and their energy levels are shown in **FIGURE 1.5**.

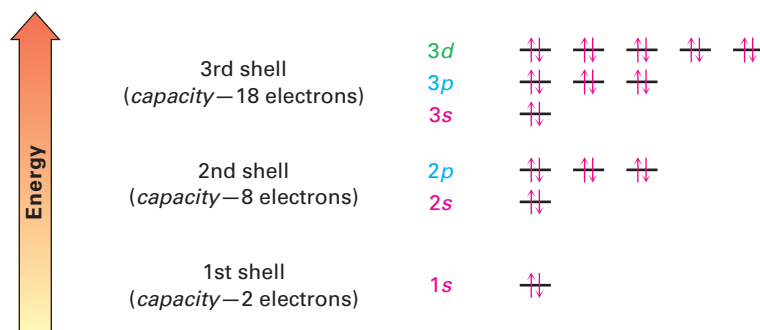
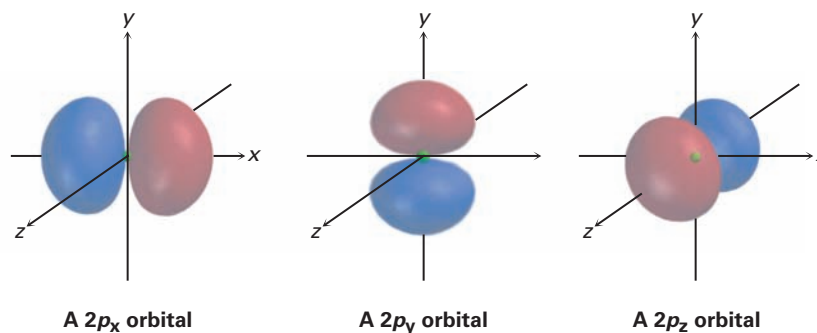


FIGURE 1.5 Energy levels of electrons in an atom. The first shell holds a maximum of 2 electrons in one $1s$ orbital; the second shell holds a maximum of 8 electrons in one $2s$ and three $2p$ orbitals; the third shell holds a maximum of 18 electrons in one $3s$, three $3p$, and five $3d$ orbitals; and so on. The two electrons in each orbital are represented by up and down arrows, $\uparrow\downarrow$. Although not shown, the energy level of the $4s$ orbital falls between $3p$ and $3d$.

The three different p orbitals within a given shell are oriented in space along mutually perpendicular directions, denoted p_x , p_y , and p_z . As shown in **FIGURE 1.6**, the two lobes of each p orbital are separated by a region of zero electron density called a **node**. Furthermore, the two orbital regions separated by the node have different algebraic signs, $+$ and $-$, in the wave function, as represented by the different colors in Figure 1.6. As we'll see in Section 1-11, the algebraic signs of the different orbital lobes have important consequences with respect to chemical bonding and chemical reactivity.

FIGURE 1.6 Shapes of the 2p orbitals. Each of the three mutually perpendicular, dumbbell-shaped orbitals has two lobes separated by a node. The two lobes have different algebraic signs in the corresponding wave function, as indicated by the different colors.



1-3 Atomic Structure: Electron Configurations

The lowest-energy arrangement, or **ground-state electron configuration**, of an atom is a listing of the orbitals occupied by its electrons. We can predict this arrangement by following three rules:

Rule 1

The lowest-energy orbitals fill up first, according to the order $1s \rightarrow 2s \rightarrow 2p \rightarrow 3s \rightarrow 3p \rightarrow 4s \rightarrow 3d$, a statement called the *aufbau principle*. Note that the $4s$ orbital lies between the $3p$ and $3d$ orbitals in energy.

Rule 2

Electrons act in some ways as if they were spinning around an axis, in somewhat the same way that the earth spins. This spin can have two orientations, denoted as up (\uparrow) and down (\downarrow). Only two electrons can occupy an orbital, and they must be of opposite spin, a statement called the *Pauli exclusion principle*.

Rule 3

If two or more empty orbitals of equal energy are available, one electron occupies each with spins parallel until all orbitals are half-full, a statement called *Hund's rule*.

Some examples of how these rules apply are shown in **TABLE 1.1**. Hydrogen, for instance, has only one electron, which must occupy the lowest-energy orbital. Thus, hydrogen has a $1s$ ground-state configuration. Carbon has six electrons and the ground-state configuration $1s^2 2s^2 2p_x^1 2p_y^1$, and so forth. Note that a superscript is used to represent the number of electrons in a particular orbital.

TABLE 1.1 Ground-State Electron Configurations of Some Elements

Element	Atomic number	Configuration	Element	Atomic number	Configuration
Hydrogen	1	$1s \uparrow$	Phosphorus	15	$3p \uparrow \uparrow \uparrow$ $3s \uparrow \downarrow$
Carbon	6	$2p \uparrow \uparrow \text{---}$ $2s \uparrow \downarrow$ $1s \uparrow \downarrow$			$2p \uparrow \uparrow \uparrow$ $2s \uparrow \downarrow$ $1s \uparrow \downarrow$

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PROBLEM 1.1

Give the ground-state electron configuration for each of the following elements:

(a) Oxygen (b) Phosphorus (c) Sulfur

PROBLEM 1.2

How many electrons does each of the following biological trace elements have in its outermost electron shell?

(a) Magnesium (b) Cobalt (c) Selenium

1-4 Development of Chemical Bonding Theory

By the mid-1800s, the new science of chemistry was developing rapidly and chemists had begun to probe the forces holding atoms together in compounds. In 1858, August Kekulé and Archibald Couper independently proposed that, in all its compounds, carbon is *tetravalent*—it always forms four bonds when it joins other elements to form stable compounds. Furthermore, said Kekulé, carbon atoms can bond to one another to form extended chains of linked atoms.

Shortly after the tetravalent nature of carbon was proposed, extensions to the Kekulé–Couper theory were made when the possibility of *multiple* bonding between atoms was suggested. Emil Erlenmeyer proposed a carbon–carbon triple bond for acetylene, and Alexander Crum Brown proposed a carbon–carbon double bond for ethylene. In 1865, Kekulé provided another major advance when he suggested that carbon chains can double back on themselves to form *rings* of atoms.

Although Kekulé and Couper were correct in describing the tetravalent nature of carbon, chemistry was still viewed in a two-dimensional way until 1874. In that year, Jacobus van't Hoff and Joseph Le Bel added a third dimension to our ideas about organic compounds. They proposed that the four bonds of carbon are not oriented randomly but have specific spatial directions. Van't Hoff went even further and suggested that the four atoms to which carbon is bonded sit at the corners of a regular tetrahedron, with carbon in the center.

A representation of a tetrahedral carbon atom is shown in **FIGURE 1.7**. Note the conventions used to show three-dimensionality: solid lines represent bonds in the plane of the page, the heavy wedged line represents a bond coming out of the page toward the viewer, and the dashed line represents a bond receding back behind the page away from the viewer. These representations will be used throughout this text.

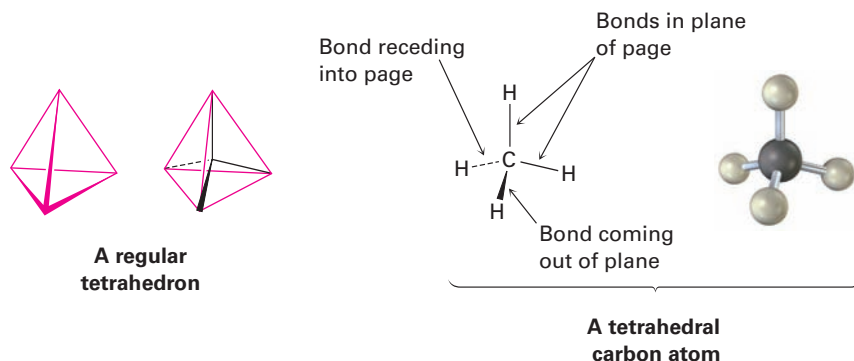


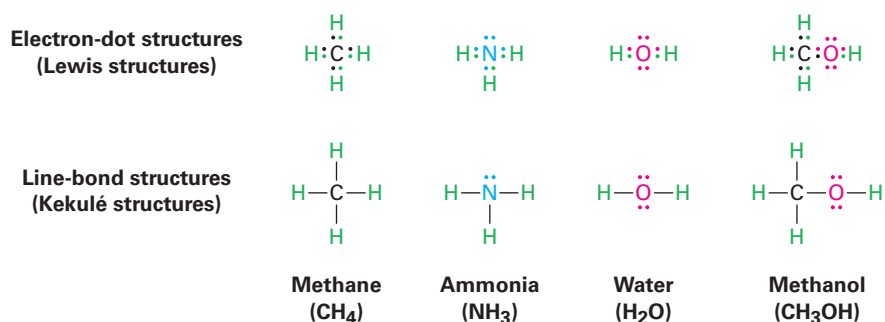
FIGURE 1.7 A representation of van't Hoff's tetrahedral carbon atom. The solid lines represent bonds in the plane of the paper, the heavy wedged line represents a bond coming out of the plane of the page, and the dashed line represents a bond going back behind the plane of the page.

Why, though, do atoms bond together, and how can bonds be described electronically? The *why* question is relatively easy to answer: atoms bond together because the compound that results is more stable and lower in energy than the separate atoms. Energy (usually as heat) is always released and flows *out of* the chemical system when a chemical bond forms. Conversely, energy must always be put *into* the system to break a chemical bond. Making bonds always releases energy, and breaking bonds always absorbs energy. The *how* question is more difficult. To answer it, we need to know more about the electronic properties of atoms.

We know through observation that eight electrons (an electron *octet*) in an atom's outermost shell, or **valence shell**, impart special stability to the noble-gas elements in group 8A of the periodic table: Ne (2 + 8); Ar (2 + 8 + 8); Kr (2 + 8 + 18 + 8). We also know that the chemistry of main-group elements is governed by their tendency to take on the electron configuration of the nearest noble gas. The alkali metals in group 1A, for example, achieve a noble-gas configuration by losing the single *s* electron from their valence shell to form a cation, while the halogens in group 7A achieve a noble-gas configuration by gaining a *p* electron to fill their valence shell and form an anion. The resultant ions are held together in compounds like $\text{Na}^+ \text{Cl}^-$ by an electrostatic attraction of unlike charges that we call an **ionic bond**.

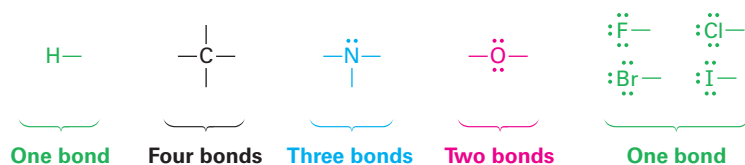
But how do elements closer to the middle of the periodic table form bonds? Look at methane, CH_4 , the main constituent of natural gas, for example. The bonding in methane is not ionic because it would take too much energy for carbon ($1s^2 2s^2 2p^2$) to either gain or lose *four* electrons to achieve a noble-gas configuration. Instead, carbon bonds to other atoms, not by gaining or losing electrons, but by *sharing* them. Such a shared-electron bond, first proposed in 1916 by G. N. Lewis, is called a **covalent bond**. The neutral collection of atoms held together by covalent bonds is called a **molecule**.

A simple way of indicating the covalent bonds in molecules is to use what are called *Lewis structures*, or **electron-dot structures**, in which the valence-shell electrons of an atom are represented as dots. Thus, hydrogen has one dot representing its *1s* electron, carbon has four dots ($2s^2 2p^2$), oxygen has six dots ($2s^2 2p^4$), and so on. A stable molecule results whenever a noble-gas configuration is achieved for all the atoms—eight dots (an octet) for main-group atoms or two dots for hydrogen. Simpler still is the use of *Kekulé structures*, or **line-bond structures**, in which two-electron covalent bonds are indicated as lines drawn between atoms.

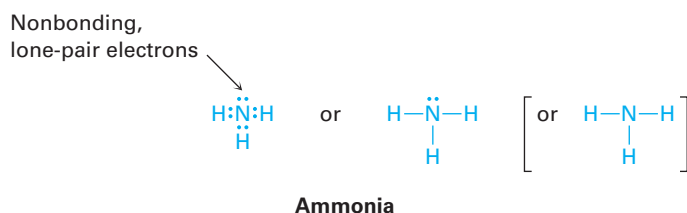


The number of covalent bonds an atom forms depends on how many additional valence electrons it needs to reach a noble-gas configuration. Hydrogen

has one valence electron ($1s$) and needs one more to reach the helium configuration ($1s^2$), so it forms one bond. Carbon has four valence electrons ($2s^2 2p^2$) and needs four more to reach the neon configuration ($2s^2 2p^6$), so it forms four bonds. Nitrogen has five valence electrons ($2s^2 2p^3$), needs three more, and forms three bonds; oxygen has six valence electrons ($2s^2 2p^4$), needs two more, and forms two bonds; and the halogens have seven valence electrons, need one more, and form one bond.



Valence electrons that are not used for bonding are called **lone-pair electrons**, or *nonbonding electrons*. The nitrogen atom in ammonia (NH_3), for instance, shares six valence electrons in three covalent bonds and has its remaining two valence electrons in a nonbonding lone pair. As a time-saving shorthand, nonbonding electrons are often omitted when drawing line-bond structures, but you still have to keep them in mind since they're often crucial in chemical reactions.



Predicting the Number of Bonds Formed by Atoms in Molecules

WORKED EXAMPLE 1.1

How many hydrogen atoms does phosphorus bond to in phosphine, PH_3 ?

Strategy

Identify the periodic group of phosphorus, and tell from that how many electrons (bonds) are needed to make an octet.

Solution

Phosphorus, like nitrogen, is in group 5A of the periodic table and has five valence electrons. It thus needs to share three more electrons to make an octet and therefore bonds to three hydrogen atoms, giving PH_3 .

Drawing Electron-Dot and Line-Bond Structures

WORKED EXAMPLE 1.2

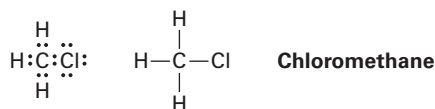
Draw both electron-dot and line-bond structures for chloromethane, CH_3Cl .

Strategy

Remember that a bond—that is, a pair of shared electrons—is represented as a line between atoms.

Solution

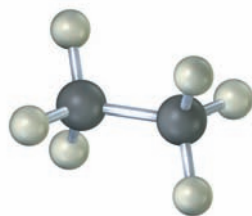
Hydrogen has one valence electron, carbon has four valence electrons, and chlorine has seven valence electrons. Thus, chloromethane is represented as

**PROBLEM 1.3**

Draw a molecule of chloroform, CHCl_3 , using solid, wedged, and dashed lines to show its tetrahedral geometry.

PROBLEM 1.4

Convert the adjacent representation of ethane, C_2H_6 , into a conventional drawing that uses solid, wedged, and dashed lines to indicate tetrahedral geometry around each carbon (gray = C, ivory = H).



Ethane

PROBLEM 1.5

What are likely formulas for the following substances?

- (a) $\text{CH}_? \text{Cl}_2$ (b) $\text{CH}_3\text{SH}_?$ (c) $\text{CH}_3\text{NH}_?$

PROBLEM 1.6

Draw line-bond structures for the following substances, showing all nonbonding electrons:

- (a) $\text{CH}_3\text{CH}_2\text{OH}$, ethanol (b) H_2S , hydrogen sulfide
(c) CH_3NH_2 , methylamine (d) $\text{N}(\text{CH}_3)_3$, trimethylamine

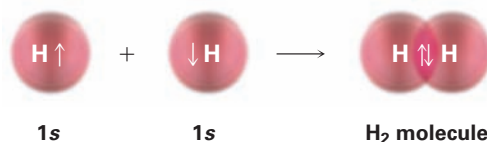
PROBLEM 1.7

Why can't an organic molecule have the formula C_2H_7 ?

1-5 Describing Chemical Bonds: Valence Bond Theory

How does electron sharing lead to bonding between atoms? Two models have been developed to describe covalent bonding: *valence bond theory* and *molecular orbital theory*. Each model has its strengths and weaknesses, and chemists tend to use them interchangeably depending on the circumstances. Valence bond theory is the more easily visualized of the two, so most of the descriptions we'll use in this book derive from that approach.

According to **valence bond theory**, a covalent bond forms when two atoms approach each other closely and a singly occupied orbital on one atom *overlaps* a singly occupied orbital on the other atom. The electrons are now paired in the overlapping orbitals and are attracted to the nuclei of both atoms, thus bonding the atoms together. In the H_2 molecule, for example, the H–H bond results from the overlap of two singly occupied hydrogen $1s$ orbitals:



The overlapping orbitals in the H_2 molecule have the elongated egg shape we might get by pressing two spheres together. If a plane were to pass through the middle of the bond, the intersection of the plane and the overlapping orbitals would be a circle. In other words, the H–H bond is *cylindrically symmetrical*, as shown in **FIGURE 1.8**. Such bonds, which are formed by the head-on overlap of two atomic orbitals along a line drawn between the nuclei, are called **sigma (σ) bonds**.

During the bond-forming reaction $2 H\cdot \rightarrow H_2$, 436 kJ/mol (104 kcal/mol) of energy is released. Because the product H_2 molecule has 436 kJ/mol less energy than the starting 2 $H\cdot$ atoms, the product is more stable than the reactants and we say that the H–H bond has a **bond strength** of 436 kJ/mol. In other words, we would have to put 436 kJ/mol of energy *into* the H–H bond to break the H_2 molecule apart into H atoms (**FIGURE 1.9**). [For convenience, we'll generally give energies in both kilocalories (kcal) and the SI unit kilojoules (kJ): 1 kJ = 0.2390 kcal; 1 kcal = 4.184 kJ.]

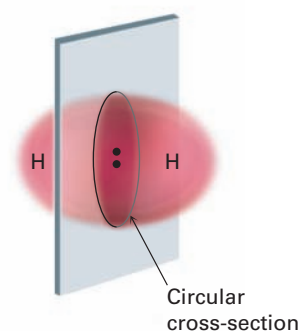
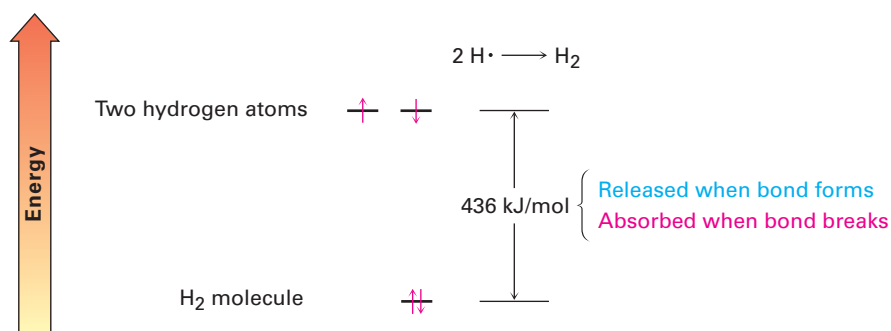


FIGURE 1.8 Cylindrical symmetry of the H–H σ bond. The intersection of a plane cutting through the σ bond is a circle.

FIGURE 1.9 Relative energy levels of two H atoms and the H_2 molecule. The H_2 molecule has 436 kJ/mol (104 kcal/mol) less energy than the two H atoms, so 436 kJ/mol of energy is released when the H–H bond forms. Conversely, 436 kJ/mol is absorbed when the H–H bond breaks.

How close are the two nuclei in the H_2 molecule? If they are too close, they will repel each other because both are positively charged, yet if they are too far apart, they won't be able to share the bonding electrons. Thus, there is an optimum distance between nuclei that leads to maximum stability (**FIGURE 1.10**). Called the **bond length**, this distance is 74 pm in the H_2 molecule. Every covalent bond has both a characteristic bond strength and bond length.

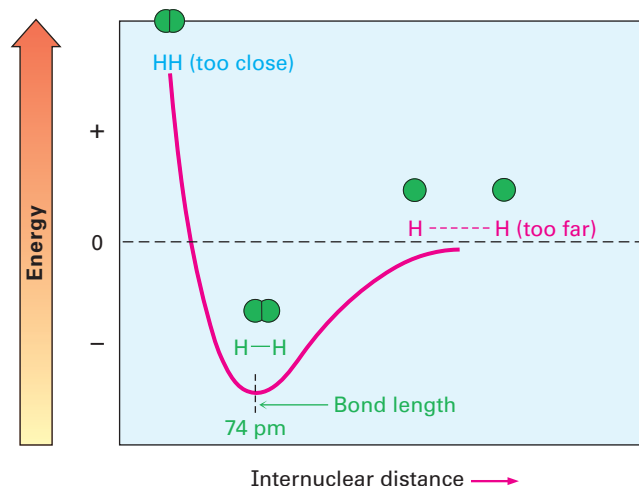


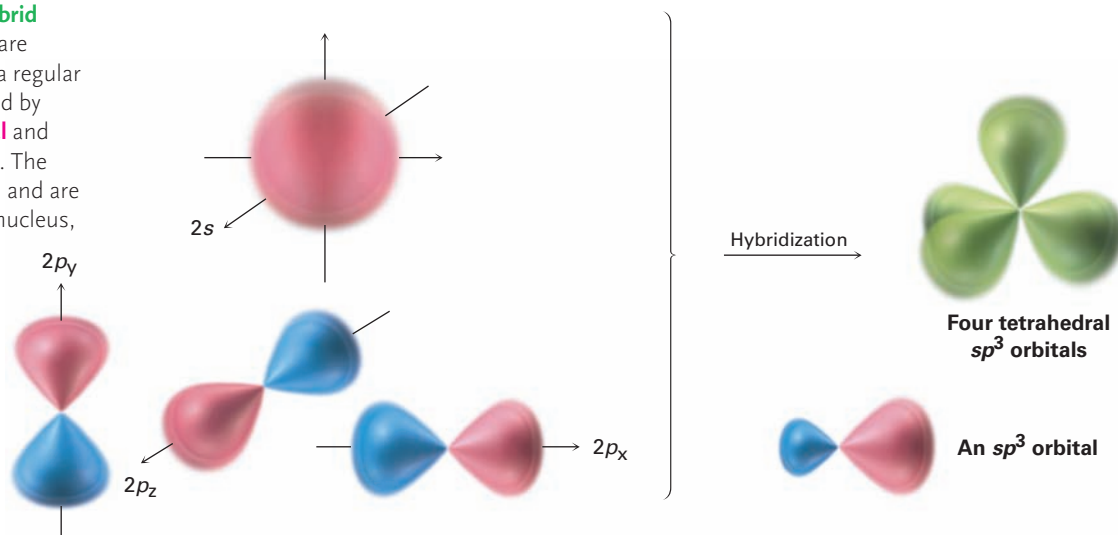
FIGURE 1.10 A plot of energy versus internuclear distance for two hydrogen atoms. The distance between nuclei at the minimum energy point is the **bond length**.

1-6 sp^3 Hybrid Orbitals and the Structure of Methane

The bonding in the hydrogen molecule is fairly straightforward, but the situation is more complicated in organic molecules with tetravalent carbon atoms. Take methane, CH_4 , for instance. As we've seen, carbon has four valence electrons ($2s^2 2p^2$) and forms four bonds. Because carbon uses two kinds of orbitals for bonding, $2s$ and $2p$, we might expect methane to have two kinds of C–H bonds. In fact, though, all four C–H bonds in methane are identical and are spatially oriented toward the corners of a regular tetrahedron, as shown previously in Figure 1.7. How can we explain this?

An answer was provided in 1931 by Linus Pauling, who showed mathematically how an s orbital and three p orbitals on an atom can combine, or *hybridize*, to form four equivalent atomic orbitals with tetrahedral orientation. Shown in **FIGURE 1.11**, these tetrahedrally oriented orbitals are called sp^3 hybrids. Note that the superscript 3 in the name sp^3 tells how many of each type of atomic orbital combine to form the hybrid, not how many electrons occupy it.

FIGURE 1.11 Four sp^3 hybrid orbitals. The four orbitals are oriented to the corners of a regular tetrahedron and are formed by combination of an s orbital and three p orbitals (red/blue). The sp^3 hybrids have two lobes and are unsymmetrical about the nucleus, giving them a directionality and allowing them to form strong bonds to other atoms.



The concept of hybridization explains *how* carbon forms four equivalent tetrahedral bonds but not *why* it does so. The shape of the hybrid orbital suggests the answer. When an s orbital hybridizes with three p orbitals, the resultant sp^3 hybrid orbitals are unsymmetrical about the nucleus. One of the two lobes is much larger than the other and can therefore overlap more effectively with an orbital from another atom when it forms a bond. As a result, sp^3 hybrid orbitals form stronger bonds than do unhybridized s or p orbitals.

The asymmetry of sp^3 orbitals arises because, as noted previously, the two lobes of a p orbital have different algebraic signs, $+$ and $-$. Thus, when a p orbital hybridizes with an s orbital, the positive p lobe adds to the s orbital but the negative p lobe subtracts from the s orbital. The resultant hybrid orbital is therefore unsymmetrical about the nucleus and is strongly oriented in one direction.

When each of the four identical sp^3 hybrid orbitals of a carbon atom overlaps with the $1s$ orbital of a hydrogen atom, four identical C–H bonds are formed and methane results. Each C–H bond in methane has a strength of 439 kJ/mol (105 kcal/mol) and a length of 109 pm. Because the four bonds

have a specific geometry, we also can define a property called the **bond angle**. The angle formed by each H–C–H is 109.5° , the so-called tetrahedral angle. Methane thus has the structure shown in **FIGURE 1.12**.

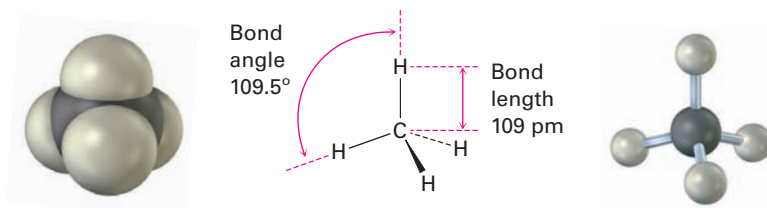
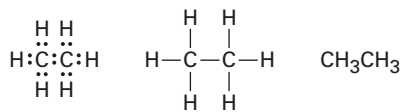


FIGURE 1.12 The structure of methane, showing its 109.5° bond angles.

1-7 sp^3 Hybrid Orbitals and the Structure of Ethane

The same kind of orbital hybridization that accounts for the methane structure also accounts for the bonding together of carbon atoms into chains and rings to make possible many millions of organic compounds. Ethane, C_2H_6 , is the simplest molecule containing a carbon–carbon bond:



Some representations of ethane

We can picture the ethane molecule by imagining that the two carbon atoms bond to each other by σ overlap of an sp^3 hybrid orbital from each (**FIGURE 1.13**). The remaining three sp^3 hybrid orbitals of each carbon overlap with the $1s$ orbitals of three hydrogens to form the six C–H bonds. The C–H bonds in ethane are similar to those in methane, although a bit weaker— 421 kJ/mol (101 kcal/mol) for ethane versus 439 kJ/mol for methane. The C–C bond is 153 pm long and has a strength of 377 kJ/mol (90 kcal/mol). All the bond angles of ethane are near, although not exactly at, the tetrahedral value of 109.5° .

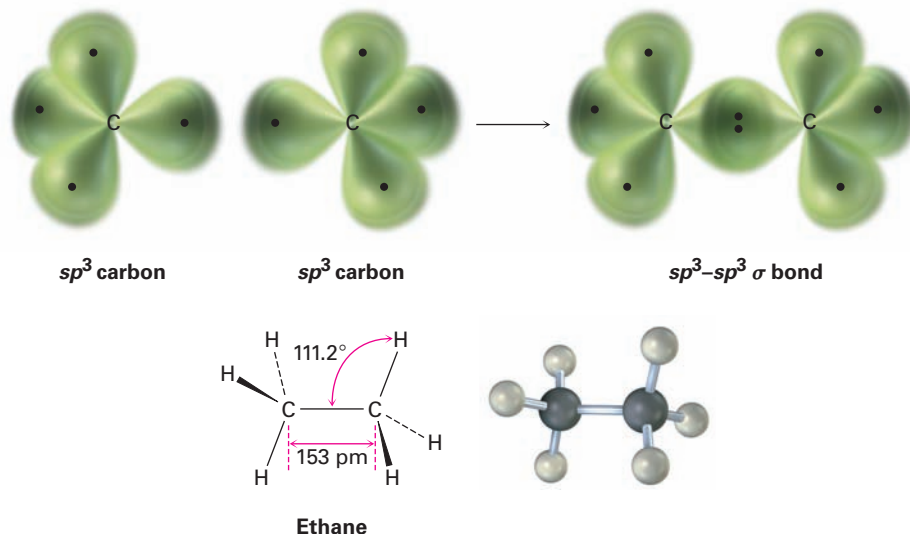


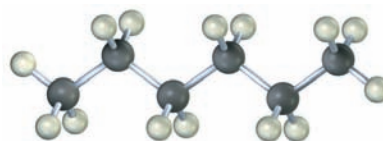
FIGURE 1.13 The structure of ethane. The carbon–carbon bond is formed by σ overlap of two sp^3 hybrid orbitals. For clarity, the smaller lobes of the sp^3 hybrid orbitals are not shown.

PROBLEM 1.8

Draw a line-bond structure for propane, $\text{CH}_3\text{CH}_2\text{CH}_3$. Predict the value of each bond angle, and indicate the overall shape of the molecule.

PROBLEM 1.9

Convert the molecular model of hexane, a component of gasoline, into a line-bond structure (gray = C, ivory = H).



Hexane

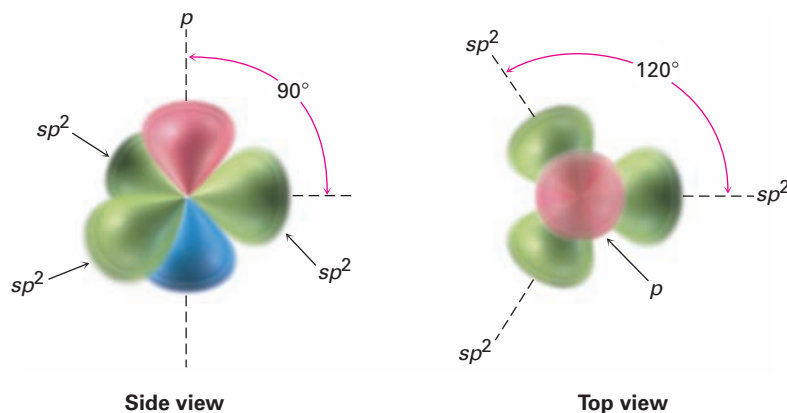
1-8 sp^2 Hybrid Orbitals and the Structure of Ethylene

The bonds we've seen in methane and ethane are called *single bonds* because they result from the sharing of one electron pair between bonded atoms. It was recognized nearly 150 years ago, however, that carbon atoms can also form *double bonds* by sharing *two* electron pairs between atoms or *triple bonds* by sharing *three* electron pairs. Ethylene, for instance, has the structure $\text{H}_2\text{C}=\text{CH}_2$ and contains a carbon–carbon double bond, while acetylene has the structure $\text{HC}\equiv\text{CH}$ and contains a carbon–carbon triple bond.

How are multiple bonds described by valence bond theory? When we discussed sp^3 hybrid orbitals in Section 1-6, we said that the four valence-shell atomic orbitals of carbon combine to form four equivalent sp^3 hybrids. Imagine instead that the $2s$ orbital combines with only *two* of the three available $2p$ orbitals. Three **sp^2 hybrid orbitals** result, and one $2p$ orbital remains unchanged. Like sp^3 hybrids, sp^2 hybrid orbitals are unsymmetrical about the nucleus and are strongly oriented in a specific direction so that they can form strong bonds. The three sp^2 orbitals lie in a plane at angles of 120° to one another, with the remaining p orbital perpendicular to the sp^2 plane, as shown in **FIGURE 1.14**.

FIGURE 1.14 sp^2 Hybridization.

The three equivalent **sp^2 hybrid orbitals** lie in a plane at angles of 120° to one another, and a single unhybridized **p orbital (red/blue)** is perpendicular to the sp^2 plane.



When two carbons with sp^2 hybridization approach each other, they form a strong σ bond by sp^2-sp^2 head-on overlap. At the same time, the unhybridized p orbitals interact by sideways overlap to form what is called a **pi (π) bond**. The combination of an sp^2-sp^2 σ bond and a $2p-2p$ π bond results in the sharing of four electrons and the formation of a carbon-carbon double bond (FIGURE 1.15). Note that the electrons in the σ bond occupy the region centered between nuclei, while the electrons in the π bond occupy regions above and below a line drawn between nuclei.

To complete the structure of ethylene, four hydrogen atoms form σ bonds with the remaining four sp^2 orbitals. Ethylene thus has a planar structure, with H-C-H and H-C-C bond angles of approximately 120° . (The actual values are 117.4° for the H-C-H bond angle and 121.3° for the H-C-C bond angle.) Each C-H bond has a length of 108.7 pm and a strength of 464 kJ/mol (111 kcal/mol).

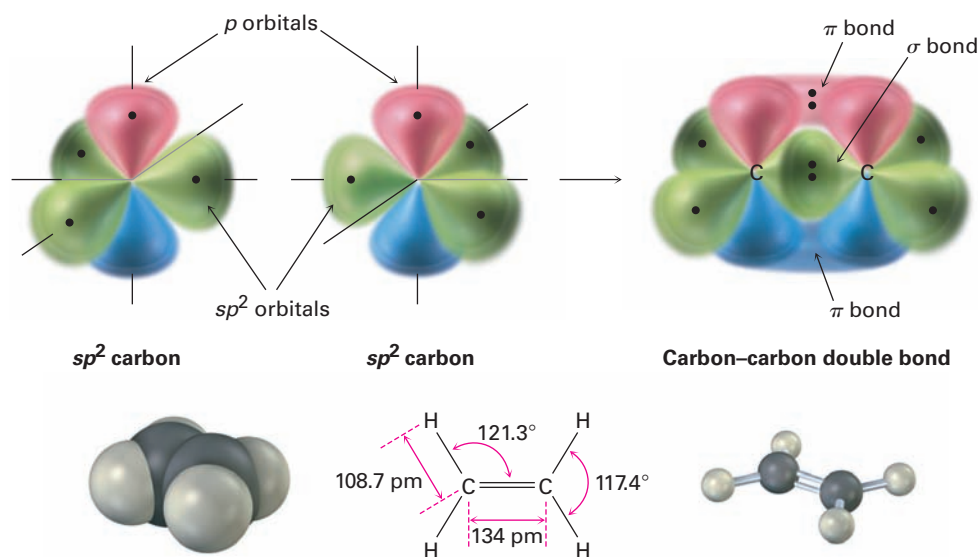


FIGURE 1.15 The structure of ethylene. One part of the double bond in ethylene results from σ (head-on) overlap of sp^2 orbitals, and the other part results from π (sideways) overlap of unhybridized p orbitals (red/blue). The π bond has regions of electron density above and below a line drawn between nuclei.

As you might expect, the carbon-carbon double bond in ethylene is both shorter and stronger than the single bond in ethane because it has four electrons bonding the nuclei together rather than two. Ethylene has a C=C bond length of 134 pm and a strength of 728 kJ/mol (174 kcal/mol) versus a C-C length of 153 pm and a strength of 377 kJ/mol for ethane. The carbon-carbon double bond is less than twice as strong as a single bond because the sideways overlap in the π part of the double bond is not as great as the head-on overlap in the σ part.

Drawing Electron-Dot and Line-Bond Structures

WORKED EXAMPLE 1.3

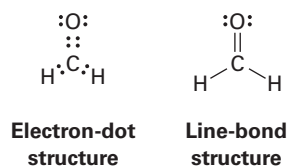
Commonly used in biology as a tissue preservative, formaldehyde, CH_2O , contains a carbon-oxygen double bond. Draw the line-bond structure of formaldehyde, and indicate the hybridization of the carbon atom.

Strategy

We know that hydrogen forms one covalent bond, carbon forms four, and oxygen forms two. Trial and error, combined with intuition, is needed to fit the atoms together.

Solution

There is only one way that two hydrogens, one carbon, and one oxygen can combine:



Like the carbon atoms in ethylene, the carbon atom in formaldehyde is in a double bond and is therefore sp^2 -hybridized.

PROBLEM 1.10

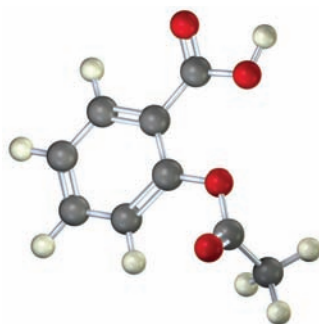
Draw a line-bond structure for propene, $\text{CH}_3\text{CH}=\text{CH}_2$; indicate the hybridization of each carbon; and predict the value of each bond angle.

PROBLEM 1.11

Draw a line-bond structure for buta-1,3-diene, $\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}_2$; indicate the hybridization of each carbon; and predict the value of each bond angle.

PROBLEM 1.12

A molecular model of aspirin (acetylsalicylic acid) is shown. Identify the hybridization of each carbon atom in aspirin, and tell which atoms have lone pairs of electrons (gray = C, red = O, ivory = H).



Aspirin
(acetylsalicylic acid)

1-9

 sp Hybrid Orbitals and the Structure of Acetylene

In addition to forming single and double bonds by sharing two and four electrons, respectively, carbon also can form a *triple* bond by sharing six electrons. To account for the triple bond in a molecule such as acetylene, $\text{H}-\text{C}\equiv\text{C}-\text{H}$, we need a third kind of hybrid orbital, an **sp hybrid**. Imagine that, instead of combining with two or three p orbitals, a carbon $2s$ orbital hybridizes with only a single p orbital. Two sp hybrid orbitals result, and two p orbitals remain

unchanged. The two *sp* orbitals are oriented 180° apart on the *x*-axis, while the remaining two *p* orbitals are perpendicular on the *y*-axis and the *z*-axis, as shown in **FIGURE 1.16**.

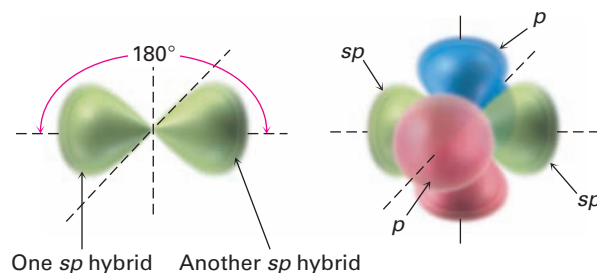


FIGURE 1.16 *sp* Hybridization. The two *sp* hybrid orbitals are oriented 180° away from each other, perpendicular to the two remaining *p* orbitals (red/blue).

When two *sp*-hybridized carbon atoms approach each other, *sp* hybrid orbitals on each carbon overlap head-on to form a strong *sp*–*sp* σ bond. At the same time, the p_z orbitals from each carbon form a p_z – p_z π bond by sideways overlap, and the p_y orbitals overlap similarly to form a p_y – p_y π bond. The net effect is the sharing of six electrons and formation of a carbon–carbon triple bond. The two remaining *sp* hybrid orbitals each form a σ bond with hydrogen to complete the acetylene molecule (**FIGURE 1.17**).

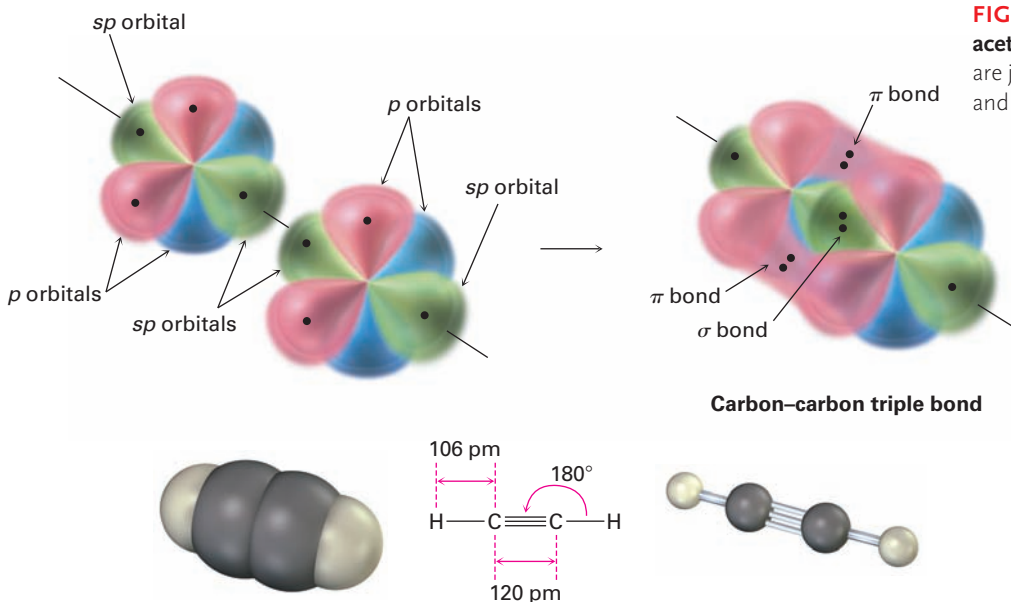


FIGURE 1.17 The structure of acetylene. The two carbon atoms are joined by one *sp*–*sp* σ bond and two *p*–*p* π bonds.

As suggested by *sp* hybridization, acetylene is a linear molecule with H–C–C bond angles of 180° . The C–H bonds have a length of 106 pm and a strength of 558 kJ/mol (133 kcal/mol). The C–C bond length in acetylene is 120 pm, and its strength is about 965 kJ/mol (231 kcal/mol), making it the shortest and strongest of any carbon–carbon bond. A comparison of *sp*, *sp*², and *sp*³ hybridization is given in **TABLE 1.2**.

TABLE 1.2 Comparison of C–C and C–H Bonds in Methane, Ethane, Ethylene, and Acetylene

Molecule	Bond	Bond strength		Bond length (pm)
		(kJ/mol)	(kcal/mol)	
Methane, CH ₄	(<i>sp</i> ³) C–H	439	105	109
Ethane, CH ₃ CH ₃	(<i>sp</i> ³) C–C (<i>sp</i> ³)	377	90	153
	(<i>sp</i> ³) C–H	421	101	109
Ethylene, H ₂ C=CH ₂	(<i>sp</i> ²) C=C (<i>sp</i> ²)	728	174	134
	(<i>sp</i> ²) C–H	464	111	109
Acetylene, HC≡CH	(<i>sp</i>) C≡C (<i>sp</i>)	965	231	120
	(<i>sp</i>) C–H	558	133	106

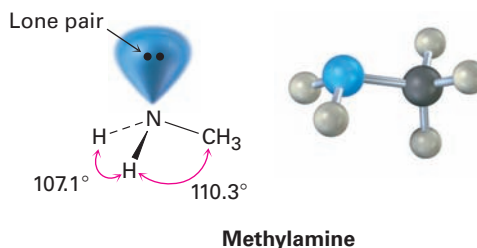
PROBLEM 1.13

Draw a line-bond structure for propyne, CH₃C≡CH. Indicate the hybridization of each carbon, and predict a value for each bond angle.

1-10 Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur

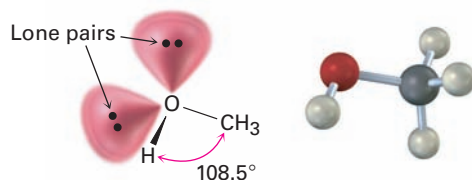
The valence bond concept of orbital hybridization described in the previous four sections is not limited to carbon. Covalent bonds formed by other elements can also be described using hybrid orbitals. Look, for instance, at the nitrogen atom in methylamine (CH₃NH₂), an organic derivative of ammonia (NH₃) and the substance responsible for the odor of rotting fish.

The experimentally measured H–N–H bond angle in methylamine is 107.1°, and the C–N–H bond angle is 110.3°, both of which are close to the 109.5° tetrahedral angle found in methane. We therefore assume that nitrogen hybridizes to form four *sp*³ orbitals, just as carbon does. One of the four *sp*³ orbitals is occupied by two nonbonding electrons, and the other three hybrid orbitals have one electron each. Overlap of these three half-filled nitrogen orbitals with half-filled orbitals from other atoms (C or H) gives methylamine. Note that the unshared lone pair of electrons in the fourth *sp*³ hybrid orbital of nitrogen occupies as much space as an N–H bond does and is very important to the chemistry of methylamine and other nitrogen-containing organic molecules.



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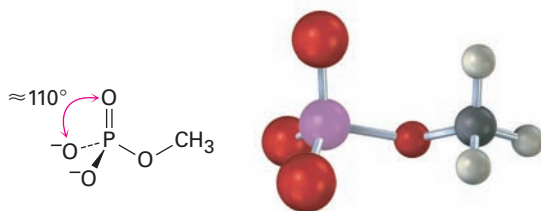
Like the carbon atom in methane and the nitrogen atom in methylamine, the oxygen atom in methanol (methyl alcohol) and many other organic molecules can be described as sp^3 -hybridized. The C–O–H bond angle in methanol is 108.5° , very close to the 109.5° tetrahedral angle. Two of the four sp^3 hybrid orbitals on oxygen are occupied by nonbonding electron lone pairs, and two are used to form bonds.



Methanol
(methyl alcohol)

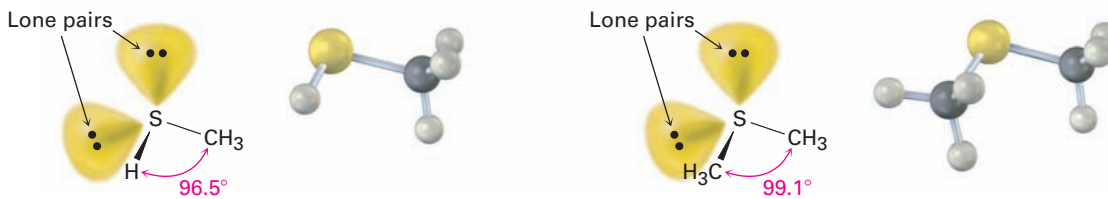
Phosphorus and sulfur are the third-row analogs of nitrogen and oxygen, and the bonding in both can be described using hybrid orbitals. Because of their positions in the third row, however, both phosphorus and sulfur can expand their outer-shell octets and form more than the typical number of covalent bonds. Phosphorus, for instance, often forms five covalent bonds, and sulfur often forms four.

Phosphorus is most commonly encountered in biological molecules in *organophosphates*, compounds that contain a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon. Methyl phosphate, $\text{CH}_3\text{OPO}_3^{2-}$, is the simplest example. The O–P–O bond angle in such compounds is typically in the range 110° to 112° , implying sp^3 hybridization for the phosphorus.



Methyl phosphate
(an organophosphate)

Sulfur is most commonly encountered in biological molecules either in compounds called *thiols*, which have a sulfur atom bonded to one hydrogen and one carbon, or in *sulfides*, which have a sulfur atom bonded to two carbons. Produced by some bacteria, methanethiol (CH_3SH) is the simplest example of a thiol, and dimethyl sulfide $[(\text{CH}_3)_2\text{S}]$ is the simplest example of a sulfide. Both can be described by approximate sp^3 hybridization around sulfur, although both have significant deviation from the 109.5° tetrahedral angle.



Methanethiol

Dimethyl sulfide

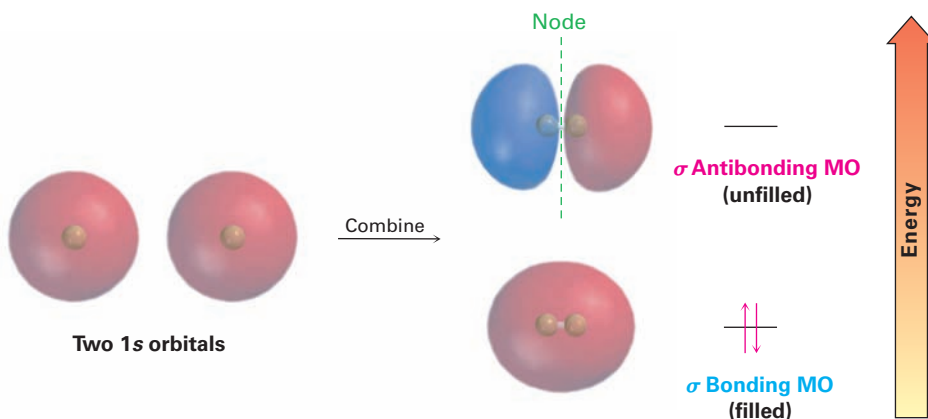


FIGURE 1.18 Molecular orbitals of H_2 . Combination of two hydrogen 1s atomic orbitals leads to two H_2 molecular orbitals. The lower-energy, **bonding MO** is filled, and the higher-energy, **antibonding MO** is unfilled.

Just as bonding and antibonding σ molecular orbitals result from the head-on combination of two s atomic orbitals in H_2 , so bonding and antibonding π molecular orbitals result from the sideways combination of two p atomic orbitals in ethylene. As shown in **FIGURE 1.19**, the lower-energy, π bonding MO has no node between nuclei and results from combination of p orbital lobes with the same algebraic sign. The higher-energy, π antibonding MO has a node between nuclei and results from combination of lobes with opposite algebraic signs. Only the bonding MO is occupied; the higher-energy, antibonding MO is vacant. We'll see in Sections 8-12 and 9-2 that molecular orbital theory is particularly useful for describing π bonds in compounds that have more than one double bond.

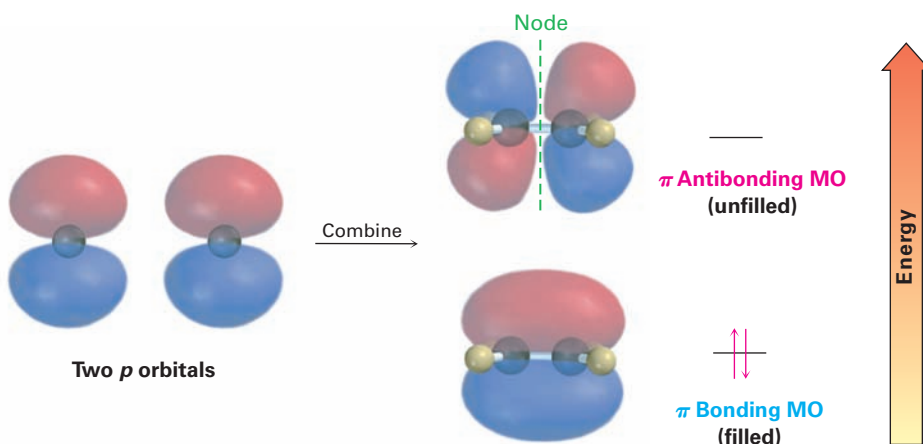
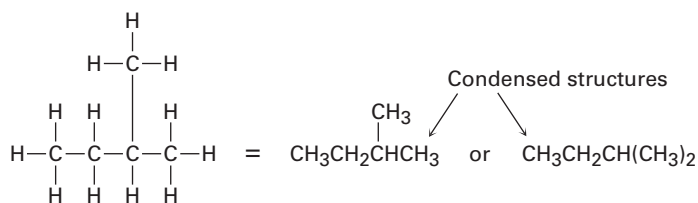


FIGURE 1.19 Molecular orbital description of the $\text{C}=\text{C}$ π bond in ethylene. The lower-energy, **π bonding MO** results from an additive combination of p orbital lobes with the same algebraic sign and is filled. The higher-energy, **π antibonding MO** results from a subtractive combination of p orbital lobes with the opposite algebraic signs and is unfilled.

1-12 Drawing Chemical Structures

Let's cover just one more point before ending this introductory chapter. In the structures we've been drawing until now, a line between atoms has represented the two electrons in a covalent bond. Drawing every bond and every atom is tedious, however, so chemists have devised several shorthand ways for writing structures. In **condensed structures**, carbon–hydrogen and carbon–carbon single bonds aren't shown; instead, they're understood. If a carbon has three hydrogens bonded to it, we write CH_3 ; if a carbon has two hydrogens

bonded to it, we write CH_2 ; and so on. The compound called 2-methylbutane, for example, is written as follows:



2-Methylbutane

Note that the horizontal bonds between carbons aren't shown in condensed structures—the CH_3 , CH_2 , and CH units are simply placed next to each other—but the vertical carbon-carbon bond in the first of the condensed structures just drawn is shown for clarity. Note also in the second of the condensed structures that the two CH_3 units attached to the CH carbon are grouped together as $(\text{CH}_3)_2$.

Even simpler than condensed structures are **skeletal structures**, such as those shown in TABLE 1.3. The rules for drawing skeletal structures are straightforward:

Rule 1

Carbon atoms aren't usually shown. Instead, a carbon atom is assumed to be at each intersection of two lines (bonds) and at the end of each line. Occasionally, a carbon atom might be indicated for emphasis or clarity.

Rule 2

Hydrogen atoms bonded to carbon aren't shown. Because carbon always has a valence of 4, we mentally supply the correct number of hydrogen atoms for each carbon.

Rule 3

Atoms other than carbon and hydrogen *are* shown.

One further comment: although such groupings as $-\text{CH}_3$, $-\text{OH}$, and $-\text{NH}_2$ are usually written with the C, O, or N atom first and the H atom second, the order of writing is sometimes inverted to $\text{H}_3\text{C}-$, $\text{HO}-$, and $\text{H}_2\text{N}-$ if needed to make the bonding connections in a molecule clearer. Larger units such as $-\text{CH}_2\text{CH}_3$ are not inverted, though; we don't write H_3CCH_2- because it would be confusing. There are, however, no well-defined rules that cover all cases; it's largely a matter of preference.

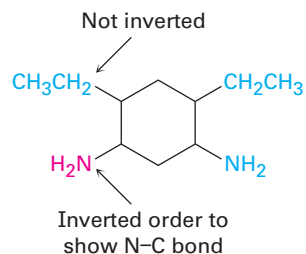
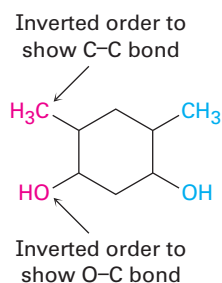
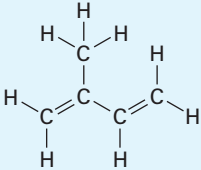
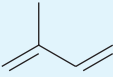
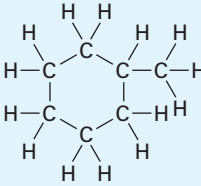
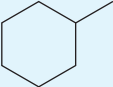
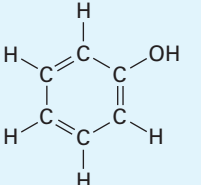
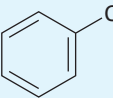


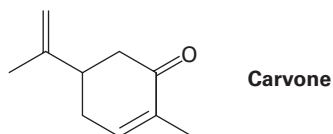
TABLE 1.3 Kekulé and Skeletal Structures for Some Compounds

Compound	Kekulé structure	Skeletal structure
Isoprene, C_5H_8		
Methylcyclohexane, C_7H_{14}		
Phenol, C_6H_6O		

Interpreting a Line-Bond Structure

WORKED EXAMPLE 1.4

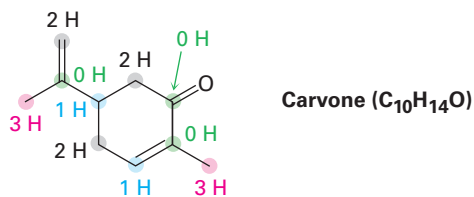
Carvone, a compound responsible for the odor of spearmint, has the following structure. Tell how many hydrogens are bonded to each carbon, and give the molecular formula of carvone.



Strategy

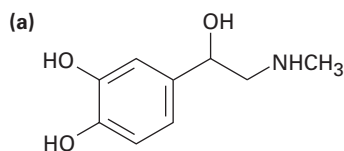
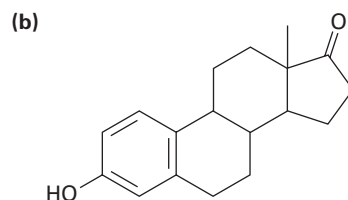
The end of a line represents a carbon atom with 3 hydrogens, CH_3 ; a two-way intersection is a carbon atom with 2 hydrogens, CH_2 ; a three-way intersection is a carbon atom with 1 hydrogen, CH ; and a four-way intersection is a carbon atom with no attached hydrogens.

Solution



PROBLEM 1.15

Tell how many hydrogens are bonded to each carbon in the following compounds, and give the molecular formula of each substance:

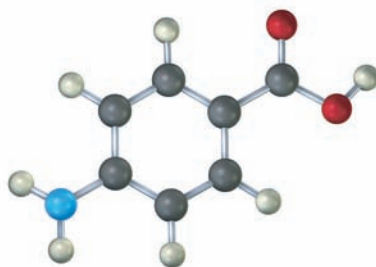
**Adrenaline****Estrone (a hormone)****PROBLEM 1.16**

Propose skeletal structures for compounds that satisfy the following molecular formulas. There is more than one possibility in each case.

(a) C_5H_{12} (b) C_2H_7N (c) C_3H_6O (d) C_4H_9Cl

PROBLEM 1.17

The following molecular model is a representation of *para*-aminobenzoic acid (PABA), the active ingredient in many sunscreens. Indicate the positions of the multiple bonds, and draw a skeletal structure (gray = C, red = O, blue = N, ivory = H).

***para*-Aminobenzoic acid (PABA)****SOMETHING EXTRA**

Organic Foods: Risk versus Benefit

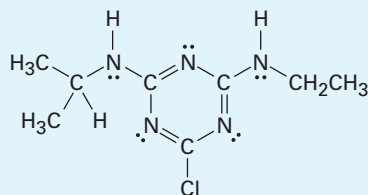
Contrary to what you may read in supermarkets or hear on television, *all* foods are organic—that is, complex mixtures of organic molecules. Even so, when applied to food, the word *organic* has come to mean an absence of synthetic chemicals, typically pesticides, antibiotics,

and preservatives. How concerned should we be about traces of pesticides in the food we eat? Or toxins in the water we drink? Or pollutants in the air we breathe?

Life is not risk-free—we all take many risks each day without thinking about it. We decide to ride a bike rather than drive, even though there is a ten times greater likelihood per mile of dying in a bicycling accident than in a car. (Author admission: I've cycled more than 70,000 miles without an accident.) We decide to walk down

stairs rather than take an elevator, even though 7000 people die from falls each year in the United States. Some of us decide to smoke cigarettes, even though it increases our chance of getting cancer by 50%. But what about risks from chemicals like pesticides?

One thing is certain: without pesticides, whether they target weeds (herbicides), insects (insecticides), or molds and fungi (fungicides), crop production would drop significantly, food prices would increase, and famines would occur in less developed parts of the world. Take the herbicide atrazine, for instance. In the United States alone, approximately 100 million pounds of atrazine are used each year to kill weeds in corn, sorghum, and sugarcane fields, greatly improving the yields of these crops. Nevertheless, the use of atrazine continues to be a concern because traces persist in the environment. Indeed, heavy atrazine exposure *can* pose health risks to humans and some animals, but the U.S. Environmental Protection Agency (EPA) is unwilling to ban its use because doing so would result in significantly lower crop yields and increased food costs and because there is no suitable alternative herbicide available.



Atrazine

How can the potential hazards from a chemical like atrazine be determined? Risk evaluation of chemicals is carried out by exposing test animals, usually mice or rats, to the chemical and then monitoring the animals for signs of harm. To limit the expense and time needed, the amounts administered are typically hundreds or thousands of times greater than those a person might normally encounter. The results obtained in animal tests are then distilled into a single number called an LD_{50} , the amount of substance per kilogram body weight that is a lethal dose for 50% of the test animals. For atrazine, the LD_{50} value is between 1 and 4 g/kg depending on the animal species. Aspirin, for comparison, has an LD_{50} of 1.1 g/kg, and ethanol (ethyl alcohol) has an LD_{50} of 10.6 g/kg.



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How dangerous is the pesticide being sprayed on this crop?

TABLE 1.4 lists values for some other familiar substances. The lower the value, the more toxic the substance. Note, though, that LD_{50} values tell only about the effects of heavy exposure for a relatively short time. They say nothing about the risks of long-term exposure, such as whether the substance can cause cancer or interfere with development in the unborn.

TABLE 1.4 Some LD_{50} Values

Substance	LD_{50} (g/kg)	Substance	LD_{50} (g/kg)
Strychnine	0.005	Chloroform	1.2
Arsenic trioxide	0.015	Iron(II) sulfate	1.5
DDT	0.115	Ethyl alcohol	10.6
Aspirin	1.1	Sodium cyclamate	17

So, should we still use atrazine? All decisions involve tradeoffs, and the answer is rarely obvious. Does the benefit of increased food production outweigh possible health risks of a pesticide? Do the beneficial effects of a new drug outweigh a potentially dangerous side effect in a small number of users? Different people will have different opinions, but an honest evaluation of facts is surely the best way to start. At present, atrazine is approved for continued use in the United States because the EPA believes that the benefits of increased food production outweigh possible health risks. At the same time, though, the use of atrazine is being phased out in Europe.



KEY WORDS

antibonding MO, 20
bond angle, 13
bond length, 11
bond strength, 11
bonding MO, 20
condensed structure, 21
covalent bond, 8
electron-dot structure, 8
electron shell, 5
ground-state electron configuration, 6
ionic bond, 8
isotope, 4
line-bond structure, 8
lone-pair electrons, 9
molecular orbital (MO) theory, 20
molecule, 8
node, 5
orbital, 4
organic chemistry, 3
 π (π) bond, 15
 σ (σ) bond, 11
skeletal structure, 22
 sp hybrid orbital, 16
 sp^2 hybrid orbital, 14
 sp^3 hybrid orbital, 12
valence bond theory, 10
valence shell, 8

SUMMARY

The purpose of this chapter has been to get you up to speed—to review some ideas about atoms, bonds, and molecular geometry. As we've seen, **organic chemistry** is the study of carbon compounds. Although a division into organic and inorganic chemistry occurred historically, there is no scientific reason for the division.

An atom consists of a positively charged nucleus surrounded by one or more negatively charged electrons. The electronic structure of an atom can be described by a quantum mechanical wave equation, in which electrons are considered to occupy **orbitals** around the nucleus. Different orbitals have different energy levels and different shapes. For example, s orbitals are spherical and p orbitals are dumbbell-shaped. The **ground-state electron configuration** of an atom can be found by assigning electrons to the proper orbitals, beginning with the lowest-energy ones.

A **covalent bond** is formed when an electron pair is shared between atoms. According to **valence bond theory**, electron sharing occurs by overlap of two atomic orbitals. According to **molecular orbital (MO) theory**, bonds result from the mathematical combination of atomic orbitals to give molecular orbitals, which belong to the entire molecule. Bonds that have a circular cross-section and are formed by head-on interaction are called **sigma (σ) bonds**; bonds formed by sideways interaction of p orbitals are called **pi (π) bonds**.

In the valence bond description, carbon uses hybrid orbitals to form bonds in organic molecules. When forming only single bonds with tetrahedral geometry, carbon uses four equivalent **sp^3 hybrid orbitals**. When forming a double bond with planar geometry, carbon uses three equivalent **sp^2 hybrid orbitals** and one unhybridized p orbital. When forming a triple bond with linear geometry, carbon uses two equivalent **sp hybrid orbitals** and two unhybridized p orbitals. Other atoms such as nitrogen, phosphorus, oxygen, and sulfur also use hybrid orbitals to form strong, oriented bonds.

Organic molecules are usually drawn using either **condensed structures** or **skeletal structures**. In condensed structures, carbon-carbon and carbon-hydrogen bonds aren't shown. In skeletal structures, only the bonds and not the atoms are shown. A carbon atom is assumed to be at the ends and at the junctions of lines (bonds), and the correct number of hydrogens is mentally supplied.

WORKING PROBLEMS

There is no surer way to learn organic chemistry than by working problems. Although careful reading and rereading of this text is important, reading alone isn't enough. You must also be able to use the information you've read and be able to apply your knowledge in new situations. Working problems gives you practice at doing this.

Each chapter in this book provides many problems of different sorts. The in-chapter problems are placed for immediate reinforcement of ideas just learned; the end-of-chapter problems provide additional practice and are of several types. They begin with a short section called "Visualizing Chemistry," which helps you "see" the microscopic world of molecules and provides practice for working and thinking in three dimensions. After the visualizations are many "Additional Problems."

Early problems are primarily of the drill type, providing an opportunity for you to practice your command of the fundamentals. Later problems tend to be more thought-provoking, and some are real challenges.

As you study organic chemistry, take the time to work the problems. Do the ones you can, and ask for help on the ones you can't. If you're stumped by a particular problem, check the accompanying *Study Guide and Solutions Manual* for an explanation that will help clarify the difficulty. Working problems takes effort, but the payoff in knowledge and understanding is immense.

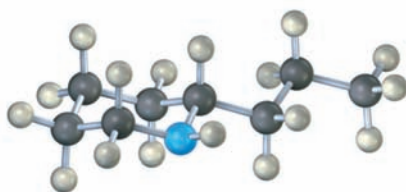
EXERCISES

VISUALIZING CHEMISTRY

(Problems 1.1–1.17 appear within the chapter.)

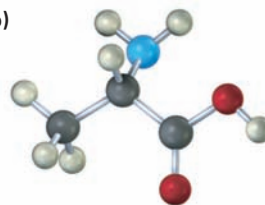
- 1.18** Convert each of the following molecular models into a skeletal structure, and give the formula of each. Only the connections between atoms are shown; multiple bonds are not indicated (gray = C, red = O, blue = N, ivory = H).

(a)



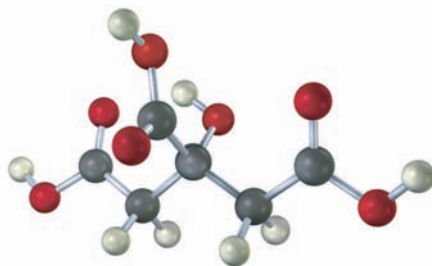
Coniine (the toxic substance in poison hemlock)

(b)

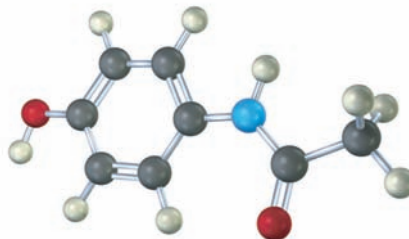


Alanine (an amino acid)

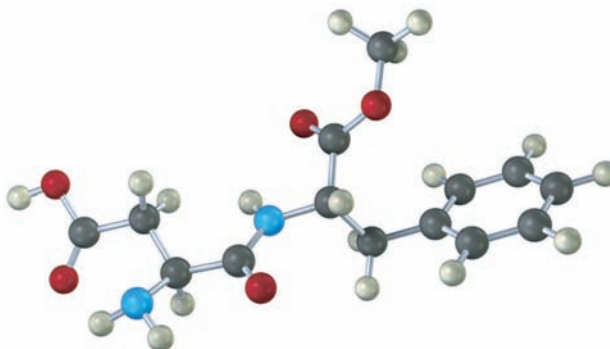
- 1.19** The following model is a representation of citric acid, a compound in the so-called citric acid cycle by which food molecules are metabolized in the body. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure by indicating the positions of multiple bonds and lone-pair electrons (gray = C, red = O, ivory = H).



- 1.20 The following model is a representation of acetaminophen, a pain reliever sold in drugstores under a variety of names, including Tylenol. Identify the hybridization of each carbon atom in acetaminophen, and tell which atoms have lone pairs of electrons (gray = C, red = O, blue = N, ivory = H).



- 1.21 The following model is a representation of aspartame, $C_{14}H_{18}N_2O_5$, known commercially under many names, including NutraSweet. Only the connections between atoms are shown; multiple bonds are not indicated. Draw a skeletal structure for aspartame, and indicate the positions of multiple bonds (gray = C, red = O, blue = N, ivory = H).



ADDITIONAL PROBLEMS

Electron Configurations

- 1.22 How many valence electrons does each of the following dietary trace elements have?
- (a) Zinc (b) Iodine (c) Silicon (d) Iron
- 1.23 Give the ground-state electron configuration for each of the following elements:
- (a) Potassium (b) Arsenic (c) Aluminum (d) Germanium

Electron-Dot and Line-Bond Structures

1.24 What are likely formulas for the following molecules?

(a) $\text{NH}_? \text{OH}$ (b) $\text{AlCl}_?$ (c) $\text{CF}_2 \text{Cl}_?$ (d) $\text{CH}_? \text{O}$

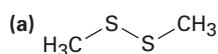
1.25 Why can't molecules with the following formulas exist?

(a) CH_5 (b) $\text{C}_2\text{H}_6\text{N}$ (c) $\text{C}_3\text{H}_5\text{Br}_2$

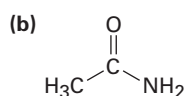
1.26 Draw an electron-dot structure for acetonitrile, $\text{C}_2\text{H}_3\text{N}$, which contains a carbon–nitrogen triple bond. How many electrons does the nitrogen atom have in its outer shell? How many are bonding, and how many are nonbonding?

1.27 Draw a line-bond structure for vinyl chloride, $\text{C}_2\text{H}_3\text{Cl}$, the starting material from which PVC [poly(vinyl chloride)] plastic is made.

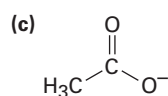
1.28 Fill in any nonbonding valence electrons that are missing from the following structures:



Dimethyl disulfide

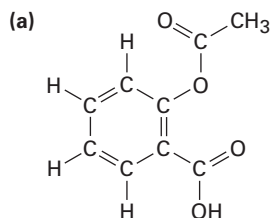


Acetamide

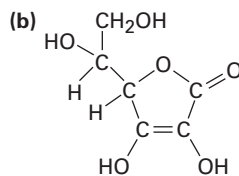


Acetate ion

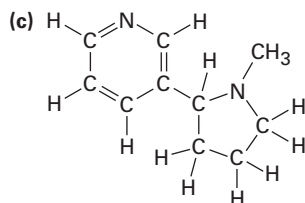
1.29 Convert the following line-bond structures into molecular formulas:



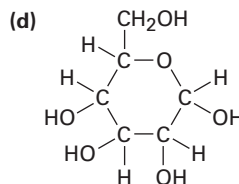
Aspirin
(acetylsalicylic acid)



Vitamin C
(ascorbic acid)



Nicotine



Glucose

1.30 Convert the following molecular formulas into line-bond structures that are consistent with valence rules:

(a) C_3H_8

(b) CH_5N

(c) $\text{C}_2\text{H}_6\text{O}$ (2 possibilities)

(d) $\text{C}_3\text{H}_7\text{Br}$ (2 possibilities)

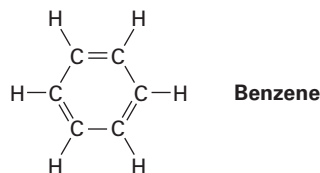
(e) $\text{C}_2\text{H}_4\text{O}$ (3 possibilities)

(f) $\text{C}_3\text{H}_9\text{N}$ (4 possibilities)

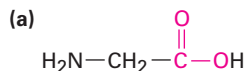
- 1.31** Draw a three-dimensional representation of the oxygen-bearing carbon atom in ethanol, $\text{CH}_3\text{CH}_2\text{OH}$, using the standard convention of solid, wedged, and dashed lines.
- 1.32** Oxaloacetic acid, an important intermediate in food metabolism, has the formula $\text{C}_4\text{H}_4\text{O}_5$ and contains three $\text{C}=\text{O}$ bonds and two $\text{O}-\text{H}$ bonds. Propose two possible structures.
- 1.33** Draw structures for the following molecules, showing lone pairs:
- (a) Acrylonitrile, $\text{C}_3\text{H}_3\text{N}$, which contains a carbon-carbon double bond and a carbon-nitrogen triple bond
- (b) Ethyl methyl ether, $\text{C}_3\text{H}_8\text{O}$, which contains an oxygen atom bonded to two carbons
- (c) Butane, C_4H_{10} , which contains a chain of four carbon atoms
- (d) Cyclohexene, C_6H_{10} , which contains a ring of six carbon atoms and one carbon-carbon double bond
- 1.34** Potassium methoxide, KOCH_3 , contains both covalent and ionic bonds. Which do you think is which?

Hybridization

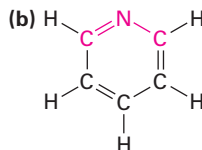
- 1.35** What is the hybridization of each carbon atom in acetonitrile (Problem 1.26)?
- 1.36** What kind of hybridization do you expect for each carbon atom in the following molecules?
- (a) Propane, $\text{CH}_3\text{CH}_2\text{CH}_3$
- (b) 2-Methylpropene, $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3\text{C}=\text{CH}_2 \end{array}$
- (c) But-1-en-3-yne, $\text{H}_2\text{C}=\text{CH}-\text{C}\equiv\text{CH}$
- (d) Acetic acid, $\begin{array}{c} \text{O} \\ || \\ \text{CH}_3\text{COH} \end{array}$
- 1.37** What is the shape of benzene, and what hybridization do you expect for each carbon?



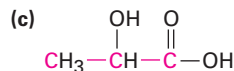
- 1.38 What values do you expect for the indicated bond angles in each of the following molecules, and what kind of hybridization do you expect for the central atom in each?



Glycine
(an amino acid)



Pyridine

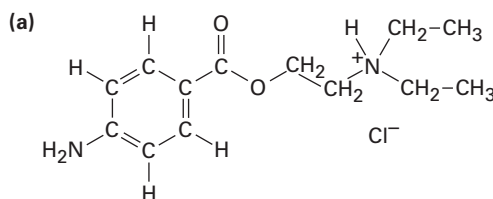


Lactic acid
(in sour milk)

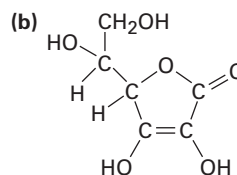
- 1.39 Propose structures for molecules that meet the following descriptions:

- (a) Contains two sp^2 -hybridized carbons and two sp^3 -hybridized carbons
 (b) Contains only four carbons, all of which are sp^2 -hybridized
 (c) Contains two sp -hybridized carbons and two sp^2 -hybridized carbons

- 1.40 What kind of hybridization do you expect for each carbon atom in the following molecules?

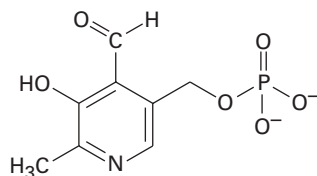


Procaine



Vitamin C
(ascorbic acid)

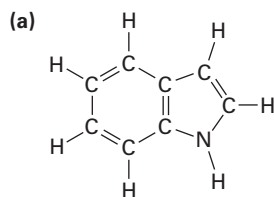
- 1.41 Pyridoxal phosphate, a close relative of vitamin B₆, is involved in a large number of metabolic reactions. Tell the hybridization, and predict the bond angles for each nonterminal atom.



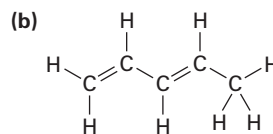
Pyridoxal phosphate

Skeletal Structures

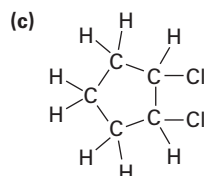
1.42 Convert the following structures into skeletal drawings:



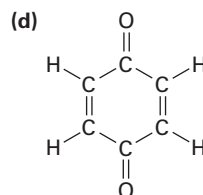
Indole



Penta-1,3-diene

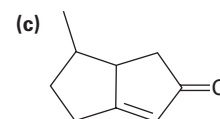
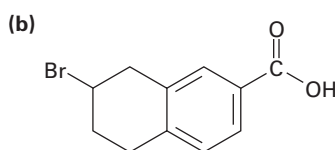
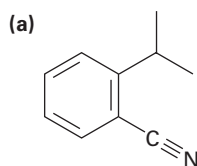


1,2-Dichlorocyclopentane

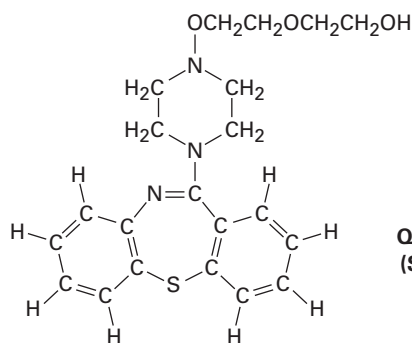


Benzoquinone

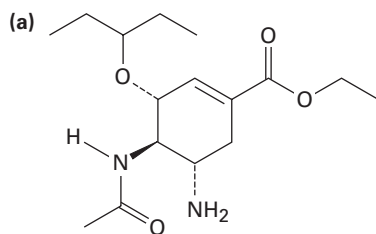
1.43 Tell the number of hydrogens bonded to each carbon atom in the following substances, and give the molecular formula of each:



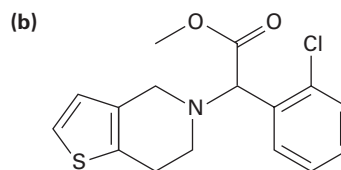
1.44 Quetiapine, marketed as Seroquel, is a heavily prescribed antipsychotic drug used in the treatment of schizophrenia and bipolar disorder. Convert the following representation into a skeletal structure, and give the molecular formula of quetiapine.

Quetiapine
(Seroquel)

- 1.45 Tell the number of hydrogens bonded to each carbon atom in (a) the anti-influenza agent oseltamivir, marketed as Tamiflu, and (b) the platelet aggregation inhibitor clopidogrel, marketed as Plavix. Give the molecular formula of each.



Oseltamivir
(Tamiflu)



Clopidogrel
(Plavix)

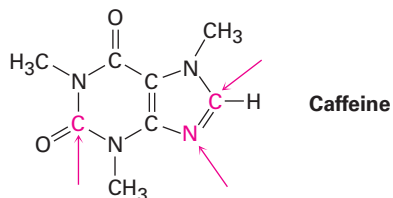
General Problems

- 1.46 Why do you suppose no one has ever been able to make cyclopentyne as a stable molecule?

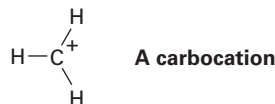


Cyclopentyne

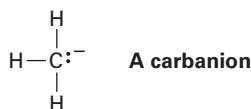
- 1.47 Allene, $\text{H}_2\text{C}=\text{C}=\text{CH}_2$, is somewhat unusual in that it has two adjacent double bonds. Draw a picture showing the orbitals involved in the σ and π bonds of allene. Is the central carbon atom sp^2 - or sp -hybridized? What about the hybridization of the terminal carbons? What shape do you predict for allene?
- 1.48 Allene (see Problem 1.47) is related structurally to carbon dioxide, CO_2 . Draw a picture showing the orbitals involved in the σ and π bonds of CO_2 , and identify the likely hybridization of carbon.
- 1.49 Complete the electron-dot structure of caffeine, showing all lone-pair electrons, and identify the hybridization of the indicated atoms.



- 1.50** Most stable organic species have tetravalent carbon atoms, but species with trivalent carbon atoms also exist. *Carbocations* are one such class of compounds.

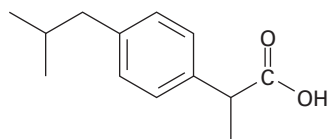
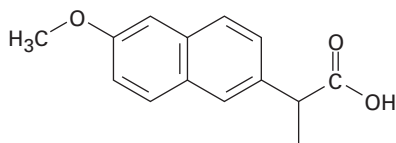
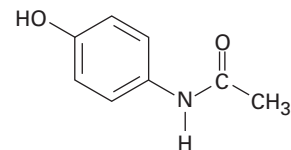


- (a) How many valence electrons does the positively charged carbon atom have?
- (b) What hybridization do you expect this carbon atom to have?
- (c) What geometry is the carbocation likely to have?
- 1.51** A *carbanion* is a species that contains a negatively charged, trivalent carbon.



- (a) What is the electronic relationship between a carbanion and a trivalent nitrogen compound such as NH_3 ?
- (b) How many valence electrons does the negatively charged carbon atom have?
- (c) What hybridization do you expect this carbon atom to have?
- (d) What geometry is the carbanion likely to have?
- 1.52** Divalent carbon species called *carbenes* are capable of fleeting existence. For example, methylene, $:\text{CH}_2$, is the simplest carbene. The two unshared electrons in methylene can be either paired in a single orbital or unpaired in different orbitals. Predict the type of hybridization you expect carbon to adopt in singlet (spin-paired) methylene and triplet (spin-unpaired) methylene. Draw a picture of each, and identify the valence orbitals on carbon.
- 1.53** There are two different substances with the formula C_4H_{10} . Draw both, and tell how they differ.
- 1.54** There are two different substances with the formula C_3H_6 . Draw both, and tell how they differ.
- 1.55** There are two different substances with the formula $\text{C}_2\text{H}_6\text{O}$. Draw both, and tell how they differ.
- 1.56** There are three different substances that contain a carbon–carbon double bond and have the formula C_4H_8 . Draw them, and tell how they differ.

- 1.57 Among the most common over-the-counter drugs you might find in a medicine cabinet are mild pain relievers such as ibuprofen (Advil, Motrin), naproxen (Aleve), and acetaminophen (Tylenol).

**Ibuprofen****Naproxen****Acetaminophen**

- (a) How many sp^3 -hybridized carbons does each molecule have?
(b) How many sp^2 -hybridized carbons does each molecule have?
(c) Can you spot any similarities in their structures?

2

Polar Covalent Bonds; Acids and Bases

CONTENTS

- 2-1 Polar Covalent Bonds: Electronegativity
- 2-2 Polar Covalent Bonds: Dipole Moments
- 2-3 Formal Charges
- 2-4 Resonance
- 2-5 Rules for Resonance Forms
- 2-6 Drawing Resonance Forms
- 2-7 Acids and Bases: The Brønsted–Lowry Definition
- 2-8 Acid and Base Strength
- 2-9 Predicting Acid–Base Reactions from pK_a Values
- 2-10 Organic Acids and Organic Bases
- 2-11 Acids and Bases: The Lewis Definition
- 2-12 Noncovalent Interactions Between Molecules

SOMETHING EXTRA

Alkaloids: From Cocaine to Dental Anesthetics



HIV protease processes proteins during the life cycle of the AIDS virus.

WHY THIS CHAPTER?

Understanding organic and biological chemistry means knowing not just *what* happens but also *why* and *how* it happens at the molecular level. In this chapter, we'll look at some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation to understand the specific reactions discussed in subsequent chapters. Topics such as bond polarity, the acid–base behavior of molecules, and hydrogen bonding are a particularly important part of that foundation.

We saw in the last chapter how covalent bonds between atoms are described, and we looked at the valence bond model, which uses hybrid orbitals to account for the observed shapes of organic molecules. Before going on to a systematic study of organic chemistry, however, we still need to review a few fundamental topics. In particular, we need to look more closely at how electrons are distributed in covalent bonds and at some of the consequences that arise when the electrons in a bond are not shared equally between atoms.

2-1 Polar Covalent Bonds: Electronegativity

Up to this point, we've treated chemical bonds as either ionic or covalent. The bond in sodium chloride, for instance, is ionic. Sodium transfers an electron to chlorine to give Na^+ and Cl^- ions, which are held together in the solid by electrostatic attractions between the unlike charges. The C–C bond in ethane, however, is covalent. The two bonding electrons are shared equally by the two equivalent carbon atoms, resulting in a symmetrical electron distribution in the bond. Most bonds, however, are neither fully ionic nor fully covalent but are somewhere between the two extremes. Such bonds are called **polar covalent bonds**, meaning that the bonding electrons are attracted more



strongly by one atom than the other so that the electron distribution between atoms is not symmetrical (FIGURE 2.1).

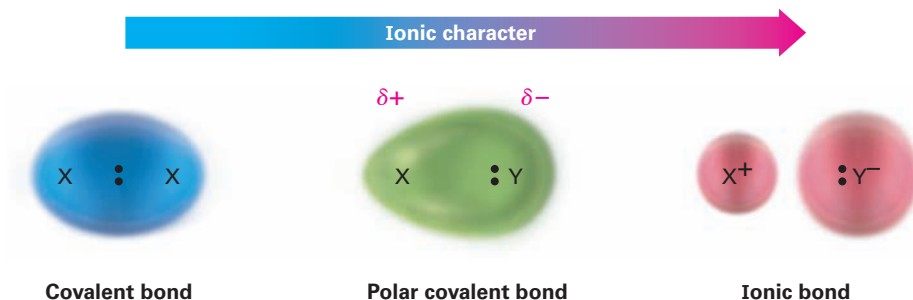


FIGURE 2.1 The continuum in bonding from covalent to ionic.

The bonding continuum is a result of an unequal distribution of bonding electrons between atoms. The symbol δ (lowercase Greek delta) means *partial* charge, either partial positive ($\delta+$) for the electron-poor atom or partial negative ($\delta-$) for the electron-rich atom.

Bond polarity is due to differences in **electronegativity (EN)**, the intrinsic ability of an atom to attract the shared electrons in a covalent bond. As shown in FIGURE 2.2, electronegativities are based on an arbitrary scale, with fluorine the most electronegative (EN = 4.0) and cesium the least (EN = 0.7). Metals on the left side of the periodic table attract electrons weakly and have lower electronegativities, while oxygen, nitrogen, and halogens on the right side of the periodic table attract electrons strongly and have higher electronegativities. Carbon, the most important element in organic compounds, has an electronegativity value of 2.5.

H 2.1																	He
Li 1.0	Be 1.6											B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	Ne
Na 0.9	Mg 1.2											Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	Ar
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.9	Ni 1.9	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	Br 2.8	Kr
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	I 2.5	Xe
Cs 0.7	Ba 0.9	La 1.0	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.9	Bi 1.9	Po 2.0	At 2.1	Rn

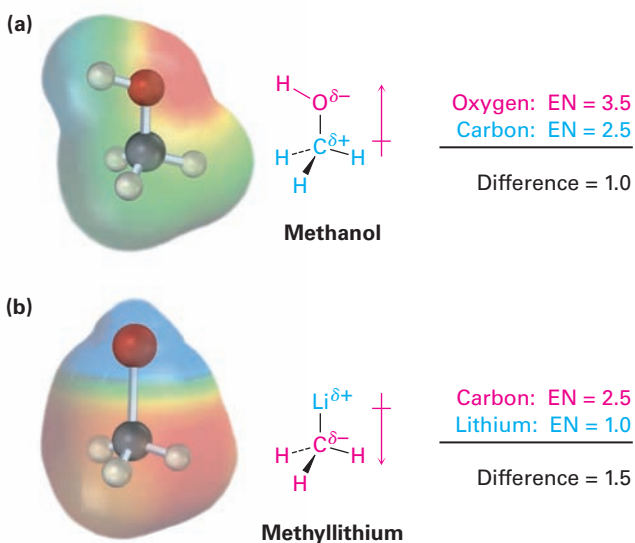
FIGURE 2.2 Electronegativity values and trends.

Electronegativity generally increases from left to right across the periodic table and decreases from top to bottom. The values are on an arbitrary scale, with F = 4.0 and Cs = 0.7. Elements in **red** are the most electronegative, those in **yellow** are medium, and those in **green** are the least electronegative.

As a rough guide, bonds between atoms whose electronegativities differ by less than 0.5 are nonpolar covalent, bonds between atoms whose electronegativities differ by 0.5 to 2 are polar covalent, and bonds between atoms whose electronegativities differ by more than 2 are largely ionic. Carbon–hydrogen bonds, for example, are relatively nonpolar because carbon (EN = 2.5) and hydrogen (EN = 2.1) have similar electronegativities. Bonds between carbon and *more* electronegative elements, such as oxygen (EN = 3.5) and nitrogen (EN = 3.0), by contrast, are polarized so that the bonding electrons are drawn away from carbon toward the electronegative atom. This leaves carbon with a partial positive charge, denoted by $\delta+$, and the electronegative atom with a partial negative charge, $\delta-$ (δ is the lowercase Greek letter delta). An example is the C–O bond in methanol, CH₃OH (FIGURE 2.3a). Bonds between carbon and *less* electronegative elements are polarized so that carbon bears a partial

negative charge and the other atom bears a partial positive charge. An example is the C–Li bond in methyllithium, CH_3Li (FIGURE 2.3b).

FIGURE 2.3 Polar covalent bonds. (a) Methanol, CH_3OH , has a polar covalent C–O bond, and (b) methyllithium, CH_3Li , has a polar covalent C–Li bond. The computer-generated representations, called electrostatic potential maps, use color to show calculated charge distributions, ranging from red (electron-rich; δ^-) to blue (electron-poor; δ^+).



Note in the representations of methanol and methyllithium in Figure 2.3 that a crossed arrow \rightarrow is used to indicate the direction of bond polarity. By convention, *electrons are displaced in the direction of the arrow*. The tail of the arrow (which looks like a plus sign) is electron-poor (δ^+), and the head of the arrow is electron-rich (δ^-).

Note also in Figure 2.3 that calculated charge distributions in molecules can be displayed visually with what are called electrostatic potential maps, which use color to indicate electron-rich (red; δ^-) and electron-poor (blue; δ^+) regions. In methanol, oxygen carries a partial negative charge and is colored red, while the carbon and hydrogen atoms carry partial positive charges and are colored blue-green. In methyllithium, lithium carries a partial positive charge (blue), while carbon and the hydrogen atoms carry partial negative charges (red). Electrostatic potential maps are useful because they show at a glance the electron-rich and electron-poor atoms in molecules. We'll make frequent use of these maps throughout the text and will see many examples of how electronic structure correlates with chemical reactivity.

When speaking of an atom's ability to polarize a bond, we often use the term *inductive effect*. An **inductive effect** is simply the shifting of electrons in a σ bond in response to the electronegativity of nearby atoms. Metals, such as lithium and magnesium, inductively donate electrons, whereas reactive non-metals, such as oxygen and nitrogen, inductively withdraw electrons. Inductive effects play a major role in understanding chemical reactivity, and we'll use them many times throughout this text to explain a variety of chemical observations.

PROBLEM 2.1

Which element in each of the following pairs is more electronegative?
(a) Li or H (b) B or Br (c) Cl or I (d) C or H

PROBLEM 2.2

Use the δ^+/δ^- convention to show the direction of expected polarity for each of the bonds indicated.

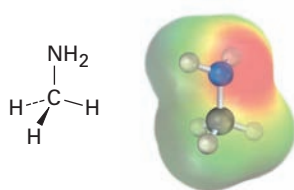
- (a) $\text{H}_3\text{C}-\text{Cl}$ (b) $\text{H}_3\text{C}-\text{NH}_2$ (c) $\text{H}_2\text{N}-\text{H}$
 (d) $\text{H}_3\text{C}-\text{SH}$ (e) $\text{H}_3\text{C}-\text{MgBr}$ (f) $\text{H}_3\text{C}-\text{F}$

PROBLEM 2.3

Use the electronegativity values shown in Figure 2.2 to rank the following bonds from least polar to most polar: $\text{H}_3\text{C}-\text{Li}$, $\text{H}_3\text{C}-\text{K}$, $\text{H}_3\text{C}-\text{F}$, $\text{H}_3\text{C}-\text{MgBr}$, $\text{H}_3\text{C}-\text{OH}$.

PROBLEM 2.4

Look at the following electrostatic potential map of methylamine, a substance responsible for the odor of rotting fish, and tell the direction of polarization of the C–N bond:



Methylamine

2-2 Polar Covalent Bonds: Dipole Moments

Just as individual bonds are often polar, molecules as a whole are often polar also. Molecular polarity results from the vector summation of all individual bond polarities and lone-pair contributions in the molecule. As a practical matter, strongly polar substances are often soluble in polar solvents like water, whereas less polar substances are insoluble in water.

Net molecular polarity is measured by a quantity called the *dipole moment* and can be thought of in the following way. Assume that there is a center of mass of all positive charges (nuclei) in a molecule and a center of mass of all negative charges (electrons). If these two centers don't coincide, then the molecule has a net polarity.

The **dipole moment**, μ (Greek mu), is defined as the magnitude of the charge Q at either end of the molecular dipole times the distance r between the charges, $\mu = Q \times r$. Dipole moments are expressed in *debyes* (D), where $1 \text{ D} = 3.336 \times 10^{-30}$ coulomb meter ($\text{C} \cdot \text{m}$) in SI units. For example, the unit charge on an electron is 1.60×10^{-19} C. Thus, if one positive charge and one negative charge are separated by 100 pm (a bit less than the length of a typical covalent bond), the dipole moment is 1.60×10^{-29} $\text{C} \cdot \text{m}$, or 4.80 D.

$$\mu = Q \times r$$

$$\mu = (1.60 \times 10^{-19} \text{ C})(100 \times 10^{-12} \text{ m}) \left(\frac{1 \text{ D}}{3.336 \times 10^{-30} \text{ C} \cdot \text{m}} \right) = 4.80 \text{ D}$$

Dipole moments for some common substances are given in **TABLE 2.1**. Of the compounds shown in the table, sodium chloride has the largest dipole moment (9.00 D) because it is ionic. Even small molecules like water ($\mu = 1.85$ D), methanol (CH_3OH ; $\mu = 1.70$ D), and ammonia ($\mu = 1.47$ D), have substantial dipole moments, however, both because they contain strongly electronegative atoms (oxygen and nitrogen) and because all three molecules have lone-pair electrons. The lone-pair electrons on oxygen and nitrogen atoms stick out into space away from the positively charged nuclei, giving rise to a considerable charge separation and making a large contribution to the dipole moment.

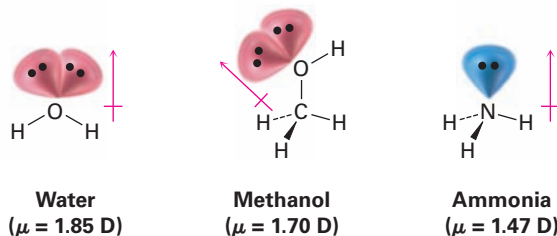

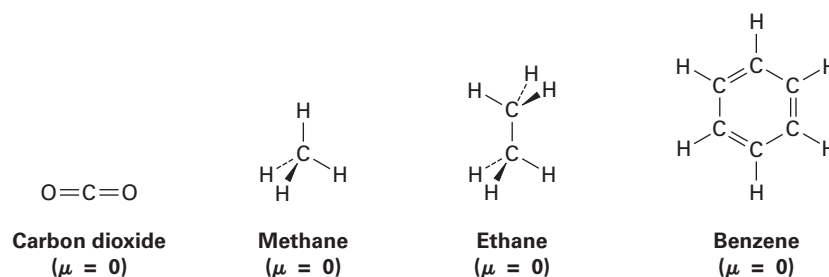


TABLE 2.1 Dipole Moments of Some Compounds

Compound	Dipole moment (D)	Compound	Dipole moment (D)
NaCl	9.00	NH ₃	1.47
CH ₂ O	2.33	CH ₃ NH ₂	1.31
CH ₃ Cl	1.87	CO ₂	0
H ₂ O	1.85	CH ₄	0
CH ₃ OH	1.70	CH ₃ CH ₃	0
CH ₃ CO ₂ H	1.70		0
CH ₃ SH	1.52	Benzene	

In contrast with water, methanol, and ammonia, molecules such as carbon dioxide, methane, ethane, and benzene have zero dipole moments. Because of the symmetrical structures of these molecules, the individual bond polarities and lone-pair contributions exactly cancel.



Predicting the Direction of a Dipole Moment

WORKED EXAMPLE 2.1

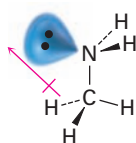
Make a three-dimensional drawing of methylamine, CH_3NH_2 , and show the direction of its dipole moment ($\mu = 1.31$).

Strategy

Look for any lone-pair electrons, and identify any atom with an electronegativity substantially different from that of carbon. (Usually, this means O, N, F, Cl, or Br.) Electron density will be displaced in the general direction of the electronegative atoms and the lone pairs.

Solution

Methylamine has an electronegative nitrogen atom with a lone pair of electrons. The dipole moment thus points generally from $-\text{CH}_3$ toward the lone pair.



Methylamine
($\mu = 1.31$)

PROBLEM 2.5

Ethylene glycol, $\text{HOCH}_2\text{CH}_2\text{OH}$, has zero dipole moment even though carbon–oxygen bonds are strongly polar and oxygen has two lone pairs of electrons. Explain.

PROBLEM 2.6

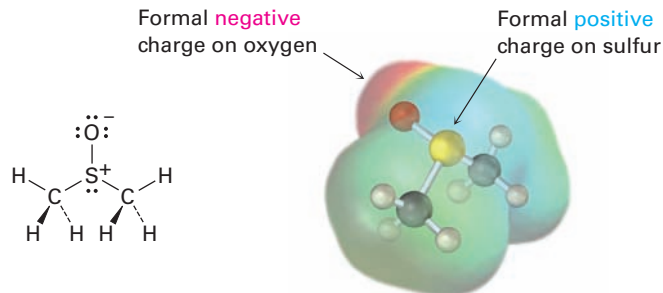
Make three-dimensional drawings of the following molecules, and predict whether each has a dipole moment. If you expect a dipole moment, show its direction.

- (a) $\text{H}_2\text{C}=\text{CH}_2$ (b) CHCl_3 (c) CH_2Cl_2 (d) $\text{H}_2\text{C}=\text{CCl}_2$

2-3 Formal Charges

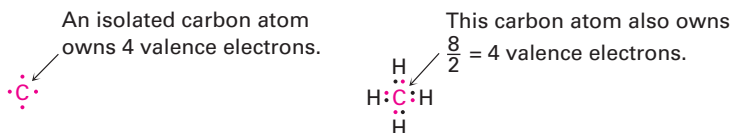
Closely related to the ideas of bond polarity and dipole moment is the concept of assigning *formal charges* to specific atoms within a molecule, particularly atoms that have an apparently “abnormal” number of bonds. Look at dimethyl sulfoxide (CH_3SOCH_3), for instance, a solvent commonly used for preserving biological cell lines at low temperature. The sulfur atom in dimethyl sulfoxide has three bonds rather than the usual two and has a formal positive charge. The oxygen atom, by contrast, has one bond rather than the usual two and has a formal negative charge. Note that an electrostatic potential map of dimethyl

sulfoxide shows the oxygen as negative (red) and the sulfur as relatively positive (blue), in accordance with the formal charges.

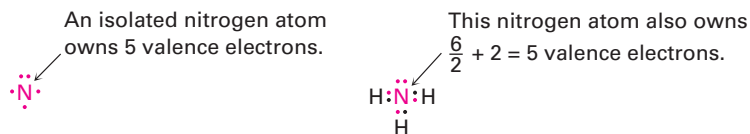


Dimethyl sulfoxide

Formal charges, as the name suggests, are a formalism and don't imply the presence of actual ionic charges in a molecule. Instead, they're a device for electron "bookkeeping" and can be thought of in the following way. A typical covalent bond is formed when each atom donates one electron. Although the bonding electrons are shared by both atoms, each atom can still be considered to own one electron for bookkeeping purposes. In methane, for instance, the carbon atom owns one electron in each of the four C–H bonds, for a total of four. Because a neutral, isolated carbon atom has four valence electrons, and because the carbon atom in methane still owns four, the methane carbon atom is neutral and has no formal charge.

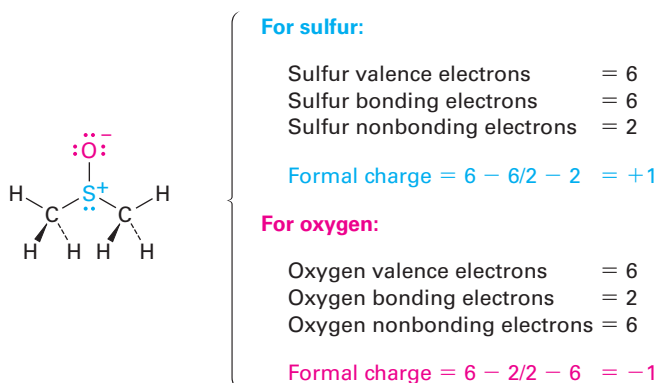


The same is true for the nitrogen atom in ammonia, which has three covalent N–H bonds and two nonbonding electrons (a lone pair). Atomic nitrogen has five valence electrons, and the ammonia nitrogen also has five—one in each of three shared N–H bonds plus two in the lone pair. Thus, the nitrogen atom in ammonia has no formal charge.



The situation is different in dimethyl sulfoxide, however. Atomic sulfur has six valence electrons, but the dimethyl sulfoxide sulfur owns only five—one in each of the two S–C single bonds, one in the S–O single bond, and two in a lone pair. Thus, the sulfur atom has formally lost an electron and therefore has a positive charge. A similar calculation for the oxygen atom shows that it has formally gained an electron and has a negative charge: atomic oxygen has

six valence electrons, but the oxygen in dimethyl sulfoxide has seven—one in the O–S bond and two in each of three lone pairs.



To express the calculations in a general way, the **formal charge** on an atom is equal to the number of valence electrons in a neutral, isolated atom minus the number of electrons owned by that bonded atom in a molecule. The number of electrons in the bonded atom, in turn, is equal to half the number of bonding electrons plus the nonbonding, lone-pair electrons.

$$\text{Formal charge} = \left(\begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in free atom} \end{array} \right) - \left(\begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in bonded atom} \end{array} \right)$$

$$= \left(\begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in free atom} \end{array} \right) - \left(\frac{\text{Number of} \\ \text{bonding electrons}}{2} + \begin{array}{c} \text{Number of} \\ \text{nonbonding} \\ \text{electrons} \end{array} \right)$$

A summary of commonly encountered formal charges and the bonding situations in which they occur is given in **TABLE 2.2**. Although only a book-keeping device, formal charges often give clues about chemical reactivity, so it's helpful to be able to identify and calculate them correctly.

TABLE 2.2 A Summary of Common Formal Charges

Atom	C			N		O		S		P
Structure										
Valence electrons	4	4	4	5	5	6	6	6	6	5
Number of bonds	3	3	3	4	2	3	1	3	1	4
Number of nonbonding electrons	1	0	2	0	4	2	6	2	6	0
Formal charge	0	+1	-1	+1	-1	+1	-1	+1	-1	+1

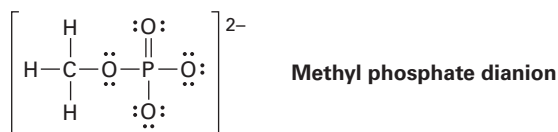
PROBLEM 2.7

Calculate formal charges for the nonhydrogen atoms in the following molecules:

- (a) Diazomethane, $\text{H}_2\text{C}=\text{N}=\ddot{\text{N}}:$ (b) Acetonitrile oxide, $\text{H}_3\text{C}-\text{C}\equiv\text{N}-\ddot{\text{O}}:$
 (c) Methyl isocyanide, $\text{H}_3\text{C}-\text{N}\equiv\text{C}:$

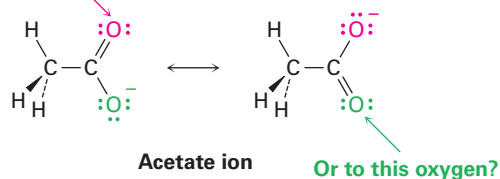
PROBLEM 2.8

Organic phosphate groups occur commonly in biological molecules. Calculate formal charges on the four O atoms in the methyl phosphate dianion.

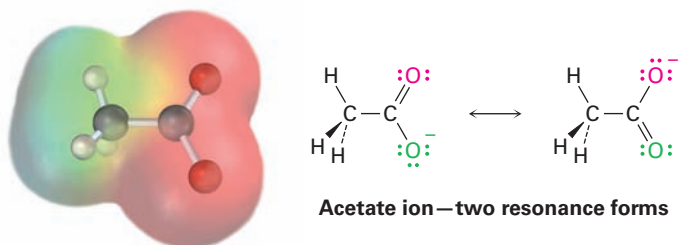
**2-4 Resonance**

Most substances can be represented unambiguously by the Kekulé line-bond structures we've been using up to this point, but an interesting problem sometimes arises. Look at the acetate ion, for instance. When we draw a line-bond structure for acetate, we need to show a double bond to one oxygen and a single bond to the other. But which oxygen is which? Should we draw a double bond to the "top" oxygen and a single bond to the "bottom" oxygen or vice versa?

Double bond to this oxygen?



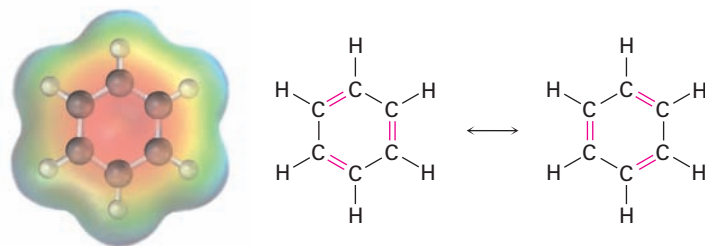
Although the two oxygen atoms in the acetate ion appear different in line-bond structures, they are in fact equivalent. Both carbon–oxygen bonds, for example, are 127 pm in length, midway between the length of a typical C–O single bond (135 pm) and a typical C=O double bond (120 pm). In other words, *neither* of the two structures for acetate is correct by itself. The true structure is intermediate between the two, and an electrostatic potential map shows that both oxygen atoms share the negative charge and have equal electron densities (red).



The two individual line-bond structures for acetate ion are called **resonance forms**, and their special resonance relationship is indicated by a double-headed arrow placed between them. *The only difference between resonance forms is the placement of the π and nonbonding valence electrons.* The atoms themselves occupy exactly the same place in both resonance forms, the connections between atoms are the same, and the three-dimensional shapes of the resonance forms are the same.

A good way to think about resonance forms is to realize that a substance like the acetate ion is no different from any other. Acetate doesn't jump back and forth between two resonance forms, spending part of the time looking like one and part of the time looking like the other. Rather, acetate has a single unchanging structure that we say is a **resonance hybrid** of the two individual forms and has characteristics of both. The only "problem" with acetate is that we can't draw it accurately using a familiar line-bond structure—line-bond structures just don't work well for resonance hybrids. The difficulty, however, is with the *representation* of acetate on paper, not with acetate itself.

Resonance is a very useful concept that we'll return to on numerous occasions throughout the rest of this book. We'll see in Section 9-2, for instance, that the six carbon-carbon bonds in so-called aromatic compounds, such as benzene, are equivalent and that benzene is best represented as a hybrid of two resonance forms. Although each individual resonance form seems to imply that benzene has alternating single and double bonds, neither form is correct by itself. The true benzene structure is a hybrid of the two individual forms, and all six carbon-carbon bonds are equivalent. This symmetrical distribution of electrons around the molecule is evident in an electrostatic potential map.



Benzene (two resonance forms)

2-5 Rules for Resonance Forms

When first dealing with resonance forms, it's useful to have a set of guidelines that describe how to draw and interpret them. The following rules should be helpful:

Rule 1

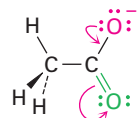
Individual resonance forms are imaginary, not real. The real structure is a composite, or resonance hybrid, of the different forms. Species such as the acetate ion and benzene are no different from any other. They have single, unchanging structures, and they do not switch back and forth between resonance forms.

The only difference between these and other substances is in the way they must be represented in drawings.

Rule 2

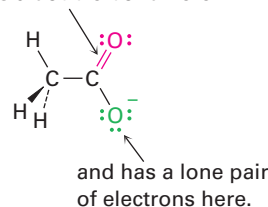
Resonance forms differ only in the placement of their π or nonbonding electrons. Neither the position nor the hybridization of any atom changes from one resonance form to another. In the acetate ion, for instance, the carbon atom is sp^2 -hybridized and the oxygen atoms remain in exactly the same place in both resonance forms. Only the positions of the π electrons in the C=O double bond and the lone-pair electrons on oxygen differ from one form to another. This movement of electrons from one resonance structure to another can be indicated by using curved arrows. *A curved arrow always indicates the movement of electrons, not the movement of atoms.* An arrow shows that a pair of electrons moves *from* the atom or bond at the tail of the arrow *to* the atom or bond at the head of the arrow.

The red curved arrow indicates that a lone pair of electrons moves from the top oxygen atom to become part of a C=O bond.

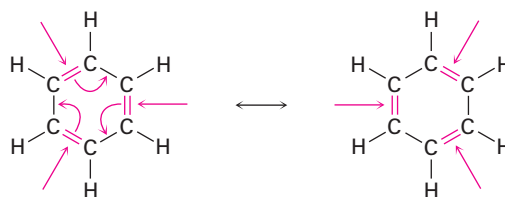


Simultaneously, two electrons from the C=O bond move onto the bottom oxygen atom to become a lone pair.

The new resonance form has a double bond here...

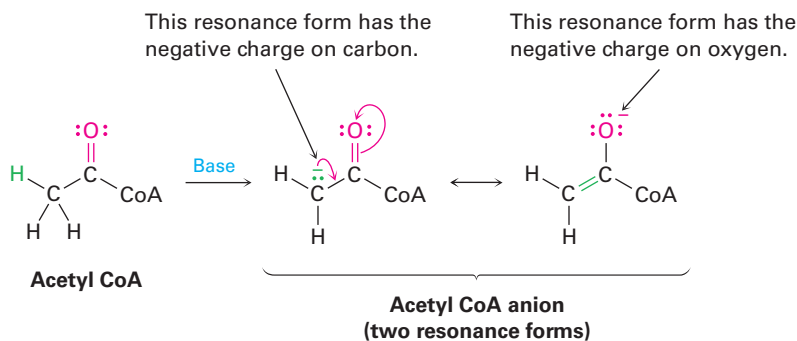


The situation with benzene is similar to that with acetate ion. The π electrons in the double bonds move, as shown with curved arrows, but the carbon and hydrogen atoms remain in place.



Rule 3

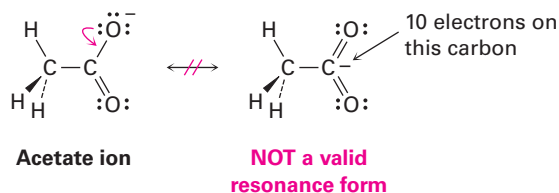
Different resonance forms of a substance don't have to be equivalent. As an example, we'll see in Chapter 17 that compounds containing a C=O double bond, such as acetyl coenzyme A, an intermediate in carbohydrate and fat metabolism, can be converted into an anion by reaction with a base. (For now, we'll abbreviate the coenzyme A part of the structure as "CoA.") The resultant anion has two resonance forms. One form contains a carbon–oxygen double bond and has a negative charge on the adjacent *carbon*, while the other contains a carbon–*carbon* double bond and has a negative charge on *oxygen*. Even though the two resonance forms aren't equivalent, both contribute to the overall resonance hybrid.



When two resonance forms are nonequivalent, the actual structure of the resonance hybrid resembles the more stable form more than it resembles the less stable form. Thus, we might expect the true structure of the acetyl CoA anion to be more like that of the form that places the negative charge on the electronegative oxygen atom rather than on carbon.

Rule 4

Resonance forms obey normal rules of valency. A resonance form is like any other structure: the octet rule still applies to second-row, main-group atoms. For example, one of the following structures for the acetate ion is not a valid resonance form because the carbon atom has five bonds and ten valence electrons:

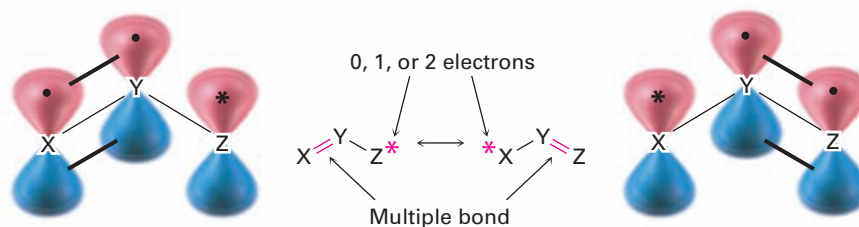


Rule 5

The resonance hybrid is more stable than any individual resonance form. In other words, resonance leads to stability. Generally speaking, the larger the number of resonance forms, the more stable a substance is because its electrons are spread out over a larger part of the molecule and are closer to more nuclei. We'll see in Chapter 9, for instance, that a benzene ring is more stable because of resonance than might otherwise be expected.

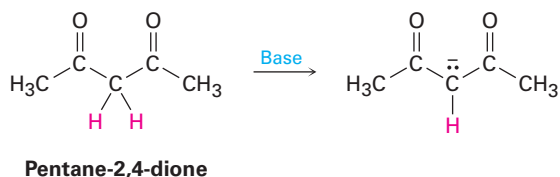
2-6 Drawing Resonance Forms

Look back at the resonance forms of the acetate ion and acetyl CoA anion shown in the previous section. The pattern seen there is a common one that leads to a useful technique for drawing resonance forms. In general, *any three-atom grouping with a p orbital on each atom has two resonance forms*:

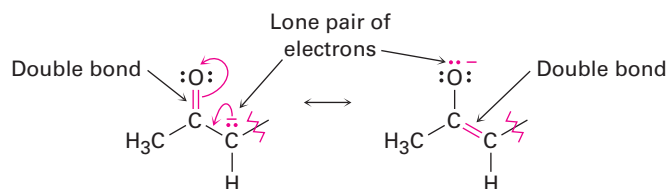


The atoms X, Y, and Z in the general structure might be C, N, O, P, S, or others, and the asterisk (*) might mean that the p orbital on atom Z is vacant, that it contains a single electron, or that it contains a lone pair of electrons. The two resonance forms differ simply by an exchange in position of the multiple bond and the asterisk from one end of the three-atom grouping to the other.

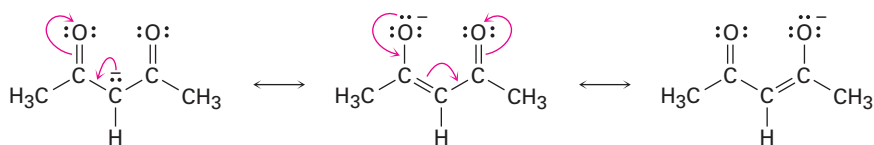
By learning to recognize such three-atom groupings within larger structures, resonance forms can be systematically generated. Look, for instance, at the anion produced when H^+ is removed from pentane-2,4-dione by reaction with a base. How many resonance structures does the resultant anion have?



The pentane-2,4-dione anion has a lone pair of electrons and a formal negative charge on the central carbon atom, next to a $\text{C}=\text{O}$ bond on the left. The $\text{O}=\text{C}-\text{C}^-$ grouping is a typical one for which two resonance structures can be drawn:



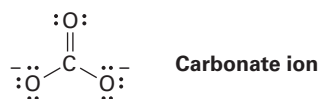
Just as there is a $\text{C}=\text{O}$ bond to the left of the lone pair, there is a second $\text{C}=\text{O}$ bond to the right. Thus, we can draw a total of three resonance structures for the pentane-2,4-dione anion:



WORKED EXAMPLE 2.2

Drawing Resonance Forms for an Anion

Draw three resonance structures for the carbonate ion, CO_3^{2-} .



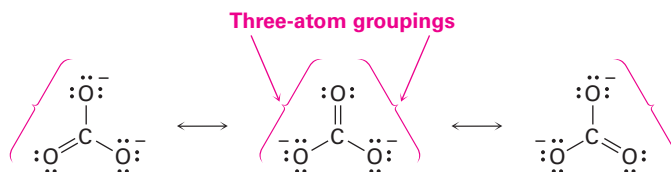
Strategy

Look for three-atom groupings that contain a multiple bond next to an atom with a p orbital. Then exchange the positions of the multiple bond and the electrons in the p orbital. In the carbonate ion, each of the singly bonded

oxygen atoms with its lone pairs and negative charge is next to the C=O double bond, giving the grouping $\text{O}=\text{C}-\text{O}^-$.

Solution

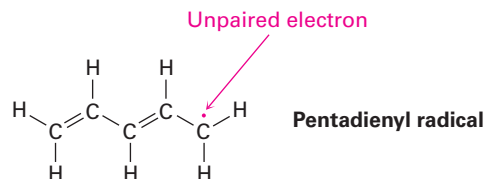
Exchanging the position of the double bond and an electron lone pair in each grouping generates three resonance structures:



Drawing Resonance Forms for a Radical

WORKED EXAMPLE 2.3

Draw three resonance forms for the pentadienyl radical, where a *radical* is a substance that contains a single, unpaired electron in one of its orbitals, denoted by a dot (\cdot).

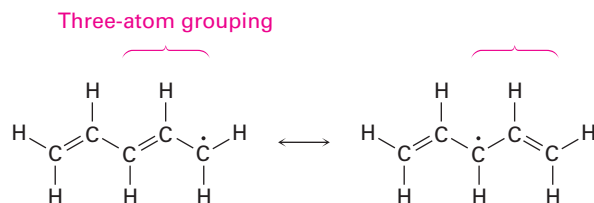


Strategy

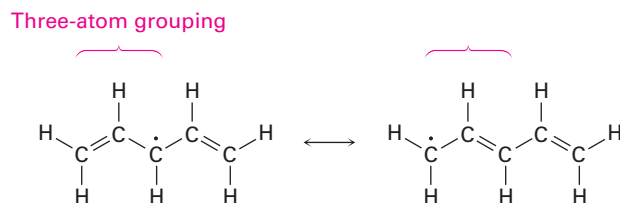
Find the three-atom groupings that contain a multiple bond next to a p orbital.

Solution

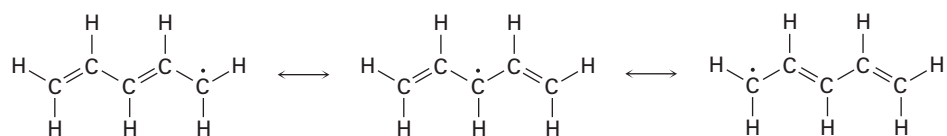
The unpaired electron is on a carbon atom next to a C=C bond, giving a typical three-atom grouping that has two resonance forms:



In the second resonance form, the unpaired electron is next to another double bond, giving another three-atom grouping and leading to another resonance form:

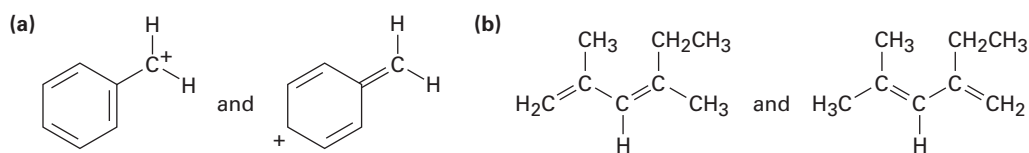


Thus, the three resonance forms for the pentadienyl radical are:



PROBLEM 2.9

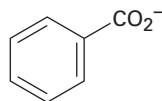
Which of the following pairs of structures represent resonance forms, and which do not? Explain.



PROBLEM 2.10

Draw the indicated number of resonance structures for each of the following species:

- The methyl phosphate dianion, $\text{CH}_3\text{OPO}_3^{2-}$ (3)
- The nitrate anion, NO_3^- (3)
- The allyl cation, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2^+$ (2)
- The benzoate anion (4)

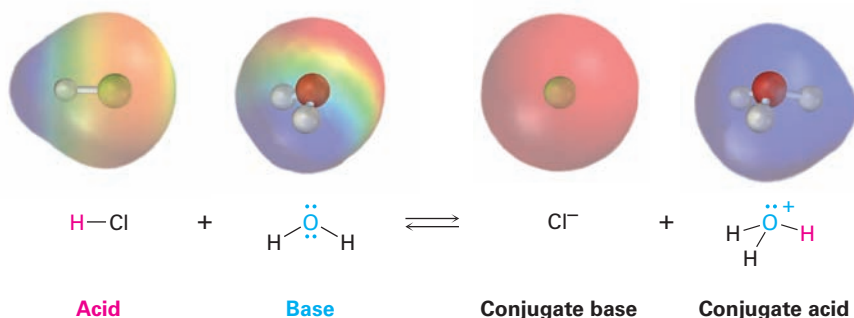


2-7 Acids and Bases: The Brønsted–Lowry Definition

Perhaps the most important of all concepts related to electronegativity and polarity is that of *acidity* and *basicity*. We'll soon see, in fact, that the acid–base behavior of organic molecules explains much of their chemistry. You may recall from your course in general chemistry that two definitions of acidity are frequently used: the *Brønsted–Lowry definition* and the *Lewis definition*. We'll look at the Brønsted–Lowry definition in this and the following three sections and then discuss the Lewis definition in Section 2-11.

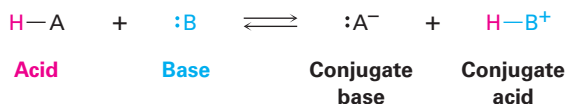
A **Brønsted–Lowry acid** is a substance that donates a hydrogen ion, H^+ , and a **Brønsted–Lowry base** is a substance that accepts a hydrogen ion. (The name *proton* is often used as a synonym for H^+ because loss of the valence electron from a neutral hydrogen atom leaves only the hydrogen nucleus—a proton.) When gaseous hydrogen chloride dissolves in water, for example, a polar HCl molecule acts as an acid and donates a proton, while a water

molecule acts as a base and accepts the proton, yielding a chloride ion (Cl^-) and a hydronium ion (H_3O^+).

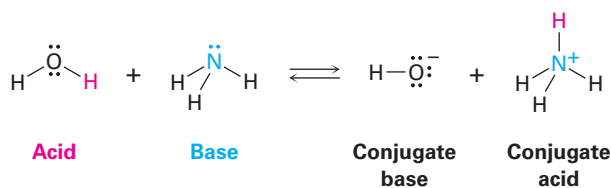
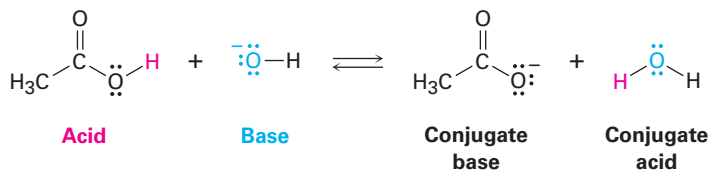


Chloride ion, the product that results when the acid HCl loses a proton, is called the **conjugate base** of the acid, and hydronium ion, the product that results when the base H₂O gains a proton, is called the **conjugate acid** of the base. Other common mineral acids, such as H₂SO₄ and HNO₃, behave similarly, as do organic acids such as acetic acid, CH₃CO₂H.

In a general sense,



For example:



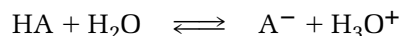
Note that water can act either as an acid or as a base, depending on the circumstances. In its reaction with HCl, water is a base that accepts a proton to give the hydronium ion, H₃O⁺. In its reaction with ammonia (NH₃), however, water is an acid that donates a proton to give ammonium ion (NH₄⁺) and hydroxide ion, HO⁻.

PROBLEM 2.11

Nitric acid (HNO₃) reacts with ammonia (NH₃) to yield ammonium nitrate. Write the reaction, and identify the acid, the base, the conjugate acid product, and the conjugate base product.

2-8 Acid and Base Strength

Different acids vary in their ability to donate H^+ . Stronger acids, such as HCl , react almost completely with water, whereas weaker acids, such as acetic acid ($\text{CH}_3\text{CO}_2\text{H}$), react only slightly. The exact strength of a given acid HA in water solution is described using the **acidity constant** (K_a) for the acid-dissociation equilibrium. Remember from general chemistry that the concentration of solvent is ignored in the equilibrium expression and that brackets [] around a substance refer to the concentration of the enclosed species in moles per liter.



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

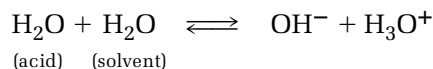
Stronger acids have their equilibria toward the right and thus have larger acidity constants, whereas weaker acids have their equilibria toward the left and have smaller acidity constants. The range of K_a values for different acids is enormous, running from about 10^{15} for the strongest acids to about 10^{-60} for the weakest. The common inorganic acids, such as H_2SO_4 , HNO_3 , and HCl , have K_a 's in the range of 10^2 to 10^9 , while organic acids generally have K_a 's in the range of 10^{-5} to 10^{-15} . As you gain more experience, you'll develop a rough feeling for which acids are "strong" and which are "weak" (always remembering that the terms are relative).

Acid strengths are normally expressed using $\text{p}K_a$ values rather than K_a values, where the **$\text{p}K_a$** is the negative common logarithm of the K_a :

$$\text{p}K_a = -\log K_a$$

A *stronger* acid (larger K_a) has a *smaller* $\text{p}K_a$, and a *weaker* acid (smaller K_a) has a *larger* $\text{p}K_a$. **TABLE 2.3** lists the $\text{p}K_a$'s of some common acids in order of their strength, and a more comprehensive table is given in Appendix B.

Note that the $\text{p}K_a$ value shown in Table 2.3 for water is 15.74, which results from the following calculation. Because water is both the acid and the solvent, the equilibrium expression is



$$\begin{aligned} K_a &= \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} = \frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]} \\ &= \frac{[1.0 \times 10^{-7}][1.0 \times 10^{-7}]}{[55.4]} = [1.8 \times 10^{-16}] \end{aligned}$$

$$\text{p}K_a = 15.74$$

The numerator in this expression is the so-called ion-product constant for water, $K_w = [\text{H}_3\text{O}^+][\text{OH}^-] = 1.00 \times 10^{-14}$, and the denominator is the molar concentration of pure water, $[\text{H}_2\text{O}] = 55.4 \text{ M}$ at 25°C . The calculation is artificial in that the concentration of "solvent" water is ignored while the concentration of "acid" water is not, but it is nevertheless useful in allowing us to make a comparison of water with other weak acids on a similar footing.

Note also in Table 2.3 that there is an inverse relationship between the acid strength of an acid and the base strength of its conjugate base. A *strong* acid has a *weak* conjugate base, and a *weak* acid has a *strong* conjugate base.

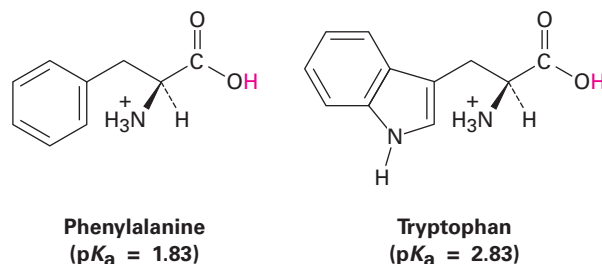
TABLE 2.3 Relative Strengths of Some Common Acids and Their Conjugate Bases

	Acid	Name	pK_a	Conjugate base	Name	
	$\text{CH}_3\text{CH}_2\text{OH}$	Ethanol	16.00	$\text{CH}_3\text{CH}_2\text{O}^-$	Ethoxide ion	
	H_2O	Water	15.74	HO^-	Hydroxide ion	
	HCN	Hydrocyanic acid	9.31	CN^-	Cyanide ion	
	H_2PO_4^-	Dihydrogen phosphate ion	7.21	HPO_4^{2-}	Hydrogen phosphate ion	
	$\text{CH}_3\text{CO}_2\text{H}$	Acetic acid	4.76	CH_3CO_2^-	Acetate ion	
	H_3PO_4	Phosphoric acid	2.16	H_2PO_4^-	Dihydrogen phosphate ion	
	HNO_3	Nitric acid	-1.3	NO_3^-	Nitrate ion	
	HCl	Hydrochloric acid	-7.0	Cl^-	Chloride ion	

To understand this inverse relationship, think about what is happening to the acidic hydrogen in an acid–base reaction. A strong acid is one that loses H^+ easily, meaning that its conjugate base holds the H^+ weakly and is therefore a weak base. A weak acid is one that loses H^+ with difficulty, meaning that its conjugate base holds the proton tightly and is therefore a strong base. The fact that HCl is a strong acid, for example, means that Cl^- does not hold H^+ tightly and is thus a weak base. Water, on the other hand, is a weak acid, meaning that OH^- holds H^+ tightly and is a strong base.

PROBLEM 2.12

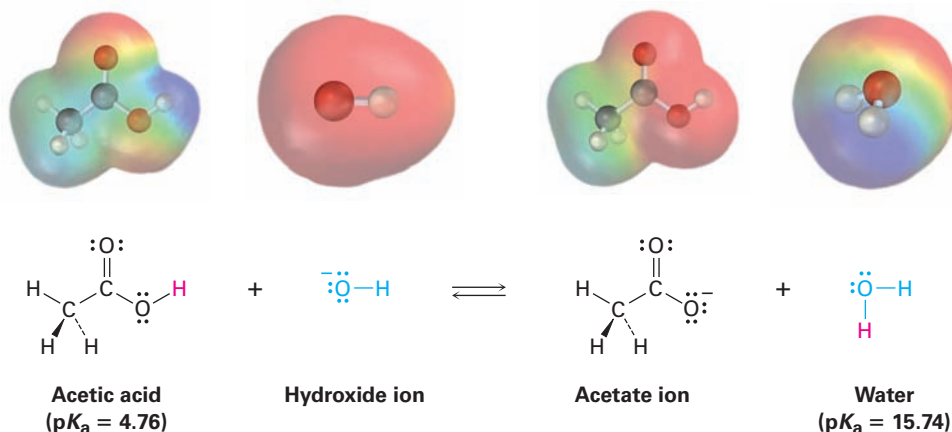
The amino acid phenylalanine has $pK_a = 1.83$, and tryptophan has $pK_a = 2.83$. Which is the stronger acid?

**PROBLEM 2.13**

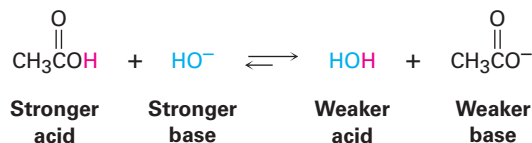
Amide ion, H_2N^- , is a much stronger base than hydroxide ion, HO^- . Which is the stronger acid, NH_3 or H_2O ? Explain.

2-9 Predicting Acid–Base Reactions from pK_a Values

Compilations of pK_a values like those in Table 2.3 and Appendix B are useful for predicting whether a given acid–base reaction will take place because H^+ will always go *from* the stronger acid *to* the stronger base. That is, an acid will donate a proton to the conjugate base of a weaker acid, and the conjugate base of a weaker acid will remove the proton from a stronger acid. Since water ($pK_a = 15.74$) is a weaker acid than acetic acid ($pK_a = 4.76$), for example, hydroxide ion holds a proton more tightly than acetate ion does. Hydroxide ion will therefore react to a large extent with acetic acid, CH_3CO_2H , to yield acetate ion and H_2O .



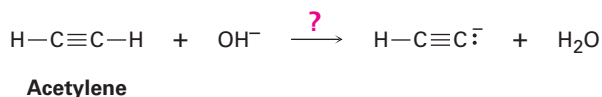
Another way to predict acid–base reactivity is to remember that the product conjugate acid in an acid–base reaction must be weaker and less reactive than the starting acid and the product conjugate base must be weaker and less reactive than the starting base. In the reaction of acetic acid with hydroxide ion, for example, the product conjugate acid (H_2O) is weaker than the starting acid (CH_3CO_2H) and the product conjugate base ($CH_3CO_2^-$) is weaker than the starting base (OH^-).



WORKED EXAMPLE 2.4

Predicting Acid Strengths from pK_a Values

Water has $pK_a = 15.74$, and acetylene has $pK_a = 25$. Which is the stronger acid? Does hydroxide ion react with acetylene?



Strategy

In comparing two acids, the one with the lower pK_a is stronger. Thus, water is a stronger acid than acetylene and gives up H^+ more easily.

Solution

Because water is a stronger acid and gives up H^+ more easily than acetylene does, the HO^- ion must have less affinity for H^+ than the $\text{HC}\equiv\text{C}^-$ ion has. In other words, the anion of acetylene is a stronger base than hydroxide ion, and the reaction will not proceed as written.

Calculating K_a from $\text{p}K_a$ **WORKED EXAMPLE 2.5**

According to the data in Table 2.3, acetic acid has $\text{p}K_a = 4.76$. What is its K_a ?

Strategy

Since $\text{p}K_a$ is the negative logarithm of K_a , it's necessary to use a calculator with an ANTILOG or INV LOG function. Enter the value of the $\text{p}K_a$ (4.76), change the sign (-4.76), and then find the antilog (1.74×10^{-5}).

Solution

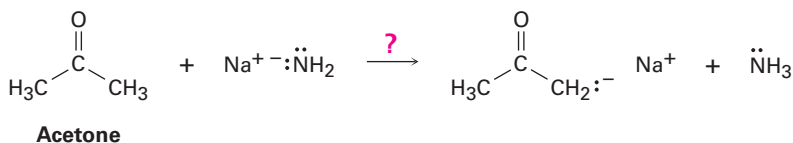
$$K_a = \text{antilog } -4.76 = 1.74 \times 10^{-5}$$

PROBLEM 2.14

Will either of the following reactions take place as written, according to the $\text{p}K_a$ data in Table 2.3?

**PROBLEM 2.15**

Ammonia, NH_3 , has $\text{p}K_a \approx 36$, and acetone has $\text{p}K_a \approx 19$. Will the following reaction take place?

**PROBLEM 2.16**

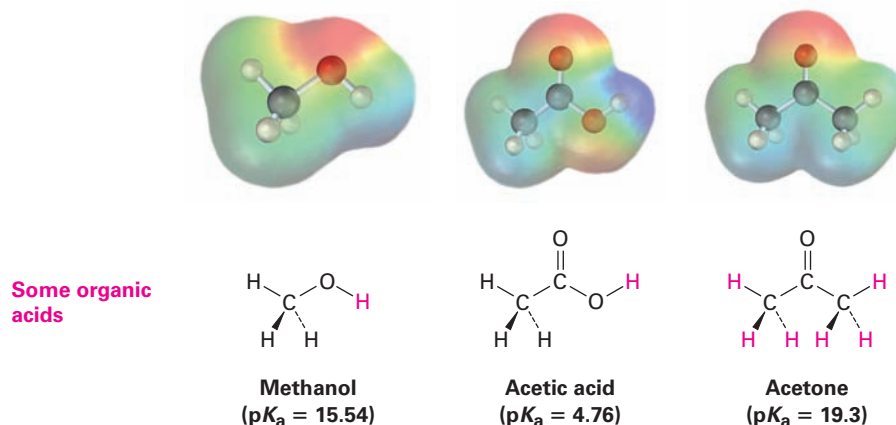
What is the K_a of HCN if its $\text{p}K_a = 9.31$?

2-10 Organic Acids and Organic Bases

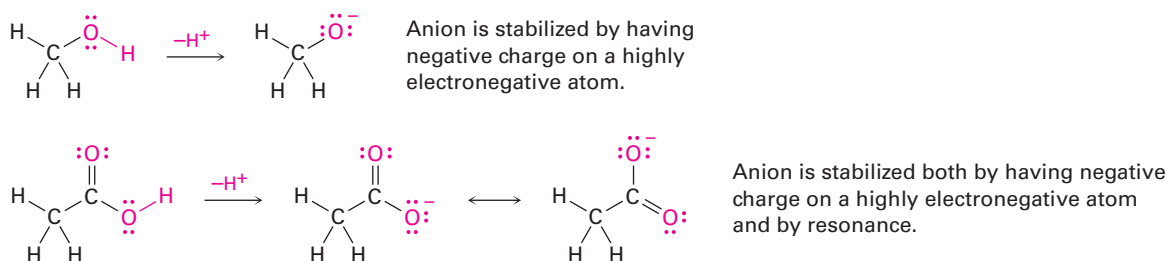
Many of the reactions we'll be seeing in future chapters, including practically all biological reactions, involve organic acids and organic bases. Although it's too early to go into the details of these processes now, you might keep the following generalities in mind:

Organic Acids

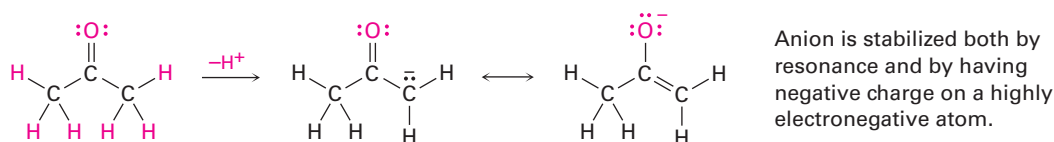
Organic acids are characterized by the presence of a positively polarized hydrogen atom (blue in electrostatic potential maps) and are of two main kinds: those acids such as methanol and acetic acid that contain a hydrogen atom bonded to an electronegative oxygen atom (O–H) and those such as acetone and acetyl CoA (Section 2-5) that contain a hydrogen atom bonded to a carbon atom next to a C=O double bond (O=C–C–H).



Methanol contains an O–H bond and is a weak acid, while acetic acid also contains an O–H bond and is a somewhat stronger acid. In both cases, acidity is due to the fact that the conjugate base resulting from loss of H^+ is stabilized by having its negative charge on a strongly electronegative oxygen atom. In addition, the conjugate base of acetic acid is stabilized by resonance (Sections 2-4 and 2-5).



The acidity of acetone, acetyl CoA, and other compounds with C=O double bonds is due to the fact that the conjugate base resulting from loss of H^+ is stabilized by resonance. In addition, one of the resonance forms stabilizes the negative charge by placing it on an electronegative oxygen atom.



Electrostatic potential maps of the conjugate bases from methanol, acetic acid, and acetone are shown in **FIGURE 2.4**. As you might expect, all three show a substantial amount of negative charge (red) on oxygen.

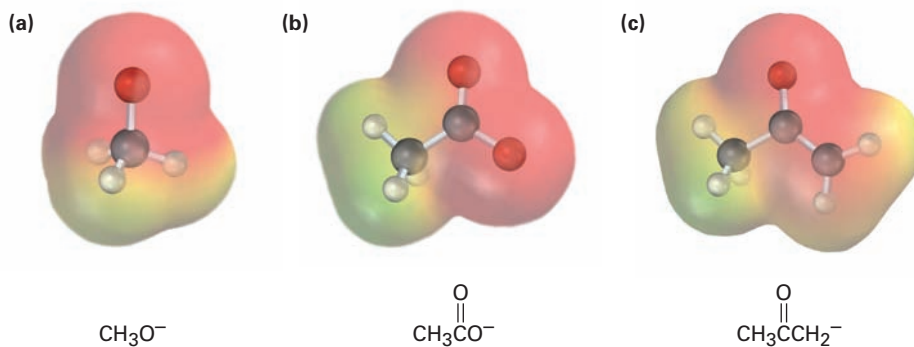
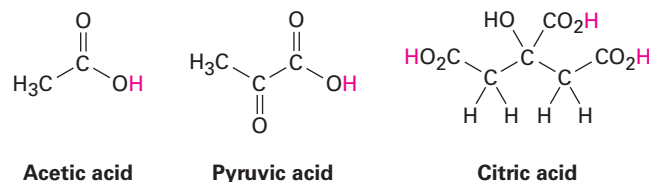


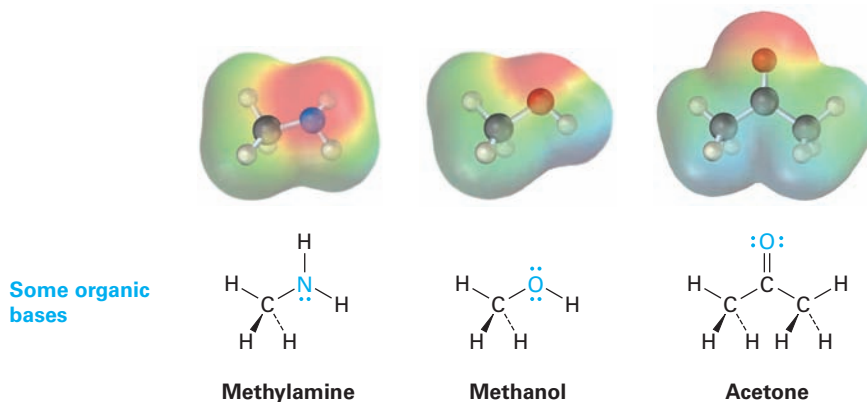
FIGURE 2.4 Electrostatic potential maps of the conjugate bases of (a) methanol, (b) acetic acid, and (c) acetone. Electronegative oxygen atoms stabilize the negative charge in all three.

Compounds called *carboxylic acids*, which contain the $-\text{CO}_2\text{H}$ grouping, occur abundantly in all living organisms and are involved in almost all metabolic pathways. Acetic acid, pyruvic acid, and citric acid are examples. You might note that at the typical pH of 7.3 found within cells, carboxylic acids are usually dissociated and exist as their carboxylate anions, $-\text{CO}_2^-$.



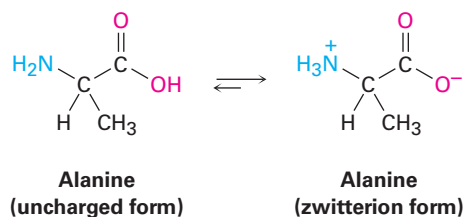
Organic Bases

Organic bases are characterized by the presence of an atom (reddish in electrostatic potential maps) with a lone pair of electrons that can bond to H^+ . Nitrogen-containing compounds such as methylamine are the most common organic bases and are involved in almost all metabolic pathways, but oxygen-containing compounds can also act as bases when reacting with a sufficiently strong acid. Note that some oxygen-containing compounds can act both as acids and as bases depending on the circumstances, just as water can. Methanol and acetone, for instance, act as *acids* when they donate a proton but as *bases* when their oxygen atom accepts a proton.



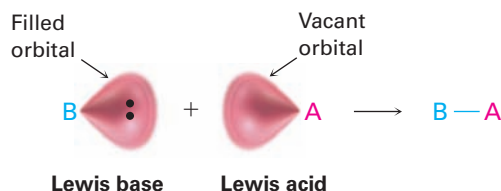
We'll soon see that substances called *amino acids*, so-named because they are both amines ($-\text{NH}_2$) and carboxylic acids ($-\text{CO}_2\text{H}$), are the building blocks from which the proteins present in all living organisms are made. Twenty different amino acids go into making up proteins; alanine is an example.

Interestingly, alanine and other amino acids exist primarily in a doubly charged form called a *zwitterion* rather than in the uncharged form. The zwitterion form arises because amino acids have both acidic and basic sites within the same molecule and therefore undergo an *internal* acid–base reaction.



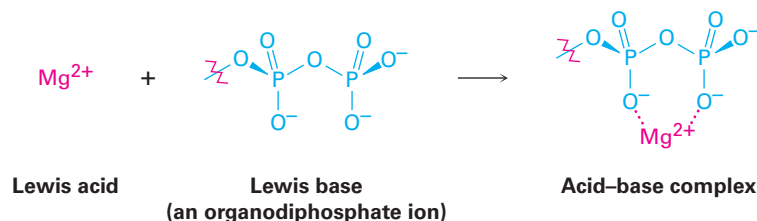
2-11 Acids and Bases: The Lewis Definition

The Lewis definition of acids and bases is broader and more encompassing than the Brønsted–Lowry definition because it's not limited to substances that donate or accept just protons. A **Lewis acid** is a substance that *accepts an electron pair*, and a **Lewis base** is a substance that *donates an electron pair*. The donated electron pair is shared between the acid and the base in a covalent bond.



Lewis Acids and the Curved Arrow Formalism

The fact that a Lewis acid is able to accept an electron pair means that it must have either a vacant, low-energy orbital or a polar bond to hydrogen so that it can donate H^+ (which has an empty $1s$ orbital). Thus, the Lewis definition of acidity includes many species in addition to H^+ . For example, various metal cations, such as Mg^{2+} , are Lewis acids because they accept a pair of electrons when they form a bond to a base. We'll see in later chapters that many metabolic reactions begin with an acid–base reaction between Mg^{2+} as a Lewis acid and an organodiphosphate or organotriphosphate ion as the Lewis base.



In the same way, compounds of group 3A elements, such as BF_3 and AlCl_3 , are Lewis acids because they have unfilled valence orbitals and can accept electron pairs from Lewis bases, as shown in **FIGURE 2.5**. Similarly, many transition-metal compounds, such as TiCl_4 , FeCl_3 , ZnCl_2 , and SnCl_4 , are Lewis acids.

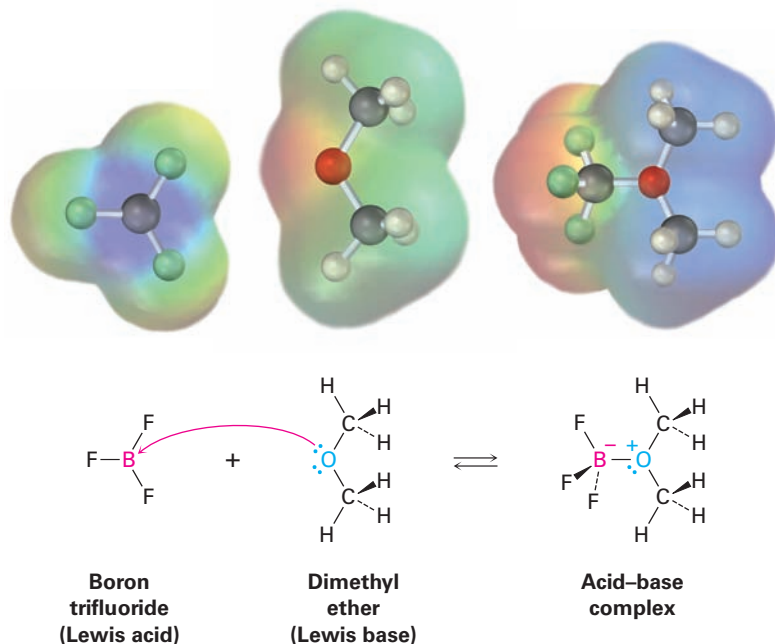
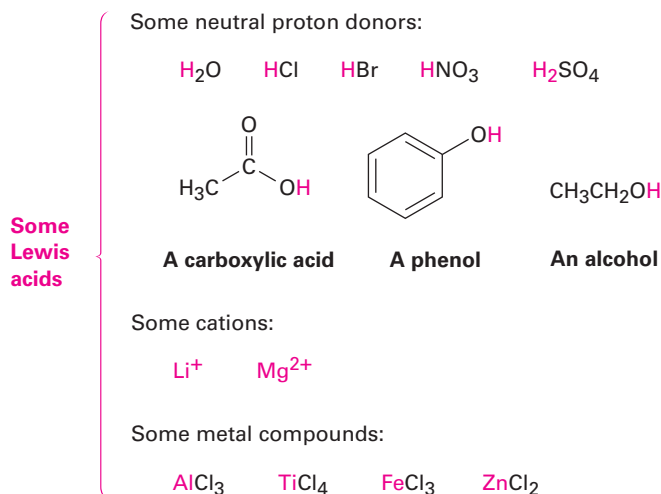


FIGURE 2.5 Reaction of boron trifluoride, a Lewis acid, with dimethyl ether, a Lewis base.

The Lewis acid accepts a pair of electrons, and the Lewis base donates a pair of nonbonding electrons. Note how the movement of electrons *from* the Lewis base *to* the Lewis acid is indicated by a curved arrow. Note also how, in electrostatic potential maps, **the boron becomes more negative (red)** after reaction because it has gained electrons and **the oxygen atom becomes more positive (blue)** because it has donated electrons.

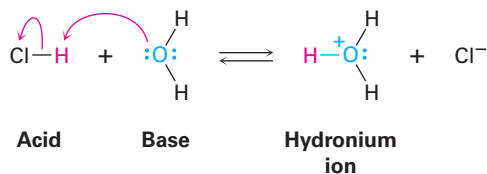
Look closely at the acid–base reaction in Figure 2.5, and note how it is shown. Dimethyl ether, the Lewis base, donates an electron pair to a vacant valence orbital of the boron atom in BF_3 , a Lewis acid. The direction of electron-pair flow from the base to the acid is shown using curved arrows, just as the direction of electron flow in going from one resonance structure to another was shown using curved arrows in Section 2-5. *A curved arrow always means that a pair of electrons moves from the atom at the tail of the arrow to the atom at the head of the arrow.* We'll use this curved-arrow notation throughout the remainder of this text to indicate electron flow during reactions.

Some further examples of Lewis acids follow:

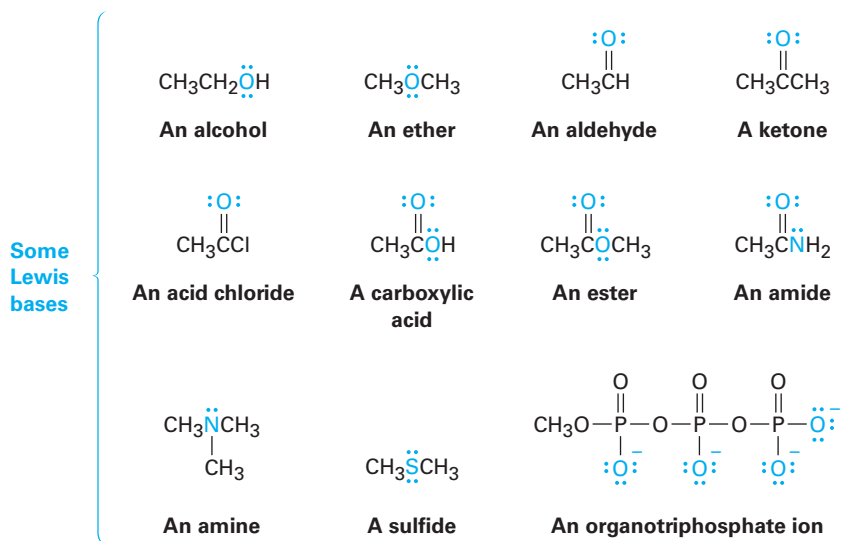


Lewis Bases

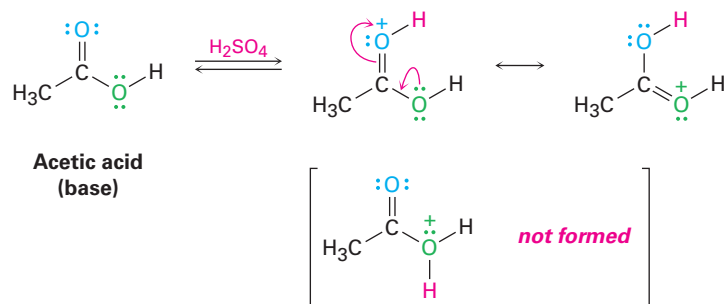
The Lewis definition of a base—a compound with a pair of nonbonding electrons that it can use in bonding to a Lewis acid—is similar to the Brønsted–Lowry definition. Thus, H_2O , with its two pairs of nonbonding electrons on oxygen, acts as a Lewis base by donating an electron pair to an H^+ in forming the hydronium ion, H_3O^+ .



In a more general sense, most oxygen- and nitrogen-containing organic compounds can act as Lewis bases because they have lone pairs of electrons. A divalent oxygen compound has two lone pairs of electrons, and a trivalent nitrogen compound has one lone pair. Note in the following examples that some compounds can act as both acids and bases, just as water can. Alcohols and carboxylic acids, for instance, act as acids when they donate an H^+ but as bases when their oxygen atom accepts an H^+ .



Note in the list of Lewis bases just given that some compounds, such as carboxylic acids, esters, and amides, have more than one atom with a lone pair of electrons and can therefore react at more than one site. Acetic acid, for example, can be protonated either on the doubly bonded oxygen atom or on the singly bonded oxygen atom. Reaction normally occurs only once in such instances, and the more stable of the two possible protonation products is formed. For acetic acid, protonation by reaction with sulfuric acid occurs on the doubly bonded oxygen because that product is stabilized by two resonance forms.



Using Curved Arrows to Show Electron Flow

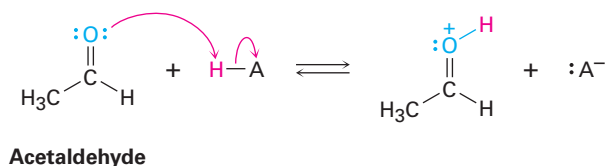
WORKED EXAMPLE 2.6

Using curved arrows, show how acetaldehyde, CH_3CHO , can act as a Lewis base.

Strategy

A Lewis base donates an electron pair to a Lewis acid. We therefore need to locate the electron lone pairs on acetaldehyde and use a curved arrow to show the movement of a pair toward the H atom of the acid.

Solution



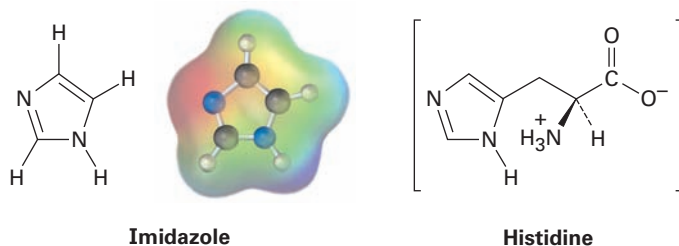
PROBLEM 2.17

Using curved arrows, show how the species in part (a) can act as Lewis bases in their reactions with HCl , and show how the species in part (b) can act as Lewis acids in their reaction with OH^- .

(a) $\text{CH}_3\text{CH}_2\text{OH}$, $\text{HN}(\text{CH}_3)_2$, $\text{P}(\text{CH}_3)_3$ (b) H_3C^+ , $\text{B}(\text{CH}_3)_3$, MgBr_2

PROBLEM 2.18

Imidazole, which forms part of the structure of the amino acid histidine, can act as both an acid and a base.



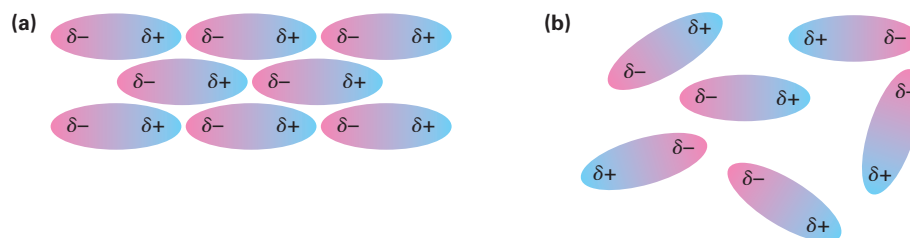
- (a) Look at the electrostatic potential map of imidazole, and identify the most acidic hydrogen atom and the more basic nitrogen atom.
- (b) Draw resonance structures for the products that result when imidazole is protonated by an acid and deprotonated by a base.

2-12 Noncovalent Interactions between Molecules

When thinking about chemical reactivity, chemists usually focus their attention on *bonds*, the covalent interactions between atoms *within* molecules. Also important, however, particularly in large biomolecules like proteins and nucleic acids, are a variety of interactions *between* molecules that strongly affect molecular properties. Collectively called intermolecular forces, van der Waals forces, or **noncovalent interactions**, they are of several different types: dipole–dipole forces, dispersion forces, and hydrogen bonds.

Dipole–dipole forces occur between polar molecules as a result of electrostatic interactions among dipoles. The forces can be either attractive or repulsive depending on the orientation of the molecules—attractive when unlike charges are together and repulsive when like charges are together. The attractive geometry is lower in energy and therefore predominates (FIGURE 2.6).

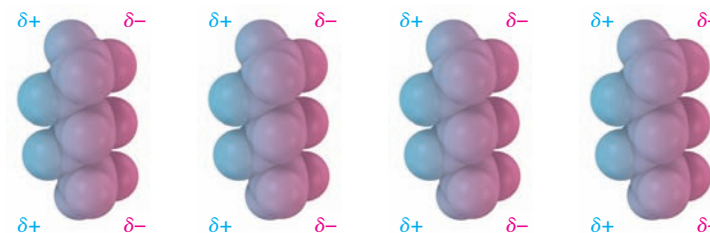
FIGURE 2.6 Dipole–dipole forces. The forces cause polar molecules (a) to attract one another when they orient with unlike charges together but (b) to repel one another when they orient with like charges together.



Dispersion forces occur between all neighboring molecules and arise because the electron distribution within molecules is constantly changing. Although uniform on a time-averaged basis, the electron distribution even in nonpolar molecules is likely to be nonuniform at any given instant. One side of a molecule may, by chance, have a slight excess of electrons relative to the opposite side, giving the molecule a temporary dipole. This temporary dipole in one molecule causes a nearby molecule to adopt a temporarily opposite dipole, with the result that a tiny attraction is induced between the two (FIGURE 2.7). Temporary molecular dipoles have only a fleeting existence and are constantly changing, but their cumulative effect is often strong enough to hold molecules close together so that a substance is a liquid or solid rather than a gas.

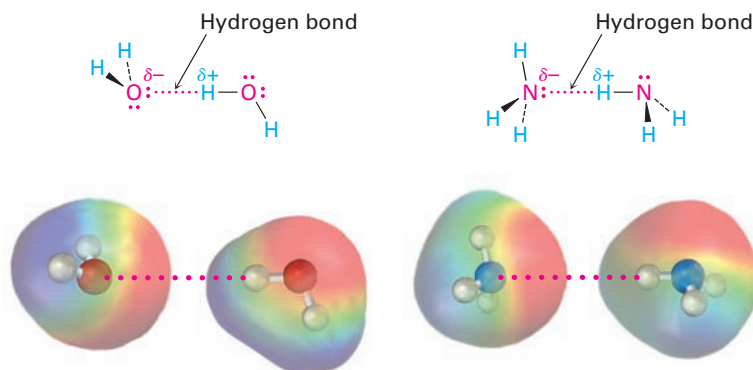
FIGURE 2.7 Dispersion forces.

Attractive forces in nonpolar molecules are caused by temporary dipoles, as shown in these models of pentane, C_5H_{12} .

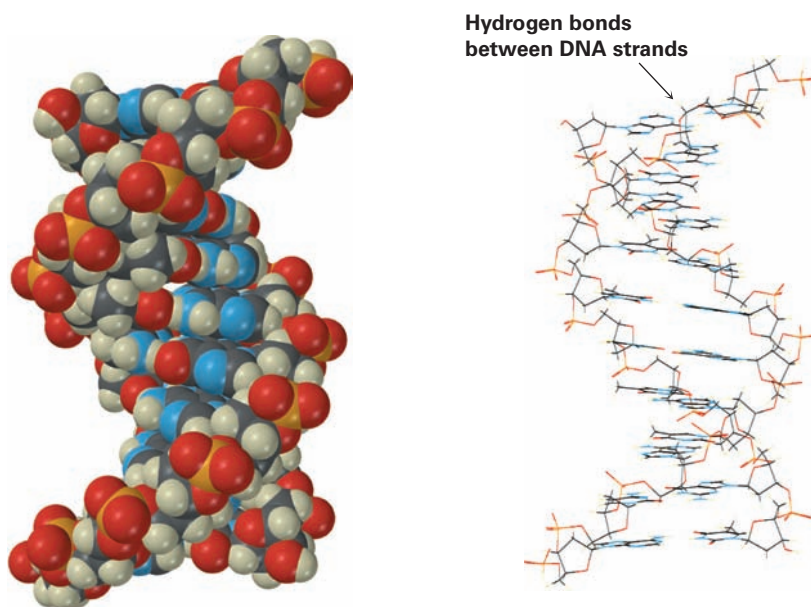


Perhaps the most important noncovalent interaction in biological molecules is the **hydrogen bond**, an attractive interaction between a hydrogen bonded to an electronegative O or N atom and an unshared electron pair on another O or N atom. In essence, a hydrogen bond is a very strong dipole–dipole interaction

involving polarized O–H or N–H bonds. Electrostatic potential maps of water and ammonia clearly show the positively polarized hydrogens (blue) and the negatively polarized oxygens and nitrogens (red).



Hydrogen-bonding has enormous consequences for living organisms. Hydrogen bonds cause water to be a liquid rather than a gas at ordinary temperatures, they hold enzymes in the shapes necessary for catalyzing biological reactions, and they cause strands of deoxyribonucleic acid (DNA) to pair up and coil into the double helix that stores genetic information.



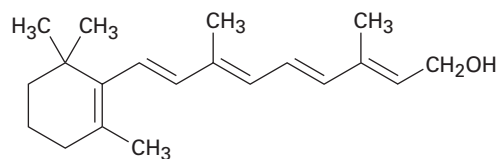
A deoxyribonucleic acid segment

One further point before leaving the subject of noncovalent interactions: biochemists frequently use the term **hydrophilic**, meaning “water-loving,” to describe a substance that is attracted to water and the term **hydrophobic**, meaning “water-fearing,” to describe a substance that is not attracted to water. Hydrophilic substances, such as table sugar, usually have a number of ionic charges or polar –OH groups in their structure so they can form hydrogen bonds, whereas hydrophobic substances, such as vegetable oil, do not have

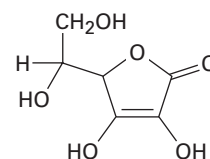
groups that form hydrogen bonds, so any attraction to water is limited to weak dispersion forces.

PROBLEM 2.19

Of the two vitamins A and C, one is hydrophilic and water-soluble while the other is hydrophobic and fat-soluble. Which do you think is which?



Vitamin A
(retinol)



Vitamin C
(ascorbic acid)

SOMETHING EXTRA

Alkaloids: From Cocaine to Dental Anesthetics

Just as ammonia (NH_3) is a weak base, there are a large number of nitrogen-containing organic compounds called *amines* that are also weak bases. In the early days of organic chemistry, basic amines derived from natural sources were known as vegetable alkali, but they are now called *alkaloids*. More than 20,000 alkaloids are known. Their study provided much of the impetus for the growth of organic chemistry in the nineteenth century and remains today an active and fascinating area of research.

Alkaloids vary widely in structure, from the simple to the enormously complex. The odor of rotting fish, for example, is caused largely by methylamine, CH_3NH_2 , a simple relative of ammonia in which one of the NH_3 hydrogens has been replaced by an

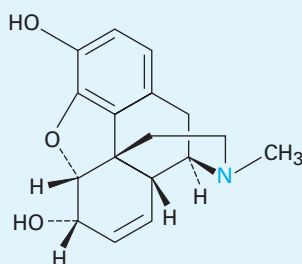


Jose Gomez/Reuters

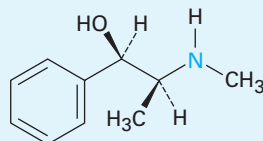
The coca bush *Erythroxylon coca*, native to upland rain forest areas of Colombia, Ecuador, Peru, Bolivia, and western Brazil, is the source of the alkaloid cocaine.

organic CH_3 group. In fact, the use of lemon juice to mask fish odors is simply an acid–base reaction of the citric acid in lemons with methylamine base in the fish.

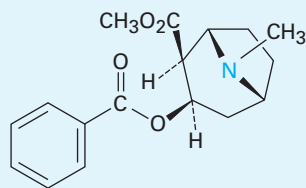
Many alkaloids have pronounced biological properties, and approximately 50% of the pharmaceutical agents used today are derived from naturally occurring amines. As just three examples, morphine, an analgesic agent, is obtained from the opium poppy *Papaver somniferum*. Ephedrine, a bronchodilator, decongestant, and appetite suppressant, is obtained from the Chinese plant *Ephedra sinica*. Cocaine, both an anesthetic and a stimulant, is obtained from the coca bush *Erythroxylon coca*, endemic to the upland rain forest areas of central South America. (And yes, there really was a small amount of cocaine in the original Coca-Cola recipe, although it was removed in 1906.)



Morphine



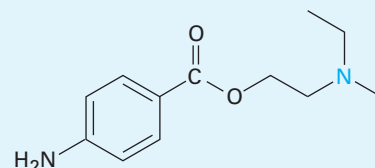
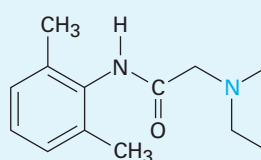
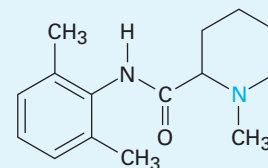
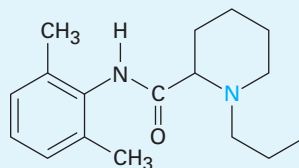
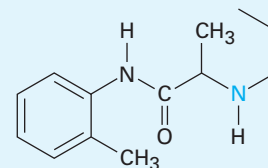
Ephedrine



Cocaine

Cocaine itself is no longer used as a medicine because it is too addictive, but its anesthetic properties provoked a search for related but nonaddictive compounds. This search ultimately resulted in the synthesis of the “caine” anesthetics that are commonly used today in dental and surgical anesthesia. Procaine, the first such compound, was synthesized in 1898 and marketed under the name Novocain. It was rapidly adopted and remains in use today as a

topical anesthetic. Other related compounds with different activity profiles followed: Lidocaine, marketed as Xylocaine, was introduced in 1943, and mepivacaine (Carbocaine) in the early 1960s. More recently, bupivacaine (Marcaine) and prilocaine (Citanest) have gained popularity. Both are quick-acting, but the effects of bupivacaine last for 3 to 6 hours while those of prilocaine fade after 45 minutes. Note some structural similarity of all the caines to cocaine itself.

Procaine
(Novocain)Lidocaine
(Xylocaine)Mepivacaine
(Carbocaine)Bupivacaine
(Marcaine)Prilocaine
(Citanest)

A recent report from the U.S. National Academy of Sciences estimates that less than 1% of all living species have been characterized. Thus, alkaloid chemistry remains today an active area of research, and innumerable substances with potentially useful properties remain to be discovered. Undoubtedly even the caine anesthetics will become obsolete at some point, perhaps supplanted by newly discovered alkaloids.



KEY WORDS

acidity constant (K_a),	44
Brønsted–Lowry acid,	42
Brønsted–Lowry base,	42
conjugate acid,	43
conjugate base,	43
dipole moment (μ),	31
electronegativity (EN),	29
formal charge,	35
hydrogen bond,	54
hydrophilic,	55
hydrophobic,	55
inductive effect,	30
Lewis acid,	50
Lewis base,	50
noncovalent interaction,	54
pK_a ,	44
polar covalent bond,	28
resonance form,	37
resonance hybrid,	37

SUMMARY

Understanding both organic and biological chemistry means knowing not just what happens but also why and how it happens at the molecular level. In this chapter, we've reviewed some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation for understanding the specific reactions that will be discussed in subsequent chapters.

Organic molecules often have **polar covalent bonds** as a result of unsymmetrical electron sharing caused by differences in the **electronegativity** of atoms. A carbon–oxygen bond is polar, for example, because oxygen attracts the shared electrons more strongly than carbon does. Carbon–hydrogen bonds are relatively nonpolar. Many molecules as a whole are also polar owing to the presence of individual polar bonds and electron lone pairs. The polarity of a molecule is measured by its **dipole moment, μ** .

Plus (+) and minus (–) signs are often used to indicate the presence of **formal charges** on atoms in molecules. Assigning formal charges to specific atoms is a bookkeeping technique that makes it possible to keep track of the valence electrons around an atom and that offers some clues about chemical reactivity.

Some substances, such as acetate ion and benzene, can't be represented by a single line-bond structure and must be considered as a **resonance hybrid** of two or more structures, neither of which is correct by itself. The only difference between two **resonance forms** is in the location of their π and nonbonding electrons. The nuclei remain in the same places in both structures, and the hybridization of the atoms remains the same.

Acidity and basicity are closely related to the ideas of polarity and electronegativity. A **Brønsted–Lowry acid** is a compound that can donate a proton (hydrogen ion, H^+), and a **Brønsted–Lowry base** is a compound that can accept a proton. The strength of a Brønsted–Lowry acid or base is expressed by its **acidity constant, K_a** , or by the negative logarithm of the acidity constant, **pK_a** . The larger the pK_a , the weaker the acid. More useful is the Lewis definition of acids and bases. A **Lewis acid** is a compound that has a low-energy empty orbital that can accept an electron pair; Mg^{2+} , BF_3 , $AlCl_3$, and H^+ are examples. A **Lewis base** is a compound that can donate an unshared electron pair; NH_3 and H_2O are examples. Most organic molecules that contain oxygen or nitrogen can act as Lewis bases toward sufficiently strong acids.

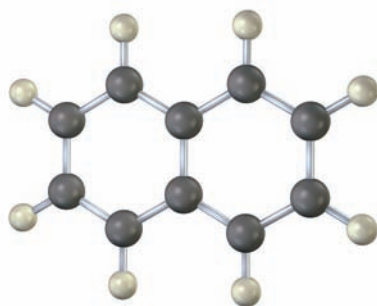
A variety of **noncovalent interactions** have a significant effect on the properties of large biomolecules. **Hydrogen-bonding**—the attractive interaction between a positively polarized hydrogen atom bonded to an O or N atom with an unshared electron pair on another O or N atom, is particularly important in giving proteins and nucleic acids their shapes.

EXERCISES

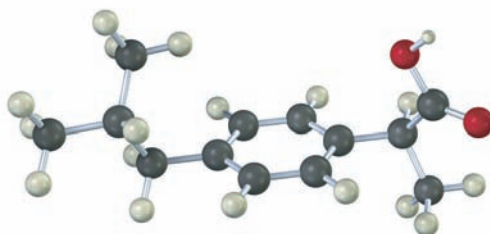
VISUALIZING CHEMISTRY

(Problems 2.1–2.19 appear within the chapter.)

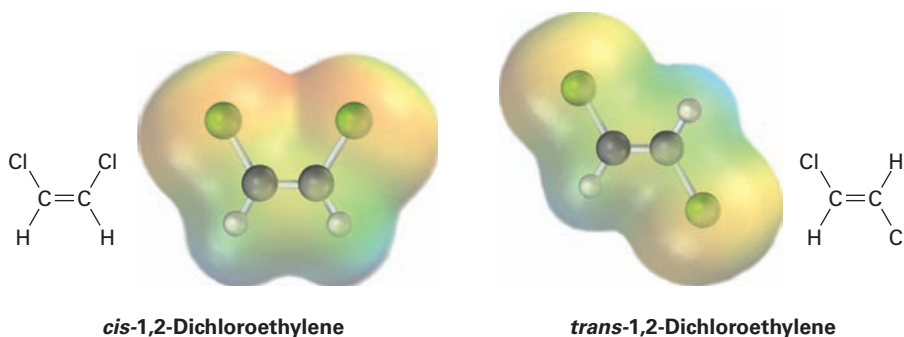
- 2.20** Fill in the multiple bonds in the following model of naphthalene, $C_{10}H_8$ (gray = C, ivory = H). How many resonance structures does naphthalene have? Draw them.



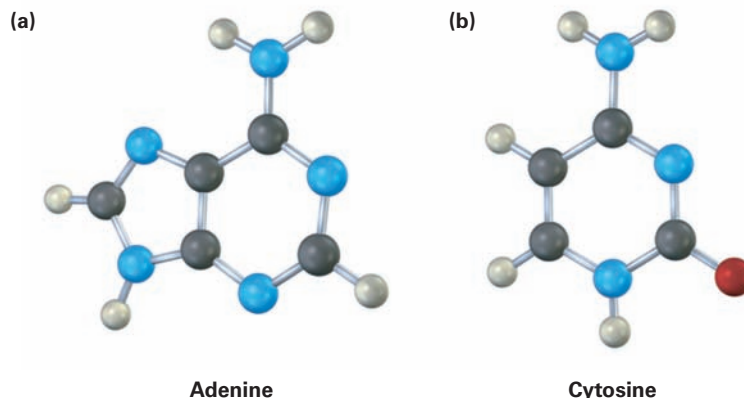
- 2.21** The following model is a representation of ibuprofen, a common over-the-counter pain reliever. Indicate the positions of the multiple bonds, and draw a skeletal structure (gray = C, red = O, ivory = H).



- 2.22** *cis*-1,2-Dichloroethylene and *trans*-dichloroethylene are *isomers*, compounds with the same formula but different chemical structures. Look at the following electrostatic potential maps, and tell whether either compound has a dipole moment.



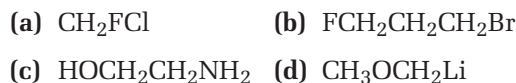
- 2.23 The following molecular models are representations of (a) adenine and (b) cytosine, constituents of DNA (deoxyribonucleic acid). Indicate the positions of multiple bonds and lone pairs for both, and draw skeletal structures (gray = C, red = O, blue = N, ivory = H).



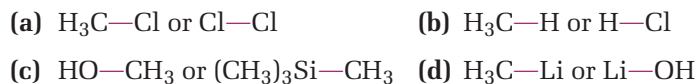
ADDITIONAL PROBLEMS

Electronegativity and Dipole Moments

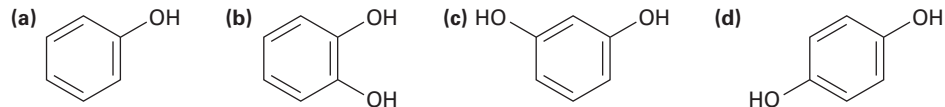
- 2.24 Identify the most electronegative element in each of the following molecules:



- 2.25 Use the electronegativity table given in Figure 2.2 on page 29 to predict which bond in each of the following pairs is more polar, and indicate the direction of bond polarity for each compound.



- 2.26 Which of the following molecules has a dipole moment? Indicate the expected direction of each.

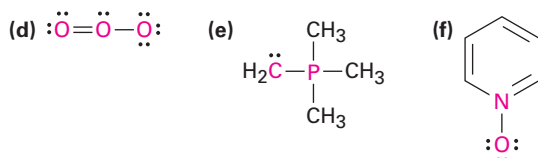
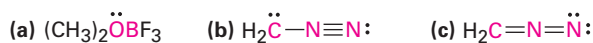


- 2.27 (a) The $\text{H}-\text{Cl}$ bond length is 136 pm. What would the dipole moment of HCl be if the molecule were 100% ionic, $\text{H}^+ \text{Cl}^-$?
 (b) The actual dipole moment of HCl is 1.08 D. What is the percent ionic character of the $\text{H}-\text{Cl}$ bond?
- 2.28 Phosgene, $\text{Cl}_2\text{C}=\text{O}$, has a smaller dipole moment than formaldehyde, $\text{H}_2\text{C}=\text{O}$, even though it contains electronegative chlorine atoms in place of hydrogen. Explain.

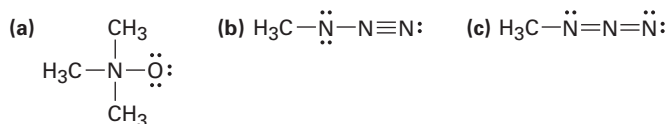
- 2.29 Fluoromethane (CH_3F , $\mu = 1.81 \text{ D}$) has a smaller dipole moment than chloromethane (CH_3Cl , $\mu = 1.87 \text{ D}$) even though fluorine is more electronegative than chlorine. Explain.
- 2.30 Methanethiol, CH_3SH , has a substantial dipole moment ($\mu = 1.52$) even though carbon and sulfur have identical electronegativities. Explain.

Formal Charges

2.31 Calculate the formal charges on the atoms shown in red.

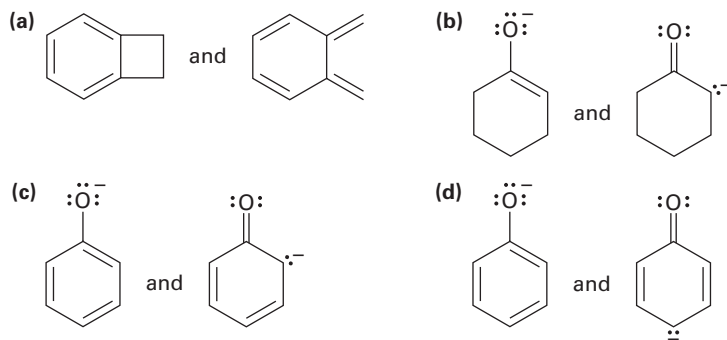


2.32 Assign formal charges to the atoms in each of the following molecules:

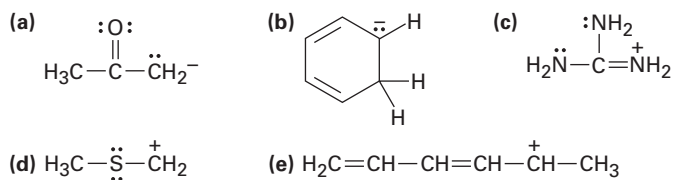


Resonance

2.33 Which of the following pairs of structures represent resonance forms?



2.34 Draw as many resonance structures as you can for the following species:

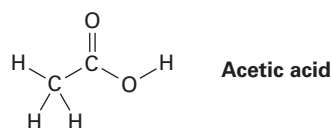


- 2.35 Cyclobutadiene is a rectangular molecule with two shorter double bonds and two longer single bonds. Why do the following structures *not* represent resonance forms?



Acids and Bases

- 2.36 Alcohols can act either as weak acids or as weak bases, just as water can. Show the reaction of methanol, CH_3OH , with a strong acid such as HCl and with a strong base such as $\text{Na}^+ \text{ } ^-\text{NH}_2$.
- 2.37 The O–H hydrogen in acetic acid is more acidic than any of the C–H hydrogens. Explain this result using resonance structures of the anions formed when a proton is removed.



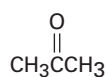
- 2.38 Draw electron-dot structures for the following molecules, indicating any unshared electron pairs. Which of the compounds are likely to act as Lewis acids and which as Lewis bases?

(a) AlBr_3 (b) $\text{CH}_3\text{CH}_2\text{NH}_2$ (c) BH_3 (d) HF (e) CH_3SCH_3 (f) TiCl_4

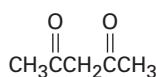
- 2.39 Write the products of the following acid–base reactions:

(a) $\text{CH}_3\text{OH} + \text{H}_2\text{SO}_4 \rightleftharpoons ?$
 (b) $\text{CH}_3\text{OH} + \text{NaNH}_2 \rightleftharpoons ?$
 (c) $\text{CH}_3\text{NH}_3^+ \text{Cl}^- + \text{NaOH} \rightleftharpoons ?$

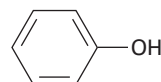
- 2.40 Rank the following substances in order of increasing acidity:



Acetone
($\text{p}K_a = 19.3$)



Pentane-2,4-dione
($\text{p}K_a = 9$)



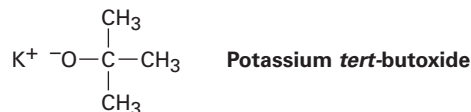
Phenol
($\text{p}K_a = 9.9$)



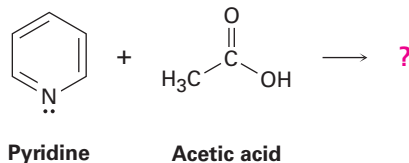
Acetic acid
($\text{p}K_a = 4.76$)

- 2.41 Which, if any, of the substances in Problem 2.40 is a strong enough acid to react almost completely with NaOH ? (The $\text{p}K_a$ of H_2O is 15.74.)
- 2.42 The ammonium ion (NH_4^+ , $\text{p}K_a = 9.25$) has a lower $\text{p}K_a$ than the methylammonium ion (CH_3NH_3^+ , $\text{p}K_a = 10.66$). Which is the stronger base, ammonia (NH_3) or methylamine (CH_3NH_2)? Explain.

- 2.43 Is *tert*-butoxide anion a strong enough base to react significantly with water? In other words, can a solution of potassium *tert*-butoxide be prepared in water? The pK_a of *tert*-butyl alcohol is approximately 18.



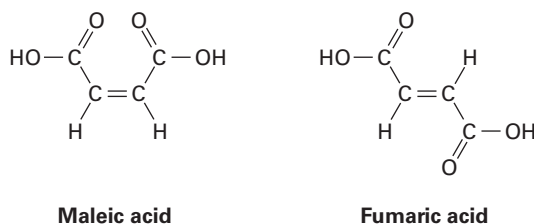
- 2.44 Predict the structure of the product formed in the reaction of the organic base pyridine with the organic acid acetic acid, and use curved arrows to indicate the direction of electron flow.



- 2.45 Calculate K_a values from the following pK_a 's:
 (a) Acetone, $pK_a = 19.3$ (b) Formic acid, $pK_a = 3.75$
- 2.46 Calculate pK_a values from the following K_a 's:
 (a) Nitromethane, $K_a = 5.0 \times 10^{-11}$ (b) Acrylic acid, $K_a = 5.6 \times 10^{-5}$
- 2.47 What is the pH of a 0.050 M solution of formic acid, $pK_a = 3.75$?
- 2.48 Sodium bicarbonate, NaHCO_3 , is the sodium salt of carbonic acid (H_2CO_3), $pK_a = 6.37$. Which of the substances shown in Problem 2.40 will react significantly with sodium bicarbonate?

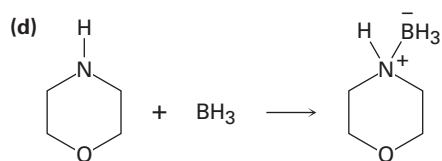
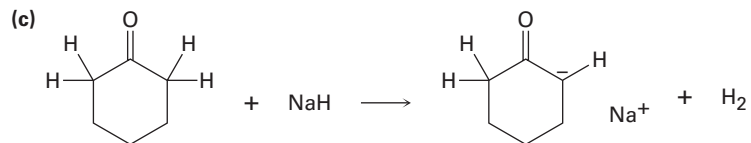
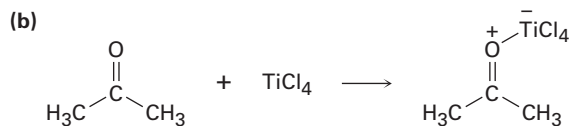
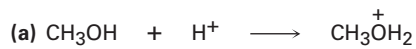
General Problems

- 2.49 Maleic acid has a dipole moment, but the closely related fumaric acid, a substance involved in the citric acid cycle by which food molecules are metabolized, does not. Explain.

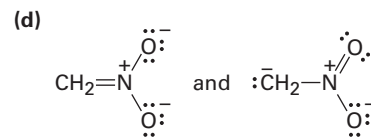
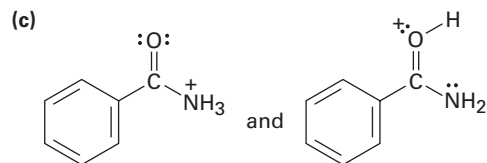
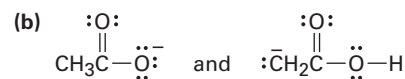
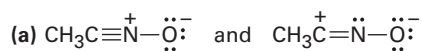


- 2.50 Assume that you have two unlabeled bottles, one of which contains phenol ($pK_a = 9.9$) and one of which contains acetic acid ($pK_a = 4.76$). In light of your answer to Problem 2.48, suggest a simple way to determine what is in each bottle.

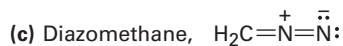
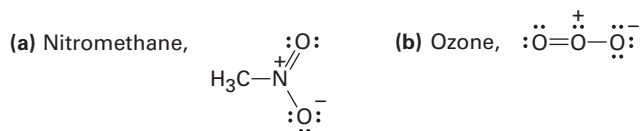
2.51 Identify the acids and bases in the following reactions:



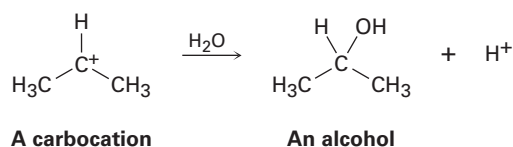
2.52 Which of the following pairs represent resonance structures?



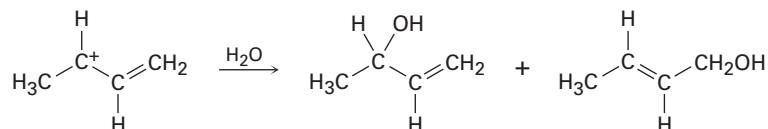
2.53 Draw as many resonance structures as you can for the following species, adding appropriate formal charges to each:



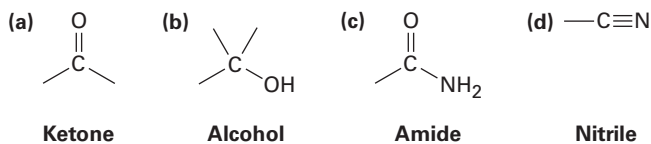
- 2.54 Carbocations, which contain a trivalent, positively charged carbon atom, react with water to give alcohols:



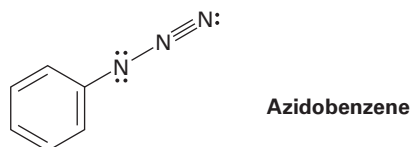
How can you account for the fact that the following carbocation gives a mixture of *two* alcohols on reaction with water?



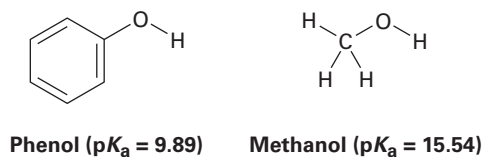
- 2.55 We'll see in the next chapter that organic molecules can be classified according to the *functional groups* they contain, where a functional group is a collection of atoms with a characteristic chemical reactivity. Use the electronegativity values given in Figure 2.2 on page 29 to predict the direction of polarization of the following functional groups.



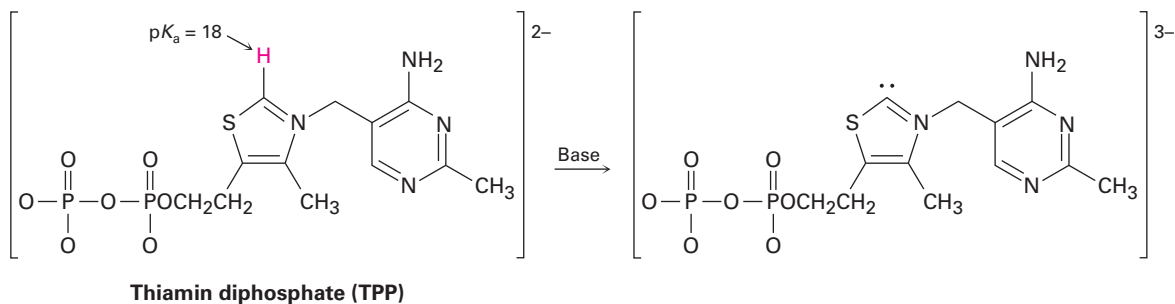
- 2.56 The *azide* functional group (Problem 2.55), such as occurs in azidobenzene, contains three adjacent nitrogen atoms. One resonance structure for azidobenzene is shown. Draw three additional resonance structures, and assign appropriate formal charges to the atoms in all four.



- 2.57 Phenol, $\text{C}_6\text{H}_5\text{OH}$, is a stronger acid than methanol, CH_3OH , even though both contain an O–H bond. Draw the structures of the anions resulting from loss of H^+ from phenol and methanol, and use resonance structures to explain the difference in acidity.

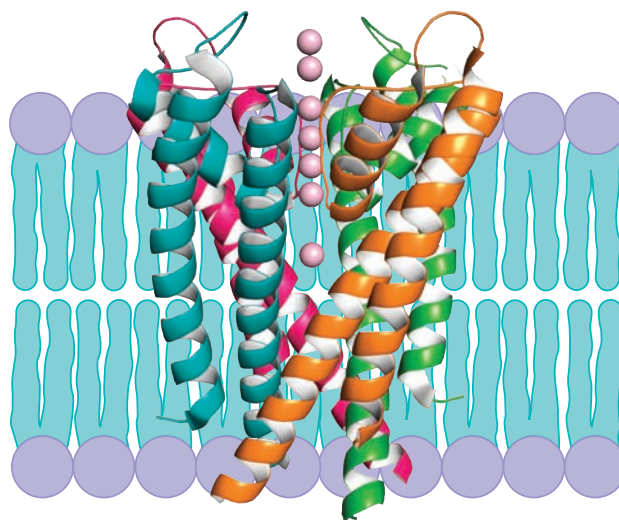


2.58 Thiamin diphosphate (TPP), a derivative of vitamin B₁ required for glucose metabolism, is a weak acid that can be deprotonated by base. Assign formal charges to the appropriate atoms in both TPP and its deprotonation product.



Organic Compounds: Alkanes and Their Stereochemistry

3



A membrane channel protein that conducts K^+ ions across cell membranes.

CONTENTS

- 3-1 Functional Groups
- 3-2 Alkanes and Alkane Isomers
- 3-3 Alkyl Groups
- 3-4 Naming Alkanes
- 3-5 Properties of Alkanes
- 3-6 Conformations of Ethane
- 3-7 Conformations of Other Alkanes

SOMETHING EXTRA

Gasoline

WHY THIS CHAPTER?

The simple organic compounds called *alkanes* are relatively unreactive and have only a minor role in a few biological processes but they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we'll use alkanes to introduce the basic approach to naming organic compounds and to take an initial look at some of the three-dimensional aspects of molecules, a topic of particular importance in understanding biological organic chemistry.

According to *Chemical Abstracts*, the publication that abstracts and indexes the chemical literature, there are more than 70 million known organic compounds. Each of these compounds has its own physical properties, such as melting point and boiling point, and each has its own chemical reactivity.

Chemists have learned through years of experience that organic compounds can be classified into families according to their structural features and that the members of a given family have similar chemical behavior. Instead of 70 million compounds with random reactivity, there are a few dozen families of organic compounds whose chemistry is reasonably predictable. We'll study the chemistry of specific families throughout much of this book, beginning in this chapter with a look at the simplest family, the *alkanes*.

3-1 Functional Groups

The structural features that make it possible to classify compounds into families are called *functional groups*. A **functional group** is a group of atoms within a molecule that has a characteristic chemical behavior. Chemically, a



given functional group behaves in nearly the same way in every molecule it's a part of. For example, compare ethylene, a plant hormone that causes fruit to ripen, with menthene, a much more complicated molecule found in peppermint oil. Both substances contain a carbon–carbon double-bond functional group, and both therefore react with Br_2 in the same way to give a product in which a Br atom has added to each of the double-bond carbons (**FIGURE 3.1**). This example is typical: *the chemistry of every organic molecule, regardless of size and complexity, is determined by the functional groups it contains.*

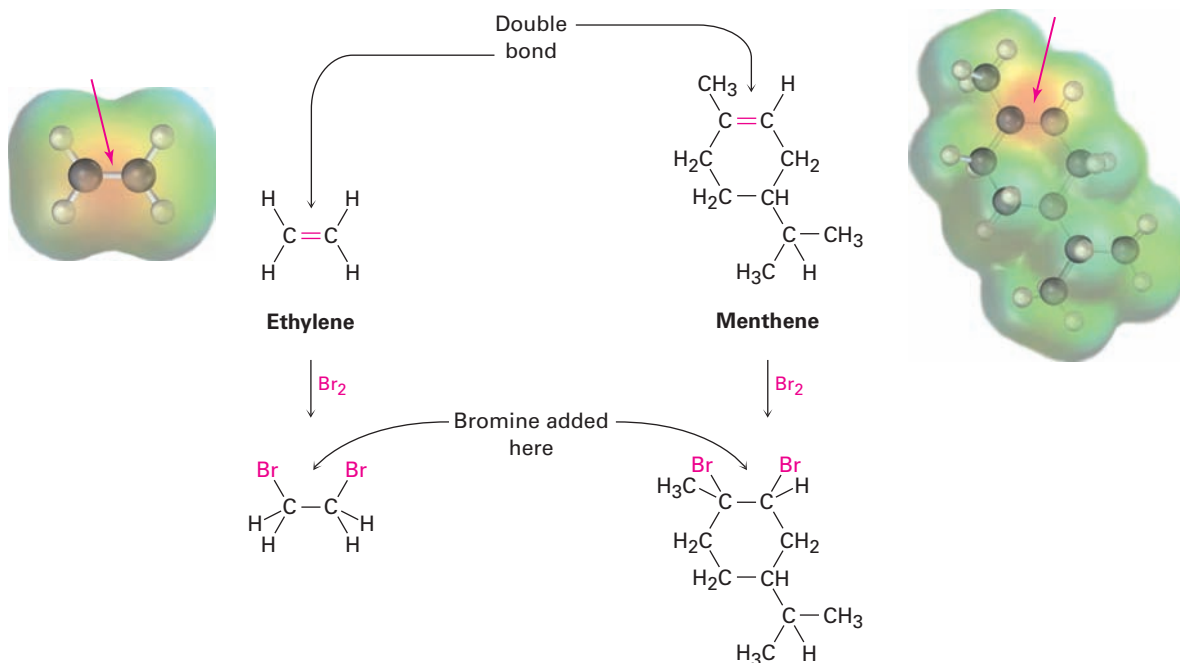


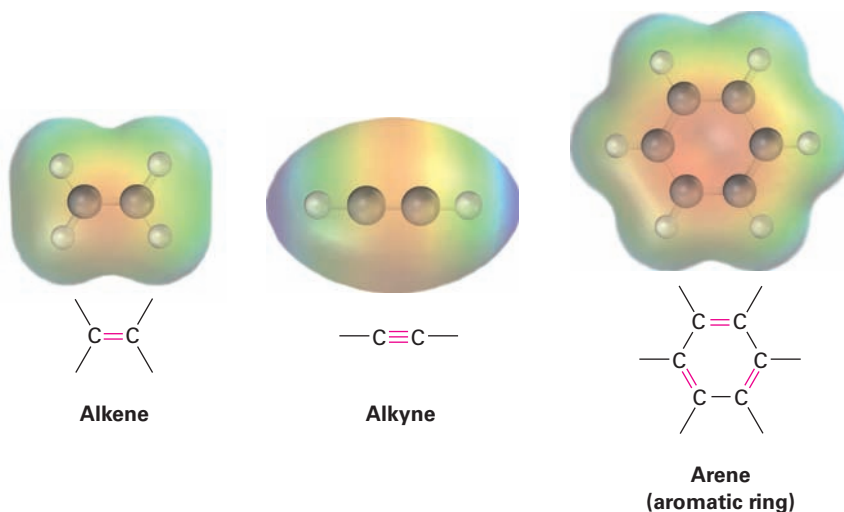
FIGURE 3.1 The reactions of ethylene and menthene with bromine. In both molecules, the carbon–carbon, double-bond functional group has a similar polarity pattern, so both molecules react with Br_2 in the same way. The size and complexity of the molecules are not important.

Look at **TABLE 3.1** on pages 62 and 63, which lists many of the common functional groups and gives simple examples of their occurrence. Some functional groups have only carbon–carbon double or triple bonds; others have halogen atoms; and still others contain oxygen, nitrogen, sulfur, or phosphorus. Much of the chemistry you'll be studying in subsequent chapters is the chemistry of these functional groups.

Functional Groups with Carbon–Carbon Multiple Bonds

Alkenes, alkynes, and arenes (aromatic compounds) all contain carbon–carbon multiple bonds. *Alkenes* have a double bond, *alkynes* have a triple bond, and *arenes* have alternating double and single bonds in a six-membered

ring of carbon atoms. Because of their structural similarities, these compounds also have chemical similarities.



Functional Groups with Carbon Singly Bonded to an Electronegative Atom

Alkyl halides (haloalkanes), alcohols, ethers, alkyl phosphates, amines, thiols, sulfides, and disulfides all have a carbon atom singly bonded to an electronegative atom—halogen, oxygen, nitrogen, or sulfur. Alkyl halides have a carbon atom bonded to halogen ($-\text{X}$), alcohols have a carbon atom bonded to the oxygen of a hydroxyl group ($-\text{OH}$), ethers have two carbon atoms bonded to the same oxygen, organophosphates have a carbon atom bonded to the oxygen of a phosphate group ($-\text{OPO}_3^{2-}$), amines have a carbon atom bonded to a nitrogen, thiols have a carbon atom bonded to the sulfur of an $-\text{SH}$ group, sulfides have two carbon atoms bonded to the same sulfur, and disulfides have carbon atoms bonded to two sulfurs that are joined together. In all cases, the bonds are polar, with the carbon atom bearing a partial positive charge (δ^+) and the electronegative atom bearing a partial negative charge (δ^-).

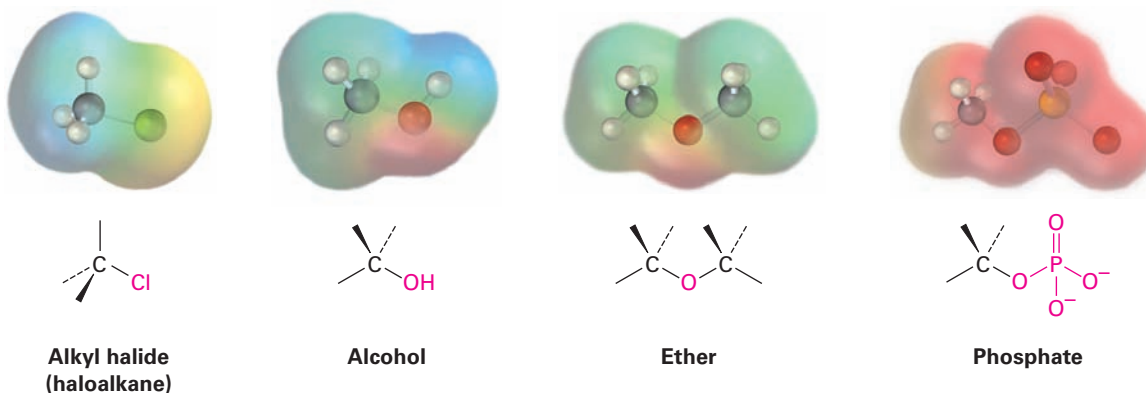


TABLE 3.1 Structures of Some Common Functional Groups

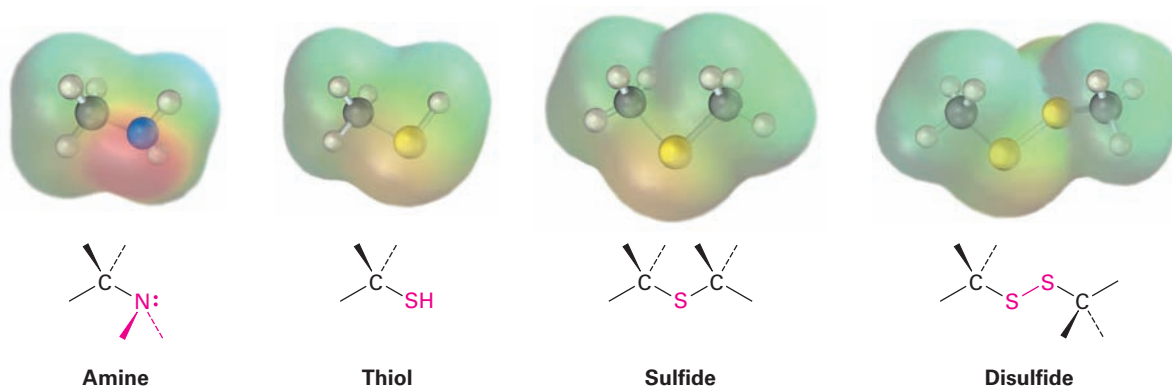
Name	Structure ^a	Name ending	Example
Alkene (double bond)		-ene	H ₂ C=CH ₂ Ethene
Alkyne (triple bond)		-yne	HC≡CH Ethyne
Arene (aromatic ring)		None	 Benzene
Halide	 (X = F, Cl, Br, I)	None	CH ₃ Cl Chloromethane
Alcohol		-ol	CH ₃ OH Methanol
Ether		ether	CH ₃ OCH ₃ Dimethyl ether
Monophosphate		phosphate	CH ₃ OPO ₃ ²⁻ Methyl phosphate
Diphosphate		diphosphate	CH ₃ OP ₂ O ₆ ³⁻ Methyl diphosphate
Amine		-amine	CH ₃ NH ₂ Methylamine
Imine (Schiff base)		None	 Acetone imine
Nitrile		-nitrile	CH ₃ C≡N Ethanenitrile
Thiol		-thiol	CH ₃ SH Methanethiol

^aThe bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule. (Continued)

TABLE 3.1 Structures of Some Common Functional Groups *continued*

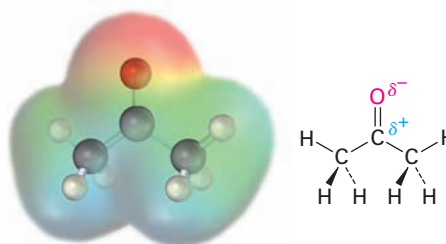
Name	Structure ^a	Name ending	Example
Sulfide		<i>sulfide</i>	CH ₃ SCH ₃ Dimethyl sulfide
Disulfide		<i>disulfide</i>	CH ₃ SSCH ₃ Dimethyl disulfide
Sulfoxide		<i>sulfoxide</i>	CH ₃ SCH ₃ Dimethyl sulfoxide
Aldehyde		<i>-al</i>	CH ₃ CHO Ethanal
Ketone		<i>-one</i>	CH ₃ COCH ₃ Propanone
Carboxylic acid		<i>-oic acid</i>	CH ₃ COOH Ethanoic acid
Ester		<i>-oate</i>	CH ₃ COOCH ₃ Methyl ethanoate
Thioester		<i>-thioate</i>	CH ₃ CSCH ₃ Methyl ethanethioate
Amide		<i>-amide</i>	CH ₃ CNH ₂ Ethanamide
Acid chloride		<i>-oyl chloride</i>	CH ₃ COCl Ethanoyl chloride
Carboxylic acid anhydride		<i>-oic anhydride</i>	CH ₃ COOCH ₃ Ethanoic anhydride

^aThe bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule.

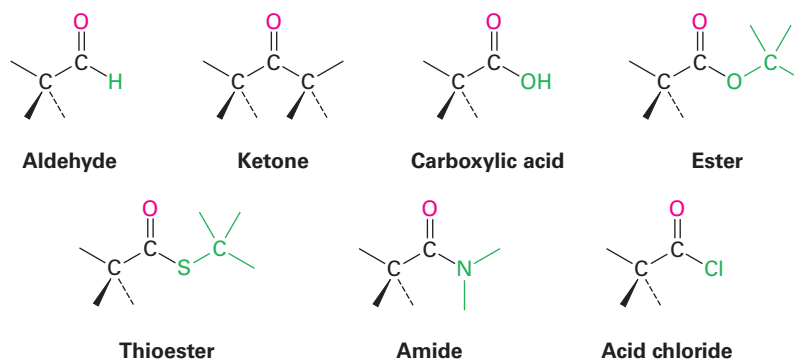


Functional Groups with a Carbon–Oxygen Double Bond (Carbonyl Groups)

The *carbonyl group*, C=O (pronounced car-bo-**neel**) is common to many of the families listed in Table 3.1. Carbonyl groups are present in a large majority of organic compounds and in practically all biological molecules. These compounds behave similarly in many respects but differ depending on the identity of the atoms bonded to the carbonyl-group carbon. Aldehydes have at least one hydrogen bonded to the C=O, ketones have two carbons bonded to the C=O, carboxylic acids have an –OH group bonded to the C=O, esters have an ether-like oxygen bonded to the C=O, thioesters have a sulfide-like sulfur bonded to the C=O, amides have an amine-like nitrogen bonded to the C=O, acid chlorides have a chlorine bonded to the C=O, and so on. The carbonyl carbon atom bears a partial positive charge (δ^+), and the oxygen bears a partial negative charge (δ^-).



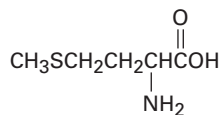
Acetone — a typical carbonyl compound



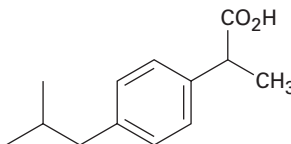
PROBLEM 3.1

Identify the functional groups in each of the following molecules:

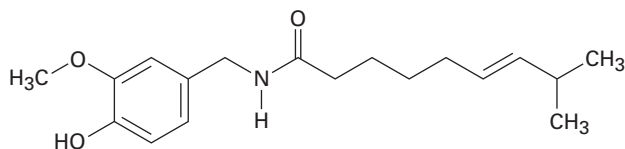
(a) Methionine, an amino acid:



(b) Ibuprofen, a pain reliever:



(c) Capsaicin, the pungent substance in chili peppers:

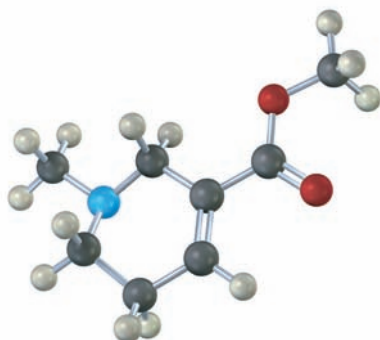
**PROBLEM 3.2**

Propose structures for simple molecules that contain the following functional groups:

- | | |
|---------------------------|----------------------|
| (a) Alcohol | (b) Aromatic ring |
| (c) Carboxylic acid | (d) Amine |
| (e) Both ketone and amine | (f) Two double bonds |

PROBLEM 3.3

Identify the functional groups in the following model of arecoline, a veterinary drug used to control worms in animals. Convert the drawing into a line-bond structure and a molecular formula (red = O, blue = N).



historical roots, the alkanes are named based on Greek numbers. The suffix *-ane* is added to the end of each name to indicate that the molecule identified is an alkane. Thus, *pentane* is the five-carbon alkane, *hexane* is the six-carbon alkane, and so on. We'll soon see that these alkane names form the basis for naming all other organic compounds, so at least the first ten should be memorized.

Drawing the Structures of Isomers

WORKED EXAMPLE 3.1

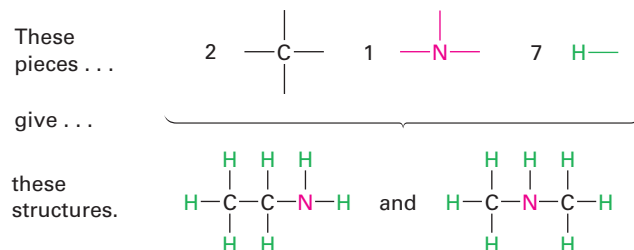
Propose structures for two isomers with the formula C_2H_7N .

Strategy

We know that carbon forms four bonds, nitrogen forms three, and hydrogen forms one. Write down the carbon atoms first, and then use a combination of trial and error plus intuition to put the pieces together.

Solution

There are two isomeric structures. One has the connection C–C–N, and the other has the connection C–N–C.



PROBLEM 3.4

Draw structures of the five isomers of C_6H_{14} .

PROBLEM 3.5

Propose structures that meet the following descriptions:

- Two isomeric esters with the formula $C_5H_{10}O_2$
- Two isomeric nitriles with the formula C_4H_7N
- Two isomeric disulfides with the formula $C_4H_{10}S_2$

PROBLEM 3.6

How many isomers are there that meet the following descriptions?

- Alcohols with the formula C_3H_8O
- Bromoalkanes with the formula C_4H_9Br
- Thioesters with the formula C_4H_8OS

3-3 Alkyl Groups

If you imagine removing a hydrogen atom from an alkane, the partial structure that remains is called an **alkyl group**. Alkyl groups are not stable compounds themselves; they are simply parts of larger compounds. Alkyl groups are named by replacing the *-ane* ending of the parent alkane with an *-yl* ending.

For example, removal of a hydrogen from methane, CH_4 , generates a *methyl* group, $-\text{CH}_3$, and removal of a hydrogen from ethane, CH_3CH_3 , generates an *ethyl* group, $-\text{CH}_2\text{CH}_3$. Similarly, removal of a hydrogen atom from the end carbon of any straight-chain alkane gives the series of straight-chain alkyl groups shown in TABLE 3.4. Combining an alkyl group with any of the functional groups listed earlier makes it possible to generate and name many thousands of compounds. For example:

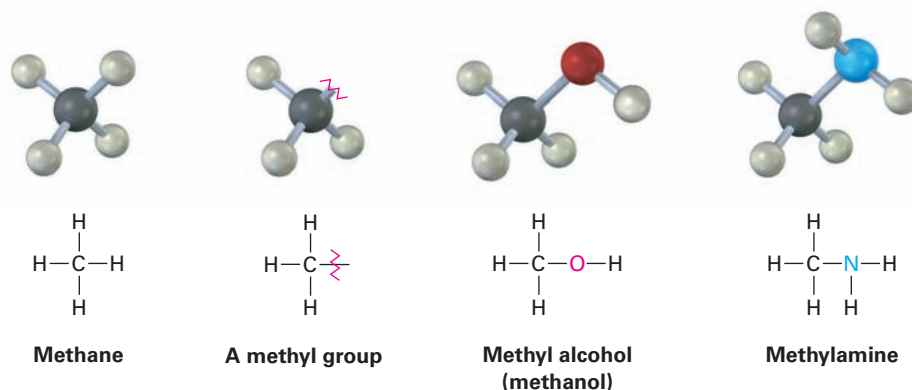
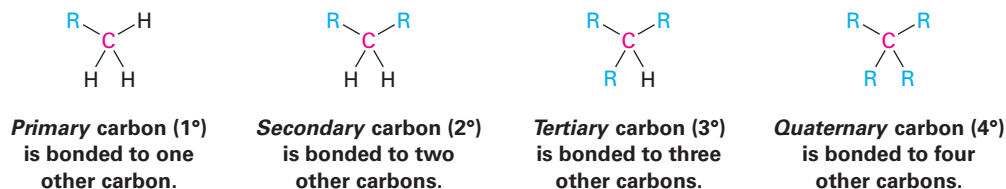


TABLE 3.4 Some Straight-Chain Alkyl Groups

Alkane	Name	Alkyl group	Name (abbreviation)
CH_4	Methane	$-\text{CH}_3$	Methyl (Me)
CH_3CH_3	Ethane	$-\text{CH}_2\text{CH}_3$	Ethyl (Et)
$\text{CH}_3\text{CH}_2\text{CH}_3$	Propane	$-\text{CH}_2\text{CH}_2\text{CH}_3$	Propyl (Pr)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$	Butane	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Butyl (Bu)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Pentane	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Pentyl, or amyl

Just as straight-chain alkyl groups are generated by removing a hydrogen from an end carbon, branched alkyl groups are generated by removing a hydrogen atom from an internal carbon. Two 3-carbon alkyl groups and four 4-carbon alkyl groups are possible (FIGURE 3.3).

One further comment about naming alkyl groups: the prefixes *sec-* (for secondary) and *tert-* (for tertiary) used for the C_4 alkyl groups in Figure 3.3 refer to the number of other carbon atoms attached to the branching carbon atom. There are four possibilities: primary (1°), secondary (2°), tertiary (3°), and quaternary (4°):



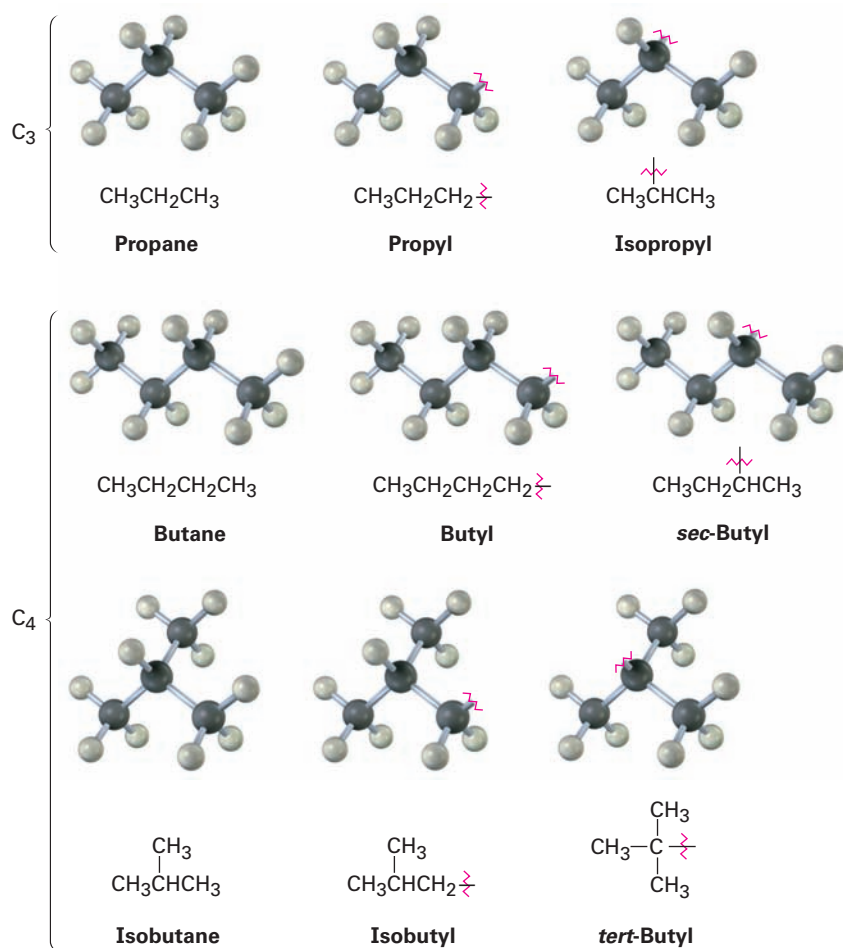
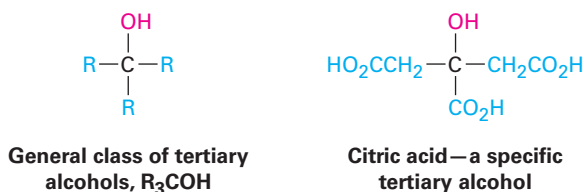


FIGURE 3.3 Alkyl groups generated from straight-chain alkanes.

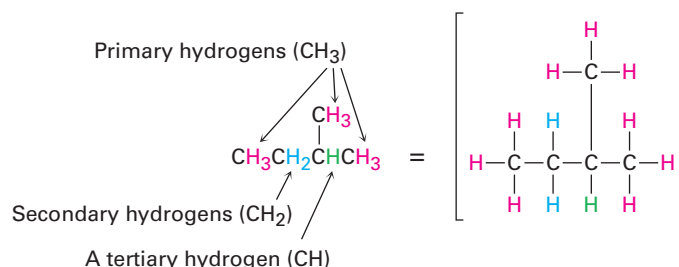
The symbol **R** is used here and throughout organic chemistry to represent a *generalized* organic group. The R group can be methyl, ethyl, propyl, or any of a multitude of others. You might think of **R** as representing the **R**est of the molecule, which isn't specified.

The terms *primary*, *secondary*, *tertiary*, and *quaternary* are routinely used in organic chemistry, and their meanings need to become second nature. For example, if we were to say, "Citric acid is a tertiary alcohol," we would mean that it has an alcohol functional group (–OH) bonded to a carbon atom that is itself bonded to three other carbons. (These other carbons may in turn connect to other functional groups.)



In addition, we also speak about hydrogen atoms as being primary, secondary, or tertiary. Primary hydrogen atoms are attached to primary carbons (RCH₃), secondary hydrogens are attached to secondary carbons (R₂CH₂), and

tertiary hydrogens are attached to tertiary carbons (R_3CH). There is, of course, no such thing as a quaternary hydrogen. (Why not?)

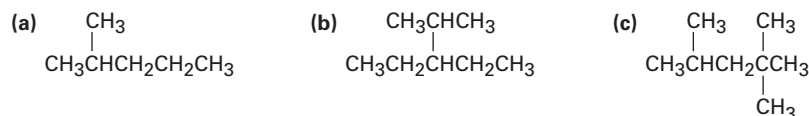


PROBLEM 3.7

Draw the eight 5-carbon alkyl groups (pentyl isomers).

PROBLEM 3.8

Identify the carbon atoms in the following molecules as primary, secondary, tertiary, or quaternary:



PROBLEM 3.9

Identify the hydrogen atoms on the compounds shown in Problem 3.8 as primary, secondary, or tertiary.

PROBLEM 3.10

Draw structures of alkanes that meet the following descriptions:

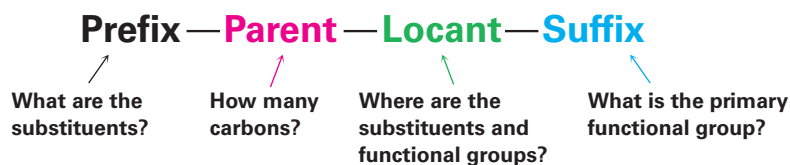
- An alkane with two tertiary carbons
- An alkane that contains an isopropyl group
- An alkane that has one quaternary and one secondary carbon

3-4 Naming Alkanes

In earlier times, when relatively few pure organic chemicals were known, new compounds were named at the whim of their discoverer. Thus, urea (CH_4N_2O) is a crystalline substance isolated from urine; morphine ($C_{17}H_{19}NO_3$) is an analgesic (painkiller) named after Morpheus, the Greek god of dreams; and acetic acid, the primary organic constituent of vinegar, is named from the Latin word for vinegar, *acetum*.

As the science of organic chemistry slowly grew in the 19th century, so too did the number of known compounds and the need for a systematic method of naming them. The system of nomenclature used by most chemists is that devised by the International Union of Pure and Applied Chemistry, or IUPAC, usually spoken as **eye-you-pac**.

A chemical name typically has four parts in the IUPAC system of nomenclature: prefix, parent, locant, and suffix. The prefix identifies the various **substituent** groups in the molecule, the parent selects a main part of the molecule and tells how many carbon atoms are in that part, the locants give the positions of the functional groups and substituents, and the suffix identifies the primary functional group.



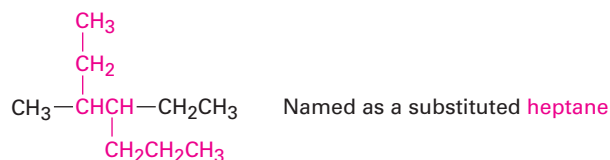
As we cover new functional groups in later chapters, the applicable IUPAC rules of nomenclature will be given. In addition, Appendix A at the back of this book gives an overall view of organic nomenclature and shows how compounds that contain more than one functional group are named. (If preferred, you can study that appendix now.) For the present, let's see how to name branched-chain alkanes and learn some general rules that are applicable to all compounds.

All but the most complex branched-chain alkanes can be named by following four steps. For a very few compounds, a fifth step is needed.

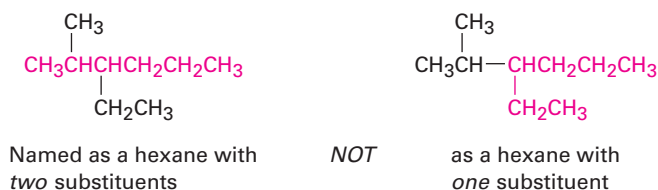
Step 1

Find the parent hydrocarbon.

- (a) Find the longest continuous chain of carbon atoms in the molecule, and use the name of that chain as the parent name. The longest chain may not always be apparent from the manner of writing; you may have to “turn corners.”



- (b) If two different chains of equal length are present, choose the one with the larger number of branch points as the parent:



Step 2**Number the atoms in the longest chain.**

- (a) Beginning at the end nearer the first branch point, number each carbon atom in the parent chain:

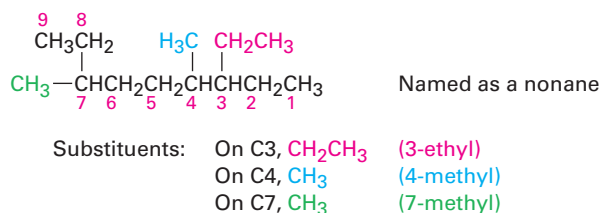


The first branch occurs at C3 in the proper system of numbering, not at C4.

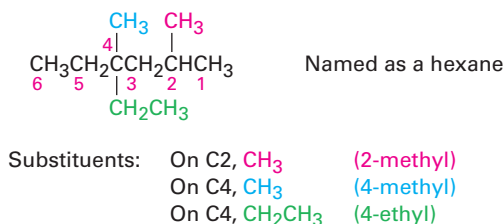
- (b) If there is branching an equal distance from both ends of the parent chain, begin numbering at the end nearer the second branch point:

**Step 3****Identify and number the substituents.**

- (a) Assign a number, or *locant*, to each substituent to locate its point of attachment to the parent chain:

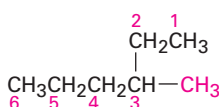
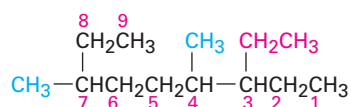
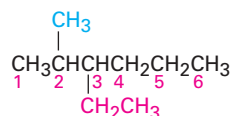
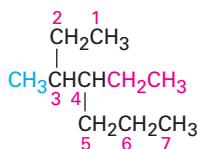
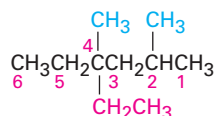


- (b) If there are two substituents on the same carbon, give them both the same number. There must be as many numbers in the name as there are substituents.

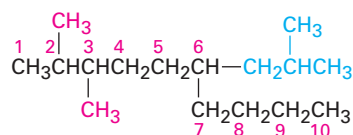
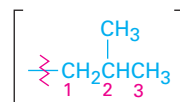
**Step 4****Write the name as a single word.**

Use hyphens to separate the different prefixes, and use commas to separate numbers. If two or more different substituents are present, cite them in alphabetical order. If two or more identical substituents are present on the parent chain, use one of the multiplier prefixes *di-*, *tri-*, *tetra-*, and so forth, but don't

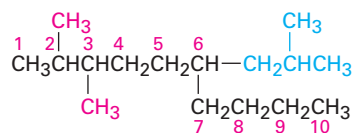
use these prefixes for alphabetizing. Full names for some of the examples we have been using follow:

**3-Methylhexane****3-Ethyl-4,7-dimethylnonane****3-Ethyl-2-methylhexane****4-Ethyl-3-methylheptane****4-Ethyl-2,4-dimethylhexane****Step 5****Name a branched substituent as though it were itself a compound.**

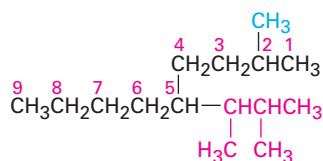
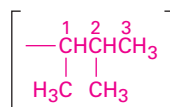
In some particularly complex cases, a fifth step is necessary. It occasionally happens that a substituent on the main chain is itself branched. In the following case, for instance, the substituent at C6 is a three-carbon chain with a methyl sub-branch. To name the compound fully, the branched substituent must first be named.

**Named as a 2,3,6-trisubstituted decane****A 2-methylpropyl group**

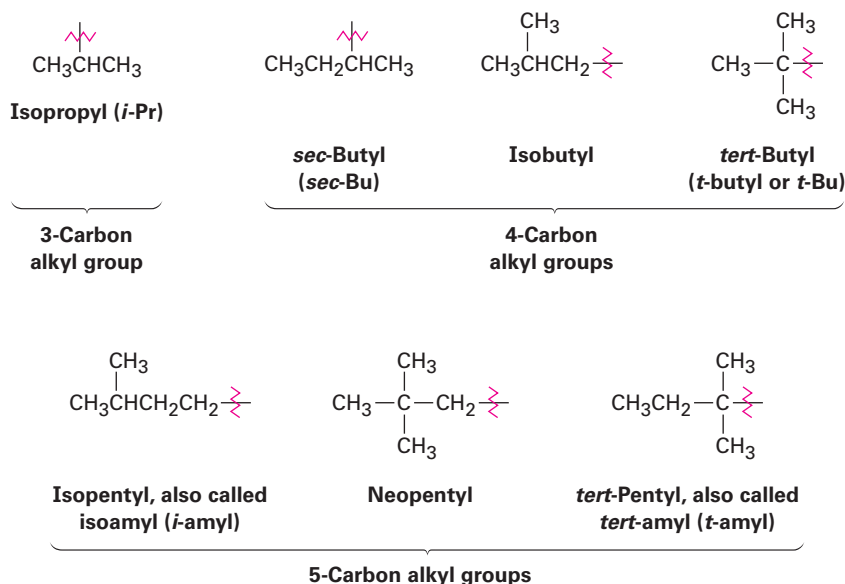
Number the branched substituent beginning at its point of its attachment to the main chain, and identify it as a 2-methylpropyl group. The substituent is alphabetized according to the first letter of its complete name, including any multiplier prefix, and is set off in parentheses when naming the entire molecule:

**2,3-Dimethyl-6-(2-methylpropyl)decane**

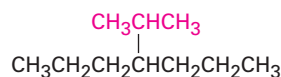
As a further example:

**5-(1,2-Dimethylpropyl)-2-methylnonane****A 1,2-dimethylpropyl group**

For historical reasons, some of the simpler branched-chain alkyl groups also have nonsystematic, common names, as noted previously.



The common names of these simple alkyl groups are so well entrenched in the chemical literature that IUPAC rules make allowance for them. Thus, the following compound is properly named either 4-(1-methylethyl)heptane or 4-isopropylheptane. There's no choice but to memorize these common names; fortunately, there are only a few of them.



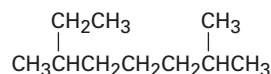
4-(1-Methylethyl)heptane or 4-Isopropylheptane

When writing an alkane name, the nonhyphenated prefix *iso-* is considered part of the alkyl-group name for alphabetizing purposes, but the hyphenated and italicized prefixes *sec-* and *tert-* are not. Thus, isopropyl and isobutyl are listed alphabetically under *i*, but *sec*-butyl and *tert*-butyl are listed under *b*.

WORKED EXAMPLE 3.2

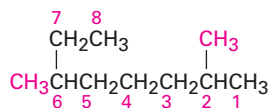
Naming Alkanes

What is the IUPAC name of the following alkane?



Strategy

Find the longest continuous carbon chain in the molecule, and use that as the parent name. This molecule has a chain of eight carbons—octane—with two methyl substituents. (You have to turn corners to see it.) Numbering from the end nearer the first methyl substituent indicates that the methyls are at C2 and C6.

Solution**2,6-Dimethyloctane****Converting a Chemical Name into a Structure****WORKED EXAMPLE 3.3**

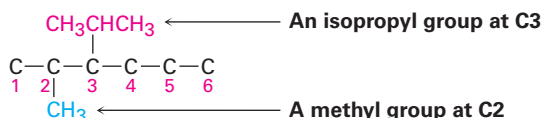
Draw the structure of 3-isopropyl-2-methylhexane.

Strategy

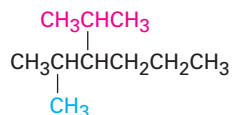
This is the reverse of Worked Example 3.2 and uses a reverse strategy. Look at the parent name (hexane), and draw its carbon structure.



Next, find the substituents (3-isopropyl and 2-methyl), and place them on the proper carbons:

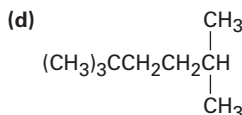
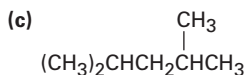
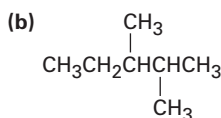


Finally, add hydrogens to complete the structure.

Solution**3-Isopropyl-2-methylhexane****PROBLEM 3.11**

Give IUPAC names for the following compounds:

(a) The three isomers of C_5H_{12}

**PROBLEM 3.12**

Draw structures corresponding to the following IUPAC names:

- (a) 3,4-Dimethylnonane (b) 3-Ethyl-4,4-dimethylheptane
 (c) 2,2-Dimethyl-4-propyloctane (d) 2,2,4-Trimethylpentane

dispersion forces between molecules (Section 2-12). Only when sufficient energy is applied to overcome these forces does the solid melt or the liquid boil. As you might expect, dispersion forces increase as molecular size increases, which accounts for the higher melting and boiling points of larger alkanes.

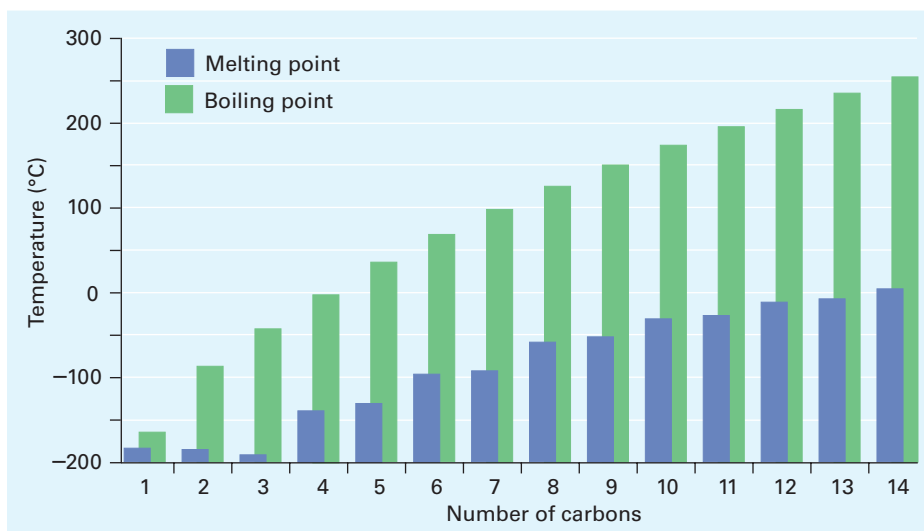


FIGURE 3.4 A plot of melting and boiling points versus number of carbon atoms for the C_1 – C_{14} straight-chain alkanes. There is a regular increase with molecular size.

Another effect seen in alkanes is that increased branching lowers an alkane's boiling point. Thus, pentane has no branches and boils at 36.1 °C, isopentane (2-methylbutane) has one branch and boils at 27.85 °C, and neopentane (2,2-dimethylpropane) has two branches and boils at 9.5 °C. Similarly, octane boils at 125.7 °C, whereas isooctane (2,2,4-trimethylpentane) boils at 99.3 °C. Branched-chain alkanes are lower boiling because they are more nearly spherical than straight-chain alkanes, have smaller surface areas, and consequently have smaller dispersion forces.

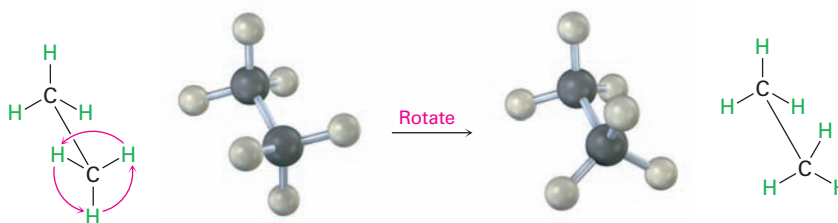
3-6 Conformations of Ethane

Up to now, we've viewed molecules primarily in a two-dimensional way and have given little thought to any consequences that might arise from the spatial arrangement of atoms in molecules. Now it's time to add a third dimension to our study. **Stereochemistry** is the branch of chemistry concerned with the three-dimensional aspects of molecules. We'll see on many occasions in future chapters that the exact three-dimensional structure of a molecule is often crucial to determining its properties and biological behavior.

We know from Section 1-5 that σ bonds are cylindrically symmetrical. In other words, the intersection of a plane cutting through a carbon–carbon single-bond orbital looks like a circle. Because of this cylindrical symmetry, rotation is possible around carbon–carbon bonds in open-chain molecules. In ethane, for instance, rotation around the C–C bond occurs freely, constantly changing the geometric relationships between the hydrogens on one carbon and those on the other (**FIGURE 3.5**).

FIGURE 3.5 Single-bond

rotation. Rotation occurs around the carbon–carbon single bond in ethane because of σ bond cylindrical symmetry.

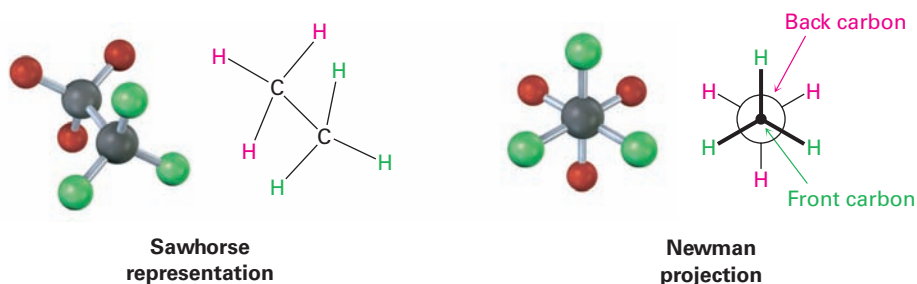


The different arrangements of atoms that result from bond rotation are called **conformations**, and molecules that have different arrangements are called conformational isomers, or **conformers**. Unlike constitutional isomers, however, different conformers often can't be isolated because they interconvert too rapidly.

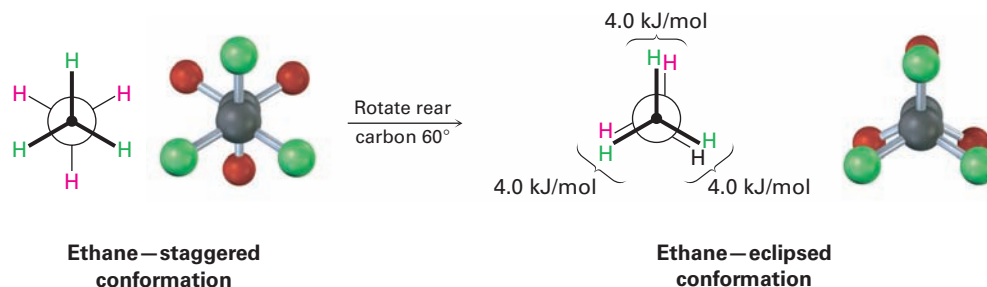
Conformational isomers are represented in two ways, as shown in **FIGURE 3.6**. A **sawhorse representation** views the carbon–carbon bond from an oblique angle and indicates spatial orientation by showing all C–H bonds. A **Newman projection** views the carbon–carbon bond directly end-on and represents the two carbon atoms by a circle. Bonds attached to the front carbon are represented by lines to the center of the circle, and bonds attached to the rear carbon are represented by lines to the edge of the circle.

FIGURE 3.6 A sawhorse representation and a Newman projection of ethane.

The sawhorse representation views the molecule from an oblique angle, while the Newman projection views the molecule end-on. Note that the molecular model of the Newman projection appears at first to have six atoms attached to a single carbon. Actually, the front carbon, with **three attached green atoms**, is directly in front of the rear carbon, with **three attached red atoms**.



Despite what we've just said, we actually don't observe *perfectly* free rotation in ethane. Experiments show that there is a small (12 kJ/mol; 2.9 kcal/mol) barrier to rotation and that some conformations are more stable than others. The lowest-energy, most stable conformation is the one in which all six C–H bonds are as far away from one another as possible—**staggered** when viewed end-on in a Newman projection. The highest-energy, least stable conformation is the one in which the six C–H bonds are as close as possible—**eclipsed** in a Newman projection. At any given instant, about 99% of ethane molecules have an approximately staggered conformation and only about 1% are near the eclipsed conformation.



The extra 12 kJ/mol of energy present in the eclipsed conformation of ethane is called **torsional strain**. Its cause has been the subject of controversy, but the major factor is an interaction between C–H bonding orbitals on one carbon with antibonding orbitals on the adjacent carbon, which stabilizes the staggered conformation relative to the eclipsed one. Because the total strain of 12 kJ/mol arises from three equal hydrogen–hydrogen eclipsing interactions, we can assign a value of approximately 4.0 kJ/mol (1.0 kcal/mol) to each single interaction. The barrier to rotation that results can be represented on a graph of potential energy versus degree of rotation in which the angle between C–H bonds on front and back carbons as viewed end-on (the *dihedral angle*) goes full circle from 0° to 360°. Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations, as shown in **FIGURE 3.7**.

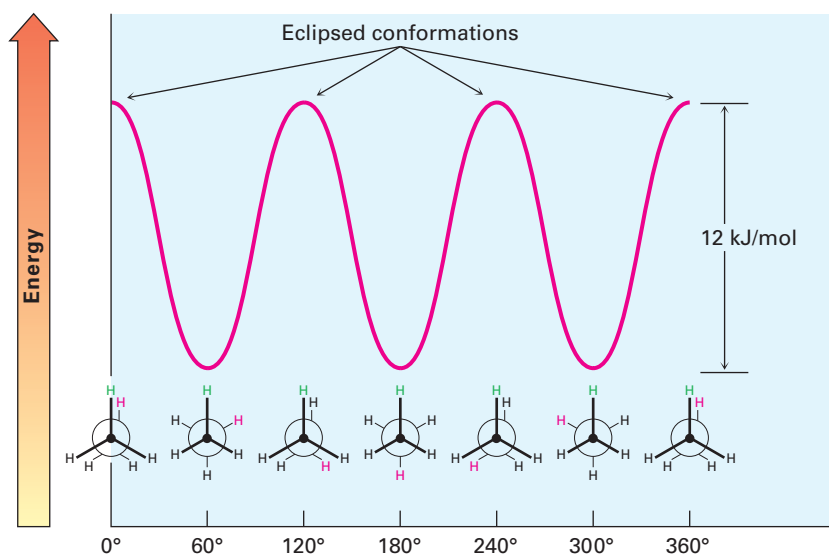


FIGURE 3.7 A graph of potential energy versus bond rotation in ethane. The staggered conformations are 12 kJ/mol lower in energy than the eclipsed conformations.

3-7 Conformations of Other Alkanes

Propane, the next higher member in the alkane series, also has a torsional barrier that results in hindered rotation around the carbon–carbon bonds. The barrier is slightly higher in propane than in ethane—a total of 14 kJ/mol (3.4 kcal/mol) versus 12 kJ/mol.

The eclipsed conformation of propane has three interactions—two ethane-type hydrogen–hydrogen interactions and one additional hydrogen–methyl interaction. Since each eclipsing H ↔ H interaction is the same as that in ethane and thus has an energy “cost” of 4.0 kJ/mol, we can assign a value of $14 - (2 \times 4.0) = 6.0$ kJ/mol (1.4 kcal/mol) to the eclipsing H ↔ CH₃ interaction (**FIGURE 3.8**).

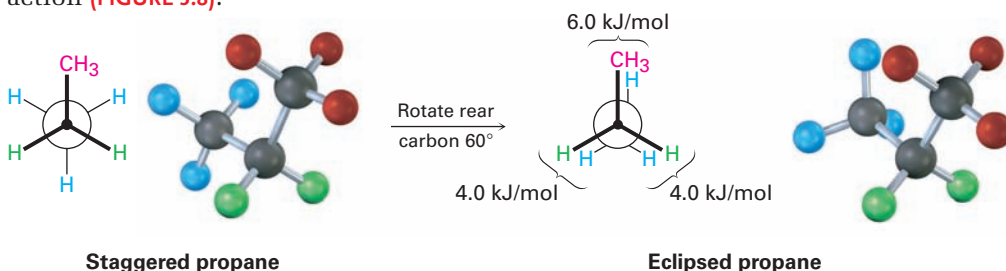
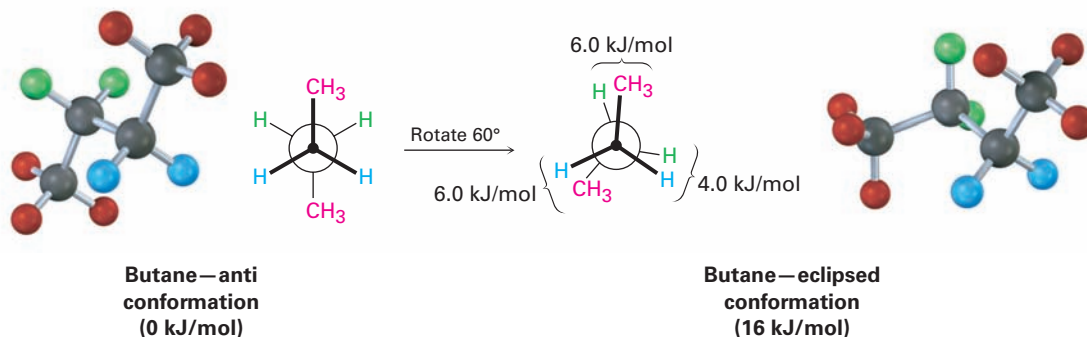
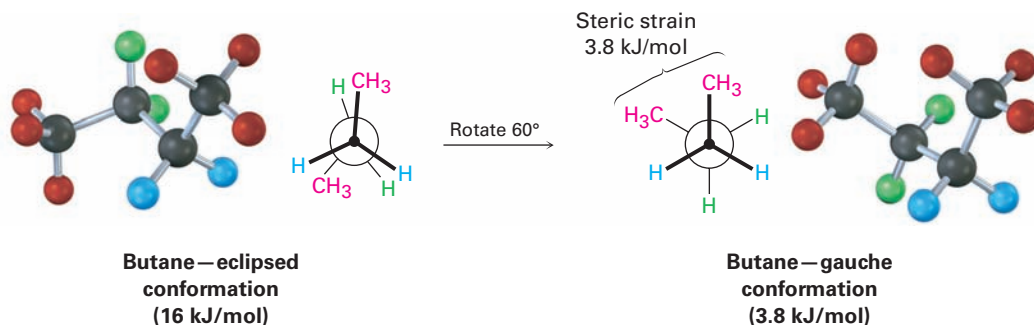


FIGURE 3.8 Newman projections of propane, showing staggered and eclipsed conformations. The staggered conformer is lower in energy by 14 kJ/mol.

The conformational situation becomes more complex for larger alkanes because not all staggered conformations have the same energy and not all eclipsed conformations have the same energy. In butane, for instance, the lowest-energy arrangement, called the **anti conformation**, is the one in which the two methyl groups are as far apart as possible— 180° away from each other. As rotation around the C2–C3 bond occurs, an eclipsed conformation is reached in which there are two $\text{CH}_3 \leftrightarrow \text{H}$ interactions and one $\text{H} \leftrightarrow \text{H}$ interaction. Using the energy values derived previously from ethane and propane, this eclipsed conformation is more strained than the anti conformation by $2 \times 6.0 \text{ kJ/mol} + 4.0 \text{ kJ/mol}$ (two $\text{CH}_3 \leftrightarrow \text{H}$ interactions plus one $\text{H} \leftrightarrow \text{H}$ interaction), for a total of 16 kJ/mol (3.8 kcal/mol).

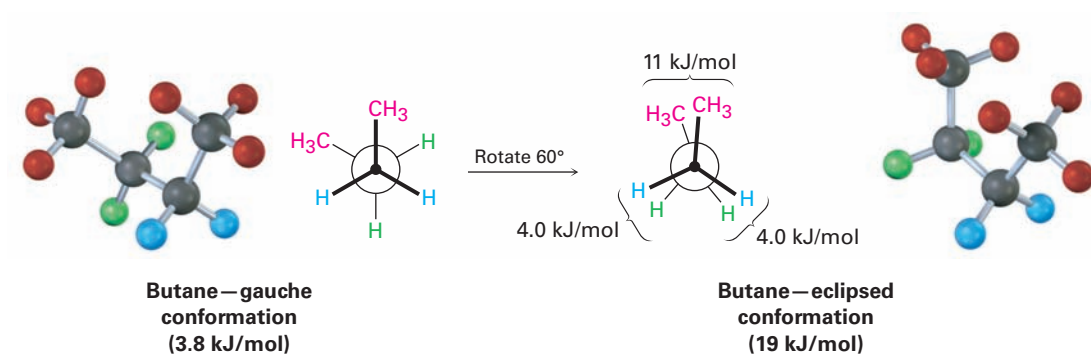


As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are 60° apart. Called the **gauche conformation**, it lies 3.8 kJ/mol (0.9 kcal/mol) higher in energy than the anti conformation even though it has no eclipsing interactions. This energy difference occurs because the hydrogen atoms of the methyl groups are near one another in the gauche conformation, resulting in what is called *steric strain*. **Steric strain** is the repulsive interaction that occurs when atoms are forced closer together than their atomic radii allow. It's the result of trying to force two atoms to occupy the same space.



As the dihedral angle between the methyl groups approaches 0° , an energy maximum is reached at a second eclipsed conformation. Because the methyl groups are forced even closer together than in the gauche conformation, both torsional strain and steric strain are present. A total strain energy of 19 kJ/mol (4.5 kcal/mol) has been estimated for this conformation, making it possible to calculate a value of 11 kJ/mol (2.6 kcal/mol) for the $\text{CH}_3 \leftrightarrow \text{CH}_3$ eclipsing

interaction: total strain of 19 kJ/mol less the strain of two H ↔ H eclipsing interactions (2×4.0 kcal/mol) equals 11 kJ/mol.



After 0° , the rotation becomes a mirror image of what we've already seen: another gauche conformation is reached, another eclipsed conformation, and finally a return to the anti conformation. A plot of potential energy versus rotation about the C2–C3 bond is shown in **FIGURE 3.9**.

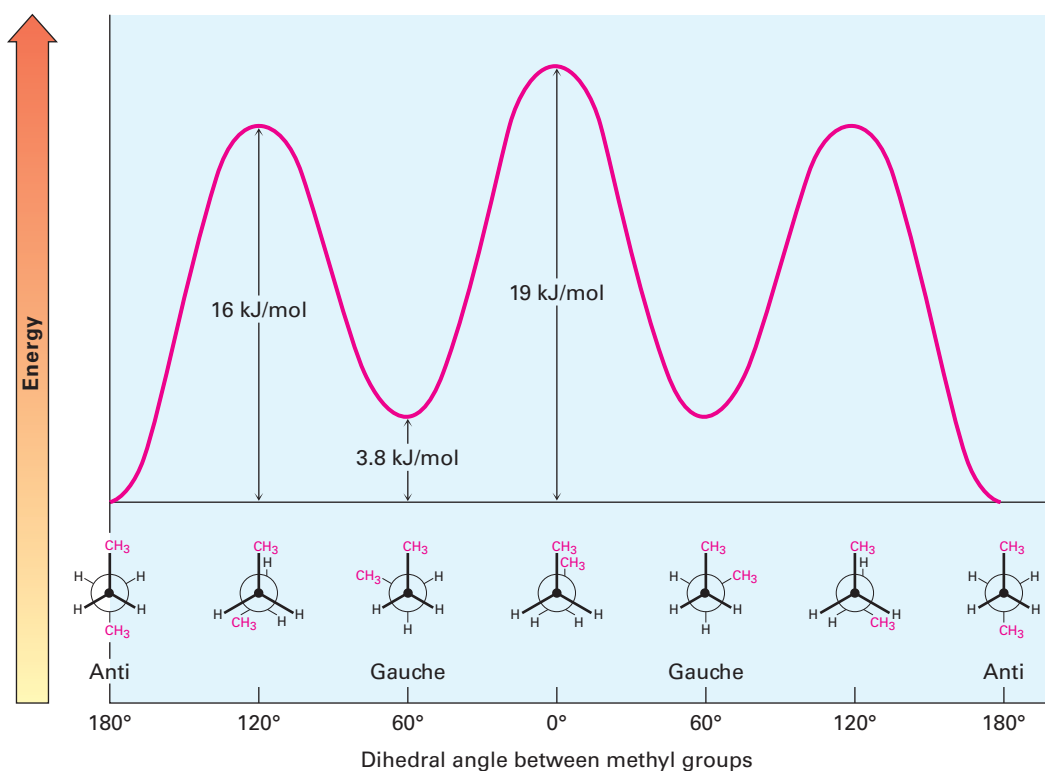


FIGURE 3.9 A plot of potential energy versus rotation for the C2–C3 bond in butane. The energy maximum occurs when the two methyl groups eclipse each other, and the energy minimum occurs when the two methyl groups are 180° apart (anti).

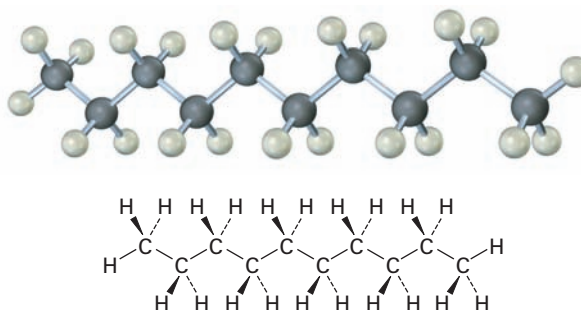
The notion of assigning definite energy values to specific interactions within a molecule is a very useful one that we'll return to in the next chapter. A summary of what we've seen thus far is given in **TABLE 3.5**.

TABLE 3.5 Energy Costs for Interactions in Alkane Conformations

Interaction	Cause	Energy cost	
		(kJ/mol)	(kcal/mol)
H \leftrightarrow H eclipsed	Torsional strain	4.0	1.0
H \leftrightarrow CH ₃ eclipsed	Mostly torsional strain	6.0	1.4
CH ₃ \leftrightarrow CH ₃ eclipsed	Torsional and steric strain	11	2.6
CH ₃ \leftrightarrow CH ₃ gauche	Steric strain	3.8	0.9

The same principles just developed for butane apply to pentane, hexane, and all higher alkanes. The most favorable conformation for any alkane has the carbon–carbon bonds in staggered arrangements, with large substituents arranged anti to one another. A generalized alkane structure is shown in **FIGURE 3.10**.

FIGURE 3.10 Alkane conformation. The most stable alkane conformation is the one in which all substituents are staggered and the carbon–carbon bonds are arranged anti, as shown in this model of decane.



One final point: saying that one particular conformation is “more stable” than another doesn’t mean that the molecule adopts and maintains only the more stable conformation. At room temperature, rotations around σ bonds occur so rapidly that all conformers are in equilibrium. At any given instant, however, a larger percentage of molecules will be found in a more stable conformation than in a less stable one.

WORKED EXAMPLE 3.4

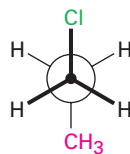
Drawing Newman Projections

Sight along the C1–C2 bond of 1-chloropropane, and draw Newman projections of the most stable and least stable conformations.

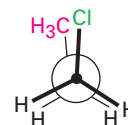
Strategy

The most stable conformation of a substituted alkane is generally a staggered one in which large groups have an anti relationship. The least stable conformation is generally an eclipsed one in which large groups are as close as possible.

Solution



Most stable (staggered)



Least stable (eclipsed)

PROBLEM 3.15

Make a graph of potential energy versus angle of bond rotation for propane, and assign values to the energy maxima.

PROBLEM 3.16

Sight along the C2–C1 bond of 2-methylpropane (isobutane), and do the following:

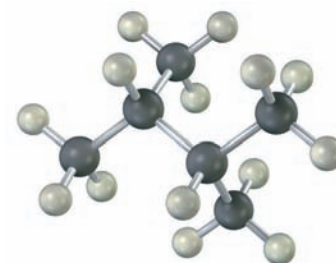
- Draw a Newman projection of the most stable conformation.
- Draw a Newman projection of the least stable conformation.
- Make a graph of energy versus angle of rotation around the C2–C1 bond.
- Assign relative values to the maxima and minima in your graph, given that an H ↔ H eclipsing interaction costs 4.0 kJ/mol and an H ↔ CH₃ eclipsing interaction costs 6.0 kJ/mol.

PROBLEM 3.17

Sight along the C2–C3 bond of 2,3-dimethylbutane, and draw a Newman projection of the most stable conformation.

PROBLEM 3.18

Draw a Newman projection along the C2–C3 bond of the adjacent conformation of 2,3-dimethylbutane, and calculate a total strain energy:

**SOMETHING EXTRA**

Gasoline

British Foreign Minister Ernest Bevin once said, “The Kingdom of Heaven runs on righteousness, but the Kingdom of Earth runs on alkanes.” (Actually, he said “runs on oil” not “runs on alkanes,” but they’re essentially the same.) By far the major sources of alkanes are the world’s natural gas and petroleum deposits. Laid down eons ago, these deposits are thought to be derived primarily from the decomposition of tiny, single-celled marine organisms called foraminifera. *Natural gas* consists chiefly of methane but also contains ethane, propane, and butane. *Petroleum* is a complex mixture of hydrocarbons that must be separated into fractions and then further refined before it can be used.

The petroleum era began in August 1859, when the world’s first oil well was drilled by Edwin Drake near Titusville, Pennsylvania. The petroleum was distilled into fractions according to boiling point, but it was high-boiling kerosene, or lamp oil, rather than gasoline that was primarily sought. Literacy was becoming

Gasoline is a finite resource. It won’t be around forever.

widespread at the time, and people wanted better light for reading than was available from candles. Gasoline was too volatile for use in lamps and was initially considered a waste by-product. The world has changed greatly since those early days, however, and it is now gasoline rather than lamp oil that is prized.

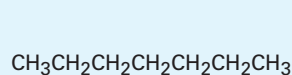
Petroleum refining begins by fractional distillation of crude oil into three principal cuts according to boiling point (bp): straight-run gasoline (bp 30–200 °C), kerosene (bp 175–300 °C), and heating oil, or diesel fuel (bp 275–400 °C). Further distillation under reduced pressure then yields lubricating oils and waxes and leaves a tarry residue of asphalt. The distillation of crude oil is only the first step in gasoline production, however. Straight-run gasoline turns out to be a poor



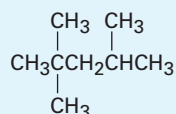
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fuel in automobiles because of engine knock, an uncontrolled combustion that can occur in a hot engine.

The *octane number* of a fuel is the measure by which its antiknock properties are judged. It was recognized long ago that straight-chain hydrocarbons are far more prone to induce engine knock than are highly branched compounds. Heptane, a particularly bad fuel, is assigned a base value of 0 octane number, and 2,2,4-trimethylpentane, commonly known as iso-octane, has a rating of 100.



Heptane
(octane number = 0)



2,2,4-Trimethylpentane
(octane number = 100)

Because straight-run gasoline burns so poorly in engines, petroleum chemists have devised numerous methods for producing higher-quality fuels. One of these methods, *catalytic cracking*, involves taking the high-boiling kerosene cut (C_{11} – C_{14}) and “cracking” it into smaller branched molecules suitable for use in gasoline. Another process, called *reforming*, is used to convert C_6 – C_8 alkanes to aromatic compounds such as benzene and toluene, which have substantially higher octane numbers than alkanes. The final product that goes in your tank has an approximate composition of 15% C_4 – C_8 straight-chain alkanes, 25–40% C_4 – C_{10} branched-chain alkanes, 10% cyclic alkanes, 10% straight-chain and cyclic alkenes, and 25% arenes (aromatics).

KEY WORDS

- aliphatic, 66
- alkane, 66
- alkyl group, 69
- anti conformation, 82
- branched-chain alkane, 67
- conformation, 80
- conformers, 80
- constitutional isomers, 67
- eclipsed conformation, 80
- functional group, 59
- gauche conformation, 82
- hydrocarbon, 66
- isomers, 67
- Newman projection, 80
- R group, 71
- saturated, 66
- staggered conformation, 80
- stereochemistry, 79
- steric strain, 82
- straight-chain alkane, 67
- substituent, 73
- torsional strain, 81

SUMMARY

Even though alkanes are relatively unreactive and rarely involved in chemical reactions, they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we’ve used alkanes to introduce the basic approach to naming organic compounds and to take an initial look at **stereochemistry**, a study of the three-dimensional aspects of molecules.

A **functional group** is a group of atoms within a larger molecule that has a characteristic chemical reactivity. Because functional groups behave approximately the same way in all molecules where they occur, the chemical reactions of an organic molecule are largely determined by its functional groups.

Alkanes are a class of **saturated hydrocarbons** with the general formula $\text{C}_n\text{H}_{2n+2}$. They contain no functional groups, are relatively inert, and can be either **straight-chain** (*normal*) or **branched**. Alkanes are named by a series of IUPAC rules of nomenclature. Compounds that have the same chemical formula but different structures are called **isomers**. More specifically, compounds such as butane and isobutane, which differ in their connections between atoms, are called **constitutional isomers**.

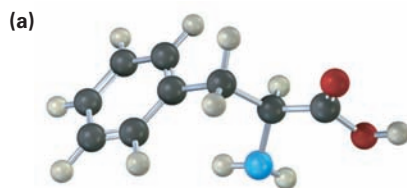
Carbon–carbon single bonds in alkanes are formed by σ overlap of carbon sp^3 hybrid orbitals. Rotation is possible around σ bonds because of their cylindrical symmetry, and alkanes therefore exist in a large number of rapidly interconverting **conformations**. **Newman projections** make it possible to visualize the spatial consequences of bond rotation by sighting directly along a carbon–carbon bond axis. Not all alkane conformations are equally stable. The **staggered** conformation of ethane is 12 kJ/mol (2.9 kcal/mol) more stable than the **eclipsed** conformation because of **torsional strain**. In general, any alkane is most stable when all its bonds are staggered.

EXERCISES

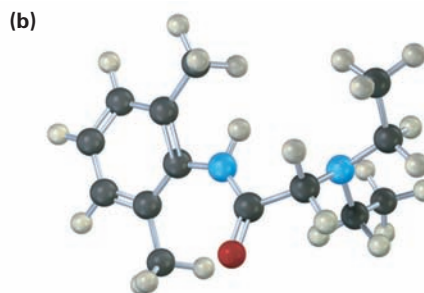
VISUALIZING CHEMISTRY

(Problems 3.1–3.18 appear within the chapter.)

- 3.19 Identify the functional groups in the following substances, and convert each drawing into a molecular formula (red = O, blue = N):

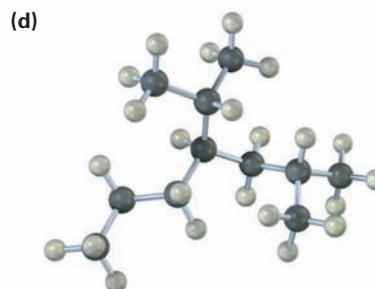
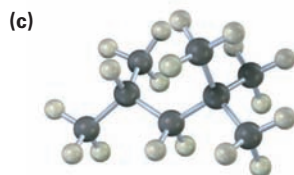
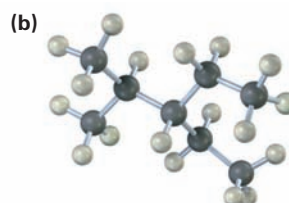
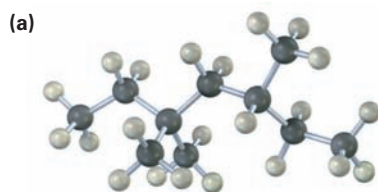


Phenylalanine

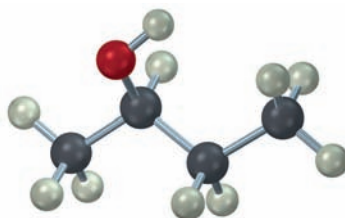


Lidocaine

- 3.20 Give IUPAC names for the following alkanes, and convert each drawing into a skeletal structure:



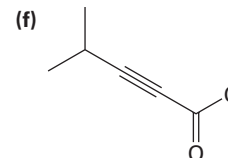
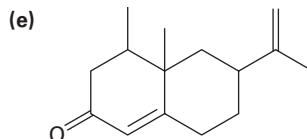
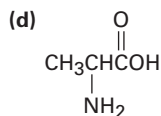
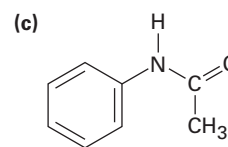
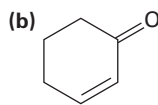
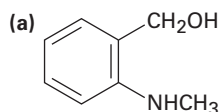
- 3.21 Draw a Newman projection along the C2–C3 bond of the following conformation of butan-2-ol.



ADDITIONAL PROBLEMS

Functional Groups

3.22 Locate and identify the functional groups in the following molecules.



3.23 Propose structures that meet the following descriptions:

- (a) A ketone with five carbons (b) A four-carbon amide
 (c) A five-carbon ester (d) An aromatic aldehyde
 (e) A keto ester (f) An amino alcohol

3.24 Propose structures for the following:

- (a) A ketone, C_4H_8O (b) A nitrile, C_5H_9N
 (c) A dialdehyde, $C_4H_6O_2$ (d) A bromoalkene, $C_6H_{11}Br$
 (e) An alkane, C_6H_{14} (f) A cyclic saturated hydrocarbon, C_6H_{12}
 (g) A diene (dialkene), C_5H_8 (h) A keto alkene, C_5H_8O

3.25 Predict the hybridization of the carbon atom in each of the following functional groups:

- (a) Ketone (b) Nitrile (c) Carboxylic acid

3.26 Draw the structures of the following molecules:

- (a) Biacetyl, $C_4H_6O_2$, a substance with the aroma of butter; it contains no rings or carbon-carbon multiple bonds.
 (b) Ethylenimine, C_2H_5N , a substance used in the synthesis of melamine polymers; it contains no multiple bonds.
 (c) Glycerol, $C_3H_8O_3$, a substance isolated from fat and used in cosmetics; it has an $-OH$ group on each carbon.

Isomers

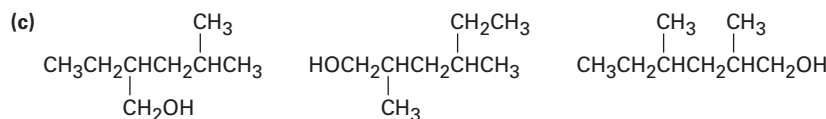
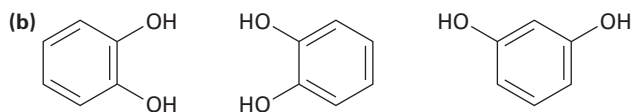
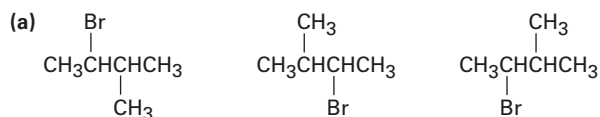
3.27 Draw structures that meet the following descriptions (there are many possibilities):

(a) Three isomers with the formula C_8H_{18}

(b) Two isomers with the formula $C_4H_8O_2$

3.28 Draw structures of the nine isomers of C_7H_{16} .

3.29 In each of the following sets, which structures represent the same compound and which represent different compounds?



3.30 There are seven constitutional isomers with the formula $C_4H_{10}O$. Draw as many as you can.

3.31 Draw as many compounds as you can that fit the following descriptions:

(a) Alcohols with formula $C_4H_{10}O$

(b) Amines with formula $C_5H_{13}N$

(c) Ketones with formula $C_5H_{10}O$

(d) Aldehydes with formula $C_5H_{10}O$

(e) Esters with formula $C_4H_8O_2$

(f) Ethers with formula $C_4H_{10}O$

3.32 Draw compounds that contain the following:

(a) A primary alcohol (b) A tertiary nitrile

(c) A secondary thiol (d) Both primary and secondary alcohols

(e) An isopropyl group (f) A quaternary carbon

Naming Compounds

3.33 Draw and name all monobromo derivatives of pentane, $C_5H_{11}Br$.

3.34 Draw and name all monochloro derivatives of 2,5-dimethylhexane, $C_8H_{17}Cl$.

3.35 Draw structures for the following:

- (a) 2-Methylheptane (b) 4-Ethyl-2,2-dimethylhexane
 (c) 4-Ethyl-3,4-dimethyloctane (d) 2,4,4-Trimethylheptane
 (e) 3,3-Diethyl-2,5-dimethylnonane (f) 4-Isopropyl-3-methylheptane

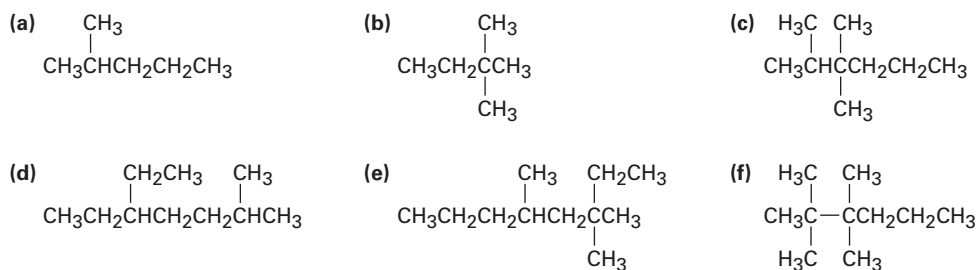
3.36 Draw a compound that:

- (a) Has only primary and tertiary carbons
 (b) Has no secondary or tertiary carbons
 (c) Has four secondary carbons

3.37 Draw a compound that:

- (a) Has nine primary hydrogens
 (b) Has only primary hydrogens

3.38 Give IUPAC names for the following compounds:



3.39 Name the five isomers of C_6H_{14} .

3.40 Explain why each of the following names is incorrect:

- (a) 2,2-Dimethyl-6-ethylheptane (b) 4-Ethyl-5,5-dimethylpentane
 (c) 3-Ethyl-4,4-dimethylhexane (d) 5,5,6-Trimethyloctane
 (e) 2-Isopropyl-4-methylheptane

3.41 Propose structures and give IUPAC names for the following:

- (a) A diethyldimethylhexane (b) A (3-methylbutyl)-substituted alkane

Conformations

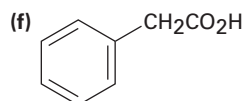
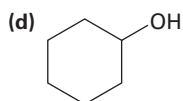
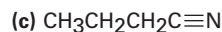
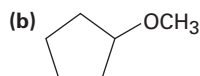
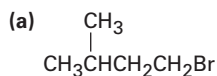
3.42 Consider 2-methylbutane (isopentane). Sighting along the C2–C3 bond:

- (a) Draw a Newman projection of the most stable conformation.
 (b) Draw a Newman projection of the least stable conformation.
 (c) If a $\text{CH}_3 \leftrightarrow \text{CH}_3$ eclipsing interaction costs 11 kJ/mol (2.5 kcal/mol) and a $\text{CH}_3 \leftrightarrow \text{CH}_3$ gauche interaction costs 3.8 kJ/mol (0.9 kcal/mol), make a quantitative plot of energy versus rotation about the C2–C3 bond.

- 3.43 What are the relative energies of the three possible staggered conformations around the C2–C3 bond in 2,3-dimethylbutane? (See Problem 3.42.)
- 3.44 Construct a qualitative potential-energy diagram for rotation about the C–C bond of 1,2-dibromoethane. Which conformation would you expect to be most stable? Label the anti and gauche conformations of 1,2-dibromoethane.
- 3.45 Which conformation of 1,2-dibromoethane (Problem 3.44) would you expect to have the largest dipole moment? The observed dipole moment of 1,2-dibromoethane is $\mu = 1.0$ D. What does this tell you about the actual conformation of the molecule?
- 3.46 Draw the most stable conformation of pentane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.
- 3.47 Draw the most stable conformation of 1,4-dichlorobutane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

General Problems

- 3.48 For each of the following compounds, draw an isomer that has the same functional groups.

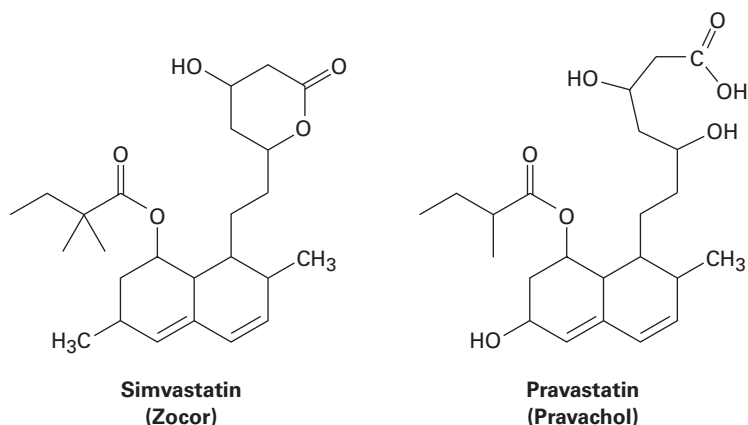


- 3.49 Malic acid, $\text{C}_4\text{H}_6\text{O}_5$, has been isolated from apples. Because this compound reacts with 2 molar equivalents of base, it is a dicarboxylic acid.
- (a) Draw at least five possible structures.
- (b) If malic acid is a secondary alcohol, what is its structure?
- 3.50 Formaldehyde, $\text{H}_2\text{C}=\text{O}$, is known to all biologists because of its usefulness as a tissue preservative. When pure, formaldehyde *trimerizes* to give trioxane, $\text{C}_3\text{H}_6\text{O}_3$, which, surprisingly enough, has no carbonyl groups. Only one monobromo derivative ($\text{C}_3\text{H}_5\text{BrO}_3$) of trioxane is possible. Propose a structure for trioxane.
- 3.51 The barrier to rotation about the C–C bond in bromoethane is 15 kJ/mol (3.6 kcal/mol).
- (a) What energy value can you assign to an H \leftrightarrow Br eclipsing interaction?
- (b) Construct a quantitative diagram of potential energy versus bond rotation for bromoethane.

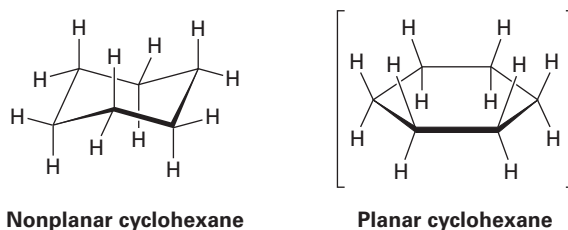
3.52 Increased substitution around a bond leads to increased strain. Take the four substituted butanes listed below, for example. For each compound, sight along the C2–C3 bond and draw Newman projections of the most stable and least stable conformations. Use the data in Table 3.5 to assign strain energy values to each conformation. Which of the eight conformations is most strained? Which is least strained?

- (a) 2-Methylbutane (b) 2,2-Dimethylbutane
(c) 2,3-Dimethylbutane (d) 2,2,3-Trimethylbutane

3.53 The cholesterol-lowering agents called statins, such as simvastatin (Zocor) and pravastatin (Pravachol), are among the most widely prescribed drugs in the world (see the Chapter 1 Introduction). Identify the functional groups in both, and tell how the two substances differ.



3.54 We'll look in the next chapter at *cycloalkanes*—saturated cyclic hydrocarbons—and we'll see that the molecules generally adopt puckered, nonplanar conformations. Cyclohexane, for instance, has a puckered shape like a lounge chair rather than a flat shape. Why?

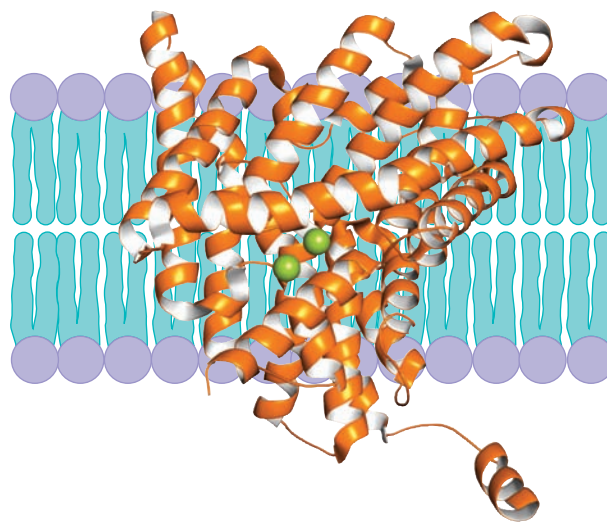


3.55 We'll see in the next chapter that there are two isomeric substances that are both named 1,2-dimethylcyclohexane. Explain.



Organic Compounds: Cycloalkanes and Their Stereochemistry

4



A membrane channel protein that conducts Cl^- ions across cell membranes.

CONTENTS

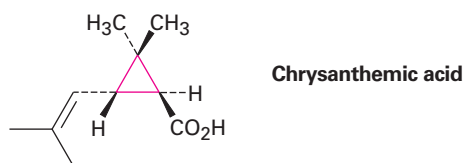
- 4-1 Naming Cycloalkanes
- 4-2 Cis–Trans Isomerism in Cycloalkanes
- 4-3 Stability of Cycloalkanes: Ring Strain
- 4-4 Conformations of Cycloalkanes
- 4-5 Conformations of Cyclohexane
- 4-6 Axial and Equatorial Bonds in Cyclohexane
- 4-7 Conformations of Monosubstituted Cyclohexanes
- 4-8 Conformations of Disubstituted Cyclohexanes
- 4-9 Conformations of Polycyclic Molecules

SOMETHING EXTRA Molecular Mechanics

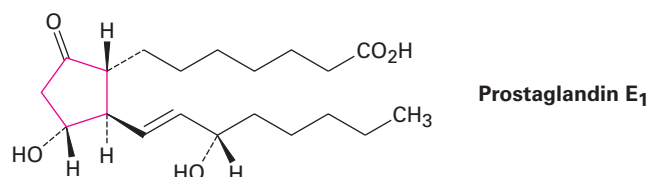
WHY THIS CHAPTER?

We'll see numerous instances in future chapters where the chemistry of a given functional group is affected by being in a ring rather than an open chain. Because cyclic molecules are so commonly encountered in most pharmaceuticals and in all classes of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids, it's important to understand the consequences of cyclic structures.

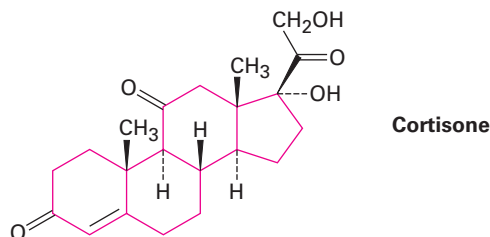
Although we've discussed only open-chain compounds up to this point, most organic compounds contain *rings* of carbon atoms. Chrysanthemic acid, for instance, whose esters occur naturally as the active insecticidal constituents of chrysanthemum flowers, contains a three-membered (cyclopropane) ring.



Prostaglandins, potent hormones that control an extraordinary variety of physiological functions in humans, contain a five-membered (cyclopentane) ring.

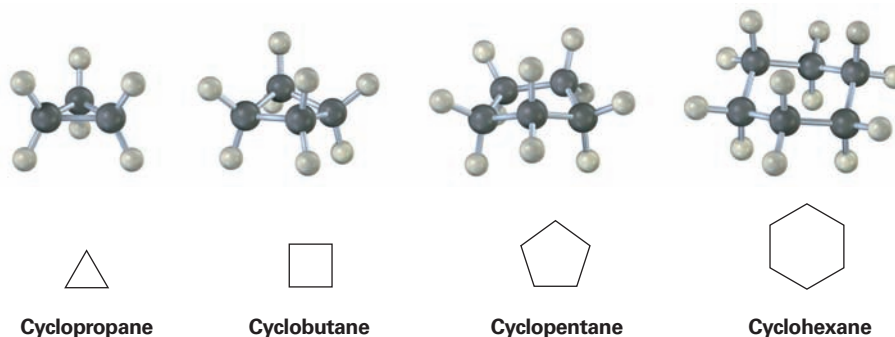


Steroids, such as cortisone, contain four rings joined together—three six-membered (cyclohexane) and one five-membered. We'll discuss steroids and their properties in more detail in Sections 23-9 and 23-10.



4-1 Naming Cycloalkanes

Saturated cyclic hydrocarbons are called **cycloalkanes**, or **alicyclic** compounds (**aliphatic cyclic**). Because cycloalkanes consist of rings of $-\text{CH}_2-$ units, they have the general formula $(\text{CH}_2)_n$, or C_nH_{2n} , and can be represented by polygons in skeletal drawings:

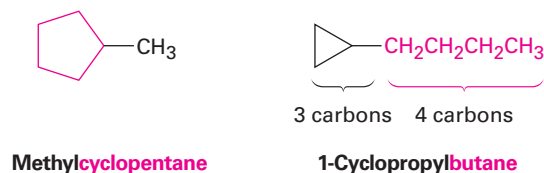


Substituted cycloalkanes are named by rules similar to those we saw in Section 3-4 for open-chain alkanes. For most compounds, there are only two steps.

Step 1

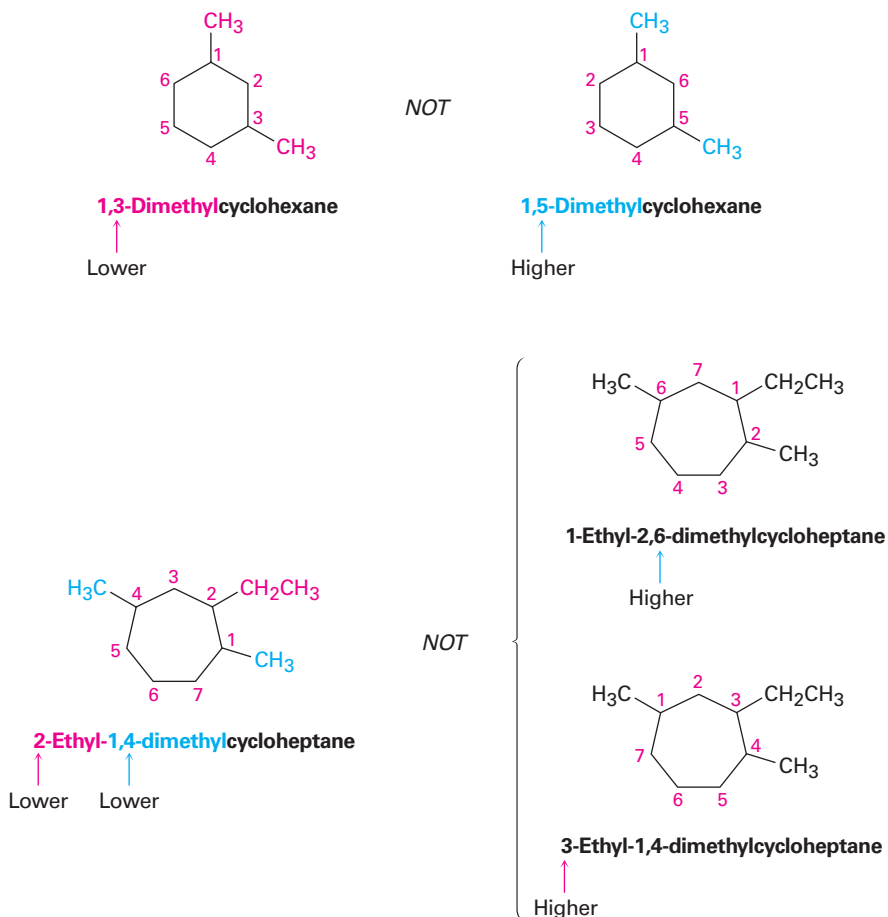
Find the parent.

Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent is greater than the number in the ring, the compound is named as a cycloalkyl-substituted alkane. For example:

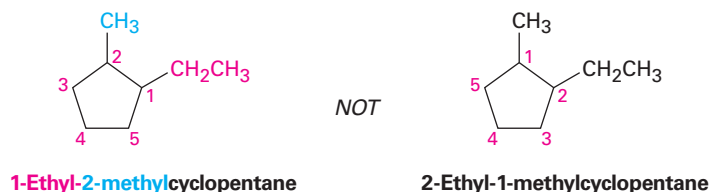


Step 2**Number the substituents, and write the name.**

For an alkyl- or halo-substituted cycloalkane, choose a point of attachment as carbon 1 and number the substituents on the ring so that the *second* substituent has as low a number as possible. If ambiguity still exists, number them so that the third or fourth substituent has as low a number as possible, until a point of difference is found.



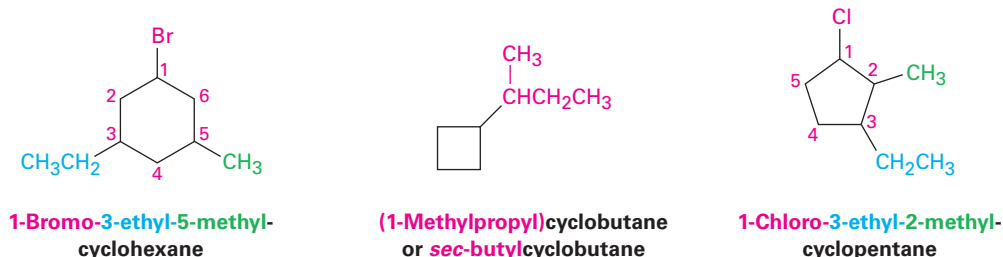
- (a) When two or more different alkyl groups that could potentially receive the same numbers are present, number them by alphabetical priority, ignoring numerical prefixes such as di- and tri-.



(b) If halogens are present, treat them just like alkyl groups:

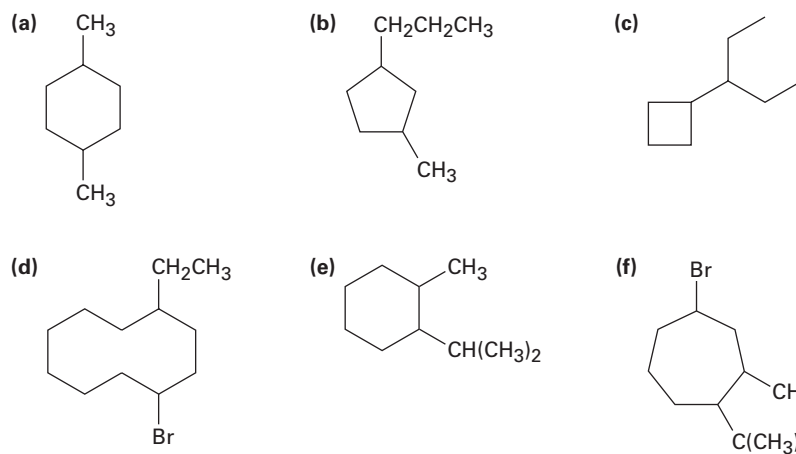


Some additional examples follow:



PROBLEM 4.1

Give IUPAC names for the following cycloalkanes:



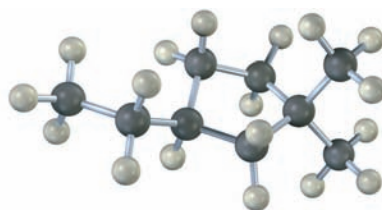
PROBLEM 4.2

Draw structures corresponding to the following IUPAC names:

- (a) 1,1-Dimethylcyclooctane (b) 3-Cyclobutylhexane
 (c) 1,2-Dichlorocyclopentane (d) 1,3-Dibromo-5-methylcyclohexane

PROBLEM 4.3

Name the following cycloalkane:



4-2 Cis-Trans Isomerism in Cycloalkanes

In many respects, the chemistry of cycloalkanes is like that of open-chain alkanes: both are nonpolar and fairly inert. There are, however, some important differences. One difference is that cycloalkanes are less flexible than open-chain alkanes. In contrast with the rotational freedom around single bonds seen in open-chain alkanes (Sections 3-6 and 3-7), there is much less freedom in cycloalkanes. Cyclopropane, for example, must be a rigid, planar molecule because three points (the carbon atoms) define a plane. No bond rotation can take place around a cyclopropane carbon-carbon bond without breaking open the ring (**FIGURE 4.1**).

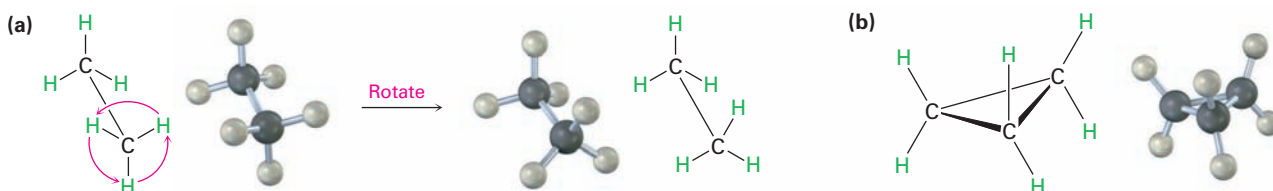


FIGURE 4.1 Bond rotation in ethane and cyclopropane. (a) Rotation occurs around the carbon-carbon bond in ethane, but (b) no rotation is possible around the carbon-carbon bonds in cyclopropane without breaking open the ring.

Larger cycloalkanes have increasing rotational freedom, and the very large rings (C_{25} and up) are so floppy that they are nearly indistinguishable from open-chain alkanes. The common ring sizes (C_3 - C_7), however, are severely restricted in their molecular motions.

Because of their cyclic structures, cycloalkanes have two faces as viewed edge-on—a “top” face and a “bottom” face. As a result, isomerism is possible in substituted cycloalkanes. For example, there are two different 1,2-dimethylcyclopropane isomers, one with the two methyl groups on the same face of the ring and one with the methyl groups on opposite faces (**FIGURE 4.2**). Both isomers are stable compounds, and neither can be converted into the other without breaking and reforming chemical bonds.

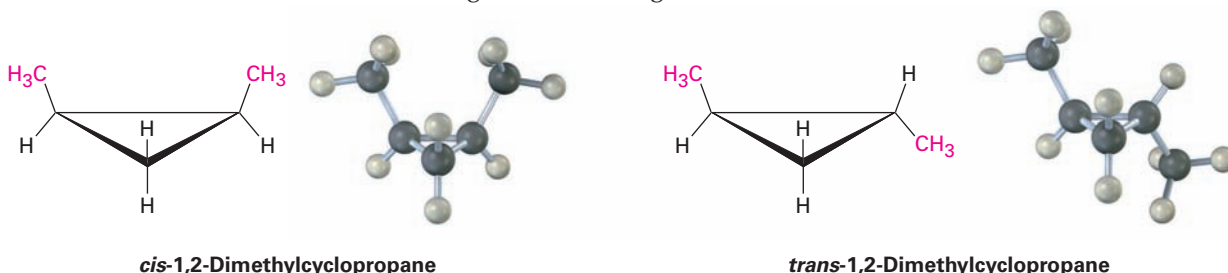
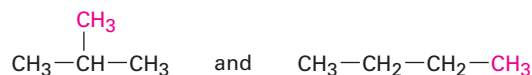


FIGURE 4.2 1,2-Dimethylcyclopropane isomers. There are two different 1,2-dimethylcyclopropane isomers, one with the methyl groups on the same face of the ring (cis) and the other with the methyl groups on opposite faces of the ring (trans). The two isomers do not interconvert.

Unlike the constitutional isomers butane and isobutane (Section 3-2), which have their atoms connected in a different order, the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, which have their atoms connected in the same order but differ in three-dimensional orientation, are called stereochemical isomers, or **stereoisomers**. As we saw in the previous chapter, the

term **stereochemistry** is used generally to refer to the three-dimensional aspects of chemical structure and reactivity.

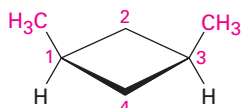
Constitutional isomers
(different connections
between atoms)



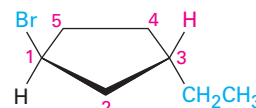
Stereoisomers
(same connections
but different three-
dimensional geometry)



The 1,2-dimethylcyclopropanes are members of a subclass of stereoisomers called **cis–trans isomers**. The prefixes *cis*- (Latin, “on the same side”) and *trans*- (Latin, “across”) are used to distinguish between them. Cis–trans isomerism is a common occurrence in substituted cycloalkanes and in many cyclic biological molecules.



cis-1,3-Dimethylcyclobutane

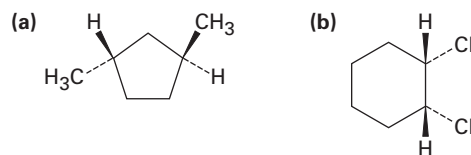


trans-1-Bromo-3-ethylcyclopentane

WORKED EXAMPLE 4.1

Naming Cycloalkanes

Name the following substances, including the *cis*- or *trans*- prefix:



Strategy

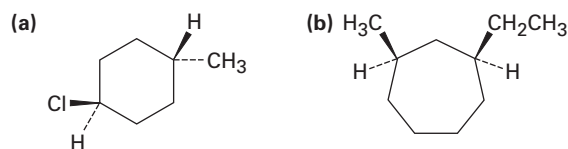
In these views, the ring is roughly in the plane of the page, a wedged bond protrudes out of the page, and a dashed bond recedes into the page. Two substituents are *cis* if they are both out of or both into the page and are *trans* if one is out of and one is into the page.

Solution

(a) *trans*-1,3-Dimethylcyclopentane (b) *cis*-1,2-Dichlorocyclohexane

PROBLEM 4.4

Name the following substances, including the *cis*- or *trans*- prefix:



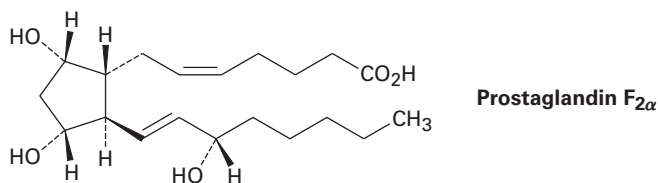
PROBLEM 4.5

Draw the structures of the following molecules:

(a) *trans*-1-Bromo-3-methylcyclohexane (b) *cis*-1,2-Dimethylcyclobutane
(c) *trans*-1-*tert*-Butyl-2-ethylcyclohexane

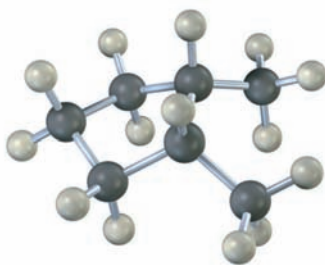
PROBLEM 4.6

Prostaglandin $F_{2\alpha}$, a hormone that causes uterine contraction during childbirth, has the following structure. Are the two hydroxyl groups ($-\text{OH}$) on the cyclopentane ring *cis* or *trans* to each other? What about the two carbon chains attached to the ring?

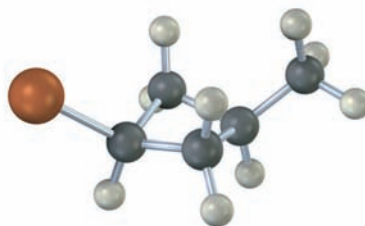
**PROBLEM 4.7**

Name the following substances, including the *cis*- or *trans*- prefix (red-brown = Br):

(a)



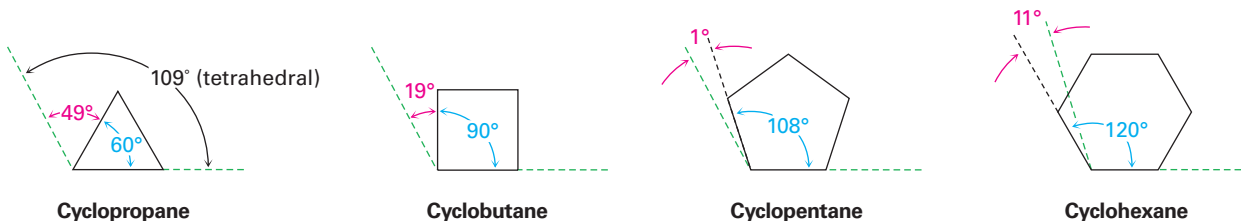
(b)



4-3 Stability of Cycloalkanes: Ring Strain

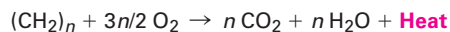
Chemists in the late 1800s knew that cyclic molecules existed, but the limitations on ring size were unclear. Although numerous compounds containing five-membered and six-membered rings were known, smaller and larger ring sizes had not been prepared despite many efforts.

A theoretical interpretation of this observation was proposed in 1885 by Adolf von Baeyer, who suggested that small and large rings might be unstable due to **angle strain**—the strain induced in a molecule when bond angles are forced to deviate from the ideal 109° tetrahedral value. Baeyer based his suggestion on the simple geometric notion that a three-membered ring (cyclopropane) should be an equilateral triangle with bond angles of 60° rather than 109° , a four-membered ring (cyclobutane) should be a square with bond angles of 90° , a five-membered ring should be a regular pentagon with bond angles of 108° , and so on. Continuing this argument, large rings should be strained by having bond angles that are much greater than 109° .



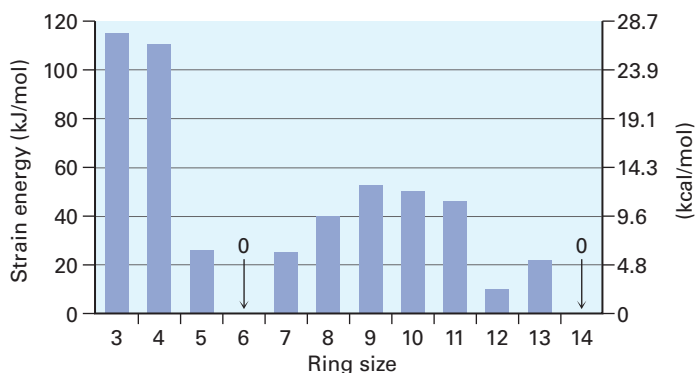
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What are the facts? To measure the amount of strain in a compound, we have to measure the total energy of the compound and then subtract the energy of a strain-free reference compound. The difference between the two values should represent the amount of extra energy in the molecule due to strain. The simplest experimental way to do this for a cycloalkane is to measure its *heat of combustion*, the amount of heat released when the compound burns completely with oxygen. The more energy (strain) the compound contains, the more energy (heat) is released on combustion.



Because the heat of combustion of a cycloalkane depends on size, we need to look at heats of combustion per CH_2 unit. Subtracting a reference value derived from a strain-free acyclic alkane and then multiplying by the number of CH_2 units in the ring gives the overall strain energy. **FIGURE 4.3** shows the results.

FIGURE 4.3 Cycloalkane strain energies. The strain energies are calculated by taking the difference between cycloalkane heat of combustion per CH_2 and acyclic alkane heat of combustion per CH_2 , and multiplying by the number of CH_2 units in a ring. Small and medium rings are strained, but cyclohexane rings and very large rings are strain-free.



The data in Figure 4.3 show that Baeyer's theory is only partially correct. Cyclopropane and cyclobutane are indeed strained, just as predicted, but cyclopentane is more strained than predicted and cyclohexane is strain-free. Cycloalkanes of intermediate size have only modest strain, and rings of more than 14 carbons are strain-free. Why is Baeyer's theory wrong?

Baeyer's theory is wrong for the simple reason that he assumed all cycloalkanes to be flat. In fact, as we'll see in the next section, most cycloalkanes are *not* flat; they adopt puckered three-dimensional conformations that allow bond angles to be nearly tetrahedral. As a result, angle strain occurs only in small rings that have little flexibility. For most ring sizes, torsional strain caused by $\text{H} \leftrightarrow \text{H}$ eclipsing interactions on adjacent carbons (Section 3-6) and steric strain caused by the repulsion between nonbonded atoms that approach too closely (Section 3-7) are the most important factors. Thus, three kinds of strain contribute to the overall energy of a cycloalkane:

Angle strain	the strain due to expansion or compression of bond angles
Torsional strain	the strain due to eclipsing of bonds on neighboring atoms
Steric strain	the strain due to repulsive interactions when atoms approach each other too closely

PROBLEM 4.8

Each $\text{H} \leftrightarrow \text{H}$ eclipsing interaction in ethane costs about 4.0 kJ/mol. How many such interactions are present in cyclopropane? What fraction of the overall

115 kJ/mol (27.5 kcal/mol) strain energy of cyclopropane is due to torsional strain?

PROBLEM 4.9

cis-1,2-Dimethylcyclopropane has more strain than *trans*-1,2-dimethylcyclopropane. How can you account for this difference? Which of the two compounds is more stable?

4-4 Conformations of Cycloalkanes

Cyclopropane

Cyclopropane is the most strained of all rings, primarily because of the angle strain caused by its 60° C–C–C bond angles. In addition, cyclopropane has considerable torsional strain because the C–H bonds on neighboring carbon atoms are eclipsed (FIGURE 4.4).

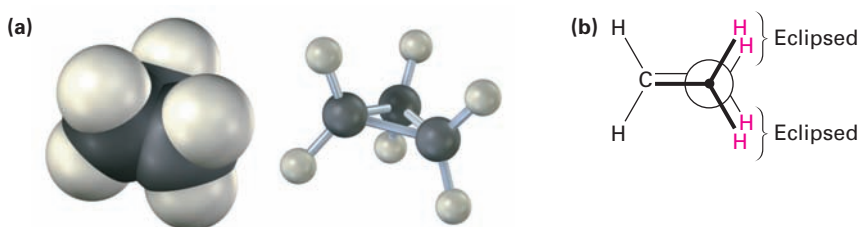
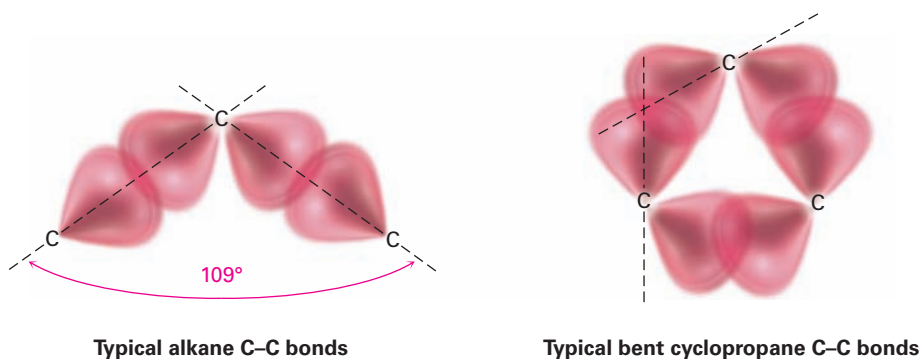


FIGURE 4.4 Structure of cyclopropane. (a) The eclipsing of neighboring C–H bonds gives rise to torsional strain. Part (b) is a Newman projection along a C–C bond.

How can the hybrid-orbital model of bonding account for the large distortion of bond angles from the normal 109° tetrahedral value to 60° in cyclopropane? The answer is that cyclopropane has *bent bonds*. In an unstrained alkane, maximum bonding is achieved when two atoms have their overlapping orbitals pointing directly toward each other. In cyclopropane, though, the orbitals can't point directly toward each other; rather, they overlap at a slight angle. The result is that cyclopropane bonds are weaker and more reactive than typical alkane bonds—255 kJ/mol (61 kcal/mol) for a C–C bond in cyclopropane versus 370 kJ/mol (88 kcal/mol) for a C–C bond in open-chain propane.



Cyclobutane

Cyclobutane has less angle strain than cyclopropane but has more torsional strain because of its larger number of ring hydrogens. As a result, the total strain for the two compounds is nearly the same—110 kJ/mol (26.4 kcal/mol) for cyclobutane versus 115 kJ/mol (27.5 kcal/mol) for cyclopropane. Cyclobutane is not quite flat but is slightly bent so that one carbon atom lies about 25° above the plane of the other three (FIGURE 4.5). The effect of this slight bend is to *increase* angle strain but to *decrease* torsional strain until a minimum-energy balance between the two opposing effects is achieved.

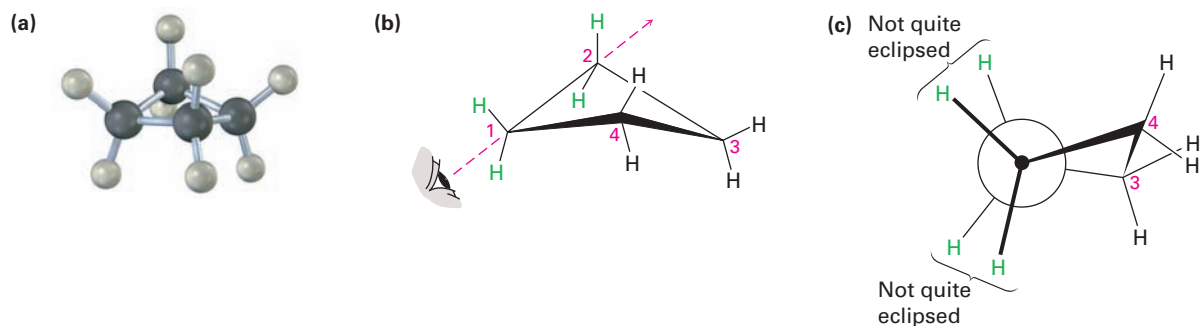


FIGURE 4.5 Conformation of cyclobutane. Part (c) is a Newman projection along a C–C bond showing that neighboring C–H bonds are not quite eclipsed.

Cyclopentane

Cyclopentane was predicted by Baeyer to be nearly strain-free, but it actually has a total strain energy of 26 kJ/mol (6.2 kcal/mol). Although planar cyclopentane has practically no angle strain, it has a large amount of torsional strain. Cyclopentane therefore twists to adopt a puckered, nonplanar conformation that strikes a balance between increased angle strain and decreased torsional strain. Four of the cyclopentane carbon atoms are in approximately the same plane, with the fifth carbon atom bent out of the plane. Most of the hydrogens are nearly staggered with respect to their neighbors (FIGURE 4.6).

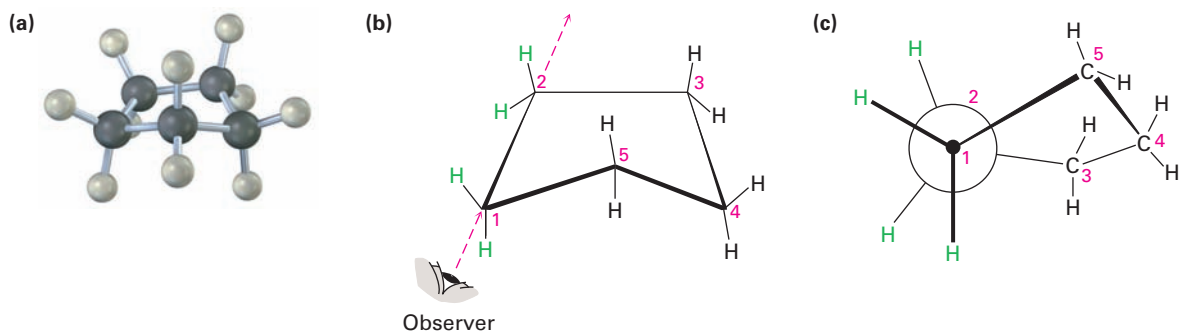


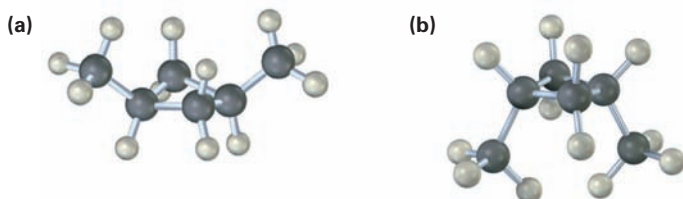
FIGURE 4.6 Conformation of cyclopentane. Carbons 1, 2, 3, and 4 are nearly coplanar, but carbon 5 is out of the plane. Part (c) is a Newman projection along the C1–C2 bond showing that neighboring C–H bonds are nearly staggered.

PROBLEM 4.10

How many H \leftrightarrow H eclipsing interactions would be present if cyclopentane were planar? Assuming an energy cost of 4.0 kJ/mol for each eclipsing interaction, how much torsional strain would planar cyclopentane have? Since the measured total strain of cyclopentane is 26 kJ/mol, how much of the torsional strain is relieved by puckering?

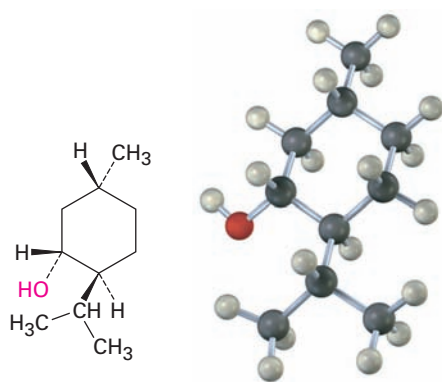
PROBLEM 4.11

Two conformations of *cis*-1,3-dimethylcyclobutane are shown. What is the difference between them, and which do you think is likely to be more stable?



4-5 Conformations of Cyclohexane

Substituted cyclohexanes are the most common cycloalkanes and occur widely in nature. A large number of compounds, including steroids and many pharmaceutical agents, have cyclohexane rings. The flavoring agent menthol, for instance, has three substituents on a six-membered ring.



Menthol

Cyclohexane adopts a strain-free, three-dimensional shape that is called a **chair conformation** because of its similarity to a lounge chair, with a back, seat, and footrest (**FIGURE 4.7**). Chair cyclohexane has neither angle strain nor

torsional strain—all C–C–C bond angles are near the 109.5° tetrahedral value, and all neighboring C–H bonds are staggered.

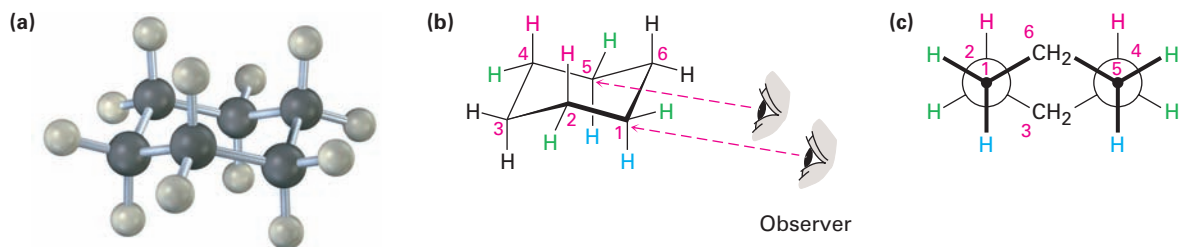


FIGURE 4.7 Strain-free chair conformation of cyclohexane. All C–C–C bond angles are 111.5° , close to the ideal 109.5° tetrahedral angle, and all neighboring C–H bonds are staggered.

The easiest way to visualize chair cyclohexane is to build a molecular model. (In fact, do it now if you have access to a model kit.) Two-dimensional drawings and computer modeling are useful, but there's no substitute for holding, twisting, and turning a three-dimensional model in your own hands.

The chair conformation of cyclohexane can be drawn in three steps:

Step 1

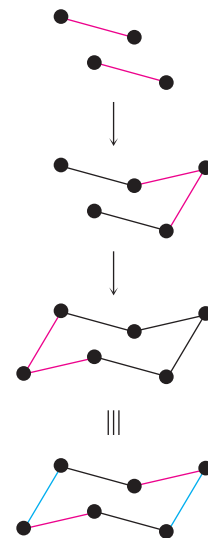
Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.

Step 2

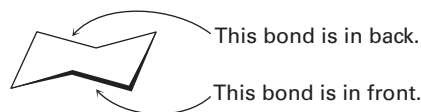
Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.

Step 3

Place the bottommost carbon atom below and to the left of the plane of the middle four, and connect the bonds. Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.

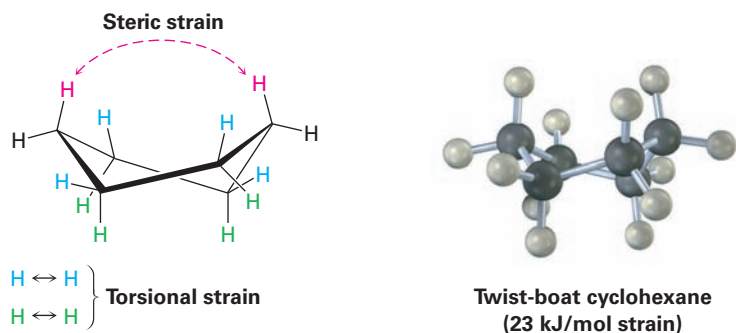


When viewing cyclohexane, it's helpful to remember that the lower bond is in front and the upper bond is in back. If this convention is not defined, an optical illusion can make it appear that the reverse is true. For clarity, all cyclohexane rings drawn in this book will have the front (lower) bond heavily shaded to indicate nearness to the viewer.



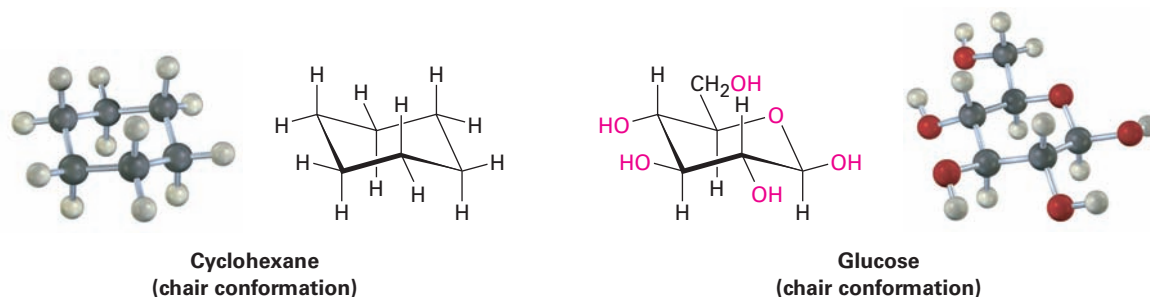
In addition to the chair conformation of cyclohexane, an alternative called the **twist-boat conformation** is also nearly free of angle strain. It does, however, have both steric strain and torsional strain and is about 23 kJ/mol

(5.5 kcal/mol) higher in energy than the chair conformation. As a result, molecules adopt the twist-boat geometry only under special circumstances.



4-6 Axial and Equatorial Bonds in Cyclohexane

The chair conformation of cyclohexane leads to many consequences. We'll see in Section 12-13, for instance, that the chemical behavior of many substituted cyclohexanes is influenced by their conformation. In addition, we'll see in Section 21-5 that simple carbohydrates, such as glucose, adopt a conformation based on the cyclohexane chair and that their chemistry is directly affected as a result.



Another consequence of the chair conformation is that there are two kinds of positions for substituents on the cyclohexane ring: *axial* positions and *equatorial* positions (FIGURE 4.8). The six **axial positions** are perpendicular to the ring, parallel to the ring axis, and the six **equatorial positions** are in the rough plane of the ring, around the ring equator.

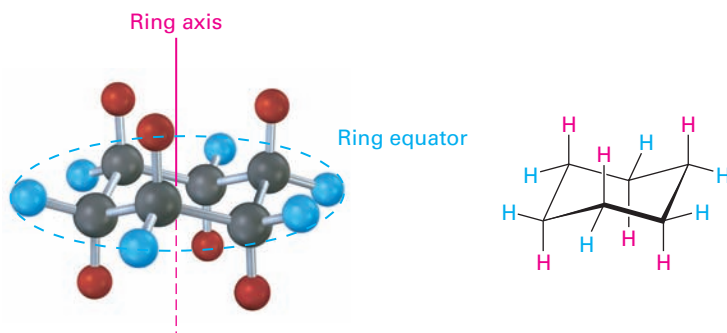
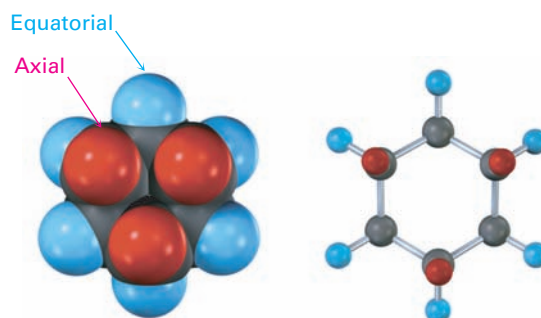


FIGURE 4.8 Axial and equatorial positions in chair cyclohexane.

The six axial hydrogens are parallel to the ring axis, and the six equatorial hydrogens are in a band around the ring equator.

As shown in Figure 4.8, each carbon atom in chair cyclohexane has one axial and one equatorial hydrogen. Furthermore, each face of the ring has three axial and three equatorial hydrogens in an alternating arrangement. For example, if the top face of the ring has axial hydrogens on carbons 1, 3, and 5, then it has equatorial hydrogens on carbons 2, 4, and 6. Exactly the reverse is true for the bottom face: carbons 1, 3, and 5 have equatorial hydrogens, but carbons 2, 4, and 6 have axial hydrogens (FIGURE 4.9).

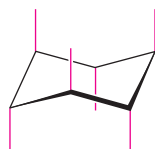
FIGURE 4.9 Alternating axial and equatorial positions in chair cyclohexane. Looking directly down the ring axis, each carbon atom has one axial and one equatorial position, and each face has alternating axial and equatorial positions.



Note that we haven't used the words *cis* and *trans* in this discussion of cyclohexane conformation. Two hydrogens on the same face of the ring are always *cis*, regardless of whether they're axial or equatorial and regardless of whether they're adjacent. Similarly, two hydrogens on opposite faces of the ring are always *trans*.

Axial and equatorial bonds can be drawn following the procedure in FIGURE 4.10. Look at a molecular model as you practice.

Axial bonds: The six axial bonds, one on each carbon, are parallel and alternate up–down.



Equatorial bonds: The six equatorial bonds, one on each carbon, come in three sets of two parallel lines. Each set is also parallel to two ring bonds. Equatorial bonds alternate between sides around the ring.



Completed cyclohexane

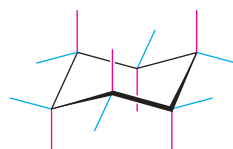


FIGURE 4.10 Procedure for drawing axial and equatorial bonds in chair cyclohexane.

Because chair cyclohexane has two kinds of positions—axial and equatorial—we might expect to find two isomeric forms of a monosubstituted cyclohexane. In fact, we don't. There is only one methylcyclohexane, one bromocyclohexane, one cyclohexanol (hydroxycyclohexane), and so on, because cyclohexane rings are *conformationally mobile* at room temperature. Different chair conformations readily interconvert, exchanging axial and

equatorial positions. This interconversion, usually called a **ring-flip**, is shown in **FIGURE 4.11**.

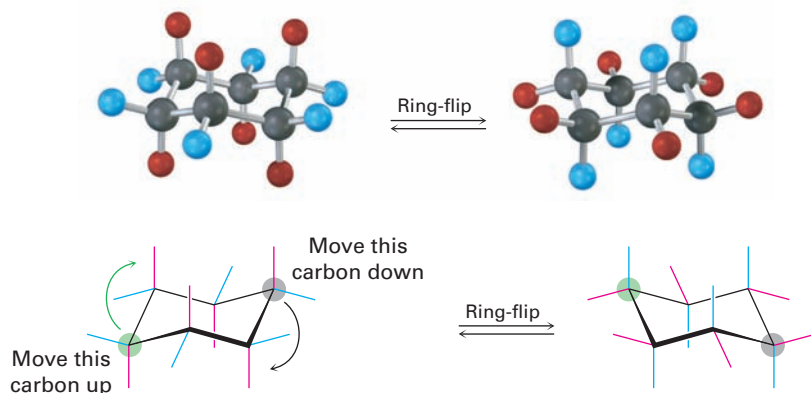
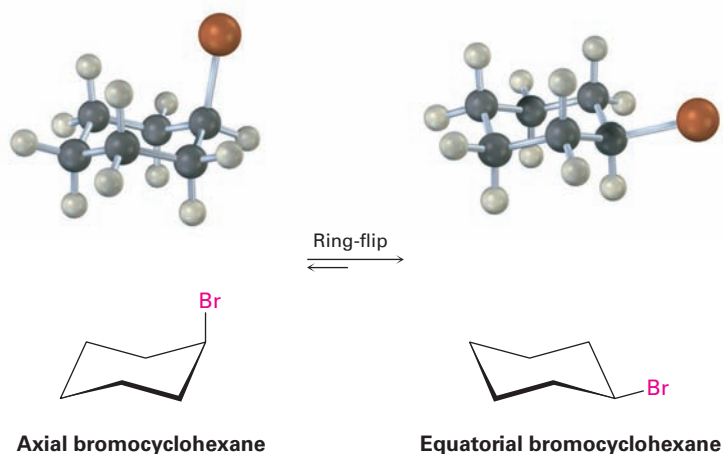


FIGURE 4.11 Ring-flip in chair cyclohexane. The ring-flip interconverts axial and equatorial positions. What is **axial** in the starting structure becomes equatorial in the ring-flipped structure, and what is **equatorial** in the starting structure is axial after ring-flip.

As shown in Figure 4.11, a chair cyclohexane can be ring-flipped by keeping the middle four carbon atoms in place while folding the two end carbons in opposite directions. In so doing, an axial substituent in one chair form becomes an equatorial substituent in the ring-flipped chair form and vice versa. For example, axial bromocyclohexane becomes equatorial bromocyclohexane after ring-flip. Since the energy barrier to chair–chair interconversion is only about 45 kJ/mol (10.8 kcal/mol), the process is rapid at room temperature and we see what appears to be a single structure rather than distinct axial and equatorial isomers.



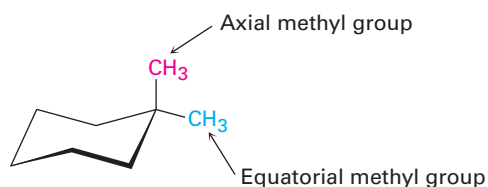
Drawing the Chair Conformation of a Substituted Cyclohexane

WORKED EXAMPLE 4.2

Draw 1,1-dimethylcyclohexane in a chair conformation, indicating which methyl group in your drawing is axial and which is equatorial.

Strategy

Draw a chair cyclohexane ring using the procedure shown in Figure 4.10, and then put two methyl groups on the same carbon. The methyl group in the rough plane of the ring is equatorial, and the one directly above or below the ring is axial.

Solution**PROBLEM 4.12**

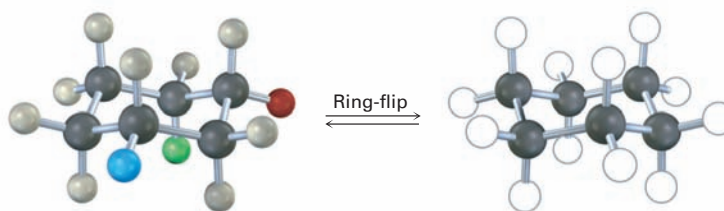
Draw two different chair conformations of cyclohexanol (hydroxycyclohexane) showing all hydrogen atoms. Identify each position as axial or equatorial.

PROBLEM 4.13

Draw two different chair conformations of *trans*-1,4-dimethylcyclohexane, and label all positions as axial or equatorial.

PROBLEM 4.14

Identify each of the colored positions—red, blue, and green—as axial or equatorial. Then carry out a ring-flip, and show the new positions occupied by each color.



4-7 Conformations of Monosubstituted Cyclohexanes

Even though cyclohexane rings flip rapidly between chair conformations at room temperature, the two conformations of a monosubstituted cyclohexane aren't equally stable. In methylcyclohexane, for instance, the equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol (1.8 kcal/mol). The same is true of other monosubstituted cyclohexanes: a substituent is almost always more stable in an equatorial position than in an axial position.

You might recall from your general chemistry course that it's possible to calculate the percentages of two isomers at equilibrium using the equation $\Delta E = -RT \ln K$, where ΔE is the energy difference between isomers, R is the gas constant [8.315 J/(K · mol)], T is the Kelvin temperature, and K is the

equilibrium constant between isomers. For example, an energy difference of 7.6 kJ/mol means that about 95% of methylcyclohexane molecules have the methyl group equatorial at any given instant and only 5% have the methyl group axial. **FIGURE 4.12** plots the relationship between energy and isomer percentages.

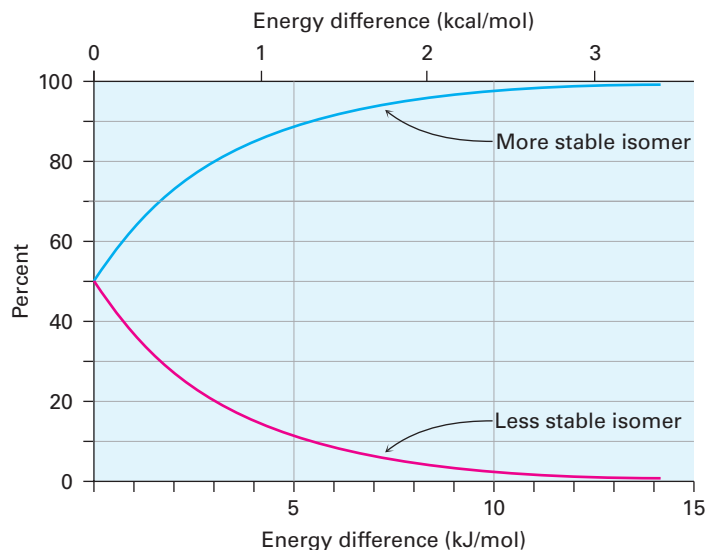


FIGURE 4.12 Plot of the percentages of two isomers at equilibrium versus the energy difference between them. The curves are calculated using the equation $\Delta E = -RT \ln K$.

The energy difference between axial and equatorial conformations is due to steric strain caused by **1,3-diaxial interactions**. The axial methyl group on C1 is too close to the axial hydrogens three carbons away on C3 and C5, resulting in 7.6 kJ/mol of steric strain (**FIGURE 4.13**).

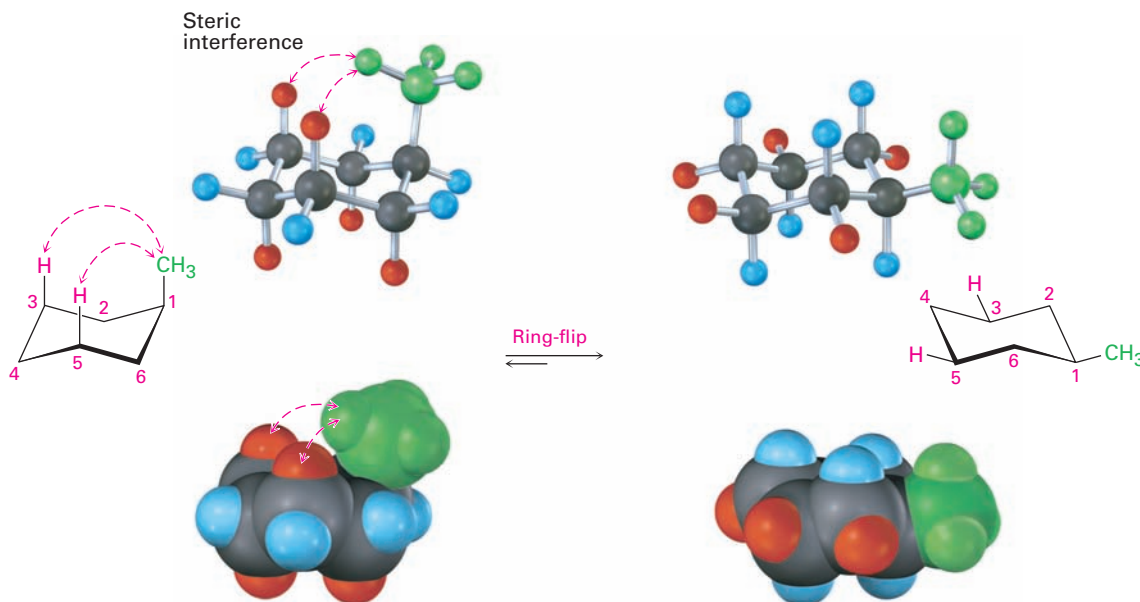
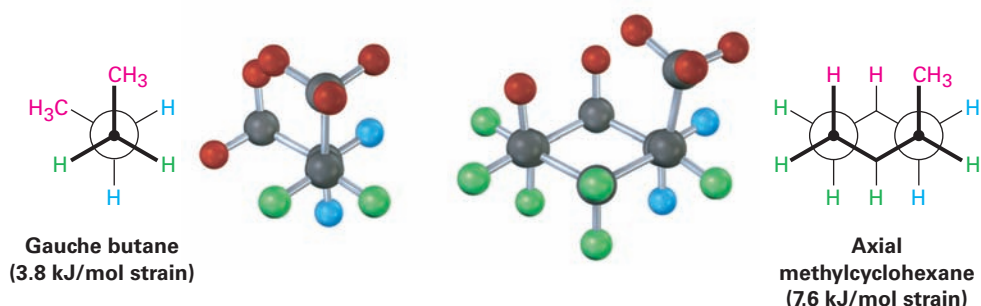


FIGURE 4.13 Interconversion of axial and equatorial methylcyclohexane. As represented in several formats, the equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol.

The 1,3-diaxial steric strain in substituted methylcyclohexane is already familiar—we saw it previously as the steric strain between methyl groups in gauche butane. Recall from Section 3-7 that gauche butane is less stable than anti butane by 3.8 kJ/mol (0.9 kcal/mol) because of steric interference between hydrogen atoms on the two methyl groups. Comparing a four-carbon fragment of axial methylcyclohexane with gauche butane shows that the steric interaction is the same in both cases (FIGURE 4.14). Because axial methylcyclohexane has two such interactions, it has $2 \times 3.8 = 7.6$ kJ/mol of steric strain. Equatorial methylcyclohexane, however, has no such interactions and is therefore more stable.

FIGURE 4.14 The origin of 1,3-diaxial interactions in methylcyclohexane. The steric strain between an axial methyl group and an axial hydrogen atom three carbons away is identical to the steric strain in gauche butane. Note that the $-\text{CH}_3$ group in methylcyclohexane moves slightly away from a true axial position to minimize the strain.



The exact amount of 1,3-diaxial steric strain in a given substituted cyclohexane depends on the nature and size of the substituent, as indicated in TABLE 4.1. Not surprisingly, the amount of steric strain increases through the series $\text{H}_3\text{C}- < \text{CH}_3\text{CH}_2- < (\text{CH}_3)_2\text{CH}- \ll (\text{CH}_3)_3\text{C}-$, paralleling the increasing size of the alkyl groups. Note that the values in Table 4.1 refer to 1,3-diaxial interactions of the substituent with a *single* hydrogen atom. These values must be doubled to arrive at the amount of strain in a mono-substituted cyclohexane.

TABLE 4.1 Steric Strain in Monosubstituted Cyclohexanes

Y	1,3-Diaxial strain		
	(kJ/mol)	(kcal/mol)	
F	0.5	0.12	
Cl, Br	1.0	0.25	
OH	2.1	0.5	
CH_3	3.8	0.9	
CH_2CH_3	4.0	0.95	
$\text{CH}(\text{CH}_3)_2$	4.6	1.1	
$\text{C}(\text{CH}_3)_3$	11.4	2.7	
C_6H_5	6.3	1.5	
CO_2H	2.9	0.7	
CN	0.4	0.1	

PROBLEM 4.15

What is the energy difference between the axial and equatorial conformations of cyclohexanol (hydroxycyclohexane)?

PROBLEM 4.16

Why do you suppose an axial cyano ($-\text{CN}$) substituent causes practically no 1,3-diaxial steric strain (0.4 kJ/mol)? Use molecular models to help with your answer.

PROBLEM 4.17

Look at Figure 4.12 on page 103, and estimate the percentages of axial and equatorial conformations present at equilibrium in bromocyclohexane.

4-8 Conformations of Disubstituted Cyclohexanes

Monosubstituted cyclohexanes are always more stable with their substituent in an equatorial position, but the situation in disubstituted cyclohexanes is more complex because the steric effects of both substituents must be taken into account. All steric interactions in both possible chair conformations must be analyzed before deciding which conformation is favored.

Let's look at 1,2-dimethylcyclohexane as an example. There are two isomers, *cis*-1,2-dimethylcyclohexane and *trans*-1,2-dimethylcyclohexane, which must be considered separately. In the *cis* isomer, both methyl groups are on the same face of the ring and the compound can exist in either of the two chair conformations shown in **FIGURE 4.15**. (It may be easier for you to see whether a compound is *cis*- or *trans*-disubstituted by first drawing the ring as a flat representation and then converting to a chair conformation.)

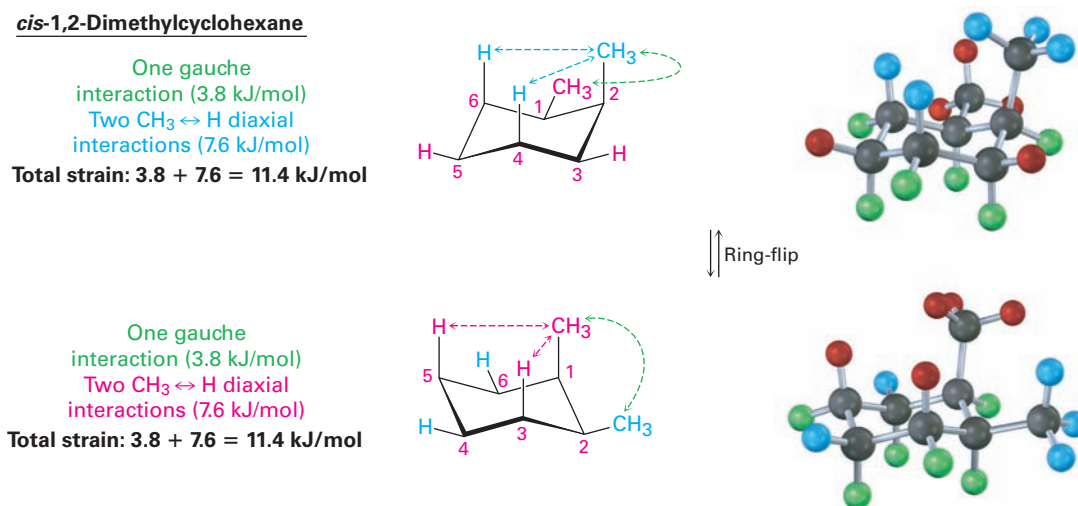


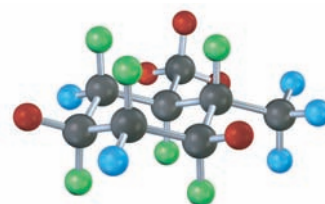
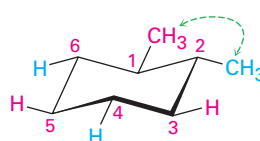
FIGURE 4.15 Conformations of *cis*-1,2-dimethylcyclohexane. The two chair conformations are equal in energy because each has one axial methyl group and one equatorial methyl group.

Both chair conformations of *cis*-1,2-dimethylcyclohexane have one axial methyl group and one equatorial methyl group. The top conformation in Figure 4.15 has an axial methyl group at C2, which has 1,3-diaxial interactions with hydrogens on C4 and C6. The ring-flipped conformation has an axial methyl group at C1, which has 1,3-diaxial interactions with hydrogens on C3 and C5. In addition, both conformations have gauche butane interactions between the two methyl groups. The two conformations are equal in energy, with a total steric strain of $3 \times 3.8 \text{ kJ/mol} = 11.4 \text{ kJ/mol}$ (2.7 kcal/mol).

In *trans*-1,2-dimethylcyclohexane, the two methyl groups are on opposite faces of the ring and the compound can exist in either of the two chair conformations shown in FIGURE 4.16. The situation here is quite different from that of the *cis* isomer. The top conformation in Figure 4.16 has both methyl groups equatorial and therefore has only a gauche butane interaction between them (3.8 kJ/mol) but no 1,3-diaxial interactions. The ring-flipped conformation, however, has both methyl groups axial. The axial methyl group at C1 interacts with axial hydrogens at C3 and C5, and the axial methyl group at C2 interacts with axial hydrogens at C4 and C6. These four 1,3-diaxial interactions produce a steric strain of $4 \times 3.8 \text{ kJ/mol} = 15.2 \text{ kJ/mol}$ and make the diaxial conformation $15.2 - 3.8 = 11.4 \text{ kJ/mol}$ less favorable than the diequatorial conformation. We therefore predict that *trans*-1,2-dimethylcyclohexane will exist almost exclusively in the diequatorial conformation.

trans-1,2-Dimethylcyclohexane

One gauche
interaction (3.8 kJ/mol)



Ring-flip

Four CH₃ ↔ H diaxial
interactions (15.2 kJ/mol)

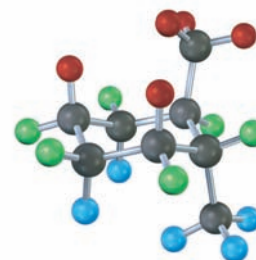
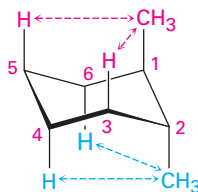
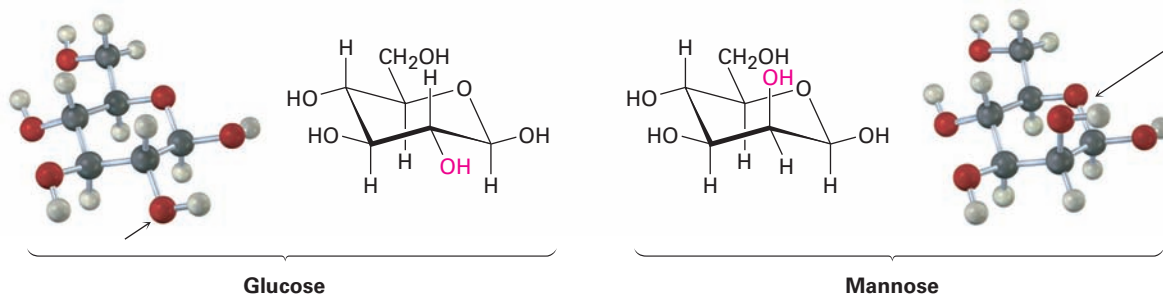


FIGURE 4.16 Conformations of *trans*-1,2-dimethylcyclohexane. The conformation with both methyl groups equatorial (top) is favored by 11.4 kJ/mol (2.7 kcal/mol) over the conformation with both methyl groups axial (bottom).

The same kind of **conformational analysis** just carried out for *cis*- and *trans*-1,2-dimethylcyclohexane can be done for any substituted cyclohexane, such as *cis*-1-*tert*-butyl-4-chlorocyclohexane (see Worked Example 4.3). As you might imagine, though, the situation becomes more complex as the number of substituents increases. For instance, compare glucose with mannose, a carbohydrate present in seaweed. Which do you think is more strained? In glucose, all substituents on the six-membered ring are equatorial, while in mannose, one of the –OH groups is axial, making mannose more strained.



A summary of the various axial and equatorial relationships among substituent groups in the different possible cis and trans substitution patterns for disubstituted cyclohexanes is given in **TABLE 4.2**.

TABLE 4.2 Axial and Equatorial Relationships in Cis- and Trans-Disubstituted Cyclohexanes

Cis/trans substitution pattern	Axial/equatorial relationships
1,2-Cis disubstituted	a,e or e,a
1,2-Trans disubstituted	a,a or e,e
1,3-Cis disubstituted	a,a or e,e
1,3-Trans disubstituted	a,e or e,a
1,4-Cis disubstituted	a,e or e,a
1,4-Trans disubstituted	a,a or e,e

Drawing the Most Stable Conformation of a Substituted Cyclohexane

WORKED EXAMPLE 4.3

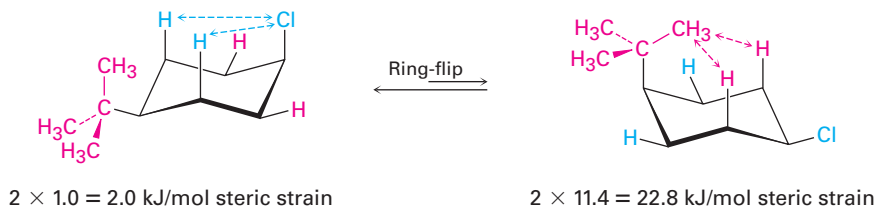
Draw the more stable chair conformation of *cis*-1-*tert*-butyl-4-chlorocyclohexane. By how much is it favored?

Strategy

Draw the two possible chair conformations, and calculate the strain energy in each. Remember that equatorial substituents cause less strain than axial substituents.

Solution

First draw the two chair conformations of the molecule:



In the conformation on the left, the *tert*-butyl group is equatorial and the chlorine is axial. In the conformation on the right, the *tert*-butyl group is axial and the chlorine is equatorial. These conformations aren't of equal energy

because an axial *tert*-butyl substituent and an axial chloro substituent produce different amounts of steric strain. Table 4.1 shows that the 1,3-diaxial interaction between a hydrogen and a *tert*-butyl group costs 11.4 kJ/mol (2.7 kcal/mol), whereas the interaction between a hydrogen and a chlorine costs only 1.0 kJ/mol (0.25 kcal/mol). An axial *tert*-butyl group therefore produces $(2 \times 11.4 \text{ kJ/mol}) - (2 \times 1.0 \text{ kJ/mol}) = 20.8 \text{ kJ/mol}$ (4.9 kcal/mol) more steric strain than does an axial chlorine, and the compound preferentially adopts the conformation with the chlorine axial and the *tert*-butyl equatorial.

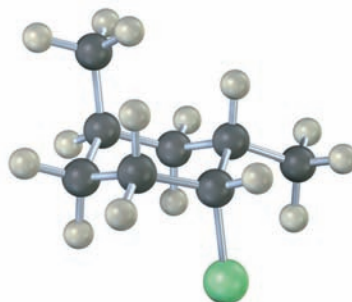
PROBLEM 4.18

Draw the more stable chair conformation of the following molecules, and estimate the amount of strain in each:

- trans*-1-Chloro-3-methylcyclohexane
- cis*-1-Ethyl-2-methylcyclohexane
- cis*-1-Bromo-4-ethylcyclohexane
- cis*-1-*tert*-Butyl-4-ethylcyclohexane

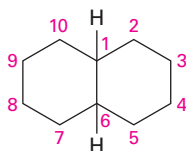
PROBLEM 4.19

Identify each substituent in the following compound as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



4-9 Conformations of Polycyclic Molecules

The last point we'll consider about cycloalkane stereochemistry is to see what happens when two or more cycloalkane rings are fused together along a common bond to construct a **polycyclic** molecule—for example, decalin.



Decalin—two fused cyclohexane rings

Decalin contains two cyclohexane rings, joined to share two carbon atoms (the *bridgehead* carbons, C1 and C6) and a common bond. Decalin can exist in either of two isomeric forms, depending on whether the rings are *trans* fused or *cis* fused. In *cis*-decalin, the hydrogen atoms at the bridgehead carbons are

on the same face of the rings; in *trans*-decalin, the bridgehead hydrogens are on opposite faces. **FIGURE 4.17** shows how both compounds can be represented using chair cyclohexane conformations. Note that *cis*- and *trans*-decalin are not interconvertible by ring-flips or other rotations. They are *cis*–*trans* stereoisomers and have the same relationship to each other that *cis*- and *trans*-1,2-dimethylcyclohexane have.

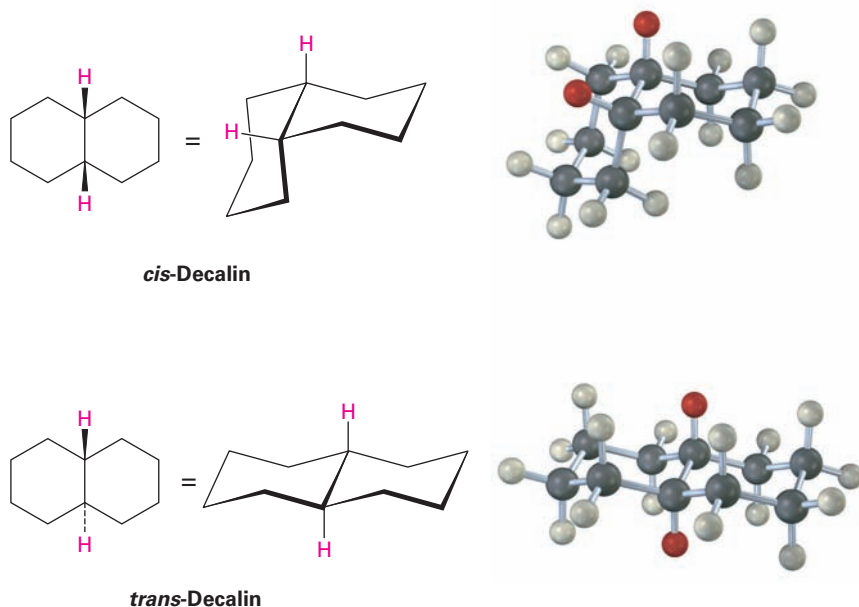
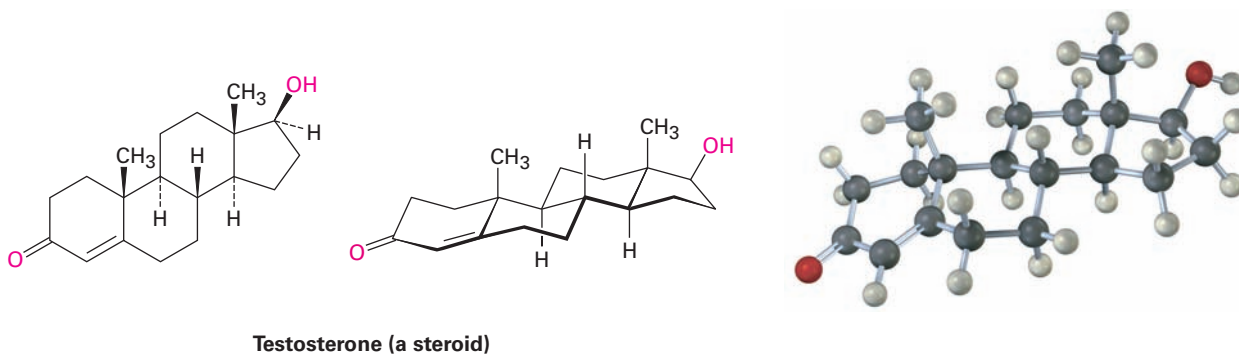


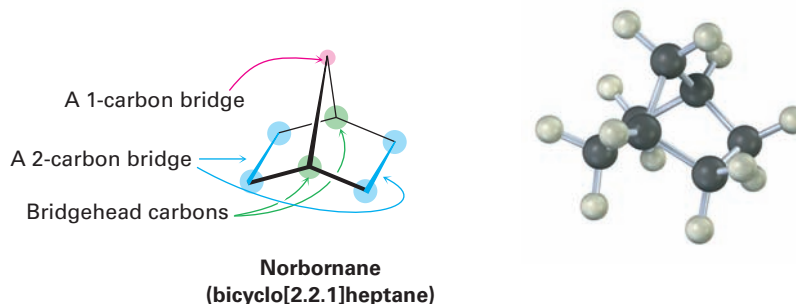
FIGURE 4.17 Representations of *cis*- and *trans*-decalin. **Hydrogen atoms** at the bridgehead carbons are on the same face of the rings in the *cis* isomer but on opposite faces in the *trans* isomer.

Polycyclic compounds are common in nature, and many valuable substances have fused-ring structures. For example, steroids, such as the male hormone testosterone, have 3 six-membered rings and 1 five-membered ring fused together. Although steroids look complicated compared with cyclohexane or decalin, the same principles that apply to the conformational analysis of simple cyclohexane rings apply equally well (and often better) to steroids.



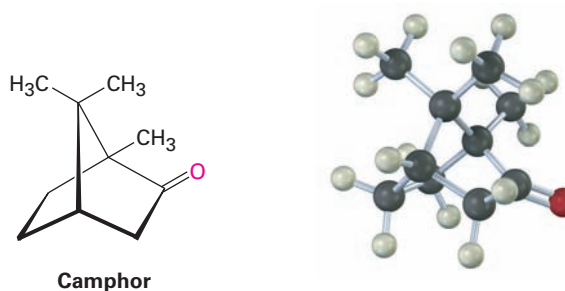
Another common ring system is the norbornane, or bicyclo[2.2.1]heptane, structure. Like decalin, norbornane is a *bicycloalkane*, so called because *two* rings would have to be broken open to generate an acyclic structure. Its systematic name, bicyclo[2.2.1]heptane, reflects the fact that the molecule has

seven carbons, is bicyclic, and has three “bridges” of 2, 2, and 1 carbon atoms connecting the two bridgehead carbons.



Norbornane has a conformationally locked boat cyclohexane ring (Section 4-5) in which carbons 1 and 4 are joined by an additional CH_2 group. Note how, in drawing this structure, a break in the rear bond indicates that the vertical bond crosses in front of it. Making a molecular model is particularly helpful when trying to see the three-dimensionality of norbornane.

Substituted norbornanes, such as camphor, are found widely in nature, and many have been important historically in developing organic structural theories.

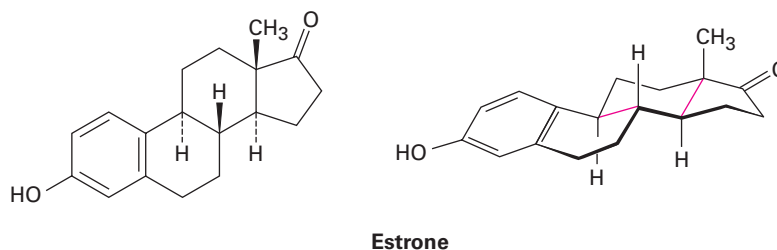


PROBLEM 4.20

Which isomer is more stable, *cis*-decalin or *trans*-decalin? Explain.

PROBLEM 4.21

Look at the following structure of the female hormone estrone, and tell whether each of the two indicated ring-fusions is *cis* or *trans*.



SOMETHING EXTRA

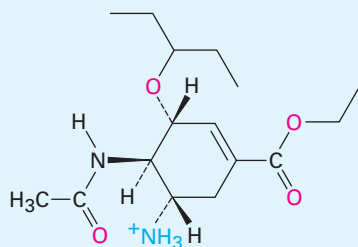
Molecular Mechanics

All the structural models in this book are computer-drawn. To make sure they accurately portray bond angles, bond lengths, torsional interactions, and steric interactions, the most stable geometry of each molecule has been calculated on a desktop computer using a commercially available *molecular mechanics* program based on work by N. L. Allinger of the University of Georgia.

The idea behind molecular mechanics is to begin with a rough geometry for a molecule and then calculate a total strain energy for that starting geometry, using mathematical equations that assign values to specific kinds of molecular interactions. Bond angles that are too large or too small cause angle strain; bond lengths that are too short or too long cause stretching or compressing strain; unfavorable eclipsing interactions around single bonds cause torsional strain; and nonbonded atoms that approach each other too closely cause steric, or *van der Waals*, strain.

$$E_{\text{total}} = E_{\text{bond stretching}} + E_{\text{angle strain}} + E_{\text{torsional strain}} + E_{\text{van der Waals}}$$

After calculating a total strain energy for the starting geometry, the program automatically changes the geometry slightly in an attempt to lower strain—



Tamiflu (oseltamivir phosphate)

FIGURE 4.18 The structure of Tamiflu (oseltamivir phosphate) and a molecular model of its minimum-energy conformation, as calculated by molecular mechanics.

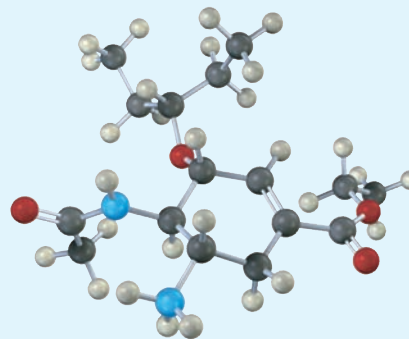


Mauro Farnaniello/Photo Researchers, Inc./Science Source

Computer programs make it possible to portray accurate representations of molecular geometry.

perhaps by lengthening a bond that is too short or decreasing an angle that is too large. Strain is recalculated for the new geometry, more changes are made, and more calculations are done. After dozens or hundreds of iterations, the calculation ultimately converges on a minimum energy that corresponds to the most favorable, least strained conformation of the molecule.

Molecular mechanics calculations have proven to be particularly useful in pharmaceutical research, where the complementary fit between a drug molecule and a receptor molecule in the body is often a key to designing new pharmaceutical agents (FIGURE 4.18).



KEY WORDS

alicyclic, 88
angle strain, 93
axial position, 99
chair conformation, 97
cis–trans isomers, 92
conformational analysis, 106
cycloalkane, 88
1,3-diaxial interaction, 103
equatorial position, 99
polycyclic compound, 108
ring-flip (cyclohexane), 101
stereochemistry, 92
stereoisomers, 91
twist-boat conformation, 98

SUMMARY

Cyclic molecules are so commonly encountered throughout organic and biological chemistry that it's important to understand the consequences of their cyclic structures. Thus, we've taken a close look at cyclic structures in this chapter.

A **cycloalkane** is a saturated cyclic hydrocarbon with the general formula C_nH_{2n} . In contrast to open-chain alkanes, where nearly free rotation occurs around C–C bonds, rotation is greatly reduced in cycloalkanes. Disubstituted cycloalkanes can therefore exist as **cis–trans isomers**. The cis isomer has both substituents on the same face of the ring; the trans isomer has substituents on opposite faces. Cis–trans isomers are just one kind of **stereoisomers**—compounds that have the same connections between atoms but different three-dimensional arrangements.

Not all cycloalkanes are equally stable. Three kinds of strain contribute to the overall energy of a cycloalkane: (1) **angle strain** is the resistance of a bond angle to compression or expansion from the normal 109° tetrahedral value, (2) torsional strain is the energy cost of having neighboring C–H bonds eclipsed rather than staggered, and (3) steric strain is the repulsive interaction that arises when two groups attempt to occupy the same space.

Cyclopropane (115 kJ/mol strain) and cyclobutane (110.4 kJ/mol strain) have both angle strain and torsional strain. Cyclopentane is free of angle strain but has a substantial torsional strain due to its large number of eclipsing interactions. Both cyclobutane and cyclopentane pucker slightly away from planarity to relieve torsional strain.

Cyclohexane is strain-free because it adopts a puckered **chair conformation**, in which all bond angles are near 109° and all neighboring C–H bonds are staggered. Chair cyclohexane has two kinds of positions: **axial** and **equatorial**. Axial positions are oriented up and down, parallel to the ring axis, while equatorial positions lie in a belt around the equator of the ring. Each carbon atom has one axial and one equatorial position.

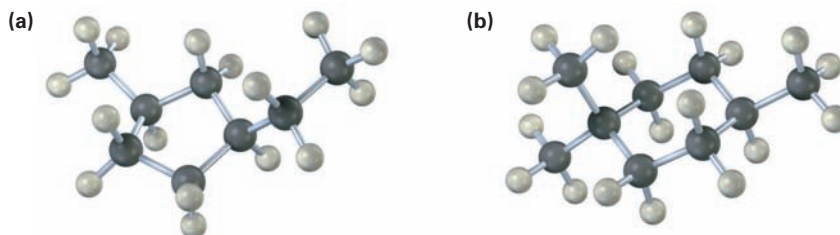
Chair cyclohexanes are conformationally mobile and can undergo a **ring-flip**, which interconverts axial and equatorial positions. Substituents on the ring are more stable in the equatorial position because axial substituents cause **1,3-diaxial interactions**. The amount of 1,3-diaxial steric strain caused by an axial substituent depends on its size.

EXERCISES

VISUALIZING CHEMISTRY

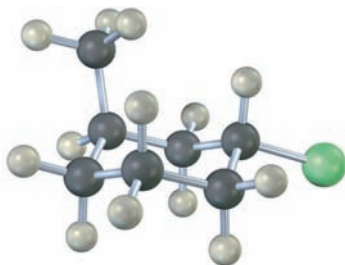
(Problems 4.1–4.21 appear within the chapter.)

4.22 Name the following cycloalkanes:

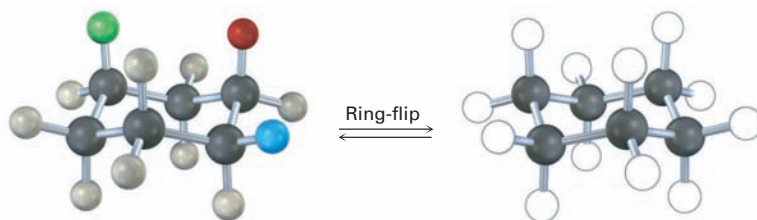


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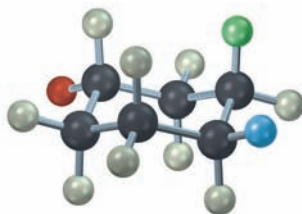
- 4.23 Name the following compound, identify each substituent as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



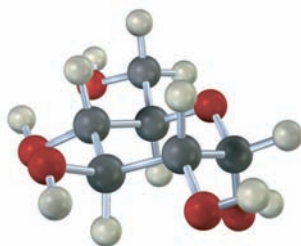
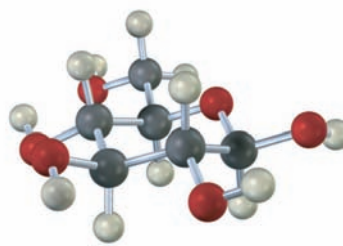
- 4.24 A trisubstituted cyclohexane with three substituents—red, green, and blue—undergoes a ring-flip to its alternative chair conformation. Identify each substituent as axial or equatorial, and show the positions occupied by the three substituents in the ring-flipped form.



- 4.25 The following cyclohexane derivative has three substituents—red, green, and blue. Identify each substituent as axial or equatorial, and identify each pair of relationships (red–blue, red–green, and blue–green) as cis or trans.



- 4.26 Glucose exists in two forms having a 36 : 64 ratio at equilibrium. Draw a skeletal structure of each, describe the difference between them, and tell which of the two you think is more stable (red = O).

 α -Glucose β -Glucose

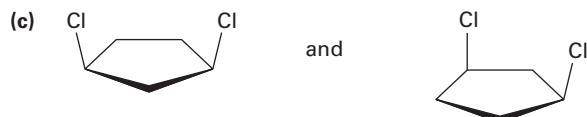
ADDITIONAL PROBLEMS

Cycloalkane Isomers

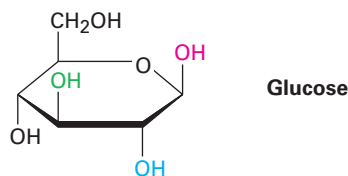
- 4.27 Draw the five cycloalkanes with the formula C_5H_{10} .
- 4.28 Draw two constitutional isomers of *cis*-1,2-dibromocyclopentane.
- 4.29 Draw a stereoisomer of *trans*-1,3-dimethylcyclobutane.
- 4.30 Tell whether the following pairs of compounds are identical, constitutional isomers, stereoisomers, or unrelated.

(a) *cis*-1,3-Dibromocyclohexane and *trans*-1,4-dibromocyclohexane

(b) 2,3-Dimethylhexane and 2,3,3-trimethylpentane



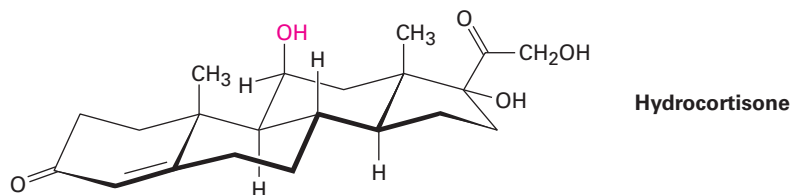
- 4.31 Draw three isomers of *trans*-1,2-dichlorocyclobutane, and label them as either constitutional isomers or stereoisomers.
- 4.32 Identify each pair of relationships among the $-OH$ groups in glucose (red–blue, red–green, red–black, blue–green, blue–black, green–black) as *cis* or *trans*.



- 4.33 Draw 1,3,5-trimethylcyclohexane using a hexagon to represent the ring. How many *cis*–*trans* stereoisomers are possible?

Cycloalkane Conformation and Stability

- 4.34 Hydrocortisone, a naturally occurring hormone produced in the adrenal glands, is often used to treat inflammation, severe allergies, and numerous other conditions. Is the indicated $-OH$ group in the molecule axial or equatorial?



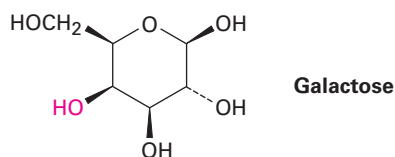
- 4.35 A 1,2-*cis* disubstituted cyclohexane, such as *cis*-1,2-dichlorocyclohexane, must have one group axial and one group equatorial. Explain.
- 4.36 A 1,2-*trans* disubstituted cyclohexane must have either both groups axial or both groups equatorial. Explain.
- 4.37 Why is a 1,3-*cis* disubstituted cyclohexane more stable than its *trans* isomer?

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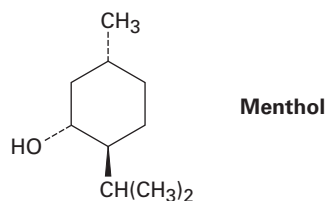
- 4.38 Which is more stable, a 1,4-trans disubstituted cyclohexane or its cis isomer?
- 4.39 *cis*-1,2-Dimethylcyclobutane is less stable than its trans isomer, but *cis*-1,3-dimethylcyclobutane is more stable than its trans isomer. Draw the most stable conformations of both, and explain.
- 4.40 From the data in Figure 4.12 and Table 4.1, estimate the percentages of molecules that have their substituents in an axial orientation for the following compounds:
- (a) Isopropylcyclohexane (b) Fluorocyclohexane
- (c) Cyclohexanecarbonitrile, C₆H₁₁CN
- 4.41 Assume that you have a variety of cyclohexanes substituted in the positions indicated. Identify the substituents as either axial or equatorial. For example, a 1,2-*cis* relationship means that one substituent must be axial and one equatorial, whereas a 1,2-*trans* relationship means that both substituents are axial or both are equatorial.
- (a) 1,3-*Trans* disubstituted (b) 1,4-*Cis* disubstituted
- (c) 1,3-*Cis* disubstituted (d) 1,5-*Trans* disubstituted
- (e) 1,5-*Cis* disubstituted (f) 1,6-*Trans* disubstituted

Cyclohexane Conformational Analysis

- 4.42 Draw the two chair conformations of *cis*-1-chloro-2-methylcyclohexane. Which is more stable, and by how much?
- 4.43 Draw the two chair conformations of *trans*-1-chloro-2-methylcyclohexane. Which is more stable?
- 4.44 Galactose, a sugar related to glucose, contains a six-membered ring in which all the substituents except the -OH group indicated below in red are equatorial. Draw galactose in its more stable chair conformation.



- 4.45 Draw the two chair conformations of menthol, and tell which is more stable.

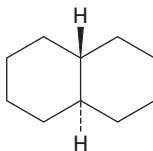


- 4.46 There are four *cis*-*trans* isomers of menthol (Problem 4.45), including the one shown. Draw the other three.

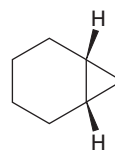
- 4.47 The diaxial conformation of *cis*-1,3-dimethylcyclohexane is approximately 23 kJ/mol (5.4 kcal/mol) less stable than the diequatorial conformation. Draw the two possible chair conformations, and suggest a reason for the large energy difference.
- 4.48 Approximately how much steric strain does the 1,3-diaxial interaction between the two methyl groups introduce into the diaxial conformation of *cis*-1,3-dimethylcyclohexane? (See Problem 4.47.)
- 4.49 In light of your answer to Problem 4.48, draw the two chair conformations of 1,1,3-trimethylcyclohexane and estimate the amount of strain energy in each. Which conformation is favored?
- 4.50 One of the two chair structures of *cis*-1-chloro-3-methylcyclohexane is more stable than the other by 15.5 kJ/mol (3.7 kcal/mol). Which is it? What is the energy cost of a 1,3-diaxial interaction between a chlorine and a methyl group?

General Problems

- 4.51 We saw in Problem 4.20 that *cis*-decalin is less stable than *trans*-decalin. Assume that the 1,3-diaxial interactions in *cis*-decalin are similar to those in axial methylcyclohexane [that is, one CH₂ ↔ H interaction costs 3.8 kJ/mol (0.9 kcal/mol)], and calculate the magnitude of the energy difference between *cis*- and *trans*-decalin.
- 4.52 Using molecular models as well as structural drawings, explain why *trans*-decalin is rigid and cannot ring-flip whereas *cis*-decalin can easily ring-flip.
- 4.53 *trans*-Decalin is more stable than its *cis* isomer, but *cis*-bicyclo[4.1.0]heptane is more stable than its *trans* isomer. Explain.

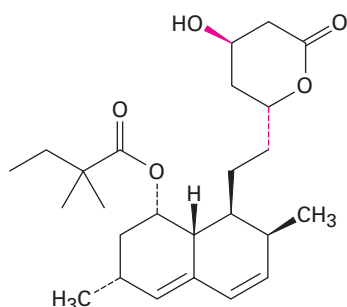


trans-Decalin

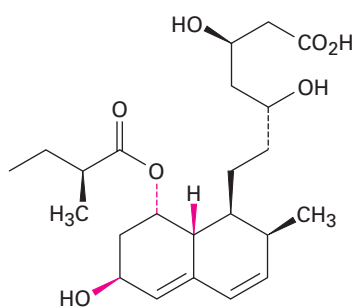


cis-Bicyclo[4.1.0]heptane

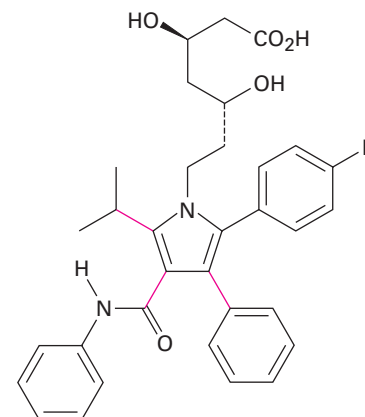
- 4.54 As mentioned in Problem 3.53, the statin drugs, such as simvastatin (Zocor), pravastatin (Pravachol), and atorvastatin (Lipitor) are the most widely prescribed drugs in the world.



Simvastatin
(Zocor)

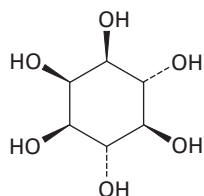


Pravastatin
(Pravachol)



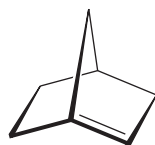
Atorvastatin
(Lipitor)

- (a) Are the two indicated bonds on simvastatin cis or trans?
- (b) What are the cis/trans relationships among the three indicated bonds on pravastatin?
- (c) Why can't the three indicated bonds on atorvastatin be identified as cis or trans?
- 4.55 *myo*-Inositol, one of the isomers of 1,2,3,4,5,6-hexahydrocyclohexane, acts as a growth factor in both animals and microorganisms. Draw the most stable chair conformation of *myo*-inositol.



myo-Inositol

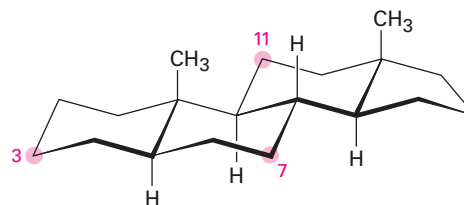
- 4.56 How many cis–trans stereoisomers of *myo*-inositol (Problem 4.55) are there? Draw the structure of the most stable isomer.
- 4.57 The German chemist J. Bredt proposed in 1935 that bicycloalkenes such as 1-norbornene, which have a double bond to the bridgehead carbon, are too strained to exist. Explain. (Making a molecular model will be helpful.)



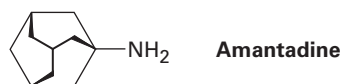
1-Norbornene

- 4.58 Tell whether each of the following substituents on a steroid is axial or equatorial. (A substituent that is “up” is on the top face of the molecule as drawn, and a substituent that is “down” is on the bottom face.)

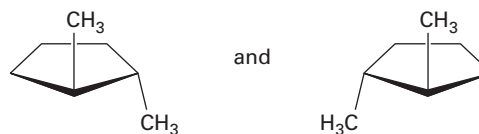
- (a) Substituent up at C3
 (b) Substituent down at C7
 (c) Substituent down at C11



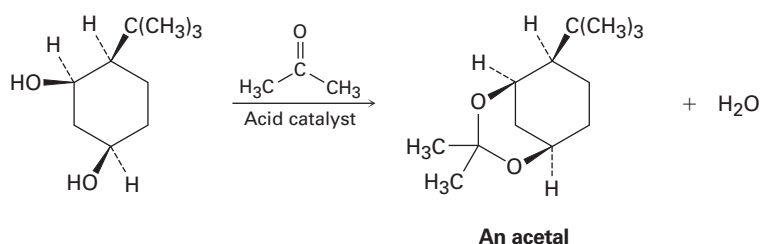
- 4.59 Amantadine is an antiviral agent that is active against influenza type A infection. Draw a three-dimensional representation of amantadine, showing the chair cyclohexane rings.



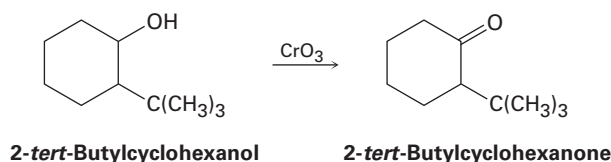
- 4.60 Here's a difficult one. There are two different substances named *trans*-1,2-dimethylcyclopentane. What is the relationship between them? (We'll explore this kind of isomerism in the next chapter.)



- 4.61 Ketones react with alcohols to yield products called *acetals*. Why does the all-cis isomer of 4-*tert*-butylcyclohexane-1,3-diol react readily with acetone and an acid catalyst to form an acetal, but other stereoisomers do not react? In formulating your answer, draw the more stable chair conformations of all four stereoisomers and the product acetal from each.



- 4.62 Alcohols undergo an *oxidation* reaction to yield carbonyl compounds on treatment with CrO_3 . For example, 2-*tert*-butylcyclohexanol gives 2-*tert*-butylcyclohexanone. If axial $-\text{OH}$ groups are generally more reactive than their equatorial isomers, which do you think reacts faster, the cis isomer of 2-*tert*-butylcyclohexanol or the trans isomer? Explain.



Stereochemistry at Tetrahedral Centers

5

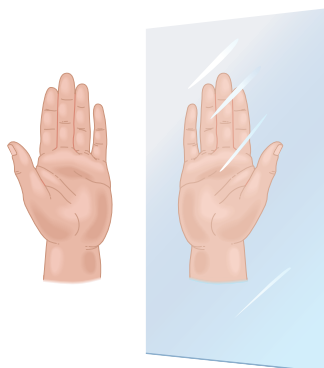


Glycogen synthase catalyzes the conversion of glucose to glycogen for energy storage.

WHY THIS CHAPTER?

Understanding the causes and consequences of molecular handedness is crucial to understanding biological chemistry. The subject can be a bit complex at first, but the material covered in this chapter nevertheless forms the basis for much of the remainder of the book.

Are you right-handed or left-handed? You may not spend much time thinking about it, but handedness plays a surprisingly large part in everything you do. Many musical instruments, such as oboes and clarinets, have a handedness to them; the last available softball glove always fits the wrong hand; left-handed people write in a “funny” way. The reason for these difficulties is that our hands aren’t identical; rather, they’re nonsuperimposable *mirror images*. When you hold a *left* hand up to a mirror, the image you see looks like a *right* hand. Try it.



Left hand

Right hand

Handedness is also important in organic and biological chemistry, where it arises primarily as a consequence of the tetrahedral stereochemistry of sp^3 -hybridized carbon atoms. Many drugs and almost all the molecules in our bodies—amino acids, carbohydrates, nucleic acids, and many more—are

CONTENTS

- 5-1 Enantiomers and the Tetrahedral Carbon
- 5-2 The Reason for Handedness in Molecules: Chirality
- 5-3 Optical Activity
- 5-4 Pasteur’s Discovery of Enantiomers
- 5-5 Sequence Rules for Specifying Configuration
- 5-6 Diastereomers
- 5-7 Meso Compounds
- 5-8 Racemic Mixtures and the Resolution of Enantiomers
- 5-9 A Review of Isomerism
- 5-10 Chirality at Nitrogen, Phosphorus, and Sulfur
- 5-11 Prochirality
- 5-12 Chirality in Nature and Chiral Environments

SOMETHING EXTRA

Chiral Drugs



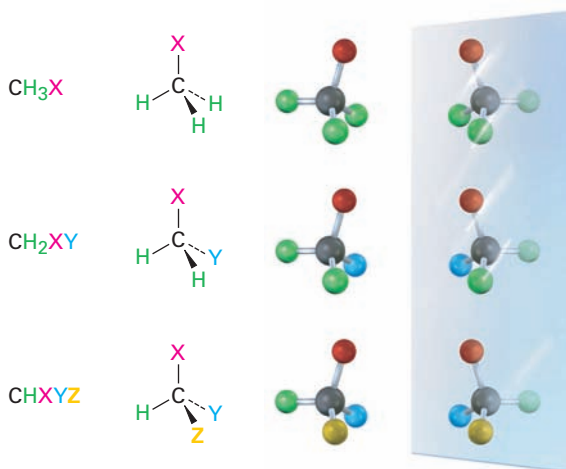
handed. Furthermore, molecular handedness makes possible the precise interactions between enzymes and their substrates that are involved in the hundreds of thousands of chemical reactions on which life is based.

5-1 Enantiomers and the Tetrahedral Carbon

What causes molecular handedness? Look at generalized molecules of the type CH_3X , CH_2XY , and CHXYZ shown in **FIGURE 5.1**. On the left are three molecules, and on the right are their images reflected in a mirror. The CH_3X and CH_2XY molecules are identical to their mirror images and thus are not handed. If you make a molecular model of each molecule and its mirror image, you'll find that you can superimpose one on the other so that all atoms coincide. The CHXYZ molecule, by contrast, is *not* identical to its mirror image. You can't superimpose a model of the molecule on a model of its mirror image for the same reason that you can't superimpose a left hand on a right hand: they simply aren't the same.

FIGURE 5.1 Tetrahedral carbon atoms and their mirror images.

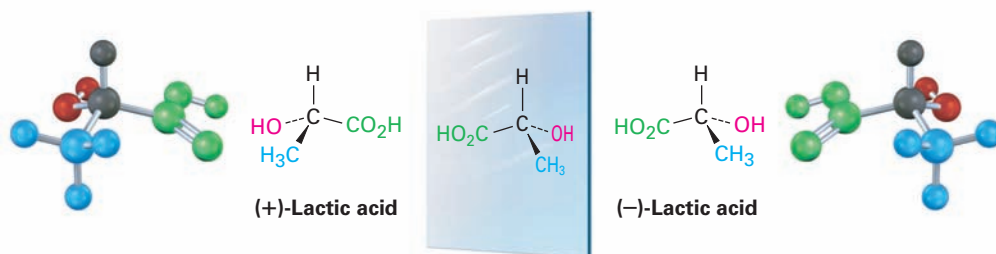
Molecules of the type CH_3X and CH_2XY are identical to their mirror images, but a molecule of the type CHXYZ is not. A CHXYZ molecule is related to its mirror image in the same way that a right hand is related to a left hand.



Molecules that are not identical to their mirror images are kinds of stereoisomers called **enantiomers** (Greek *enantio*, meaning “opposite”). Enantiomers are related to each other as a right hand is related to a left hand and result whenever a tetrahedral carbon is bonded to four different substituents (one need not be H). For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups ($-\text{H}$, $-\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2\text{H}$) bonded to the central carbon atom. The enantiomers are called (+)-lactic acid and (–)-lactic acid. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.



Lactic acid: a molecule of general formula CHXYZ



No matter how hard you try, you can't superimpose a molecule of (+)-lactic acid on a molecule of (–)-lactic acid. If any two groups match up, say –H and –CO₂H, the remaining two groups don't match (FIGURE 5.2).

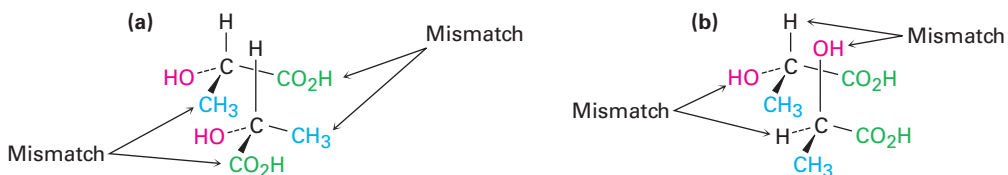


FIGURE 5.2 Attempts at superimposing the mirror-image forms of lactic acid. (a) When the –H and –OH substituents match up, the –CO₂H and –CH₃ substituents don't; (b) when –CO₂H and –CH₃ match up, –H and –OH don't. Regardless of how the molecules are oriented, they aren't identical.

5-2 The Reason for Handedness in Molecules: Chirality

A molecule that is not identical to its mirror image is said to be **chiral** (ky-ral, from the Greek *cheir*, meaning “hand”). You can't take a chiral molecule and its enantiomer and place one on the other so that all atoms coincide.

How can you predict whether a given molecule is or is not chiral? A *molecule is not chiral if it has a plane of symmetry*. A plane of symmetry is a plane that cuts through the middle of a molecule (or any object) in such a way that one half of the molecule or object is a mirror image of the other half. A coffee mug, for example, has a plane of symmetry. If you were to cut the mug in half, one half would be a mirror image of the other half. A hand, however, does not have a plane of symmetry. One “half” of a hand is not a mirror image of the other half (FIGURE 5.3).

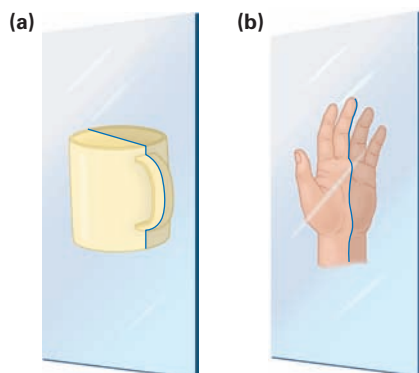
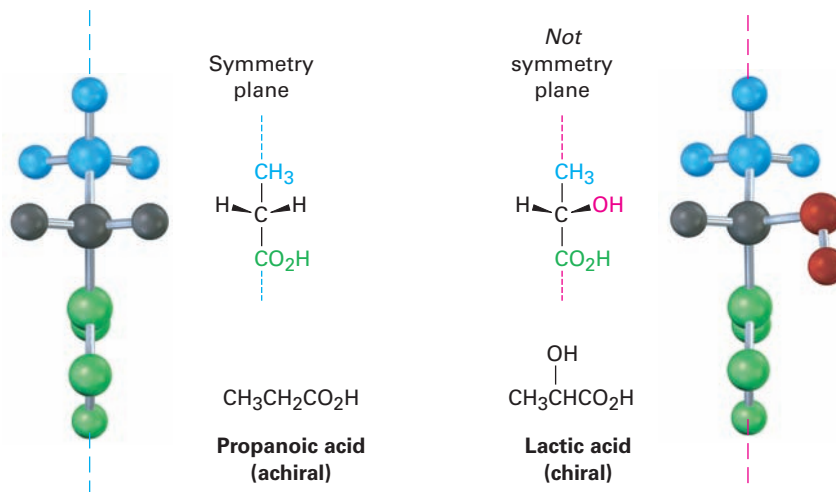


FIGURE 5.3 The meaning of **symmetry plane**. (a) An object like the coffee mug has a symmetry plane cutting through it so that right and left halves are mirror images. (b) An object like a hand does not have a symmetry plane; the right half of a hand is not a mirror image of the left half.

A molecule that has a plane of symmetry in any conformation must be identical to its mirror image and hence must be nonchiral, or **achiral**. Thus, propanoic acid, $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$, has a plane of symmetry when lined up as shown in **FIGURE 5.4** and is achiral, while lactic acid, $\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H}$, has no plane of symmetry in any conformation and is chiral.

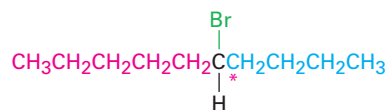
FIGURE 5.4 The achiral propanoic acid molecule versus the chiral lactic acid molecule.

Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other side. Lactic acid has no such symmetry plane.



The most common, although not the only, cause of chirality in an organic molecule is the presence of a tetrahedral carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are referred to as **chirality centers**, although other terms, such as stereocenter, asymmetric center, and stereogenic center, have also been used. Note that *chirality* is a property of an entire molecule, whereas a chirality *center* is the cause of chirality.

Detecting a chirality center in a complex molecule takes practice because it's not always immediately apparent whether four different groups are bonded to a given carbon. The differences don't necessarily appear right next to the chirality center. For example, 5-bromodecane is a chiral molecule because four different groups are bonded to C5, the chirality center (marked with an asterisk). A butyl substituent is similar to a pentyl substituent, but it isn't identical. The difference isn't apparent until four carbon atoms away from the chirality center, but there's still a difference.



5-Bromodecane (chiral)

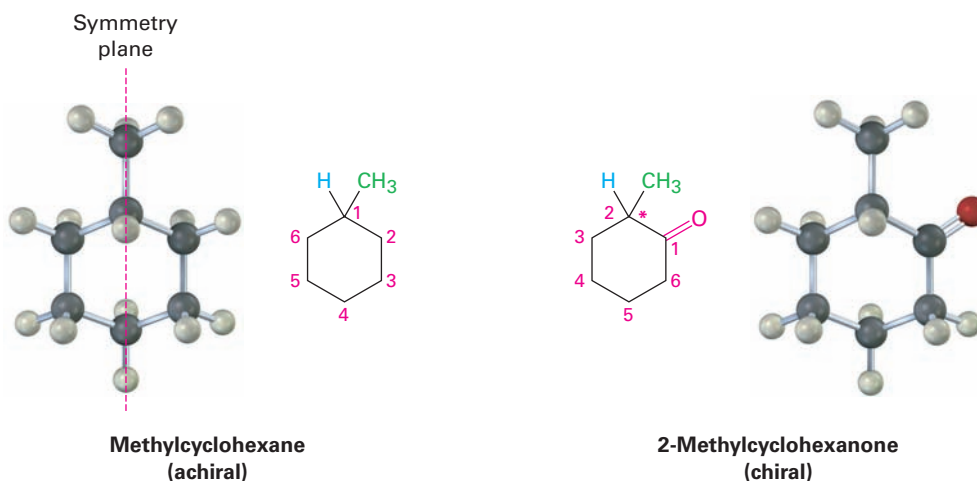
Substituents on carbon 5

- H
- Br
- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (butyl)
- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (pentyl)

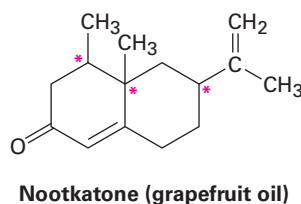
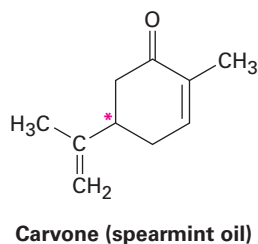
As other possible examples, look at methylcyclohexane and 2-methylcyclohexanone. Methylcyclohexane is achiral because no carbon atom in the molecule is bonded to four different groups. You can immediately eliminate all

–CH₂– carbons and the –CH₃ carbon from consideration, but what about C1 on the ring? The C1 carbon atom is bonded to a –CH₃ group, to an –H atom, and to C2 and C6 of the ring. Carbons 2 and 6 are equivalent, however, as are carbons 3 and 5. Thus, the C6–C5–C4 “substituent” is equivalent to the C2–C3–C4 substituent, and methylcyclohexane is achiral. Another way of reaching the same conclusion is to realize that methylcyclohexane has a symmetry plane, which passes through the methyl group and through C1 and C4 of the ring.

The situation is different for 2-methylcyclohexanone. 2-Methylcyclohexanone has no symmetry plane and is chiral because C2 is bonded to four different groups: a –CH₃ group, an –H atom, a –COCH₂– ring bond (C1), and a –CH₂CH₂– ring bond (C3).



Several more examples of chiral molecules are shown below. Check for yourself that the labeled carbons are chirality centers. You might note that carbons in –CH₂–, –CH₃, C=O, C=C, and C≡C groups can't be chirality centers. (Why not?)



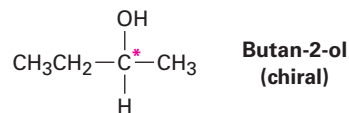
Drawing the Three-Dimensional Structure of a Chiral Molecule

WORKED EXAMPLE 5.1

Draw the structure of a chiral alcohol.

Strategy

An alcohol is a compound that contains the –OH functional group. To make an alcohol chiral, we need to have four different groups bonded to a single carbon atom, say –H, –OH, –CH₃, and –CH₂CH₃.

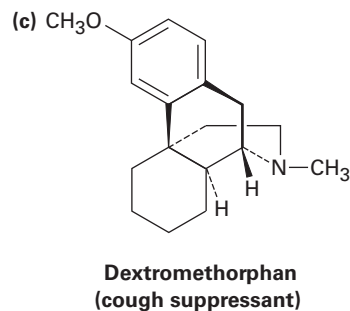
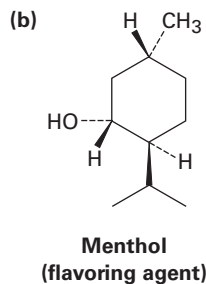
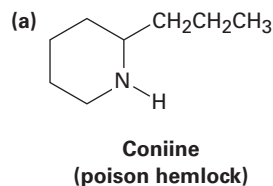
Solution**PROBLEM 5.1**

Which of the following objects are chiral?

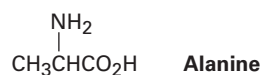
- (a) Soda can (b) Screwdriver (c) Screw (d) Shoe

PROBLEM 5.2

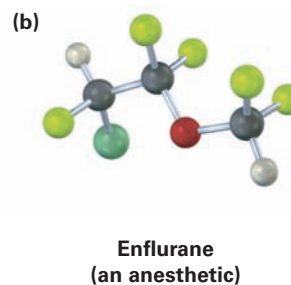
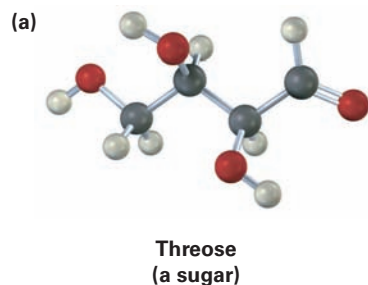
Which of the following molecules are chiral? Identify the chirality center(s) in each.

**PROBLEM 5.3**

Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.

**PROBLEM 5.4**

Identify the chirality centers in the following molecules (green = Cl, yellow-green = F):



5-3 Optical Activity

The study of chirality originated in the early 19th century during investigations by the French physicist Jean-Baptiste Biot into the nature of *plane-polarized light*. A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a beam of ordinary light passes through a device called a *polarizer*, however, only the light waves oscillating in a single plane pass through and the light is said to be plane-polarized. Light waves in all other planes are blocked out.

Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is *rotated* through an angle, α . Not all organic substances exhibit this property, but those that do are said to be **optically active**.

The angle of rotation can be measured with an instrument called a *polarimeter*, represented in **FIGURE 5.5**. A solution of optically active organic molecules is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the polarization plane occurs. The light then goes through a second polarizer, called the *analyzer*. By rotating the analyzer until the light passes through *it*, we can find the new plane of polarization and can tell to what extent rotation has occurred.

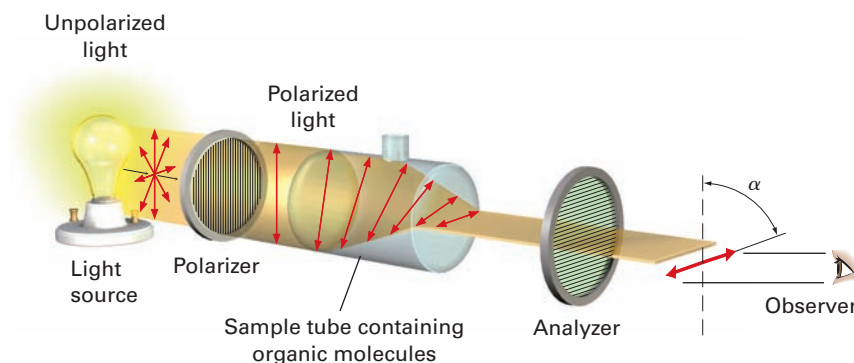


FIGURE 5.5 Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.

In addition to determining the extent of rotation, we can also find the direction. From the vantage point of the observer looking directly at the analyzer, some optically active molecules rotate polarized light to the left (counterclockwise) and are said to be **levorotatory**, whereas others rotate polarized light to the right (clockwise) and are said to be **dextrorotatory**. By convention, rotation to the left is given a minus sign ($-$) and rotation to the right is given a plus sign ($+$). ($-$)-Morphine, for instance, is levorotatory, and ($+$)-sucrose is dextrorotatory.

The extent of rotation observed in a polarimetry experiment depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample pathlength. If the concentration of sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation doubles. It also happens that the angle of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The **specific rotation**, $[\alpha]_D$,

of a compound is defined as the observed rotation when light of 589.6 nanometer (nm; 1 nm = 10^{-9} m) wavelength is used with a sample pathlength l of 1 decimeter (dm; 1 dm = 10 cm) and a sample concentration c of 1 g/cm³. (Light of 589.6 nm, the so-called sodium D line, is the yellow light emitted from common sodium street lamps.)

$$[\alpha]_{\text{D}} = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

When optical rotation data are expressed in this standard way, the specific rotation, $[\alpha]_{\text{D}}$, is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has $[\alpha]_{\text{D}} = +3.82$, and (–)-lactic acid has $[\alpha]_{\text{D}} = -3.82$. That is, the two enantiomers rotate plane-polarized light to the same extent but in opposite directions. Note that the units of specific rotation are [(deg · cm²)/g] but that values are usually expressed without the units. Some additional examples are listed in TABLE 5.1.

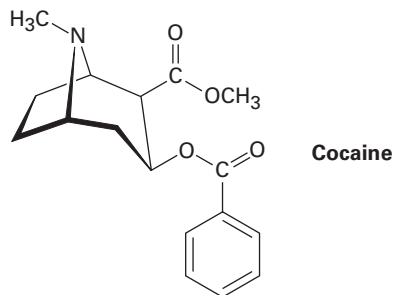
TABLE 5.1 Specific Rotation of Some Organic Molecules

Compound	$[\alpha]_{\text{D}}$	Compound	$[\alpha]_{\text{D}}$
Penicillin V	+233	Cholesterol	–31.5
Sucrose	+66.47	Morphine	–132
Camphor	+44.26	Cocaine	–16
Chloroform	0	Acetic acid	0

WORKED EXAMPLE 5.2

Calculating an Optical Rotation

A 1.20 g sample of cocaine, $[\alpha]_{\text{D}} = -16$, was dissolved in 7.50 mL of chloroform and placed in a sample tube having a pathlength of 5.00 cm. What was the observed rotation?



Strategy

Since $[\alpha]_{\text{D}} = \frac{\alpha}{l \times c}$

then $\alpha = l \times c \times [\alpha]_{\text{D}}$

where $[\alpha]_{\text{D}} = -16$, $l = 5.00 \text{ cm} = 0.500 \text{ dm}$, and $c = 1.20 \text{ g}/7.50 \text{ cm}^3 = 0.160 \text{ g/cm}^3$.

Solution

$$\alpha = (-16) (0.500) (0.160) = -1.3^\circ$$

PROBLEM 5.5

Is cocaine (Worked Example 5.2) dextrorotatory or levorotatory?

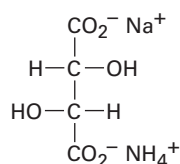
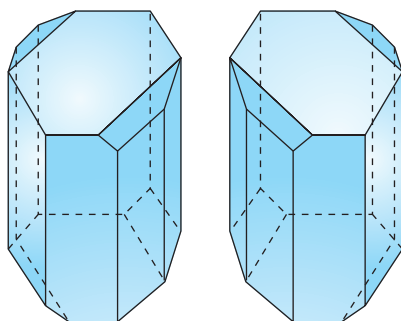
PROBLEM 5.6

A 1.50 g sample of coniine, the toxic extract of poison hemlock, was dissolved in 10.0 mL of ethanol and placed in a sample cell with a 5.00 cm path-length. The observed rotation at the sodium D line was $+1.21^\circ$. Calculate $[\alpha]_D$ for coniine.

5-4 Pasteur's Discovery of Enantiomers

Little was done after Biot's discovery of optical activity until 1848, when Louis Pasteur began work on a study of crystalline tartaric acid salts derived from wine. On crystallizing a concentrated solution of sodium ammonium tartrate below 28°C , Pasteur made the surprising observation that two distinct kinds of crystals precipitated. Furthermore, the two kinds of crystals were nonsuperimposable mirror images and were related in the same way that a right hand is related to a left hand.

Working carefully with tweezers, Pasteur was able to separate the crystals into two piles, one of "right-handed" crystals and one of "left-handed" crystals, like those shown in **FIGURE 5.6**. Although the original sample, a 50:50 mixture of right and left, was optically inactive, solutions of the crystals from each of the sorted piles were optically active and their specific rotations were equal in amount but opposite in sign.



Sodium ammonium tartrate

FIGURE 5.6 Drawings of sodium ammonium tartrate crystals taken from Pasteur's original sketches. One of the crystals is dextrorotatory in solution, and the other is levorotatory.

Pasteur was far ahead of his time. Although the structural theory of Kekulé had not yet been proposed, Pasteur explained his results by speaking of the molecules themselves, saying, "There is no doubt that [in the *dextro* tartaric acid] there exists an asymmetric arrangement having a nonsuperimposable image. It is no less certain that the atoms of the *levo* acid possess precisely the inverse asymmetric arrangement." Pasteur's vision was extraordinary, for it was not until 25 years later that his ideas regarding the asymmetric carbon atom were confirmed.

Today, we would describe Pasteur's work by saying that he had discovered enantiomers. Enantiomers, also called *optical isomers*, have identical physical properties, such as melting point and boiling point, but differ in the direction in which their solutions rotate plane-polarized light.

5-5 Sequence Rules for Specifying Configuration

Structural drawings provide a visual representation of stereochemistry, but a written method for indicating the three-dimensional arrangement, or **configuration**, of substituents at a chirality center is also needed. The method used employs a set of *sequence rules* to rank the four groups attached to the chirality center and then looks at the handedness with which those groups are attached. Called the **Cahn–Ingold–Prelog rules** after the chemists who proposed them, the sequence rules are as follows:

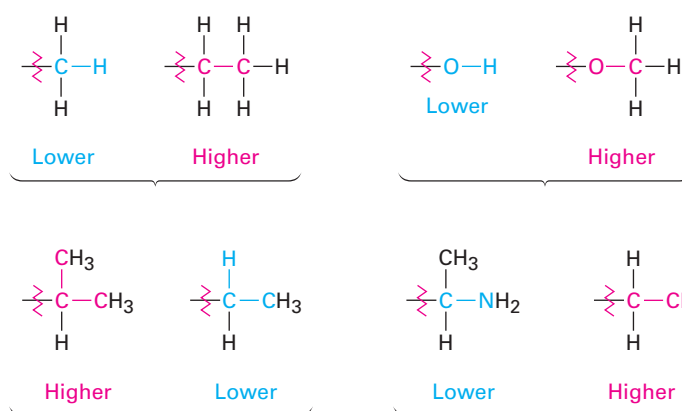
Rule 1

Look at the four atoms directly attached to the chirality center, and rank them according to atomic number. The atom with the highest atomic number has the highest ranking (first), and the atom with the lowest atomic number (usually hydrogen) has the lowest ranking (fourth). When different isotopes of the same element are compared, such as deuterium (^2H) and protium (^1H), the heavier isotope ranks higher than the lighter isotope. Thus, atoms commonly found in organic compounds have the following order.



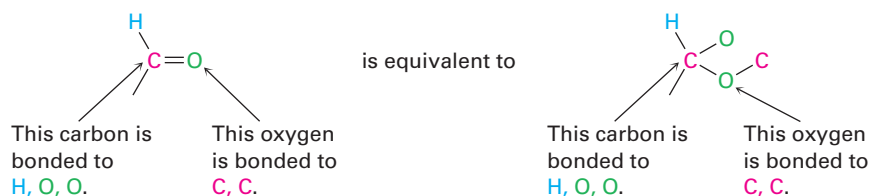
Rule 2

If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found. A $-\text{CH}_2\text{CH}_3$ substituent and a $-\text{CH}_3$ substituent are equivalent by rule 1 because both have carbon as the first atom. By rule 2, however, ethyl ranks higher than methyl because ethyl has a *carbon* as its highest second atom, while methyl has only *hydrogen* as its second atom. Look at the following pairs of examples to see how the rule works:

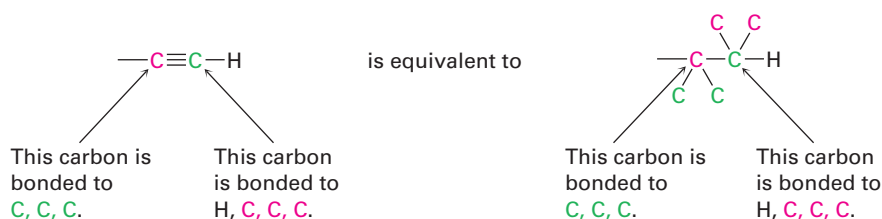
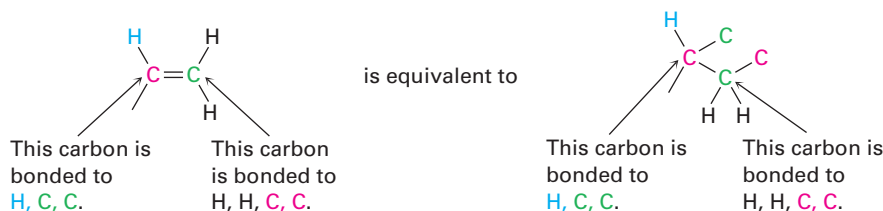


Rule 3

Multiple-bonded atoms are equivalent to the same number of single-bonded atoms. For example, an aldehyde substituent ($-\text{CH}=\text{O}$), which has a carbon atom *doubly* bonded to *one* oxygen, is equivalent to a substituent having a carbon atom *singly* bonded to *two* oxygens:



As further examples, the following pairs are equivalent:



Having ranked the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) points directly back, away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel (**FIGURE 5.7**). If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent ($1 \rightarrow 2 \rightarrow 3$) is clockwise, we say that the chirality center has the **R configuration** (Latin *rectus*, meaning “right”). If an arrow from $1 \rightarrow 2 \rightarrow 3$ is counterclockwise, the chirality center has the **S configuration** (Latin *sinister*, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a *Right* (clockwise) turn.

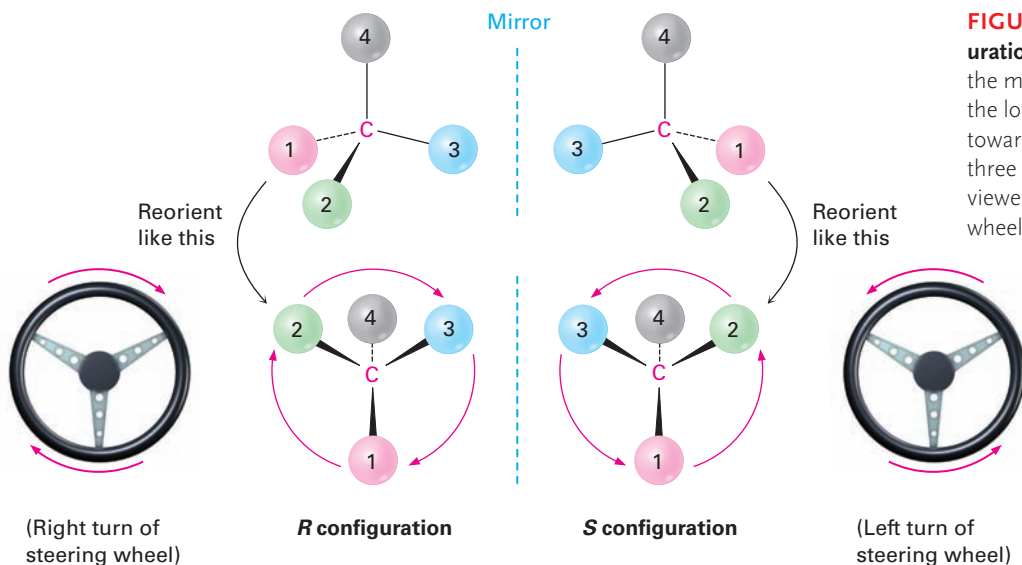
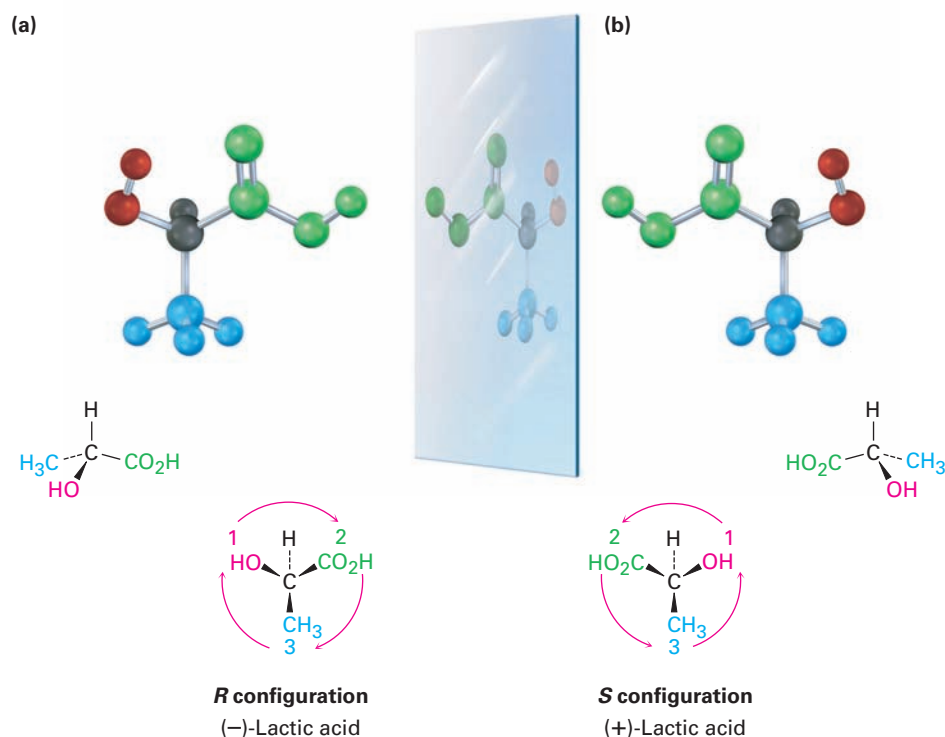


FIGURE 5.7 Assigning configuration to a chirality center. When the molecule is oriented so that the lowest-ranked group (4) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel $1 \rightarrow 2 \rightarrow 3$ is clockwise (right turn), the center has the **R configuration**. If the direction of travel $1 \rightarrow 2 \rightarrow 3$ is counterclockwise (left turn), the center is **S**.

Look at (–)-lactic acid in **FIGURE 5.8** for an example of how to assign configuration. Sequence rule 1 says that –OH is ranked 1 and –H is ranked 4, but it doesn't allow us to distinguish between –CH₃ and –CO₂H because both groups have carbon as their first atom. Sequence rule 2, however, says that –CO₂H ranks higher than –CH₃ because O (the highest second atom in –CO₂H) outranks H (the highest second atom in –CH₃). Now, turn the molecule so that the fourth-ranked group (–H) is oriented toward the rear, away from the observer. Since a curved arrow from 1 (–OH) to 2 (–CO₂H) to 3 (–CH₃) is clockwise (right turn of the steering wheel), (–)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.

FIGURE 5.8 Assigning configuration to (a) (*R*)-(–)-lactic acid and (b) (*S*)-(+)-lactic acid.



Further examples are provided by naturally occurring (–)-glyceraldehyde and (+)-alanine, which both have an *S* configuration as shown in **FIGURE 5.9**. Note that the sign of optical rotation, (+) or (–), is not related to the *R,S* designation. (*S*)-Glyceraldehyde happens to be levorotatory (–), and (*S*)-alanine happens to be dextrorotatory (+). There is no simple correlation between *R,S* configuration and direction or magnitude of optical rotation.

One additional point needs to be mentioned: the matter of **absolute configuration**. How do we know that the assignments of *R* and *S* configuration are correct in an *absolute*, rather than a relative, sense? Since we can't see the molecules themselves, how do we know that the *R* configuration belongs to the levorotatory enantiomer of lactic acid? This difficult question was solved in 1951, when an X-ray diffraction method for determining the absolute spatial arrangement of atoms in a molecule was found. Based on those results, we can say with certainty that the *R,S* conventions are correct.

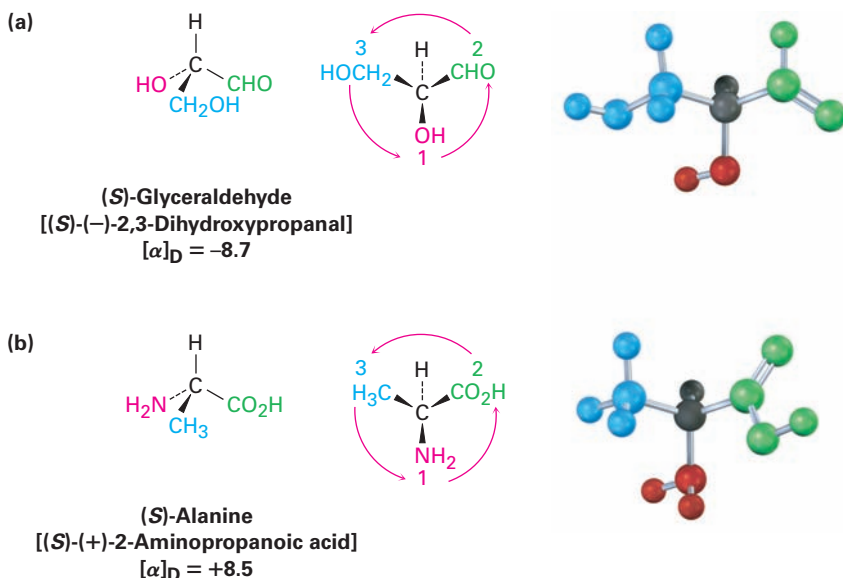
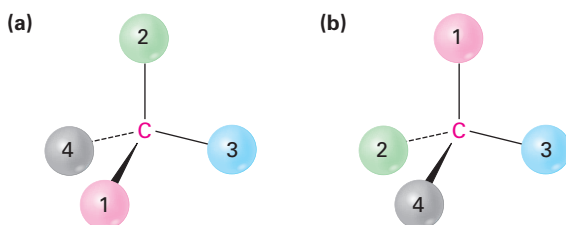


FIGURE 5.9 Assigning configuration to (a) (-)-glyceraldehyde and (b) (+)-alanine. Both happen to have the *S* configuration, although one is levorotatory and the other is dextrorotatory.

Assigning Configuration to a Chirality Center

WORKED EXAMPLE 5.3

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

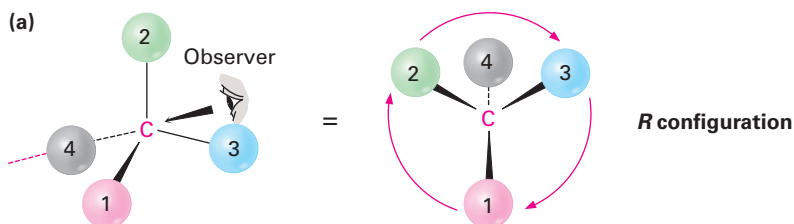


Strategy

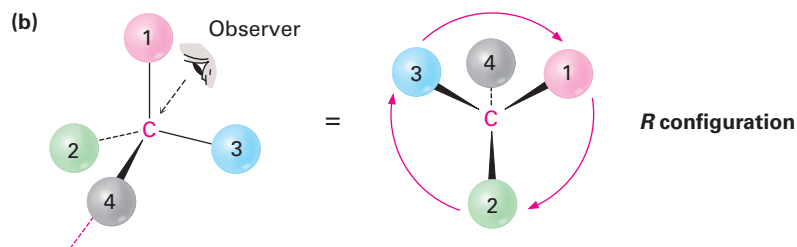
It takes practice to be able to visualize and orient a chirality center in three dimensions. You might start by indicating where the observer must be located— 180° opposite the lowest-ranked group. Then imagine yourself in the position of the observer, and redraw what you would see.

Solution

In (a), you would be located in front of the page toward the top right of the molecule, and you would see group 2 to your left, group 3 to your right, and group 1 below you. This corresponds to an *R* configuration.



In (b), you would be located behind the page toward the top left of the molecule from your point of view, and you would see group 3 to your left, group 1 to your right, and group 2 below you. This also corresponds to an *R* configuration.



WORKED EXAMPLE 5.4

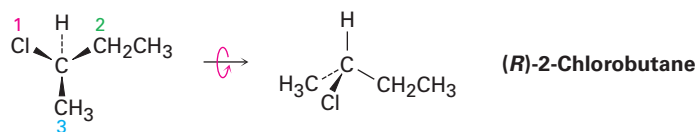
Drawing the Three-Dimensional Structure of an Enantiomer

Draw a tetrahedral representation of (*R*)-2-chlorobutane.

Strategy

Begin by ranking the four substituents bonded to the chirality center: (1) –Cl, (2) –CH₂CH₃, (3) –CH₃, (4) –H. To draw a tetrahedral representation of the molecule, orient the lowest-ranked group (–H) away from you and imagine that the other three groups are coming out of the page toward you. Then place the remaining three substituents such that the direction of travel 1 → 2 → 3 is clockwise (right turn), and tilt the molecule toward you to bring the rear hydrogen into view. Using molecular models is a great help in working problems of this sort.

Solution



PROBLEM 5.7

Which member in each of the following sets ranks higher?

- (a) –H or –Br (b) –Cl or –Br (c) –CH₃ or –CH₂CH₃
 (d) –NH₂ or –OH (e) –CH₂OH or –CH₃ (f) –CH₂OH or –CH=O

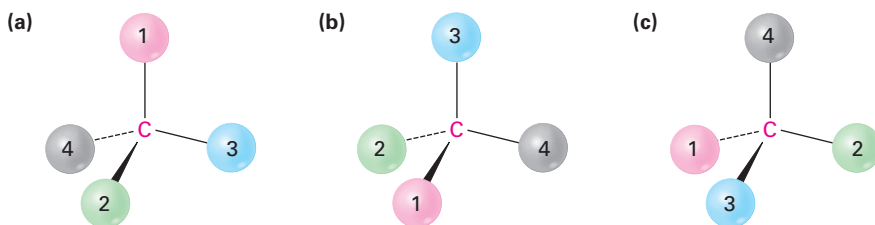
PROBLEM 5.8

Rank the substituents in each of the following sets according to the Cahn–Ingold–Prelog rules:

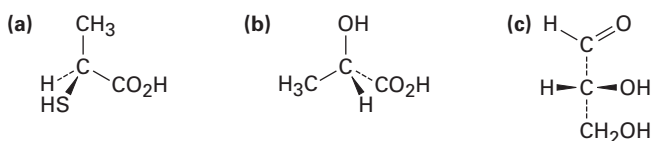
- (a) –H, –OH, –CH₂CH₃, –CH₂CH₂OH
 (b) –CO₂H, –CO₂CH₃, –CH₂OH, –OH
 (c) –CN, –CH₂NH₂, –CH₂NHCH₃, –NH₂
 (d) –SH, –CH₂SCH₃, –CH₃, –SSCH₃

PROBLEM 5.9

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

**PROBLEM 5.10**

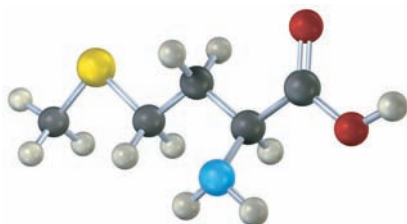
Assign *R* or *S* configuration to the chirality center in each of the following molecules:

**PROBLEM 5.11**

Draw a tetrahedral representation of (*S*)-pentan-2-ol (2-hydroxypentane).

PROBLEM 5.12

Assign *R* or *S* configuration to the chirality center in the following molecular model of the amino acid methionine (blue = N, yellow = S):



5-6 Diastereomers

Molecules like lactic acid, alanine, and glyceraldehyde are relatively simple because each has only one chirality center and only two stereoisomers. The situation becomes more complex, however, with molecules that have more than one chirality center. As a general rule, a molecule with n chirality centers can have up to 2^n stereoisomers (although it may have fewer, as we'll see shortly). Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for example. Since threonine has two chirality centers (C2 and C3), there are

four possible stereoisomers, as shown in **FIGURE 5.10**. Check for yourself that the *R,S* configurations are correct.

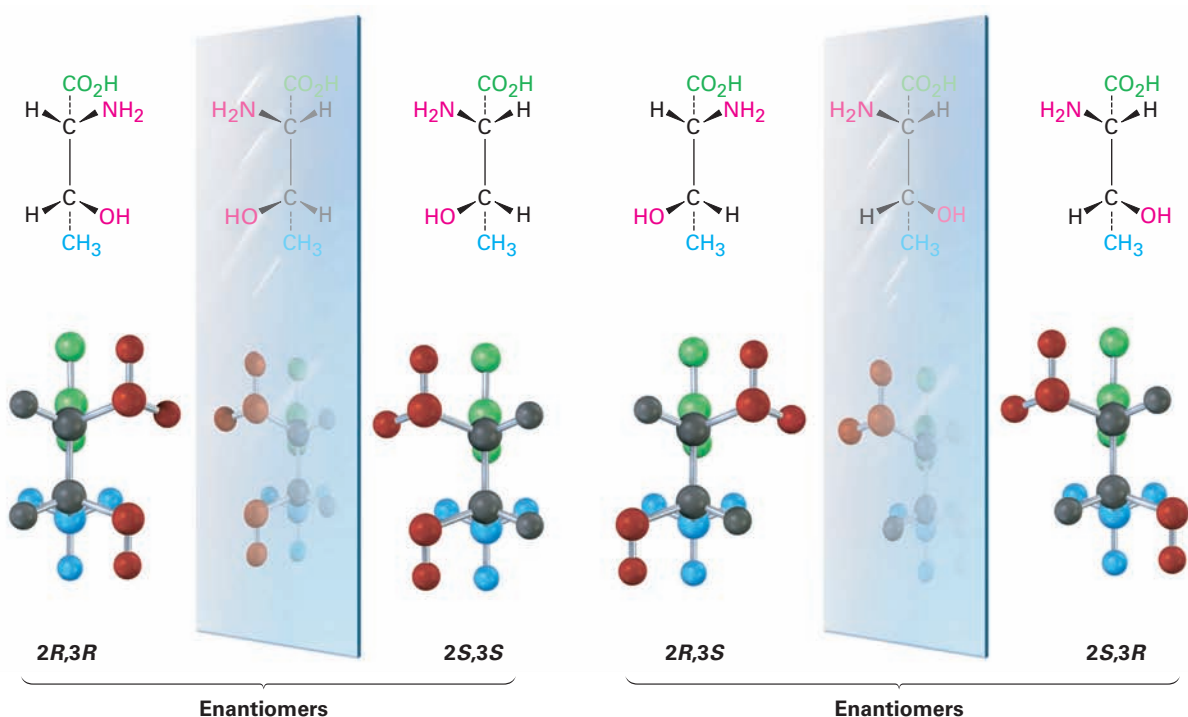


FIGURE 5.10 The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

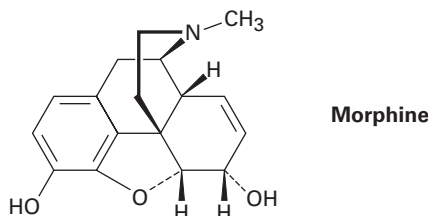
The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The *2R,3R* stereoisomer is the mirror image of *2S,3S*, and the *2R,3S* stereoisomer is the mirror image of *2S,3R*. But what is the relationship between any two stereoisomers that are not mirror images? What, for instance, is the relationship between the *2R,3R* isomer and the *2R,3S* isomer? They are stereoisomers, yet they aren't enantiomers. To describe such a relationship, we need a new term—*diastereomer*.

Diastereomers are stereoisomers that are not mirror images. Since we used the right hand/left hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and your friend's hand look *similar*, but they aren't identical and they aren't mirror images. The same is true of diastereomers: they're similar, but they aren't identical and they aren't mirror images.

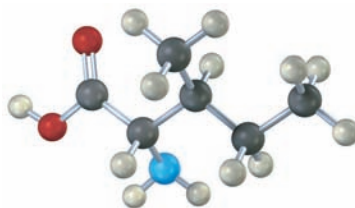
Note carefully the difference between enantiomers and diastereomers: enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. A full description of the four stereoisomers of threonine is given in **TABLE 5.2**. Of the four, only the *2S,3R* isomer, $[\alpha]_D = -28.3$, occurs naturally in plants and animals and is an essential human nutrient. This result is typical: most biological molecules are chiral, and usually only one stereoisomer is found in nature.

PROBLEM 5.14

How many chirality centers does morphine have? How many stereoisomers of morphine are possible in principle?

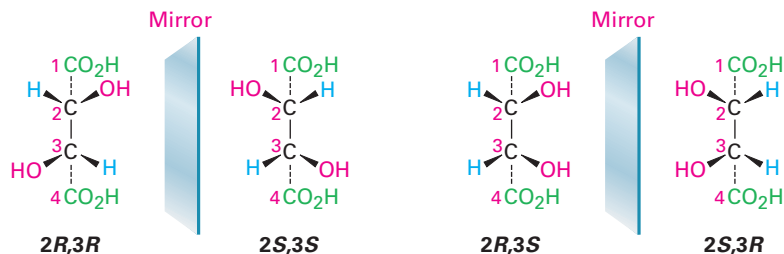
**PROBLEM 5.15**

Assign *R,S* configuration to each chirality center in the following molecular model of the amino acid isoleucine:

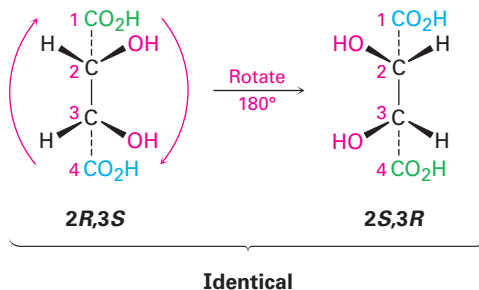


5-7 Meso Compounds

Let's look at another example of a compound with more than one chirality center: the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The *2R,3R* and *2S,3S* structures are nonsuperimposable mirror images and therefore represent a pair of enantiomers. A close look at the *2R,3S* and *2S,3R* structures, however, shows that they *are* superimposable, and thus identical, as can be seen by rotating one structure 180°.



The $2R,3S$ and $2S,3R$ structures are identical because the molecule has a plane of symmetry and is therefore achiral. The symmetry plane cuts through the C2–C3 bond, making one half of the molecule a mirror image of the other half (FIGURE 5.11). Because of the plane of symmetry, the molecule is achiral despite the fact that it has two chirality centers. Compounds that are achiral, yet contain chirality centers, are called **meso compounds** (*me-zo*). Thus, tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

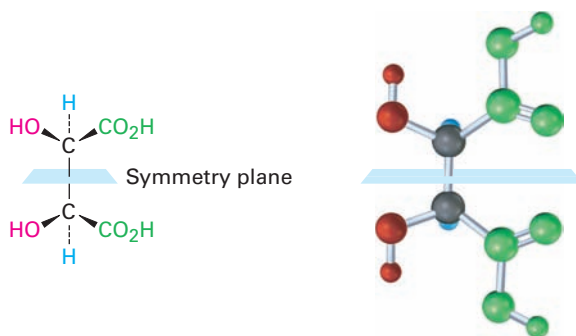


FIGURE 5.11 Symmetry of *meso*-tartaric acid. A symmetry plane through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral.

Some physical properties of the three stereoisomers are listed in TABLE 5.3. The (+)- and (–)-tartaric acids have identical melting points, solubilities, and densities, but they differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (–) forms. It has no mirror-image relationship to (+)- and (–)-tartaric acids, is a different compound altogether, and has different physical properties.

TABLE 5.3 Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm ³)	Solubility at 20 °C (g/100 mL H ₂ O)
(+)	168–170	+12	1.7598	139.0
(–)	168–170	–12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

Distinguishing Chiral Compounds from Meso Compounds

WORKED EXAMPLE 5.5

Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

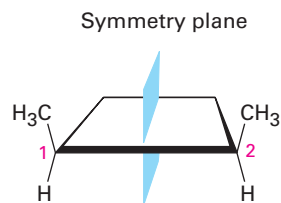
Strategy

To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for the presence or absence of a symmetry plane. Not all molecules with chirality centers are chiral overall—meso compounds are an exception.

Solution

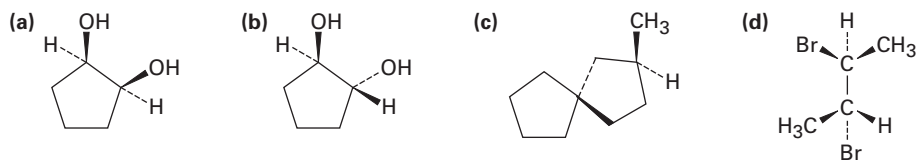
A look at the structure of *cis*-1,2-dimethylcyclobutane shows that both methyl-bearing ring carbons (C1 and C2) are chirality centers. Overall, though, the

compound is achiral because there is a symmetry plane bisecting the ring between C1 and C2. Thus, *cis*-1,2-dimethylcyclobutane is a meso compound.



PROBLEM 5.16

Which of the following structures represent meso compounds?



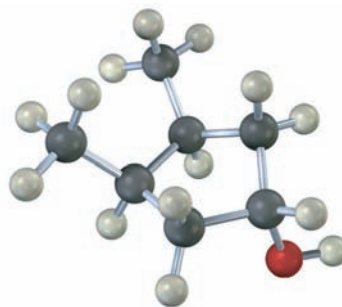
PROBLEM 5.17

Which of the following have a meso form? (Recall that the *-ol* suffix refers to an alcohol, ROH.)

(a) Butane-2,3-diol (b) Pentane-2,3-diol (c) Pentane-2,4-diol

PROBLEM 5.18

Does the following structure represent a meso compound? If so, indicate the symmetry plane.



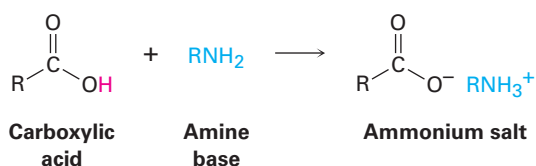
5-8 Racemic Mixtures and the Resolution of Enantiomers

To end this discussion of stereoisomerism, let's return for a last look at Pasteur's pioneering work, described in Section 5-4. Pasteur took an optically inactive tartaric acid salt and found that he could crystallize from it two optically active forms having what we would now call the *2R,3R* and

2*S*,3*S* configurations. But what was the optically inactive form he started with? It couldn't have been *meso*-tartaric acid, because *meso*-tartaric acid is a different chemical compound and can't interconvert with the two chiral enantiomers without breaking and re-forming chemical bonds.

The answer is that Pasteur started with a 50:50 *mixture* of the two chiral tartaric acid enantiomers. Such a mixture is called a **racemate** (**ra**-suh-mate), or *racemic mixture*, and is denoted by either the symbol (\pm) or the prefix *d,l* to indicate an equal mixture of dextrorotatory and levorotatory forms. Racemates show no optical rotation because the (+) rotation from one enantiomer exactly cancels the (–) rotation from the other. Through luck, Pasteur was able to separate, or **resolve**, racemic tartaric acid into its (+) and (–) enantiomers. Unfortunately, the fractional crystallization technique he used doesn't work for most racemates, so other methods are needed.

The most common method of resolution uses an acid–base reaction between the racemate of a chiral carboxylic acid (RCO₂H) and an amine base (RNH₂) to yield an ammonium salt:



To understand how this method of resolution works, let's see what happens when a racemic mixture of chiral acids, such as (+)- and (–)-lactic acids, reacts with an achiral amine base, such as methylamine, CH₃NH₂. Stereochemically, the situation is analogous to what happens when left and right hands (chiral) pick up a ball (achiral). Both left and right hands pick up the ball equally well, and the products—ball in right hand versus ball in left hand—are mirror images. In the same way, both (+)- and (–)-lactic acid react with methylamine equally well, and the product is a racemic mixture of the two enantiomers methylammonium (+)-lactate and methylammonium (–)-lactate (**FIGURE 5.12**).

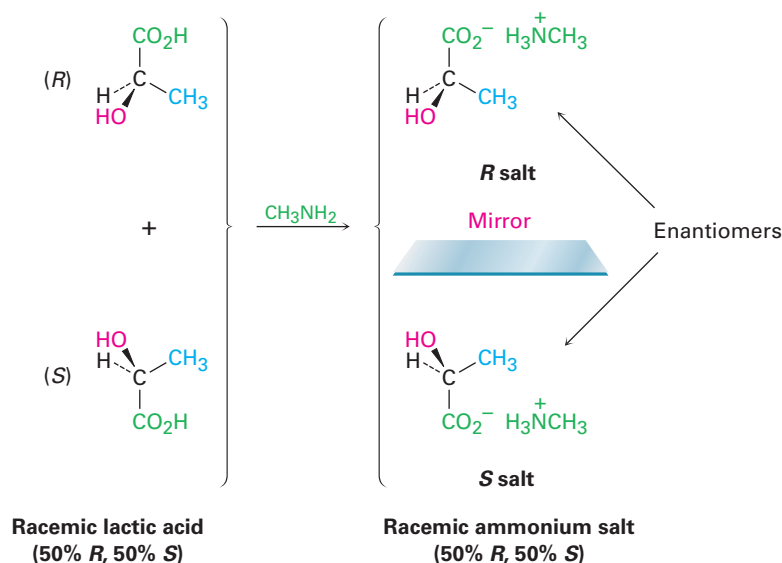


FIGURE 5.12 Reaction of racemic lactic acid with achiral methylamine. The reaction leads to a racemic mixture of ammonium salts.

Now let's see what happens when the racemic mixture of (+)- and (–)-lactic acids reacts with a single enantiomer of a chiral amine base, such as (*R*)-1-phenylethylamine. Stereochemically, the situation is analogous to what happens when left and right hands (chiral) put on a right-handed glove (*also chiral*). Left and right hands don't put on the right-handed glove in the same way, so the products—right hand in right glove versus left hand in right glove—are not mirror images; they're similar but different.

In the same way, (+)- and (–)-lactic acids react with (*R*)-1-phenylethylamine to give two different products (FIGURE 5.13). (*R*)-Lactic acid reacts with (*R*)-1-phenylethylamine to give the *R,R* salt, and (*S*)-lactic acid reacts with the *R* amine to give the *S,R* salt. *The two salts are diastereomers*. They have different chemical and physical properties, and it may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with a strong acid then allows us to isolate the two pure enantiomers of lactic acid and to recover the chiral amine for reuse.

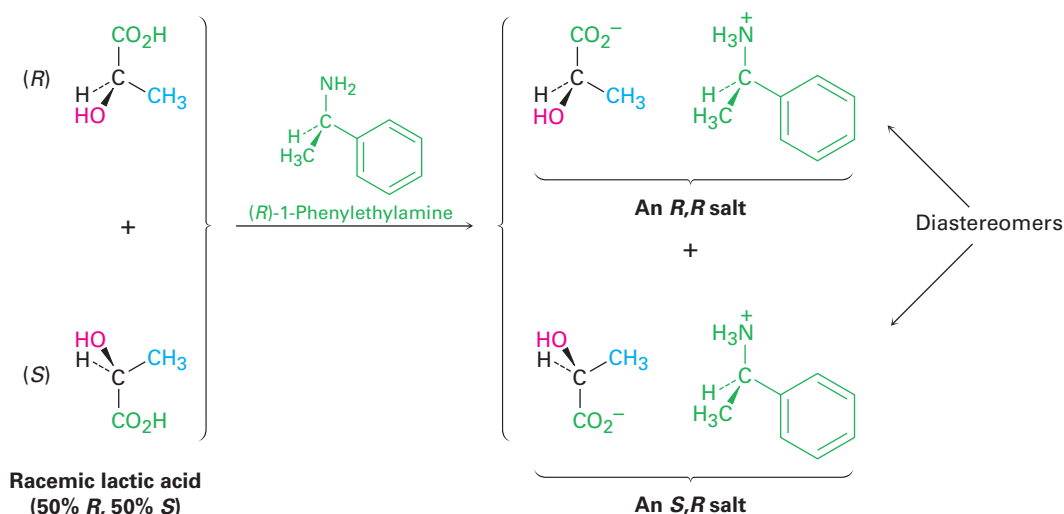
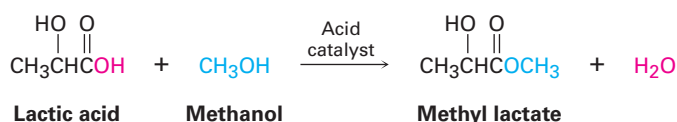


FIGURE 5.13 Reaction of racemic lactic acid with (*R*)-1-phenylethylamine. The reaction yields a mixture of diastereomeric ammonium salts, which have different properties and can be separated.

WORKED EXAMPLE 5.6

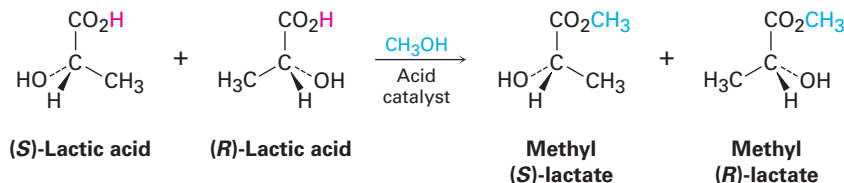
Predicting the Chirality of a Reaction Product

We'll see in Section 16-3 that carboxylic acids (RCO₂H) react with alcohols (R'OH) to form esters (RCO₂R'). Suppose that (±)-lactic acid reacts with CH₃OH to form the ester, methyl lactate. What stereochemistry would you expect the product(s) to have? What is the relationship of the products?

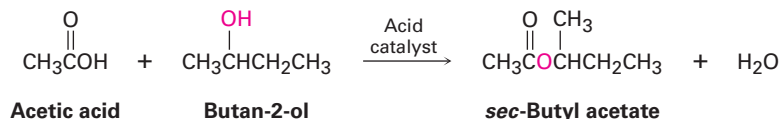


Solution

Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products:

**PROBLEM 5.19**

Suppose that acetic acid ($\text{CH}_3\text{CO}_2\text{H}$) reacts with (*S*)-butan-2-ol to form an ester (see Worked Example 5.6). What stereochemistry would you expect the product(s) to have, assuming that the singly bonded oxygen atom comes from the alcohol rather than the acid? What is the relationship of the products?

**PROBLEM 5.20**

What stereoisomers would result from reaction of (\pm)-lactic acid with (*S*)-1-phenylethylamine, and what is the relationship between them?

5-9 A Review of Isomerism

As noted on several previous occasions, isomers are compounds with the same chemical formula but different structures. We've seen several kinds of isomers in the past few chapters, and it's a good idea at this point to see how they relate to one another (FIGURE 5.14).

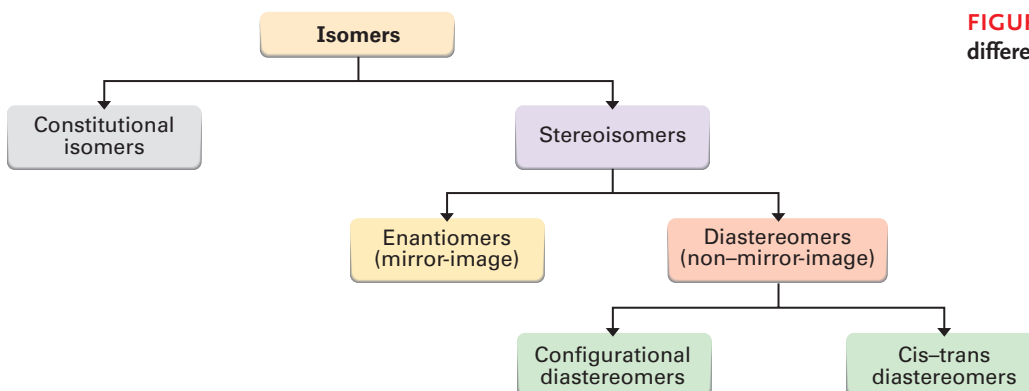
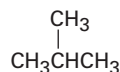


FIGURE 5.14 Summary of the different kinds of isomers.

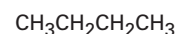
There are two fundamental types of isomers, both of which we've now encountered: constitutional isomers and stereoisomers.

- **Constitutional isomers** (Section 3-2) are compounds whose atoms are connected differently. Among the kinds of constitutional isomers we've seen are skeletal, functional, and positional isomers.

Different carbon skeletons



and



2-Methylpropane

Butane

Different functional groups



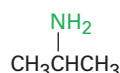
and



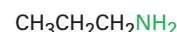
Ethyl alcohol

Dimethyl ether

Different position of functional groups



and



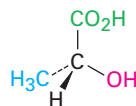
Isopropylamine

Propylamine

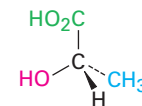
- **Stereoisomers** (Section 4-2) are compounds whose atoms are connected in the same order but with a different spatial arrangement. Among the kinds of stereoisomers we've seen are enantiomers, diastereomers, and cis–trans isomers of cycloalkanes. Actually, cis–trans isomers are just a subclass of diastereomers because they are non–mirror-image stereoisomers:

Enantiomers

(nonsuperimposable mirror-image stereoisomers)



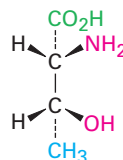
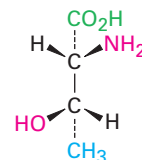
(R)-Lactic acid



(S)-Lactic acid

Diastereomers

(nonsuperimposable non–mirror-image stereoisomers)

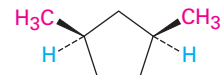
(2*R*,3*R*)-2-Amino-3-hydroxybutanoic acid(2*R*,3*S*)-2-Amino-3-hydroxybutanoic acid

Configurational diastereomers

Cis–trans diastereomers (substituents on same side or opposite side of double bond or ring)

*trans*-1,3-Dimethylcyclopentane

and

*cis*-1,3-Dimethylcyclopentane

PROBLEM 5.21

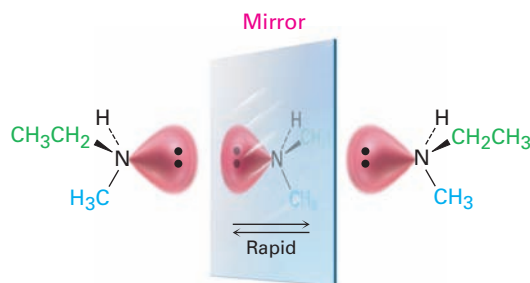
What kinds of isomers are the following pairs?

- (a) (S)-5-Chlorohex-2-ene [$\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}(\text{Cl})\text{CH}_3$] and chlorocyclohexane
 (b) (2*R*,3*R*)-2,3-Dibromopentane and (2*S*,3*R*)-2,3-dibromopentane

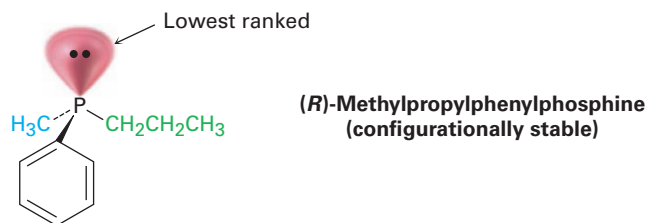
5-10 Chirality at Nitrogen, Phosphorus, and Sulfur

Although the most common cause of chirality is the presence of four different substituents bonded to a tetrahedral atom, that atom doesn't necessarily have to be carbon. Nitrogen, phosphorus, and sulfur are all commonly encountered in organic molecules, and all can be chirality centers. We know, for instance, that trivalent nitrogen is tetrahedral, with its lone pair of electrons acting as the fourth "substituent" (Section 1-10). Is trivalent nitrogen chiral? Does a compound such as ethylmethylamine exist as a pair of enantiomers?

The answer is both yes and no. Yes in principle, but no in practice. Most trivalent nitrogen compounds undergo a rapid umbrella-like inversion that interconverts enantiomers, so we can't isolate individual enantiomers except in special cases.

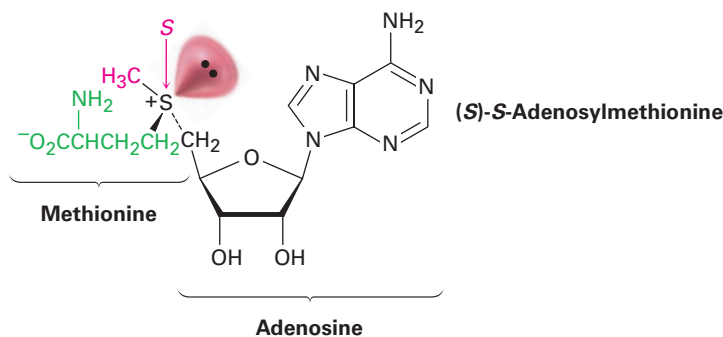


A similar situation occurs in trivalent phosphorus compounds, or *phosphines*. It turns out, though, that inversion at phosphorus is substantially slower than inversion at nitrogen, so stable chiral phosphines *can* be isolated. (*R*)- and (*S*)-methylpropylphenylphosphine, for example, are configurationally stable for several hours at 100 °C. We'll see the importance of phosphine chirality in Section 19-3 in connection with the synthesis of chiral amino acids.



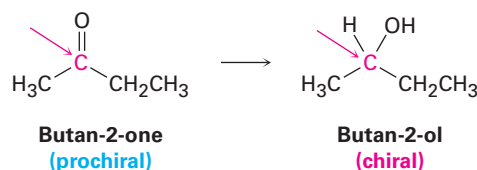
Divalent sulfur compounds are achiral, but trivalent sulfur compounds called *sulfonium ions* (R_3S^+) can be chiral. Like phosphines, sulfonium ions undergo relatively slow inversion, so chiral sulfonium ions are configurationally stable and can be isolated. Perhaps the best known example is the coenzyme *S*-adenosylmethionine, the so-called biological methyl donor, which is involved in many metabolic pathways as a source of CH_3 groups. (The "S" in the name *S*-adenosylmethionine stands for *sulfur* and means that the adenosyl group is attached to the sulfur atom of the amino acid methionine.) The molecule has *S* stereochemistry at sulfur and is configurationally stable for

several days at room temperature. Its *R* enantiomer is also known but is not biologically active.

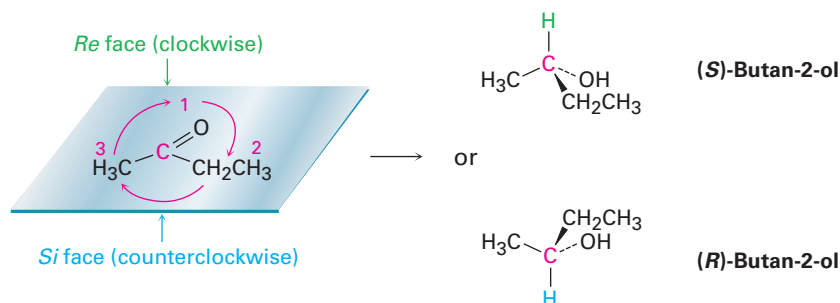


5-11 Prochirality

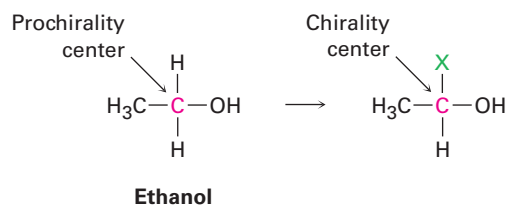
Closely related to the concept of chirality, and particularly important in biological chemistry, is the notion of *prochirality*. A molecule is said to be **prochiral** if it can be converted from achiral to chiral in a single chemical step. For instance, an unsymmetrical ketone like butan-2-one is prochiral because it can be converted to the chiral alcohol butan-2-ol by addition of hydrogen, as we'll see in Section 13-3.



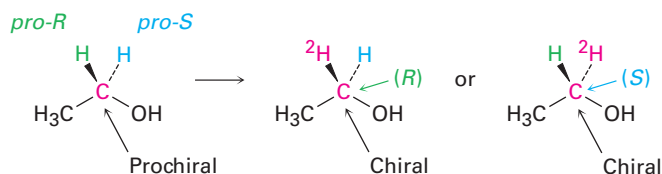
Which enantiomer of butan-2-ol is produced depends on which face of the planar carbonyl group undergoes reaction. To distinguish between the possibilities, we use the stereochemical descriptors *Re* and *Si*. Rank the three groups attached to the trigonal, sp^2 -hybridized carbon, and imagine curved arrows from the highest to second-highest to third-highest ranked substituents. The face on which the arrows curve clockwise is designated *Re* (similar to *R*), and the face on which the arrows curve counterclockwise is designated *Si* (similar to *S*). In this particular example, addition of hydrogen from the *Re* faces gives (*S*)-butan-2-ol, and addition from the *Si* face gives (*R*)-butan-2-ol.



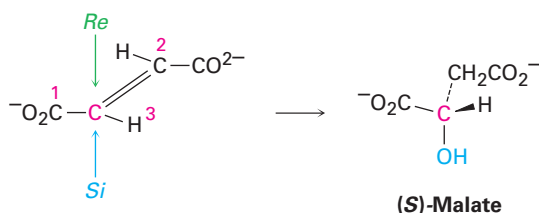
In addition to compounds with planar, sp^2 -hybridized atoms, compounds with tetrahedral, sp^3 -hybridized atoms can also be prochiral. An sp^3 -hybridized atom is said to be a **prochirality center** if, by changing one of its attached groups, it becomes a chirality center. The $-CH_2OH$ carbon atom of ethanol, for instance, is a prochirality center because changing one of its attached $-H$ atoms converts it into a chirality center.



To distinguish between the two identical atoms (or groups of atoms) on a prochirality center, we imagine a change that will raise the ranking of one atom over the other without affecting its rank with respect to other attached groups. On the $-CH_2OH$ carbon of ethanol, for instance, we might imagine replacing one of the 1H atoms (protium) by 2H (deuterium). The newly introduced 2H atom ranks higher than the remaining 1H atom, but it remains lower than other groups attached to the carbon. Of the two identical atoms in the original compound, that atom whose replacement leads to an *R* chirality center is said to be **pro-*R*** and that atom whose replacement leads to an *S* chirality center is said to be **pro-*S***.

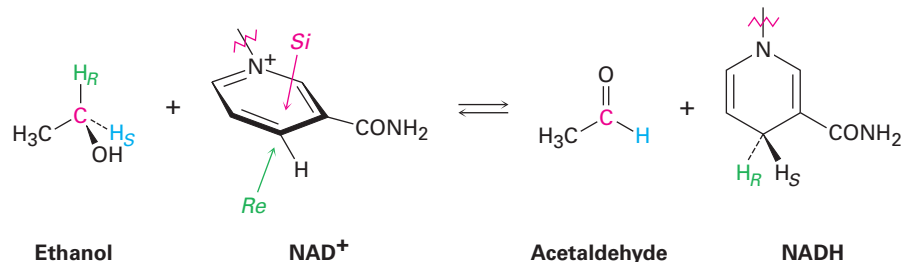


A large number of biological reactions involve prochiral compounds. One of the steps in the citric acid cycle by which food is metabolized, for instance, is the addition of H_2O to fumarate to give malate. Addition of $-OH$ occurs on the *Si* face of a fumarate carbon and gives (*S*)-malate as product.

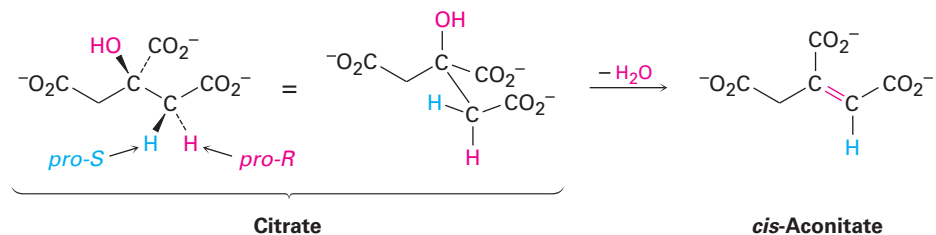


As another example, studies with deuterium-labeled substrates have shown that the reaction of ethanol with the coenzyme nicotinamide adenine dinucleotide (NAD^+) catalyzed by yeast alcohol dehydrogenase occurs with

exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of NAD^+ .

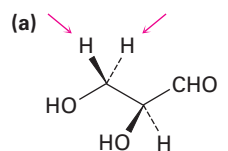


Determining the stereochemistry of reactions at prochirality centers is a powerful method for studying detailed mechanisms in biochemical reactions. As just one example, the conversion of citrate to *cis*-aconitate in the citric acid cycle has been shown to occur with loss of a *pro-R* hydrogen, implying that the OH and H groups leave from opposite sides of the molecule.

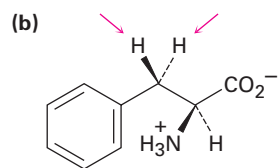


PROBLEM 5.22

Identify the indicated hydrogens in the following molecules as *pro-R* or *pro-S*:



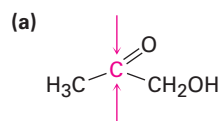
(S)-Glyceraldehyde



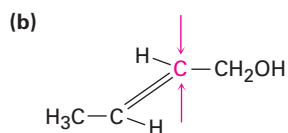
Phenylalanine

PROBLEM 5.23

Identify the indicated faces in the following molecules as *Re* or *Si*:



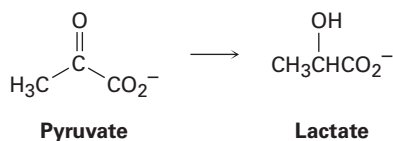
Hydroxyacetone



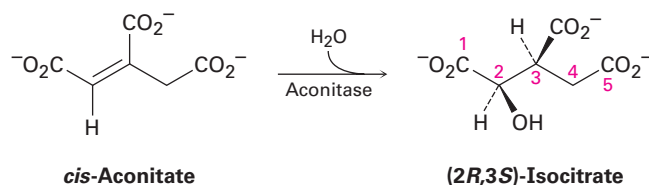
Crotyl alcohol

PROBLEM 5.24

The lactic acid that builds up in tired muscles is formed from pyruvate. If the reaction occurs with addition of hydrogen to the *Re* face of pyruvate, what is the stereochemistry of the product?

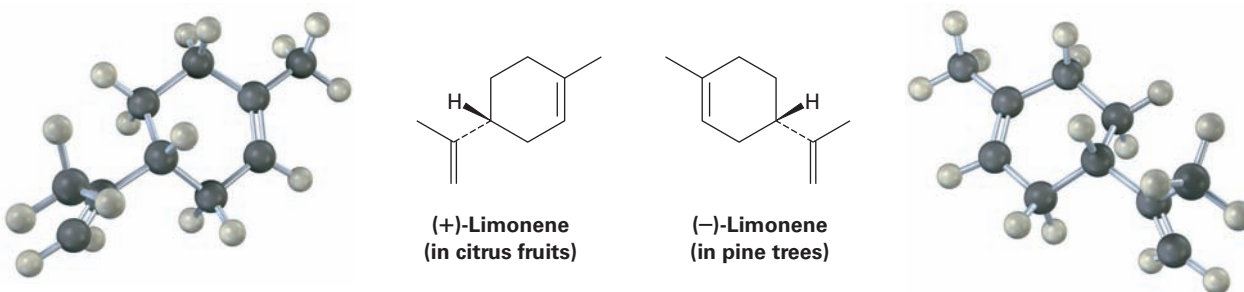
**PROBLEM 5.25**

The aconitase-catalyzed addition of water to *cis*-aconitate in the citric acid cycle occurs with the following stereochemistry. Does the addition of the OH group occur on the *Re* or the *Si* face of the substrate? What about the addition of the H? Do the H and OH groups add from the same side of the double bond or from opposite sides?



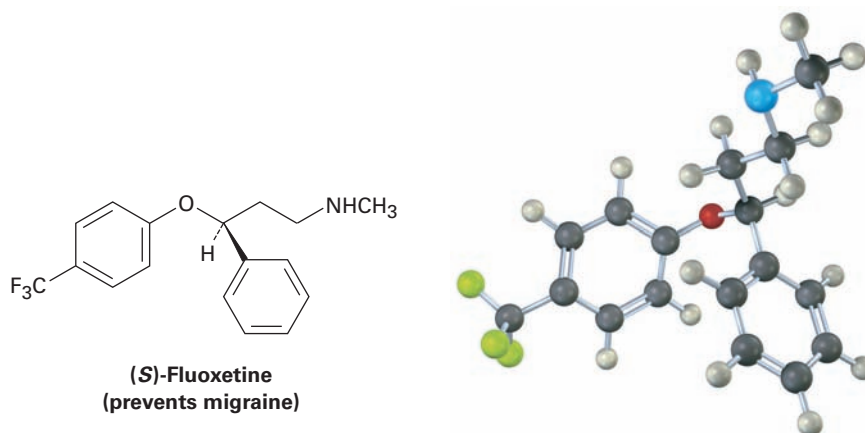
5-12 Chirality in Nature and Chiral Environments

Although the different enantiomers of a chiral molecule have the same physical properties, they usually have different biological properties. For example, the (+) enantiomer of limonene has the odor of oranges and lemons, but the (–) enantiomer has the odor of pine trees.



More dramatic examples of how a change in chirality can affect the biological properties of a molecule are found in many drugs, such as fluoxetine, a heavily prescribed medication sold under the trade name Prozac. Racemic

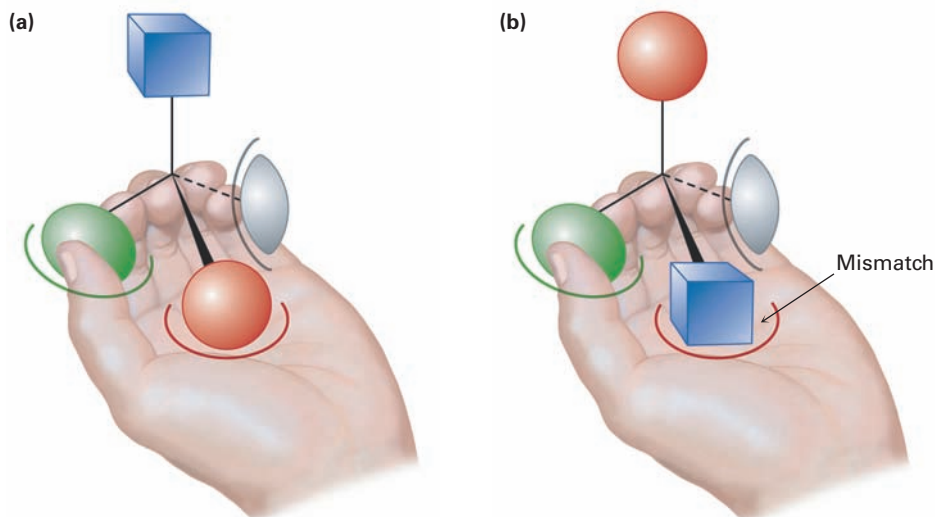
fluoxetine is an extraordinarily effective antidepressant but has no activity against migraine. The pure *S* enantiomer, however, works remarkably well in preventing migraine. Other examples of how chirality affects biological properties are given in the *Something Extra* at the end of this chapter.



Why do different enantiomers have different biological properties? To have a biological effect, a substance typically must fit into an appropriate receptor that has an exactly complementary shape. But because biological receptors are chiral, only one enantiomer of a chiral substrate can fit in, just as only a right hand can fit into a right-handed glove. The mirror-image enantiomer will be a misfit, like a left hand in a right-handed glove. A representation of the interaction between a chiral molecule and a chiral biological receptor is shown in **FIGURE 5.15**. One enantiomer fits the receptor perfectly, but the other does not.

FIGURE 5.15 Interaction of a chiral object with a chiral receptor.

A left hand interacts with a chiral object much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: **green thumb, red palm, and gray pinkie finger, with the blue substituent exposed.** **(b)** The other enantiomer, however, doesn't fit into the hand in the same way. When the green thumb and gray pinkie finger interact appropriately, the palm holds a blue substituent rather than a red one, with the **red substituent exposed.**



The hand-in-glove fit of a chiral substrate into a chiral receptor is relatively straightforward, but it's less obvious how a prochiral substrate can undergo a selective reaction. Take the reaction of ethanol with NAD^+ catalyzed by yeast alcohol dehydrogenase. As we saw at the end of Section 5-11, the reaction occurs with exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of the NAD^+ carbon.

We can understand this result by imagining that the chiral enzyme receptor again has three binding sites, as was previously the case in Figure 5.15. When green and gray substituents of a prochiral substrate are held appropriately, however, only one of the two red substituents—say, the *pro-S* one—is also held while the other, *pro-R*, substituent is exposed for reaction.

We describe the situation by saying that the receptor provides a **chiral environment** for the substrate. In the absence of a chiral environment, the two red substituents are chemically identical, but in the presence of the chiral environment, they are chemically distinctive (FIGURE 5.16a). The situation is similar to what happens when you pick up a coffee mug. By itself, the mug has a plane of symmetry and is achiral. When you pick up the mug, however, your hand provides a chiral environment so one side becomes much more accessible and easier to drink from than the other (FIGURE 5.16b).

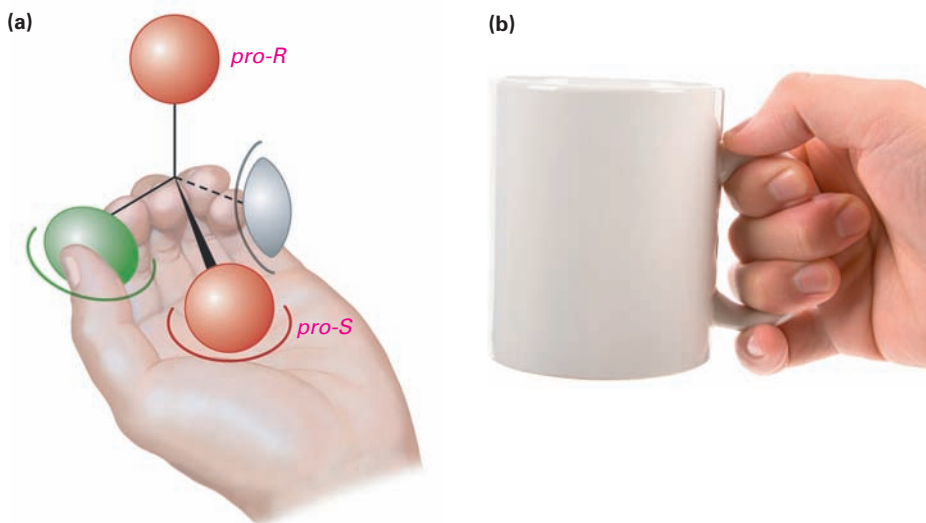


FIGURE 5.16 The meaning of chiral environment. (a) When a prochiral molecule is held in a chiral environment, the **two seemingly identical substituents** are distinguishable. (b) Similarly, when an achiral coffee mug is held in the chiral environment of your hand, it's much easier to drink from one side than the other because the two sides of the mug are now distinguishable.

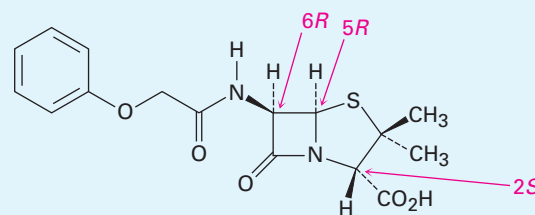
SOMETHING EXTRA

Chiral Drugs

The hundreds of different pharmaceutical agents approved for use by the U.S. Food and Drug Administration come from many sources. Many drugs are isolated directly from plants or bacteria, and others are made by chemical modification of naturally occurring compounds. An estimated 33%, however, are made entirely in the laboratory and have no relatives in nature.

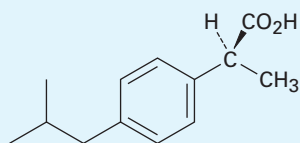
Those drugs that come from natural sources, either directly or after chemical modification, are usually chiral and are generally found only as a single enantiomer rather than as a racemate. Penicillin V, for example, an

antibiotic isolated from the *Penicillium* mold, has the $2S,5R,6R$ configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.

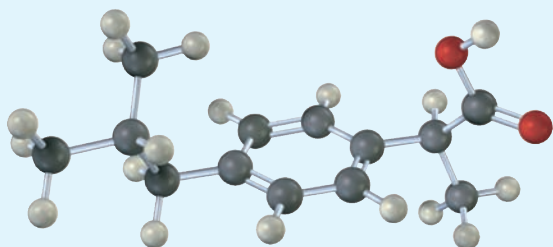


Penicillin V ($2S,5R,6R$ configuration)

In contrast to drugs from natural sources, those drugs that are made entirely in the laboratory either are achiral or, if chiral, are often produced and sold as racemates. Ibuprofen, for example, has one chirality center and is sold commercially under such trade names as Advil, Nuprin, and Motrin as a 50:50 mixture of *R* and *S*. It turns out, however, that only the *S* enantiomer is active as an analgesic and anti-inflammatory agent. The *R* enantiomer of ibuprofen is inactive, although it is slowly converted in the body to the active *S* form.



(*S*)-Ibuprofen
(an active analgesic agent)



Not only is it chemically wasteful to synthesize and administer an enantiomer that does not serve the intended purpose, many instances are now known where the presence of the “wrong” enantiomer in a racemic mixture either affects the body’s ability to utilize the “right” enantiomer or has unintended pharmacological effects of



Heath Robbins/Photomica/Getty Images

The *S* enantiomer of ibuprofen soothes the aches and pains of athletic injuries much more effectively than the *R* enantiomer.

its own. The presence of (*R*)-ibuprofen in the racemic mixture, for instance, slows the rate at which the *S* enantiomer takes effect in the body, from 12 minutes to 38 minutes.

To get around this problem, pharmaceutical companies attempt to devise methods of *enantioselective synthesis*, which allow them to prepare only a single enantiomer rather than a racemic mixture. Viable methods have been developed for the preparation of (*S*)-ibuprofen, which is now being marketed in Europe. We’ll look further into enantioselective synthesis in the Chapter 14 *Something Extra* and find out more about how ibuprofen functions in the Chapter 9 *Something Extra*.

KEY WORDS

- absolute configuration, 124
- achiral, 116
- Cahn–Ingold–Prelog rules, 122
- chiral, 115
- chiral environment, 143
- chirality center, 116
- configuration, 122

SUMMARY

In this chapter, we’ve looked at some of the causes and consequences of molecular handedness—a topic of particular importance in understanding biological chemistry. The subject can be a bit complex but is so important that it’s worthwhile spending the time needed to become familiar with it.

An object or molecule that is not superimposable on its mirror image is said to be **chiral**, meaning “handed.” A chiral molecule is one that does not have a plane of symmetry cutting through it so that one half is a mirror image of the other half. The most common cause of chirality in organic molecules is the presence of a tetrahedral, sp^3 -hybridized carbon atom bonded to four different groups—a so-called **chirality center**. Chiral compounds can exist as a

pair of nonsuperimposable mirror-image stereoisomers called **enantiomers**. Enantiomers are identical in all physical properties except for their **optical activity**, or direction in which they rotate plane-polarized light.

The stereochemical **configuration** of a chirality center can be specified as either *R* (*rectus*) or *S* (*sinister*) by using the **Cahn–Ingold–Prelog rules**. First rank the four substituents on the chiral carbon atom, and then orient the molecule so that the lowest-ranked group points directly back. If a curved arrow drawn in the direction of decreasing rank (1 → 2 → 3) for the remaining three groups is clockwise, the chirality center has the *R* configuration. If the direction is counterclockwise, the chirality center has the *S* configuration.

Some molecules have more than one chirality center. Enantiomers have opposite configuration at all chirality centers, whereas **diastereomers** have the same configuration in at least one center but opposite configurations at the others. **Epimers** are diastereomers that differ in configuration at only one chirality center. A compound with *n* chirality centers can have a maximum of 2^n stereoisomers.

Meso compounds contain chirality centers but are achiral overall because they have a plane of symmetry. Racemic mixtures, or **racemates**, are 50:50 mixtures of (+) and (–) enantiomers. Racemates and individual diastereomers differ in their physical properties, such as solubility, melting point, and boiling point.

A molecule is **prochiral** if it can be converted from achiral to chiral in a single chemical step. A prochiral sp^2 -hybridized atom has two faces, described as either *Re* or *Si*. An sp^3 -hybridized atom is a **prochirality center** if, by changing one of its attached atoms, a chirality center results. The atom whose replacement leads to an *R* chirality center is **pro-*R***, and the atom whose replacement leads to an *S* chirality center is **pro-*S***.

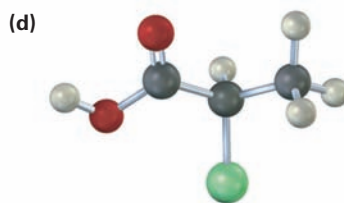
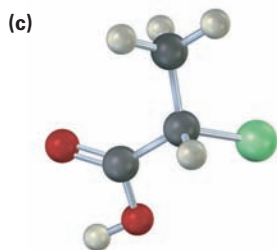
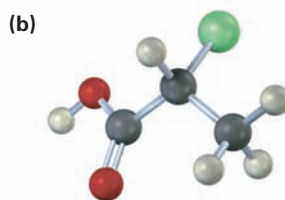
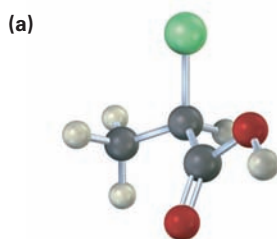
dextrorotatory,	119
diastereomers,	128
enantiomers,	114
epimers,	129
levorotatory,	119
meso compound,	131
optically active,	119
<i>pro-R</i> configuration,	139
<i>pro-S</i> configuration,	139
prochiral,	138
prochirality center,	139
<i>R</i> configuration,	123
racemate,	133
<i>Re</i> face,	138
resolution,	133
<i>S</i> configuration,	123
<i>Si</i> face,	138
specific rotation, $[\alpha]_D$,	119

EXERCISES

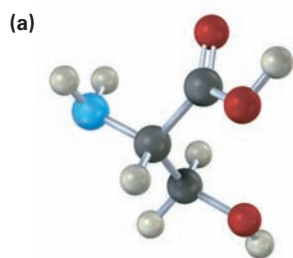
VISUALIZING CHEMISTRY

(Problems 5.1–5.25 appear within the chapter.)

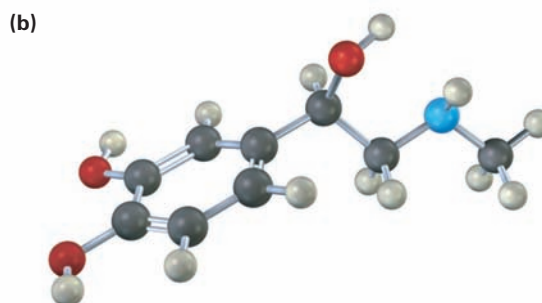
5.26 Which of the following structures are identical? (Green = Cl.)



5.27 Assign *R* or *S* configuration to the chirality centers in the following molecules (blue = N):

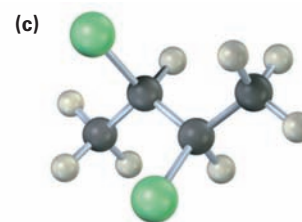
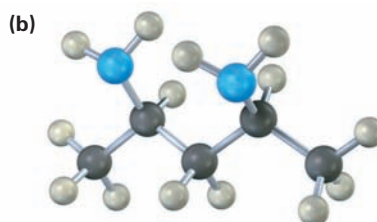
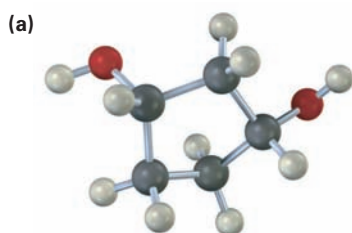


Serine

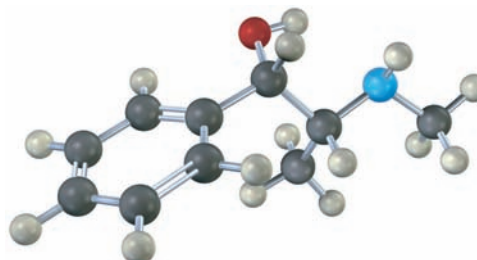


Adrenaline

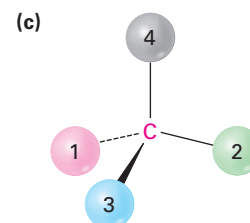
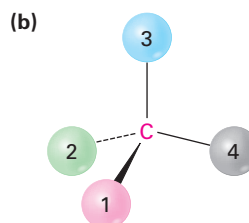
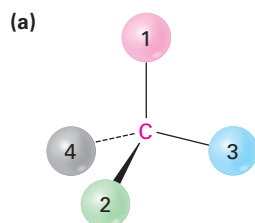
5.28 Which, if any, of the following structures represent meso compounds? (Blue = N, green = Cl.)



5.29 Assign *R* or *S* configuration to each chirality center in pseudoephedrine, an over-the-counter decongestant found in cold remedies (blue = N).



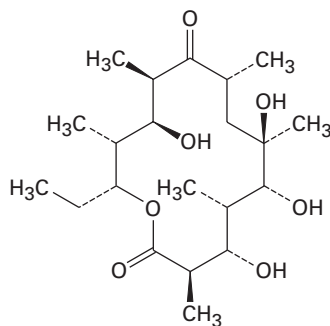
5.30 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



ADDITIONAL PROBLEMS

Chirality and Optical Activity

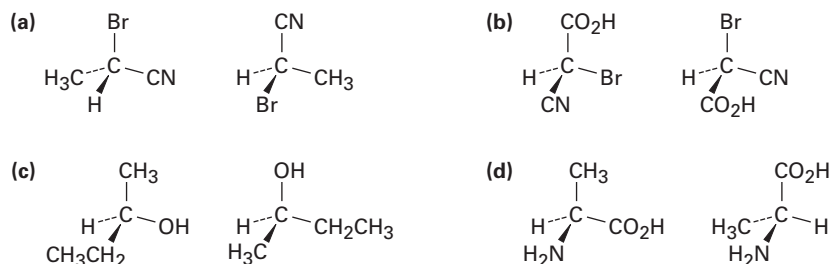
- 5.31 Which of the following objects are chiral?
- (a) A basketball (b) A fork (c) A wine glass
 (d) A golf club (e) A spiral staircase (f) A snowflake
- 5.32 Which of the following compounds are chiral? Draw them, and label the chirality centers.
- (a) 2,4-Dimethylheptane (b) 5-Ethyl-3,3-dimethylheptane
 (c) *cis*-1,4-Dichlorocyclohexane
- 5.33 Draw chiral molecules that meet the following descriptions:
- (a) A chloroalkane, $C_5H_{11}Cl$ (b) An alcohol, $C_6H_{14}O$
 (c) An alkene, C_6H_{12} (d) An alkane, C_8H_{18}
- 5.34 Eight alcohols have the formula $C_5H_{12}O$. Draw them. Which are chiral?
- 5.35 Draw compounds that fit the following descriptions:
- (a) A chiral alcohol with four carbons
 (b) A chiral carboxylic acid with the formula $C_5H_{10}O_2$
 (c) A compound with two chirality centers
 (d) A chiral aldehyde with the formula C_3H_5BrO
- 5.36 Erythronolide B is the biological precursor of erythromycin, a broad-spectrum antibiotic. How many chirality centers does erythronolide B have? Identify them.



Erythronolide B

Assigning Configuration to Chirality Centers

5.37 Which of the following pairs of structures represent the same enantiomer, and which represent different enantiomers?

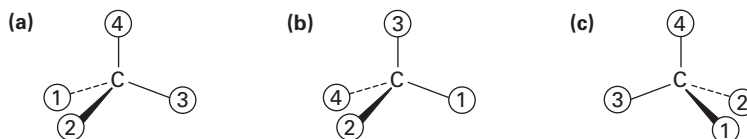


5.38 What is the relationship between the specific rotations of (2*R*,3*R*)-dichloropentane and (2*S*,3*S*)-dichloropentane? Between (2*R*,3*S*)-dichloropentane and (2*R*,3*R*)-dichloropentane?

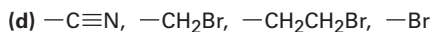
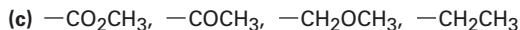
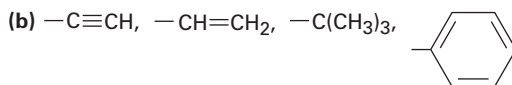
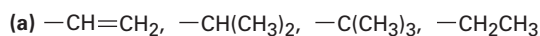
5.39 What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-octane-2,4-diol? (A diol is a compound with two –OH groups.)

5.40 What are the stereochemical configurations of the two diastereomers of (2*S*,4*R*)-octane-2,4-diol? (A diol is a compound with two –OH groups.)

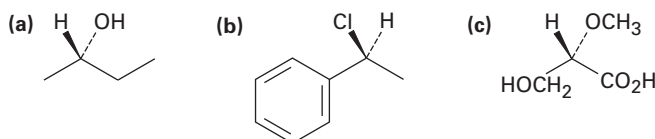
5.41 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



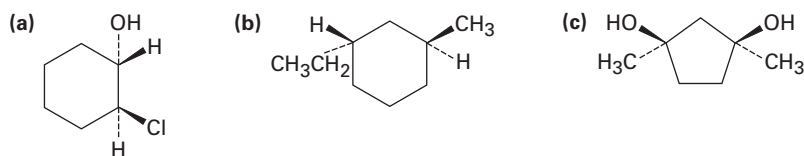
5.42 Assign Cahn–Ingold–Prelog rankings to the following sets of substituents:



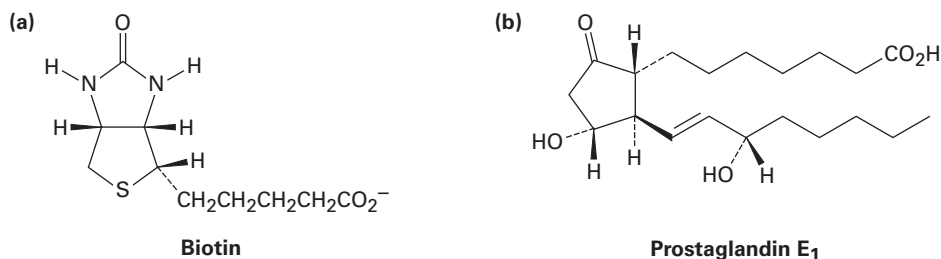
5.43 Assign *R* or *S* configurations to the chirality centers in the following molecules:



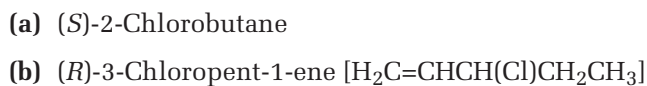
5.44 Assign *R* or *S* configuration to each chirality center in the following molecules:



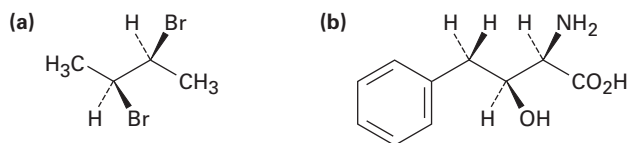
5.45 Assign *R* or *S* configuration to each chirality center in the following biological molecules:



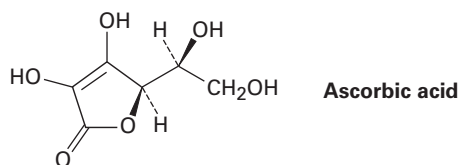
5.46 Draw tetrahedral representations of the following molecules:



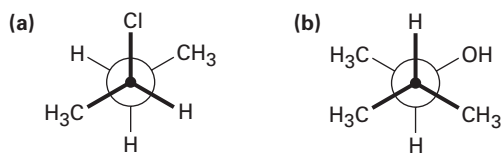
5.47 Assign *R* or *S* configuration to each chirality center in the following molecules:



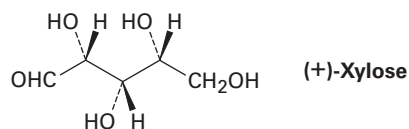
5.48 Assign *R* or *S* configurations to the chirality centers in ascorbic acid (vitamin C).



5.49 Assign *R* or *S* stereochemistry to the chirality centers in the following Newman projections:

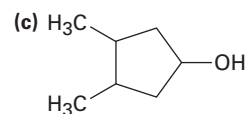
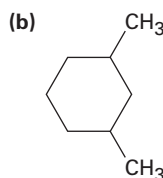
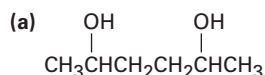


- 5.50 Xylose is a common sugar found in many types of wood, including maple and cherry. Because it is much less prone to cause tooth decay than sucrose, xylose has been used in candy and chewing gum. Assign *R* or *S* configurations to the chirality centers in xylose.

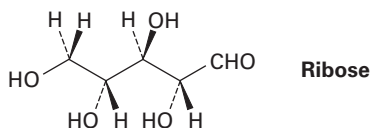


Meso Compounds

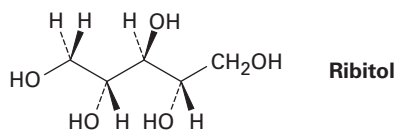
- 5.51 Draw examples of the following:
- A meso compound with the formula C_8H_{18}
 - A meso compound with the formula C_9H_{20}
 - A compound with two chirality centers, one *R* and the other *S*
- 5.52 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:



- 5.53 Draw the structure of a meso compound that has five carbons and three chirality centers.
- 5.54 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:

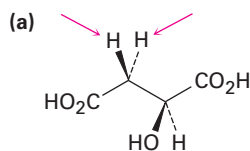


- How many chirality centers does ribose have? Identify them.
 - How many stereoisomers of ribose are there?
 - Draw the structure of the enantiomer of ribose.
 - Draw the structure of a diastereomer of ribose.
- 5.55 On reaction with hydrogen gas with a platinum catalyst, ribose (Problem 5.54) is converted into ribitol. Is ribitol optically active or inactive? Explain.

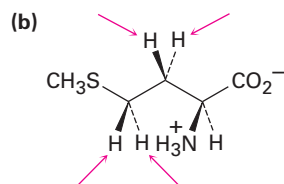


Prochirality

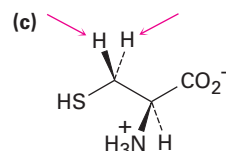
- 5.56 Identify the indicated hydrogens in the following molecules as *pro-R* or *pro-S*:



Malic acid

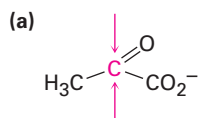


Methionine

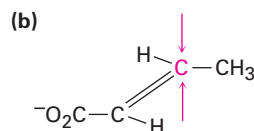


Cysteine

- 5.57 Identify the indicated faces in the following molecules as *Re* or *Si*:

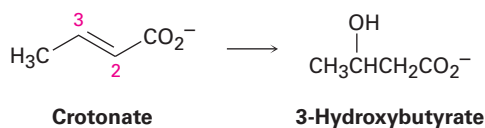


Pyruvate

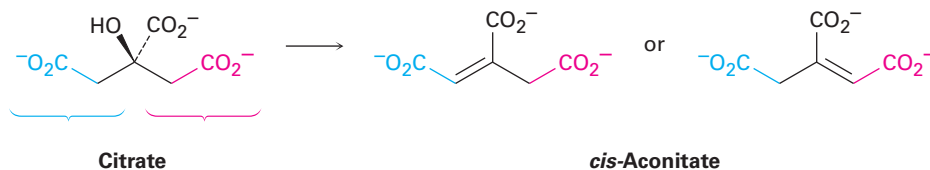


Crotonate

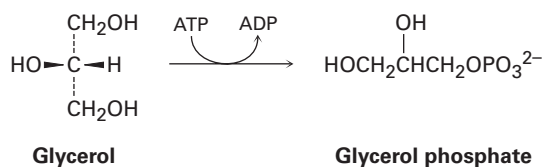
- 5.58 One of the steps in fat metabolism is the hydration of crotonate to yield 3-hydroxybutyrate. The reaction occurs by addition of $-OH$ to the *Si* face at C3, followed by protonation at C2, also from the *Si* face. Draw the product of the reaction, showing the stereochemistry of each step.



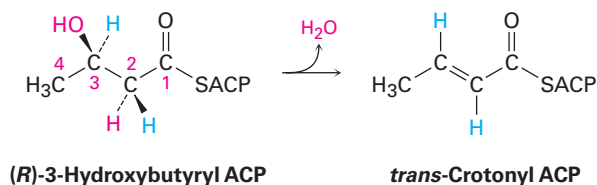
- 5.59 The dehydration of citrate to yield *cis*-aconitate, a step in the citric acid cycle, involves the *pro-R* "arm" of citrate rather than the *pro-S* arm. Which of the following two products is formed?



- 5.60 The first step in the metabolism of glycerol, formed by digestion of fats, is phosphorylation of the *pro-R* $-CH_2OH$ group by reaction with adenosine triphosphate (ATP) to give the corresponding glycerol phosphate plus adenosine diphosphate (ADP). Show the stereochemistry of the product.

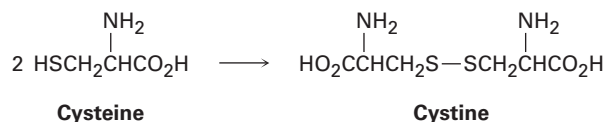


- 5.61 One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotonyl ACP. Does the reaction remove the *pro-R* or the *pro-S* hydrogen from C2?

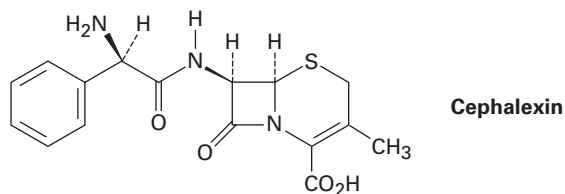


General Problems

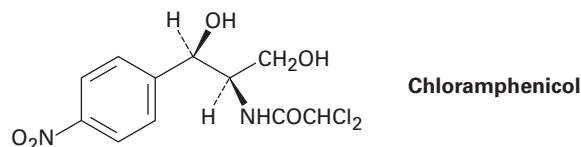
- 5.62 Draw all possible stereoisomers of cyclobutane-1,2-dicarboxylic acid, and indicate the interrelationships. Which, if any, are optically active? Do the same for cyclobutane-1,3-dicarboxylic acid.
- 5.63 Draw tetrahedral representations of the two enantiomers of the amino acid cysteine, $\text{HSCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$, and identify each as *R* or *S*.
- 5.64 The naturally occurring form of the amino acid cysteine (Problem 5.63) has the *S* configuration at its chirality center. On treatment with a mild oxidizing agent, two cysteines join to give cystine, a disulfide. Assuming that the chirality center is not affected by the reaction, is cystine optically active? Explain.



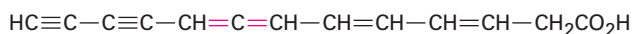
- 5.65 Draw tetrahedral representations of the following molecules:
- (a) The *2S,3R* enantiomer of 2,3-dibromopentane
- (b) The meso form of heptane-2,5-diol
- 5.66 Assign *R,S* configurations to the chiral centers in cephalixin, trade-named Keflex, the most widely prescribed antibiotic in the U.S.



- 5.67 Chloramphenicol, a powerful antibiotic isolated in 1947 from the *Streptomyces venezuelae* bacterium, is active against a broad spectrum of bacterial infections and is particularly valuable against typhoid fever. Assign *R,S* configurations to the chirality centers in chloramphenicol.

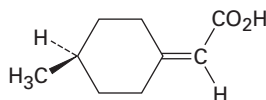


- 5.68 *Allenes* are compounds with adjacent carbon–carbon double bonds. Many allenes are chiral, even though they don't contain chirality centers. Mycomycin, for example, a naturally occurring antibiotic isolated from the bacterium *Nocardia acidophilus*, is chiral and has $[\alpha]_D = -130$. Explain why mycomycin is chiral.



Mycomycin

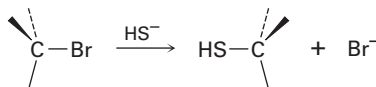
- 5.69 Long before chiral allenes were known (Problem 5.68), the resolution of 4-methylcyclohexylideneacetic acid into two enantiomers had been carried out. Why is it chiral? What geometric similarity does it have to allenes?



4-Methylcyclohexylideneacetic acid

- 5.70 (*S*)-1-Chloro-2-methylbutane undergoes light-induced reaction with Cl_2 to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane.
- (a) Write the reaction, showing the correct stereochemistry of the reactant.
- (b) One of the two products is optically active, but the other is optically inactive. Which is which?
- 5.71 How many stereoisomers of 2,4-dibromo-3-chloropentane are there? Draw them, and indicate which are optically active.

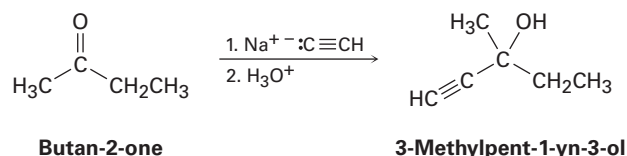
- 5.72** Draw both *cis*- and *trans*-1,4-dimethylcyclohexane in their more stable chair conformations.
- (a) How many stereoisomers are there of *cis*-1,4-dimethylcyclohexane, and how many of *trans*-1,4-dimethylcyclohexane?
- (b) Are any of the structures chiral?
- (c) What are the stereochemical relationships among the various stereoisomers of 1,4-dimethylcyclohexane?
- 5.73** Draw both *cis*- and *trans*-1,3-dimethylcyclohexane in their more stable chair conformations.
- (a) How many stereoisomers are there of *cis*-1,3-dimethylcyclohexane, and how many of *trans*-1,3-dimethylcyclohexane?
- (b) Are any of the structures chiral?
- (c) What are the stereochemical relationships among the various stereoisomers of 1,3-dimethylcyclohexane?
- 5.74** *cis*-1,2-Dimethylcyclohexane is optically inactive even though it has two chirality centers. Explain.
- 5.75** We'll see in Chapter 12 that alkyl halides react with hydrosulfide ion (HS^-) to give a product whose stereochemistry is *inverted* from that of the reactant.



**An alkyl
bromide**

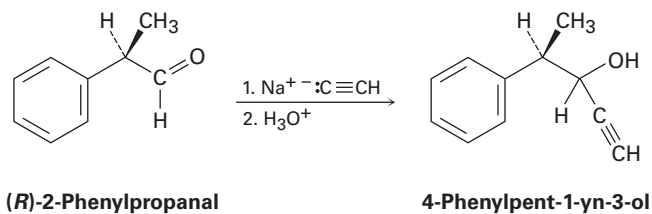
Draw the reaction of (*S*)-2-bromobutane with HS^- ion to yield butane-2-thiol, $\text{CH}_3\text{CH}_2\text{CH}(\text{SH})\text{CH}_3$. Is the stereochemistry of the product *R* or *S*?

- 5.76** Ketones react with sodium acetylide (the sodium salt of acetylene, $\text{Na}^+ \text{:C}\equiv\text{CH}$) to give alcohols. For example, the reaction of sodium acetylide with butan-2-one yields 3-methylpent-1-yn-3-ol:



- (a) Is the product chiral?
- (b) Assuming that the reaction takes place with equal likelihood from both *Re* and *Si* faces of the carbonyl group, is the product optically active? Explain.

- 5.77 Imagine that a reaction similar to that in Problem 5.76 is carried out between sodium acetylide and (*R*)-2-phenylpropanal to yield 4-phenylpent-1-yn-3-ol:



- (a) Is the product chiral?
- (b) Draw both major and minor reaction products, assuming that the reaction takes place preferentially from the *Re* face of the carbonyl group. Is the product mixture optically active? Explain.

6

An Overview of Organic Reactions

CONTENTS

- 6-1 Kinds of Organic Reactions
- 6-2 How Organic Reactions Occur: Mechanisms
- 6-3 Radical Reactions
- 6-4 Polar Reactions
- 6-5 An Example of a Polar Reaction: Addition of H₂O to Ethylene
- 6-6 Using Curved Arrows in Polar Reaction Mechanisms
- 6-7 Describing a Reaction: Equilibria, Rates, and Energy Changes
- 6-8 Describing a Reaction: Bond Dissociation Energies
- 6-9 Describing a Reaction: Energy Diagrams and Transition States
- 6-10 Describing a Reaction: Intermediates
- 6-11 A Comparison between Biological Reactions and Laboratory Reactions

SOMETHING EXTRA

Where Do Drugs Come From?



Protein kinase A catalyzes the phosphorylation of various amino acids in proteins.

WHY THIS CHAPTER?

All chemical reactions, whether they take place in the laboratory or in living organisms, follow the same “rules.” Reactions in living organisms often look more complex than laboratory reactions because of the size of the biomolecules and the involvement of biological catalysts called *enzymes*, but the principles governing all reactions are the same.

To understand both organic and biological chemistry, it's necessary to know not just *what* occurs but also *why* and *how* chemical reactions take place. In this chapter, we'll start with an overview of the fundamental kinds of organic reactions, we'll see why reactions occur, and we'll see how reactions can be described. Once this background is out of the way, we'll be ready to begin studying the details of organic and biological chemistry.

When first approached, organic chemistry might seem overwhelming. It's not so much that any one part is difficult to understand; it's that there are so many parts: tens of millions of compounds, dozens of functional groups, and an apparently endless number of reactions. With study, though, it becomes evident that there are only a few fundamental ideas that underlie all organic reactions. Far from being a collection of isolated facts, organic chemistry is a beautifully logical subject that is unified by a few broad themes. When these themes are understood, learning organic chemistry becomes easier and memorization is minimized. The aim of this book is to describe the themes and clarify the patterns that unify organic chemistry.

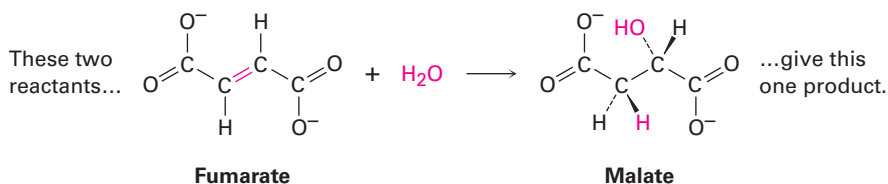
6-1 Kinds of Organic Reactions

Organic chemical reactions can be organized broadly in two ways—by *what* kinds of reactions occur and by *how* those reactions occur. Let's look first at

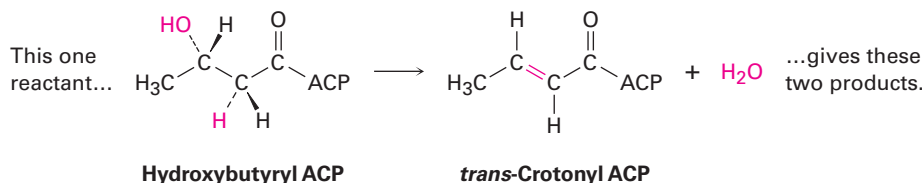


the kinds of reactions that take place. There are four general types of organic reactions: *additions*, *eliminations*, *substitutions*, and *rearrangements*.

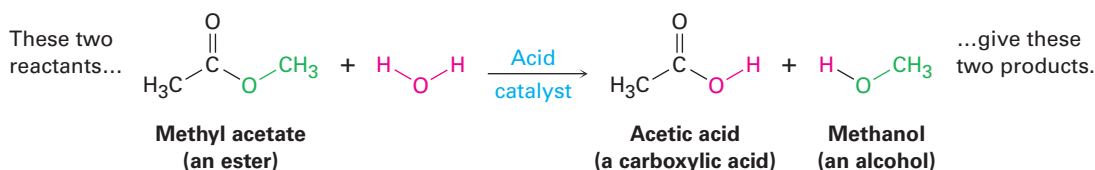
- **Addition reactions** occur when two reactants add together to form a single product with no atoms “left over.” An example is the reaction of fumarate with water to yield malate, a step in the citric acid cycle of food metabolism.



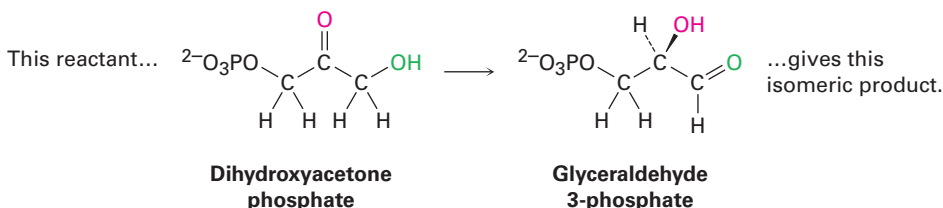
- **Elimination reactions** are, in a sense, the opposite of addition reactions. They occur when a single reactant splits into two products, often with formation of a small molecule such as water. An example is the reaction of hydroxybutyryl ACP to yield *trans*-crotonyl ACP plus water, a step in the biosynthesis of fat molecules. (The abbreviation ACP stands for “acyl carrier protein.”)



- **Substitution reactions** occur when two reactants exchange parts to give two new products. An example is the reaction of an ester such as methyl acetate with water to yield a carboxylic acid plus an alcohol. Similar reactions occur in many biological pathways, including the metabolism of dietary fats.

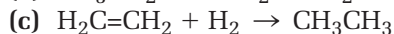
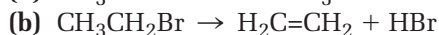
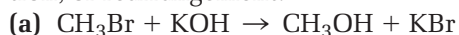


- **Rearrangement reactions** occur when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product. An example is the conversion of dihydroxyacetone phosphate into its constitutional isomer glyceraldehyde 3-phosphate, a step in the glycolysis pathway by which carbohydrates are metabolized.



PROBLEM 6.1

Classify each of the following reactions as an addition, elimination, substitution, or rearrangement:

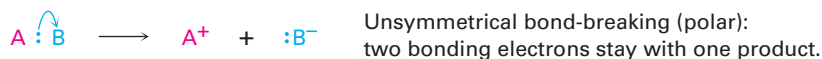
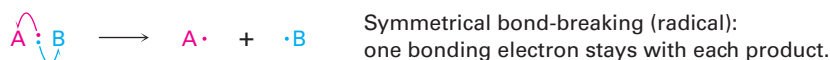


6-2 How Organic Reactions Occur: Mechanisms

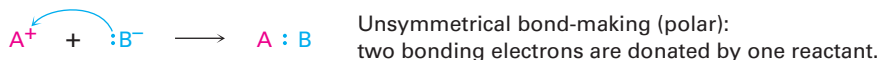
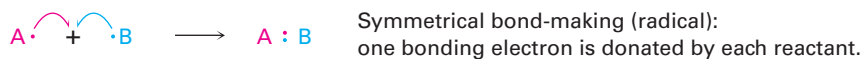
Having looked at some general kinds of reactions that take place, let's now see how reactions occur. An overall description of how a reaction occurs is called a **reaction mechanism**. A mechanism describes in detail exactly what takes place at each stage of a chemical transformation—which bonds are broken and in what order, which bonds are formed and in what order, and what the relative rates of the steps are. A complete mechanism must also account for all reactants used and all products formed.

All chemical reactions involve bond-breaking and bond-making. When two molecules come together, react, and yield products, specific bonds in the reactant molecules are broken and specific bonds in the product molecules are formed. Fundamentally, there are two ways in which a covalent two-electron bond can break: a bond can break in an electronically *symmetrical* way so that one electron remains with each product fragment, or a bond can break in an electronically *unsymmetrical* way so that both bonding electrons remain with one product fragment, leaving the other with a vacant orbital. The symmetrical cleavage is said to be *homolytic*, and the unsymmetrical cleavage is said to be *heterolytic*.

We'll develop the point in more detail later, but you might note for now that the movement of *one* electron in the symmetrical process is indicated using a half-headed, or "fishhook," arrow (\frown), whereas the movement of *two* electrons in the unsymmetrical process is indicated using a full-headed curved arrow (\curvearrowright).



Just as there are two ways in which a bond can break, there are two ways in which a covalent two-electron bond can form. A bond can form in an electronically symmetrical way if one electron is donated to the new bond by each reactant or in an unsymmetrical way if both bonding electrons are donated by one reactant.



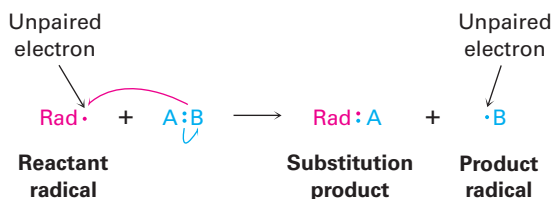
Processes that involve symmetrical bond-breaking and bond-making are called **radical reactions**. A **radical**, often called a **free radical**, is a neutral chemical species that contains an odd number of electrons and thus has a single, unpaired electron in one of its orbitals. Processes that involve unsymmetrical bond-breaking and bond-making are called **polar reactions**. Polar reactions involve species that have an even number of electrons and thus have only electron pairs in their orbitals. Polar processes are by far the more common reaction type in both organic and biological chemistry, and a large part of this book is devoted to their description.

In addition to polar and radical reactions, there is a third, less commonly encountered process called a *pericyclic reaction*. Rather than explain pericyclic reactions now, though, we'll look at them more carefully in Section 8-14 and Chapter 26.

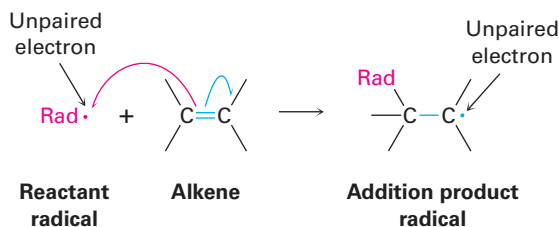
6-3 Radical Reactions

Radical reactions are not as common as polar reactions but are nevertheless important in some industrial processes and biological pathways. Let's see briefly how they occur.

A radical is highly reactive because it contains an atom with an odd number of electrons (usually seven) in its valence shell rather than a stable, noble-gas octet. A radical can achieve a valence-shell octet in several ways. For example, the radical might abstract an atom and one bonding electron from another reactant, leaving behind a new radical. The net result is a radical substitution reaction:

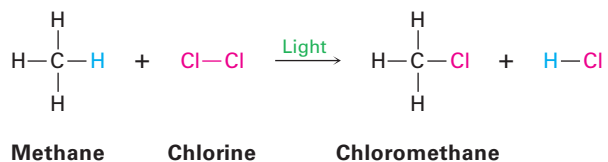


Alternatively, a reactant radical might add to a double bond, taking one electron from the double bond and leaving one behind to form a new radical. The net result is a radical addition reaction:



An example of an industrially useful radical reaction is the chlorination of methane to yield chloromethane. This substitution reaction is the

first step in the preparation of the solvents dichloromethane (CH_2Cl_2) and chloroform (CHCl_3).

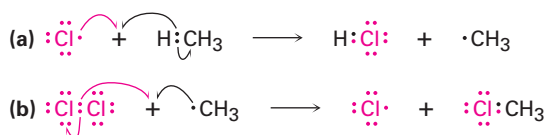


Like many radical reactions in the laboratory, methane chlorination requires three kinds of steps: *initiation*, *propagation*, and *termination*.

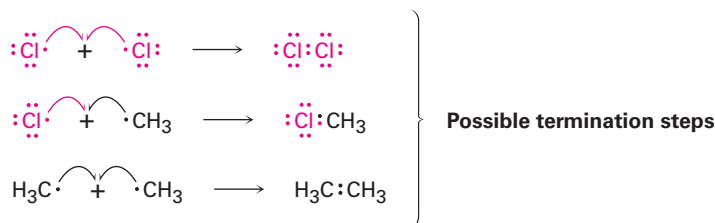
Initiation Irradiation with ultraviolet light begins the reaction by breaking the relatively weak Cl–Cl bond of a small number of Cl_2 molecules to give a few reactive chlorine radicals.



Propagation Once produced, a reactive chlorine radical collides with a methane molecule in a propagation step, abstracting a hydrogen atom to give HCl and a methyl radical ($\cdot\text{CH}_3$). This methyl radical reacts further with Cl_2 in a second propagation step to give the product chloromethane plus a new chlorine radical, which cycles back and repeats the first propagation step. Thus, once the sequence has been initiated, it becomes a self-sustaining cycle of repeating steps **(a)** and **(b)**, making the overall process a *chain reaction*.



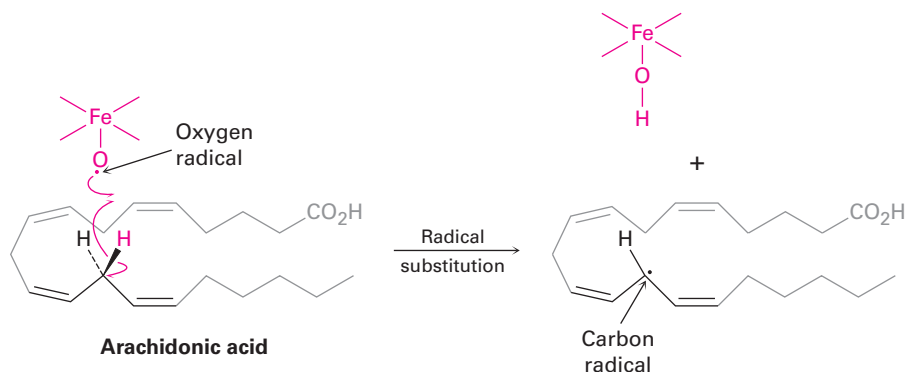
Termination Occasionally, two radicals might collide and combine to form a stable product. When that happens, the reaction cycle is broken and the chain is ended. Such termination steps occur infrequently, however, because the concentration of radicals in the reaction at any given moment is very small. Thus, the likelihood that two radicals will collide is also small.



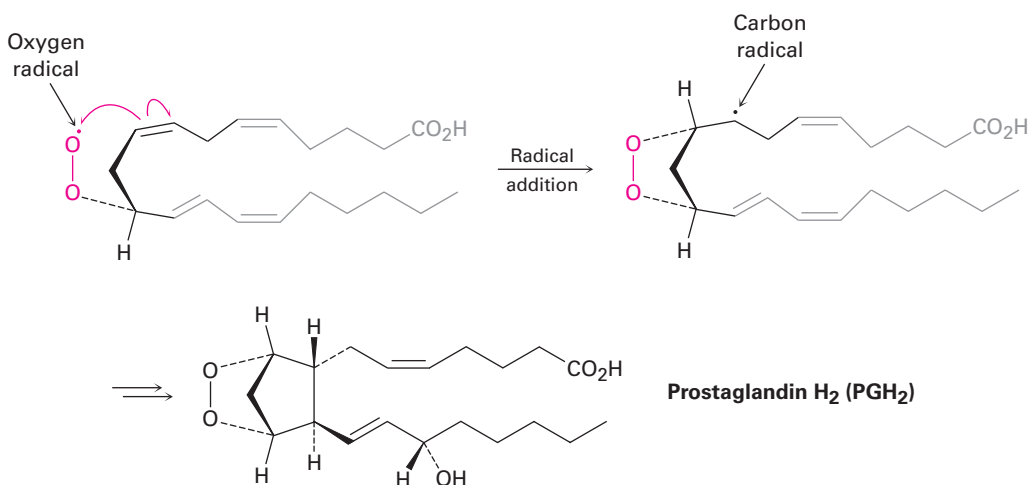
As a biological example of a radical reaction, look at the synthesis of *prostaglandins*, a large class of molecules found in virtually all body tissues and fluids. A number of pharmaceuticals are based on or derived from prostaglandins,

including medicines that induce labor during childbirth, reduce intraocular pressure in glaucoma, control bronchial asthma, and help treat congenital heart defects.

Prostaglandin biosynthesis is initiated by abstraction of a hydrogen atom from arachidonic acid by an iron–oxygen radical, thereby generating a new carbon radical in a substitution reaction. Don't be intimidated by the size of the molecules; focus on the changes occurring in each step. To help you do that, the unchanged part of the molecule is “ghosted,” with only the reactive part clearly visible.



Following the initial abstraction of a hydrogen atom, the carbon radical then reacts with O_2 to give an oxygen radical, which reacts with a C=C bond within the same molecule in an addition reaction. Several further transformations ultimately yield prostaglandin H_2 .

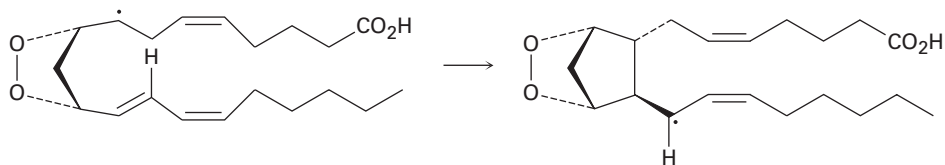


PROBLEM 6.2

Radical chlorination of alkanes is not generally useful because mixtures of products often result when more than one kind of C–H bond is present in the substrate. Draw and name all monochloro substitution products $C_6H_{13}Cl$ you might obtain by reaction of 2-methylpentane with Cl_2 .

PROBLEM 6.3

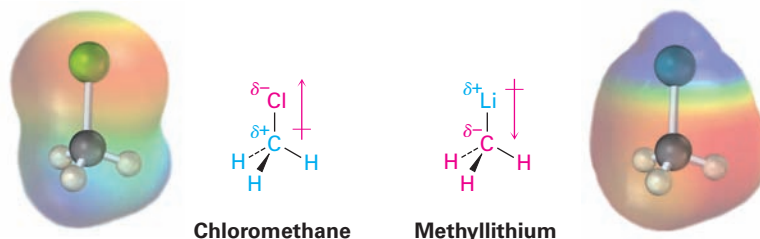
Using a curved arrow, propose a mechanism for formation of the cyclopentane ring of prostaglandin H_2 .

**6-4 Polar Reactions**

Polar reactions occur because of the electrical attraction between positively polarized and negatively polarized centers on functional groups in molecules. To see how these reactions take place, let's first recall the discussion of polar covalent bonds in Section 2-1 and then look more deeply into the effects of bond polarity on organic molecules.

Most organic compounds are electrically neutral: they have no net charge, either positive or negative. We saw in Section 2-1, however, that certain bonds within a molecule, particularly the bonds in functional groups, are polar. Bond polarity is a consequence of an unsymmetrical electron distribution in a bond and is due to the difference in electronegativity of the bonded atoms.

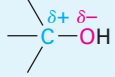
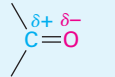

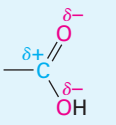
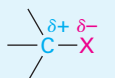
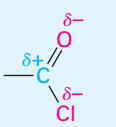
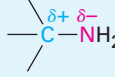
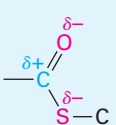
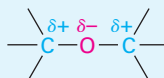
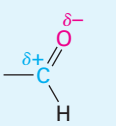
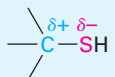
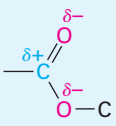
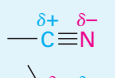
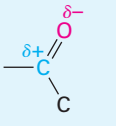
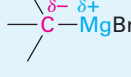
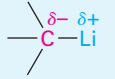
Elements such as oxygen, nitrogen, fluorine, and chlorine are more electronegative than carbon, so a carbon atom bonded to one of these atoms has a partial positive charge (δ^+). Conversely, metals are less electronegative than carbon, so a carbon atom bonded to a metal has a partial negative charge (δ^-). Electrostatic potential maps of chloromethane and methyl lithium illustrate these charge distributions, showing that the carbon atom in chloromethane is electron-poor (blue) while the carbon in methyl lithium is electron-rich (red).



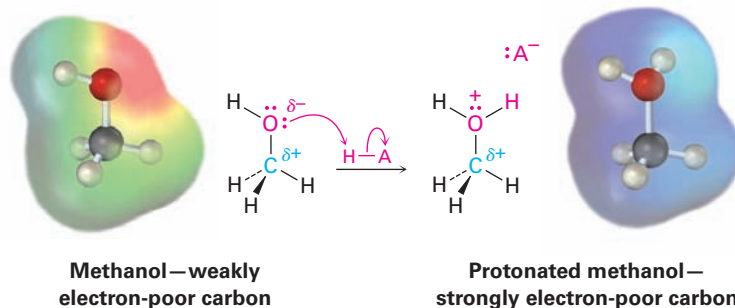
The polarity patterns of some common functional groups are shown in **TABLE 6.1**. Note that carbon is always positively polarized except when it is bonded to a metal.

This discussion of bond polarity is oversimplified in that we've considered only bonds that are inherently polar due to differences in electronegativity. Polar bonds can also result from the interaction of functional groups with acids or bases. Take an alcohol such as methanol, for example. In neutral methanol, the carbon atom is somewhat electron-poor because the electronegative oxygen attracts the electrons in the C–O bond. On protonation of the methanol oxygen by an acid, however, a full positive charge on oxygen attracts the electrons in the C–O bond much more strongly and makes the carbon

TABLE 6.1 Polarity Patterns in Some Common Functional Groups

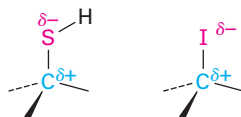
Compound type	Functional group structure	Compound type	Functional group structure
Alcohol		Carbonyl	
Alkene	 Symmetrical, nonpolar	Carboxylic acid	
Alkyl halide		Carboxylic acid chloride	
Amine		Thioester	
Ether		Aldehyde	
Thiol		Ester	
Nitrile		Ketone	
Grignard reagent			
Alkyl lithium			

much more electron-poor. We'll see numerous examples throughout this book of reactions that are catalyzed by acids because of the resultant increase in bond polarity on protonation.



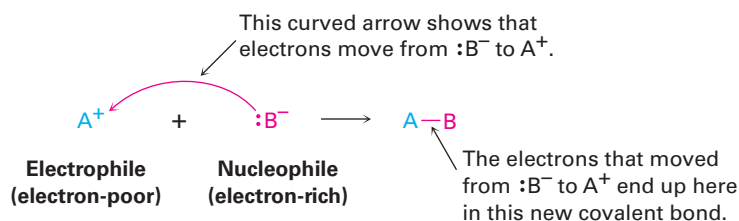
Yet a further consideration is the *polarizability* (as opposed to polarity) of atoms in a molecule. As the electric field around a given atom changes because

of changing interactions with solvent or other polar molecules nearby, the electron distribution around that atom also changes. The measure of this response to an external electrical influence is called the polarizability of the atom. Larger atoms with more, loosely held electrons are more polarizable, and smaller atoms with fewer, tightly held electrons are less polarizable. Thus, sulfur is more polarizable than oxygen, and iodine is more polarizable than chlorine. The effect of this higher polarizability for sulfur and iodine is that carbon–sulfur and carbon–iodine bonds, although nonpolar according to electronegativity values (Figure 2.2 on page 29), nevertheless usually react as if they were polar.



What does functional-group polarity mean with respect to chemical reactivity? Because unlike charges attract, the fundamental characteristic of all polar organic reactions is that electron-rich sites react with electron-poor sites. Bonds are made when an electron-rich atom donates a pair of electrons to an electron-poor atom, and bonds are broken when one atom leaves with both electrons from the former bond.

As we saw in Section 2-11, chemists indicate the movement of an electron pair during a polar reaction by using a curved, full-headed arrow. A curved arrow shows where electrons move when reactant bonds are broken and product bonds are formed. It means that an electron pair moves *from* the atom (or bond) at the tail of the arrow *to* the atom at the head of the arrow during the reaction.



In referring to the electron-rich and electron-poor species involved in polar reactions, chemists use the words *nucleophile* and *electrophile*. A **nucleophile** is a substance that is “nucleus-loving.” (Remember that a nucleus is positively charged.) A nucleophile has a negatively polarized, electron-rich atom and can form a bond by donating a pair of electrons to a positively polarized, electron-poor atom. Nucleophiles can be either neutral or negatively charged; ammonia, water, hydroxide ion, and chloride ion are examples.

An **electrophile**, by contrast, is “electron-loving.” An electrophile has a positively polarized, electron-poor atom and can form a bond by accepting a pair of electrons from a nucleophile. Electrophiles can be either neutral or positively charged. Acids (H^+ donors), alkyl halides, and carbonyl compounds are examples (FIGURE 6.1).

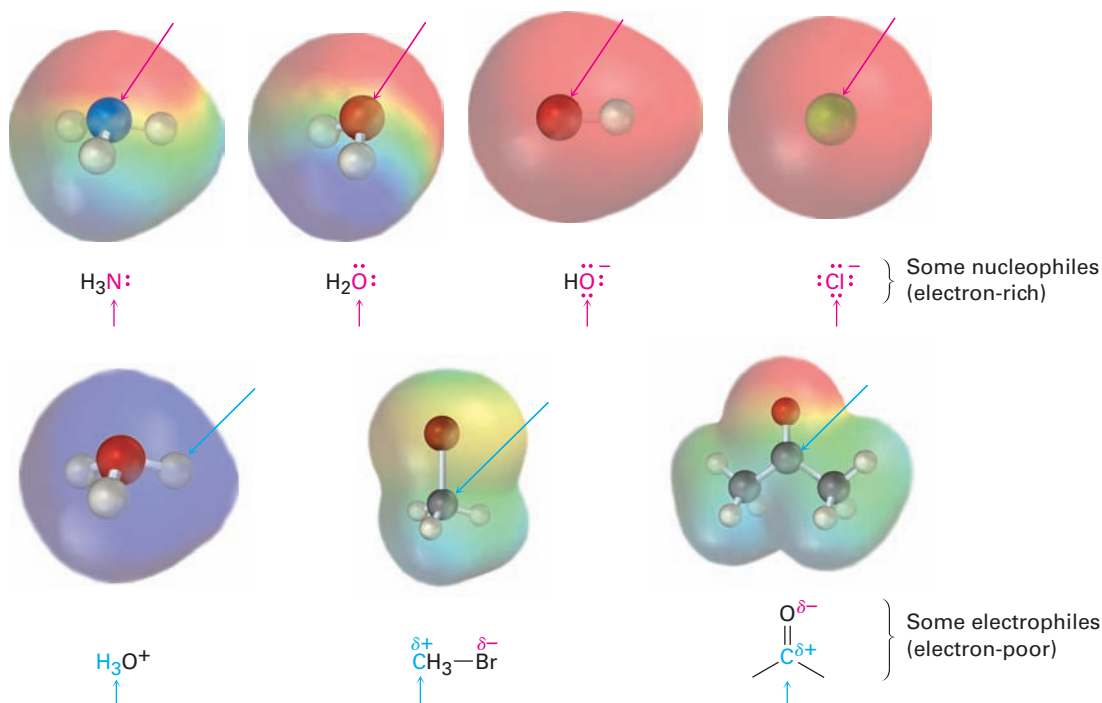


FIGURE 6.1 Some nucleophiles and electrophiles. Electrostatic potential maps identify the nucleophilic (negative) and electrophilic (positive) atoms.

Note that neutral compounds can often react either as nucleophiles or as electrophiles, depending on the circumstances. After all, if a compound is neutral yet has an electron-rich nucleophilic site, it must also have a corresponding electron-poor electrophilic site. Water, for instance, acts as an electrophile when it donates H^+ but acts as a nucleophile when it donates a nonbonding pair of electrons. Similarly, a carbonyl compound acts as an electrophile when it reacts at its positively polarized carbon atom, yet acts as a nucleophile when it reacts at its negatively polarized oxygen atom.

If the definitions of nucleophiles and electrophiles sound similar to those given in Section 2-11 for Lewis acids and Lewis bases, that's because there is indeed a correlation. Lewis bases are electron donors and behave as nucleophiles, whereas Lewis acids are electron acceptors and behave as electrophiles. Thus, much of organic chemistry is explainable in terms of acid-base reactions. The main difference is that the words *acid* and *base* are used broadly in all fields of chemistry, while the words *nucleophile* and *electrophile* are used primarily in organic chemistry when bonds to carbon are involved.

Identifying Electrophiles and Nucleophiles

WORKED EXAMPLE 6.1

Which of the following species is likely to behave as a nucleophile and which as an electrophile?

- (a) NO_2^+ (b) CN^- (c) CH_3NH_2 (d) $(\text{CH}_3)_3\text{S}^+$

Strategy

A nucleophile has an electron-rich site, either because it is negatively charged or because it has a functional group containing an atom that has a lone pair of electrons. An electrophile has an electron-poor site, either because it is

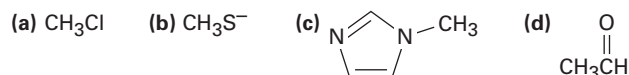
positively charged or because it has a functional group containing an atom that is positively polarized.

Solution

- (a) NO_2^+ (nitronium ion) is likely to be an electrophile because it is positively charged.
- (b) $:\text{C}\equiv\text{N}^-$ (cyanide ion) is likely to be a nucleophile because it is negatively charged.
- (c) CH_3NH_2 (methylamine) might be either a nucleophile or an electrophile depending on the circumstances. The lone pair of electrons on the nitrogen atom makes methylamine a potential nucleophile, while positively polarized N–H hydrogens make methylamine a potential acid (electrophile).
- (d) $(\text{CH}_3)_3\text{S}^+$ (trimethylsulfonium ion) is likely to be an electrophile because it is positively charged.

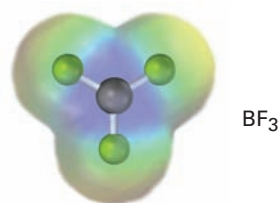
PROBLEM 6.4

Which of the following species are likely to be nucleophiles and which electrophiles?



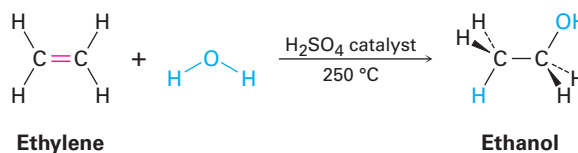
PROBLEM 6.5

An electrostatic potential map of boron trifluoride is shown. Is BF_3 likely to be a nucleophile or an electrophile? Draw a Lewis structure for BF_3 , and explain your answer.



6-5 An Example of a Polar Reaction: Addition of H_2O to Ethylene

Let's look at a typical polar process—the acid-catalyzed addition reaction of an alkene, such as ethylene, with water to give an alcohol. When ethylene is heated to $250\text{ }^\circ\text{C}$ with water and a strong acid catalyst such as H_2SO_4 , ethanol is produced. Related processes that add water to a double bond and give an alcohol occur throughout biochemistry.



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The reaction is an example of a polar reaction type known as an *electrophilic addition reaction* and can be understood using the general ideas discussed in the previous section. Let's begin by looking at the two reactants.

What do we know about ethylene? We know from Section 1-8 that a carbon-carbon double bond results from orbital overlap of two sp^2 -hybridized carbon atoms. The σ part of the double bond results from sp^2-sp^2 overlap, and the π part results from $p-p$ overlap.

What kind of chemical reactivity might we expect of a C=C bond? We know that alkanes, such as ethane, are relatively inert because the valence electrons are tied up in strong, nonpolar C-C and C-H bonds. Furthermore, the bonding electrons in alkanes are relatively inaccessible to approaching reactants because they are sheltered in σ bonds between nuclei. The electronic situation in alkenes is quite different, however. For one thing, double bonds have a greater electron density than single bonds—four electrons in a double bond versus only two in a single bond. Furthermore, the electrons in the π bond are accessible to approaching reactants because they are located above and below the plane of the double bond rather than being sheltered between nuclei (FIGURE 6.2). As a result, the double bond is nucleophilic and the chemistry of alkenes is dominated by reactions with electrophiles.

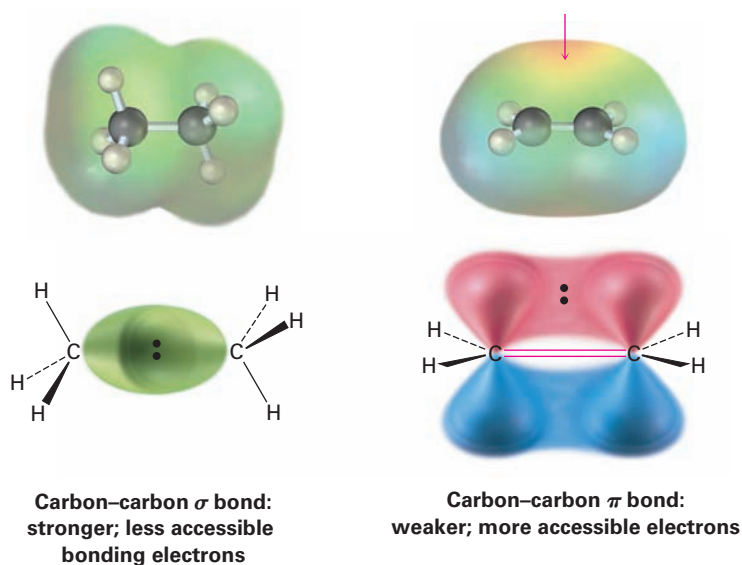


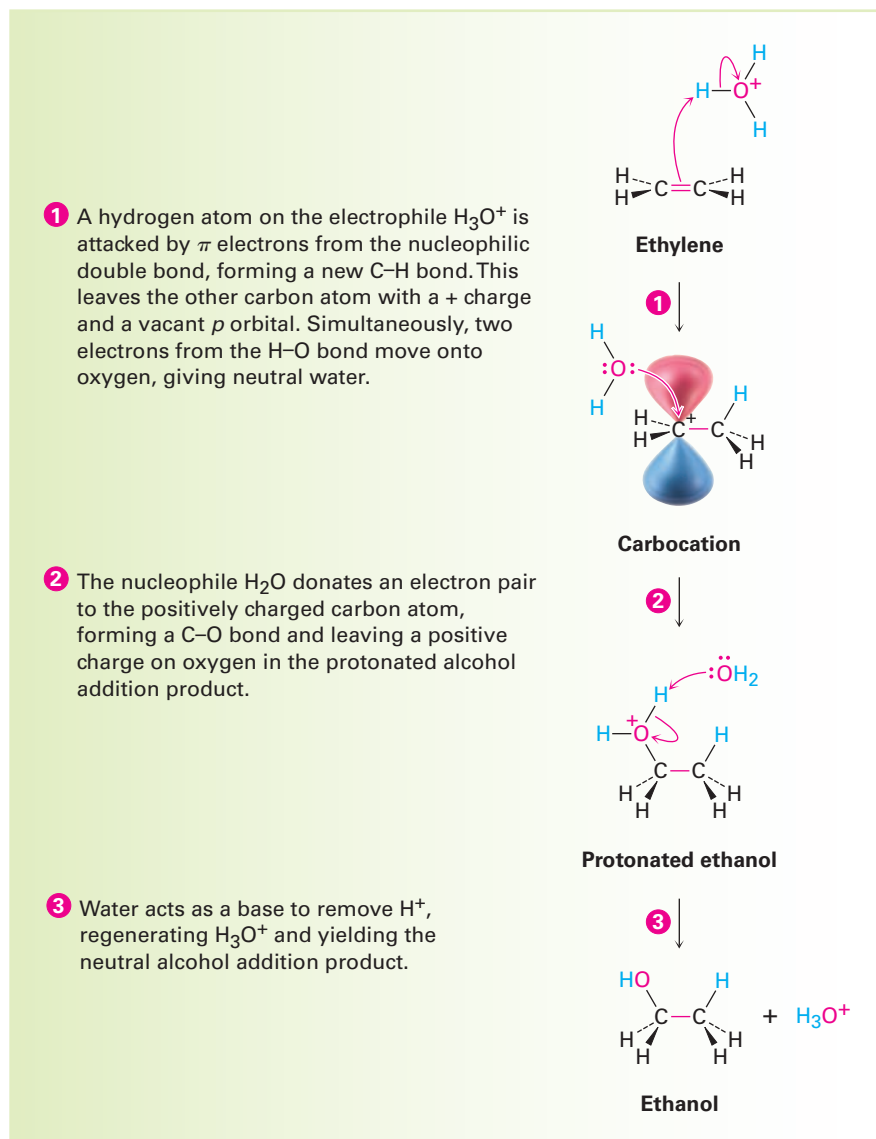
FIGURE 6.2 Comparison of carbon-carbon single and double bonds. A double bond is both more accessible to approaching reactants than a single bond and more electron-rich (more nucleophilic). An electrostatic potential map of ethylene indicates that the double bond is the region of **highest negative charge**.

What about the second reactant, H₂O? In the presence of a strong acid such as H₂SO₄, water is protonated to give the hydronium ion H₃O⁺, itself a strong acid and electrophile. Thus, the reaction between H₃O⁺ and ethylene is a typical electrophile-nucleophile combination, characteristic of all polar reactions.

We'll see more details about alkene electrophilic addition reactions shortly, but for the present we can imagine the reaction as taking place by the pathway shown in FIGURE 6.3. The reaction begins when the alkene nucleophile donates a pair of electrons from its C=C bond to H₃O⁺ to form a new C-H bond plus H₂O, as indicated by the path of the curved arrows in the first step of Figure 6.3. One curved arrow begins at the middle of the double bond (the source of the electron pair) and points to a hydrogen atom in H₃O⁺ (the atom to which a bond will form). This arrow indicates that a new C-H bond forms using electrons from the former C=C bond. Simultaneously, a second

curved arrow begins in the middle of the H–O bond and points to the O, indicating that the H–O bond breaks and the electrons from that bond remain with the O atom, giving neutral H₂O.

FIGURE 6.3 Mechanism of the acid-catalyzed electrophilic addition reaction of ethylene and H₂O. The reaction takes place in three steps, all of which involve electrophile–nucleophile interactions.



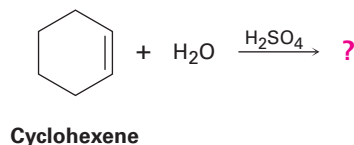
When one of the alkene carbon atoms bonds to the incoming hydrogen of H₃O⁺, the other carbon atom, having lost its share of the double-bond electrons, now has only six valence electrons and is left with a formal positive charge. This positively charged species—a carbon-cation, or **carbocation**—is itself an electrophile that can accept an electron pair from nucleophilic H₂O in a second step, forming a C–O bond and yielding a protonated alcohol addition product. Once again, a curved arrow in Figure 6.3 shows the electron-pair movement, in this case from O to the positively charged carbon. Finally, a second water molecule acts as a base to remove H⁺ from the protonated addition product, regenerating H₃O⁺ catalyst and giving the neutral alcohol.

The electrophilic addition of H₂O to ethylene is only one example of a polar process; we'll study many others in detail in later chapters. But

regardless of the details of individual reactions, all polar reactions take place between an electron-poor site and an electron-rich site and involve the donation of an electron pair from a nucleophile to an electrophile.

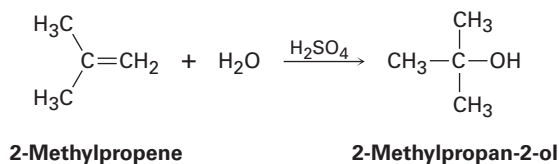
PROBLEM 6.6

What product would you expect from acid-catalyzed reaction of cyclohexene with H₂O?



PROBLEM 6.7

Acid-catalyzed reaction of H₂O with 2-methylpropene yields 2-methylpropan-2-ol. What is the structure of the carbocation formed during the reaction? Show the mechanism of the reaction.

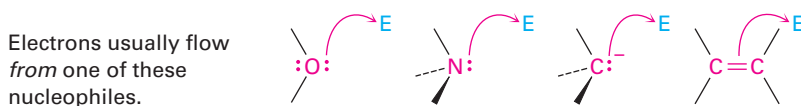


6-6 Using Curved Arrows in Polar Reaction Mechanisms

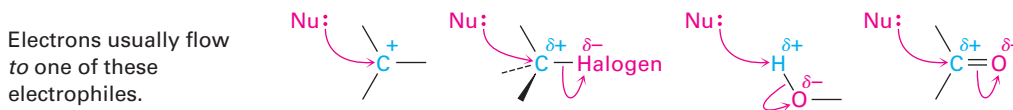
It takes practice to use curved arrows properly in reaction mechanisms like that in Figure 6.3, but there are a few rules and a few common patterns you should look for that will help you become more proficient:

Rule 1

Electrons move *from* a nucleophilic source (Nu: or Nu⁻) *to* an electrophilic sink (E or E⁺). The nucleophilic source must have an electron pair available, usually either as a lone pair or in a multiple bond. For example:

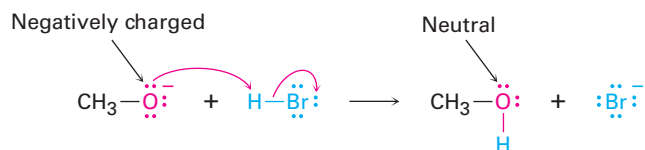


The electrophilic sink must be able to accept an electron pair, usually because it has either a positively charged atom or a positively polarized atom in a functional group. For example:

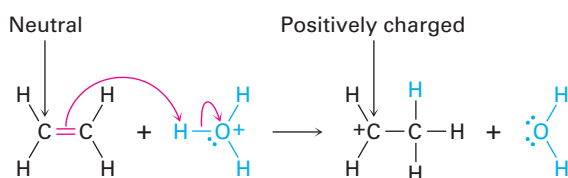


Rule 2

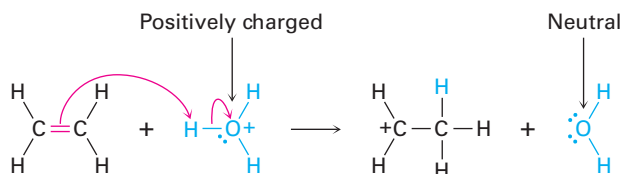
The nucleophile can be either negatively charged or neutral. If the nucleophile is negatively charged, the atom that donates an electron pair becomes neutral in the product. For example:



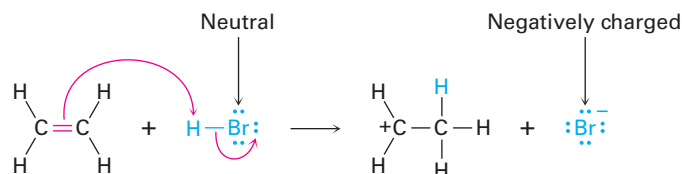
If the nucleophile is neutral, the atom that donates the electron pair acquires a positive charge in the product. For example:

**Rule 3**

The electrophile can be either positively charged or neutral. If the electrophile is positively charged, the atom bearing that charge becomes neutral after accepting an electron pair. For example:



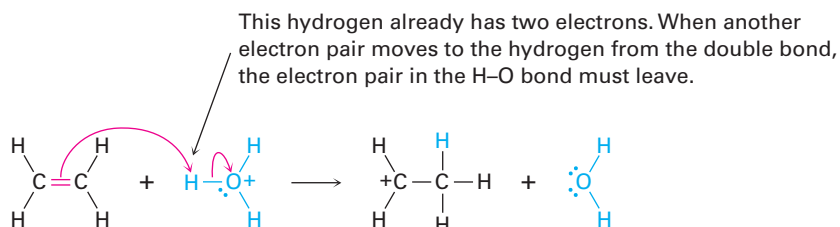
If the electrophile is neutral, the atom that ultimately accepts the electron pair acquires a negative charge. For this to happen, however, the negative charge must be stabilized by being on an electronegative atom such as oxygen, nitrogen, or a halogen. Carbon and hydrogen do not typically stabilize a negative charge. For example:



The result of Rules 2 and 3 together is that charge is conserved during the reaction. A negative charge in one of the reactants gives a negative charge in one of the products, and a positive charge in one of the reactants gives a positive charge in one of the products.

Rule 4

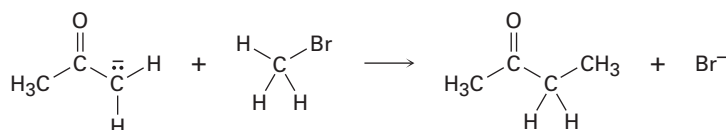
The octet rule must be followed. That is, no second-row atom can be left with ten electrons (or four for hydrogen). If an electron pair moves *to* an atom that already has an octet (or two for hydrogen), another electron pair must simultaneously move *from* that atom to maintain the octet. When two electrons move from the C=C bond of ethylene to the hydrogen atom of H_3O^+ , for instance, two electrons must leave that hydrogen. This means that the H–O bond must break and the electrons must stay with the oxygen, giving neutral water.



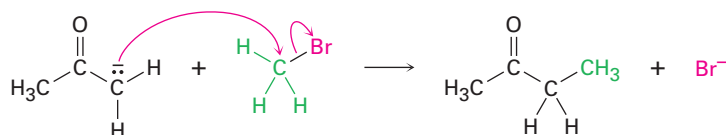
Worked Example 6.2 gives another example of drawing curved arrows.

Using Curved Arrows in Reaction Mechanisms**WORKED EXAMPLE 6.2**

Add curved arrows to the following polar reaction to show the flow of electrons:

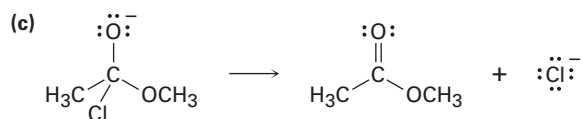
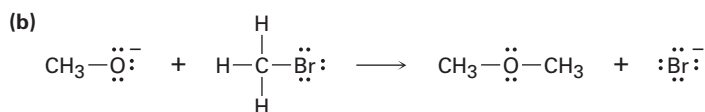
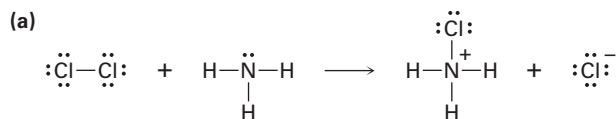
**Strategy**

Look at the reaction, and identify the bonding changes that have occurred. In this case, a C–Br bond has broken and a C–C bond has formed. The formation of the C–C bond involves donation of an electron pair from the nucleophilic carbon atom of the reactant on the left to the electrophilic carbon atom of CH_3Br , so we draw a curved arrow originating from the lone pair on the negatively charged C atom and pointing to the C atom of CH_3Br . At the same time that the C–C bond forms, the C–Br bond must break so that the octet rule is not violated. We therefore draw a second curved arrow from the C–Br bond to Br. The bromine is now a stable Br^- ion.

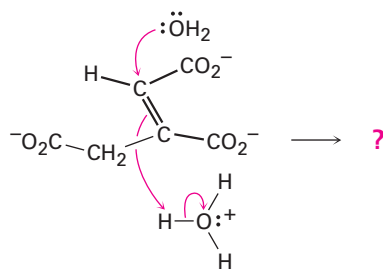
Solution

PROBLEM 6.8

Add curved arrows to the following polar reactions to indicate the flow of electrons in each:

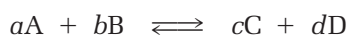
**PROBLEM 6.9**

Predict the products of the following polar reaction, a step in the citric acid cycle for food metabolism, by interpreting the flow of electrons indicated by the curved arrows.



6-7 Describing a Reaction: Equilibria, Rates, and Energy Changes

Every chemical reaction can go in either forward or reverse direction. Reactants can go forward to products, and products can revert to reactants. As you may remember from your general chemistry course, the position of the resulting chemical equilibrium is expressed by an equation in which K_{eq} , the equilibrium constant, is equal to the product concentrations multiplied together, divided by the reactant concentrations multiplied together, with each concentration raised to the power of its coefficient in the balanced equation. For the generalized reaction

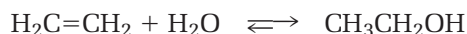


we have

$$K_{\text{eq}} = \frac{[\text{C}]^c [\text{D}]^d}{[\text{A}]^a [\text{B}]^b}$$

The value of the equilibrium constant tells which side of the reaction arrow is energetically favored. If K_{eq} is much larger than 1, then the product concentration term $[\text{C}]^c [\text{D}]^d$ is much larger than the reactant concentration term $[\text{A}]^a [\text{B}]^b$ and the reaction proceeds as written from left to right. If K_{eq} is near 1, appreciable amounts of both reactant and product are present at equilibrium. And if K_{eq} is much smaller than 1, the reaction does not take place as written but instead goes in the reverse direction, from right to left.

In the reaction of ethylene with H_2O , for example, we can write the following equilibrium expression and determine experimentally that the equilibrium constant at room temperature is approximately 25.

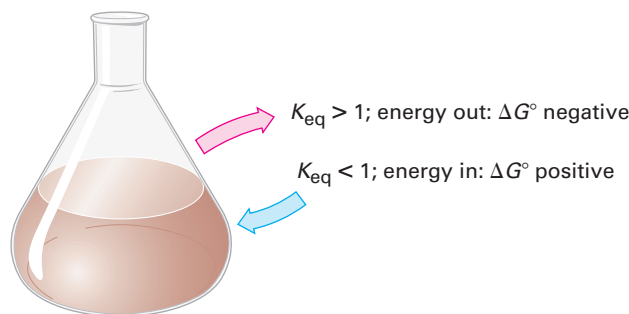


$$K_{\text{eq}} = \frac{[\text{CH}_3\text{CH}_2\text{OH}]}{[\text{H}_2\text{C}=\text{CH}_2][\text{H}_2\text{O}]} = 25$$

Because K_{eq} is a bit larger than 1, the reaction proceeds as written but a substantial amount of unreacted ethylene remains at equilibrium. For practical purposes, an equilibrium constant greater than about 10^3 is needed for the amount of reactant left over to be barely detectable (less than 0.1%).

What determines the magnitude of the equilibrium constant? For a reaction to have a favorable equilibrium constant and proceed as written, the energy of the products must be lower than the energy of the reactants. In other words, energy must be released. The situation is analogous to that of a rock poised precariously in a high-energy position near the top of a hill. When it rolls downhill, the rock releases energy until it reaches a more stable, low-energy position at the bottom.

The energy change that occurs during a chemical reaction is called the **Gibbs free-energy change (ΔG)** and is equal to the free energy of the products minus the free energy of the reactants: $\Delta G = G_{\text{products}} - G_{\text{reactants}}$. For a favorable reaction, ΔG has a negative value, meaning that energy is lost by the chemical system and released to the surroundings. Such reactions are said to be **exergonic**. For an unfavorable reaction, ΔG has a positive value, meaning that energy is absorbed by the chemical system *from* the surroundings. Such reactions are said to be **endergonic**.



You might also recall from general chemistry that the *standard* free-energy change for a reaction is denoted ΔG° , where the superscript $^\circ$ means that the reaction is carried out under standard conditions, with pure substances in

their most stable form at 1 atm pressure and a specified temperature, usually 298 K. For biological reactions, the standard free-energy change is symbolized ΔG° and refers to a reaction carried out at pH = 7.0 with solute concentrations of 1.0 M.

Because the equilibrium constant, K_{eq} , and the standard free-energy change, ΔG° , both measure whether a reaction is favorable, they are mathematically related by the equation

$$\Delta G^\circ = -RT \ln K_{\text{eq}} \quad \text{or} \quad K_{\text{eq}} = e^{-\Delta G^\circ/RT}$$

where

$$R = 8.314 \text{ J}/(\text{K}\cdot\text{mol}) = 1.987 \text{ cal}/(\text{K}\cdot\text{mol})$$

$$T = \text{kelvin temperature}$$

$$e = 2.718$$

$$\ln K_{\text{eq}} = \text{natural logarithm of } K_{\text{eq}}$$

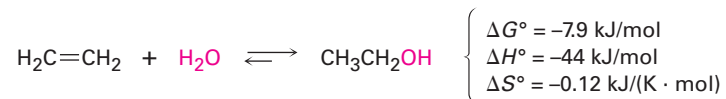
For example, the reaction of ethylene with H_2O has $K_{\text{eq}} = 25$, so $\Delta G^\circ = -7.9 \text{ kJ/mol}$ (-1.9 kcal/mol) at 298 K:

$$\begin{aligned} K_{\text{eq}} = 25 \quad \text{and} \quad \ln K_{\text{eq}} = 3.2 \\ \Delta G^\circ = -RT \ln K_{\text{eq}} = -[8.314 \text{ J}/(\text{K}\cdot\text{mol})] (298 \text{ K}) (3.2) \\ = -7,900 \text{ J/mol} = -7.9 \text{ kJ/mol} \end{aligned}$$

The free-energy change ΔG is made up of two terms, an *enthalpy* term, ΔH , and a temperature-dependent *entropy* term, $T\Delta S$. Of the two terms, the enthalpy term is often larger and more dominant.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

For the reaction of ethylene with H_2O at room temperature (298 K), the approximate values are



The **enthalpy change, ΔH** , also called the **heat of reaction**, is a measure of the change in total bonding energy during a reaction. If ΔH is negative, as in the reaction of H_2O with ethylene, the products have less energy than the reactants. Thus, the products are more stable and have stronger bonds than the reactants, heat is released, and the reaction is said to be **exothermic**. If ΔH is positive, the products are less stable and have weaker bonds than the reactants, heat is absorbed, and the reaction is said to be **endothermic**. For example, if a certain reaction breaks reactant bonds with a total strength of 380 kJ/mol and forms product bonds with a total strength of 400 kJ/mol, then ΔH for the reaction is -20 kJ/mol and the reaction is exothermic.

The **entropy change, ΔS** , is a measure of the change in the amount of molecular randomness, or freedom of motion, that accompanies a reaction. For example, in an elimination reaction of the type



there is more freedom of movement and molecular randomness in the products than in the reactant because one molecule has split into two. Thus, there is a net increase in entropy during the reaction and ΔS has a positive value.

On the other hand, for an addition reaction of the type



the opposite is true. Because such reactions restrict the freedom of movement of two molecules by joining them together, the product has less randomness than the reactants and ΔS has a negative value. The reaction of ethylene and H_2O to yield ethanol, which has $\Delta S^\circ = -120 \text{ J}/(\text{K}\cdot\text{mol})$, is an example. TABLE 6.2 describes the thermodynamic terms more fully.

TABLE 6.2 Explanation of Thermodynamic Quantities: $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$

Term	Name	Explanation
ΔG°	Gibbs free-energy change	The energy difference between reactants and products. When ΔG° is negative, the reaction is exergonic , has a favorable equilibrium constant, and can occur spontaneously. When ΔG° is positive, the reaction is endergonic , has an unfavorable equilibrium constant, and cannot occur spontaneously.
ΔH°	Enthalpy change	The heat of reaction, or difference in strength between the bonds broken in a reaction and the bonds formed. When ΔH° is negative, the reaction releases heat and is exothermic . When ΔH° is positive, the reaction absorbs heat and is endothermic .
ΔS°	Entropy change	The change in molecular randomness during a reaction. When ΔS° is negative, randomness decreases. When ΔS° is positive, randomness increases.

Knowing the value of K_{eq} for a reaction is useful, but it's important to realize the limitations. An equilibrium constant tells only the *position* of the equilibrium, or how much product is theoretically possible. It doesn't tell the *rate* of reaction, or how fast the equilibrium is established. Some reactions are extremely slow even though they have favorable equilibrium constants. Gasoline is stable at room temperature, for instance, because the rate of its reaction with oxygen is slow at 298 K. Only at higher temperatures, such as contact with a lighted match, does gasoline react rapidly with oxygen and undergo complete conversion to the equilibrium products water and carbon dioxide. Rates (*how fast* a reaction occurs) and equilibria (*how much* a reaction occurs) are entirely different.

Rate → Is the reaction fast or slow?

Equilibrium → In what direction does the reaction proceed?

PROBLEM 6.10

Which reaction is more energetically favored, one with $\Delta G^\circ = -44 \text{ kJ/mol}$ or one with $\Delta G^\circ = +44 \text{ kJ/mol}$?

PROBLEM 6.11

Which reaction is likely to be more exergonic, one with $K_{\text{eq}} = 1000$ or one with $K_{\text{eq}} = 0.001$?

6-8 Describing a Reaction: Bond Dissociation Energies

We've just seen that heat is released (negative ΔH) when a bond is formed because the products are more stable and have stronger bonds than the reactants. Conversely, heat is absorbed (positive ΔH) when a bond is broken because the products are less stable and have weaker bonds than the reactants. The amount of energy needed to break a given bond to produce two radical fragments when the molecule is in the gas phase at 25 °C is a quantity called *bond strength*, or **bond dissociation energy** (D).

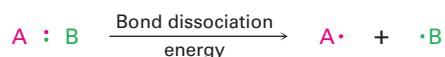
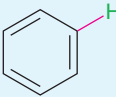
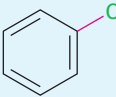
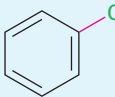
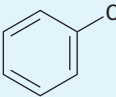
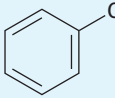
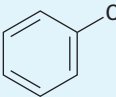
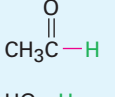
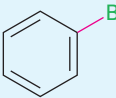
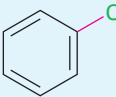
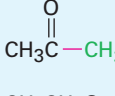


TABLE 6.3 Some Bond Dissociation Energies, D

Bond	D (kJ/mol)	Bond	D (kJ/mol)	Bond	D (kJ/mol)
H—H	436	(CH ₃) ₃ C—I	227	C ₂ H ₅ —CH ₃	370
H—F	570	H ₂ C=CH—H	464	(CH ₃) ₂ CH—CH ₃	369
H—Cl	431	H ₂ C=CH—Cl	396	(CH ₃) ₃ C—CH ₃	363
H—Br	366	H ₂ C=CHCH ₂ —H	369	H ₂ C=CH—CH ₃	426
H—I	298	H ₂ C=CHCH ₂ —Cl	298	H ₂ C=CHCH ₂ —CH ₃	318
Cl—Cl	242		472	H ₂ C=CH ₂	728
Br—Br	194		400		427
I—I	152		375		325
CH ₃ —H	439		300		374
CH ₃ —Cl	350		336	HO—H	497
CH ₃ —Br	294		464	HO—OH	211
CH ₃ —I	239	HC≡C—H	558	CH ₃ O—H	440
CH ₃ —OH	385	CH ₃ —CH ₃	377	CH ₃ S—H	366
CH ₃ —NH ₂	386			C ₂ H ₅ O—H	441
C ₂ H ₅ —H	421				352
C ₂ H ₅ —Cl	352			CH ₃ CH ₂ O—CH ₃	355
C ₂ H ₅ —Br	293			NH ₂ —H	450
C ₂ H ₅ —I	233			H—CN	528
C ₂ H ₅ —OH	391				
(CH ₃) ₂ CH—H	410				
(CH ₃) ₂ CH—Cl	354				
(CH ₃) ₂ CH—Br	299				
(CH ₃) ₃ C—H	400				
(CH ₃) ₃ C—Cl	352				
(CH ₃) ₃ C—Br	293				

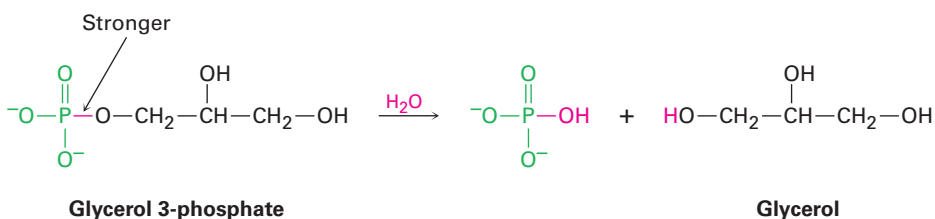
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Each specific bond has its own characteristic strength, and extensive tables of data are available. For example, a C–H bond in methane has a bond dissociation energy $D = 439.3$ kJ/mol (105.0 kcal/mol), meaning that 439.3 kJ/mol must be added to break a C–H bond of methane to give the two radical fragments $\cdot\text{CH}_3$ and $\cdot\text{H}$. Conversely, 439.3 kJ/mol of energy is released when a methyl radical and a hydrogen atom combine to form methane. **TABLE 6.3** lists some other bond strengths.

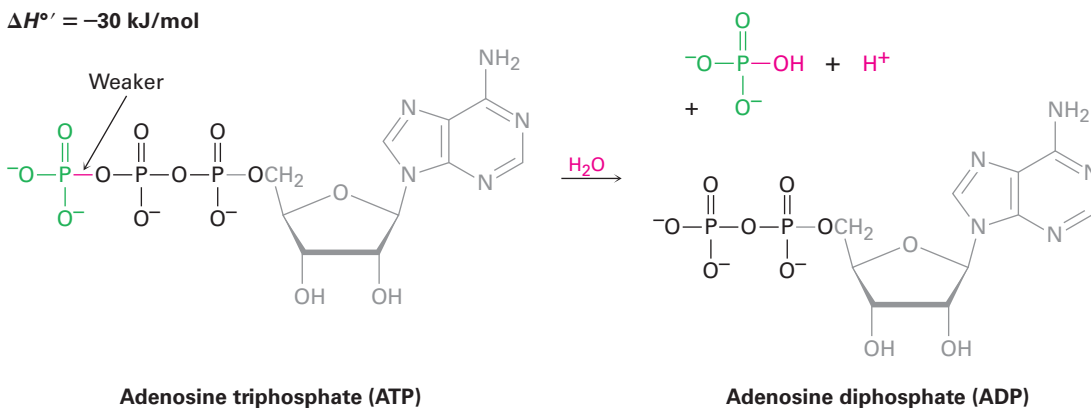
Think again about the connection between bond strengths and chemical reactivity. In an exothermic reaction, more heat is released than is absorbed. But because making bonds in the products releases heat and breaking bonds in the reactants absorbs heat, the bonds in the products must be stronger than the bonds in the reactants. In other words, exothermic reactions are favored by products with strong bonds and by reactants with weak, easily broken bonds.

Sometimes, particularly in biochemistry, reactive substances that undergo highly exothermic reactions, such as ATP (adenosine triphosphate), are referred to as “energy-rich” or “high-energy” compounds. Such a label doesn’t mean that ATP is special or different from other compounds; it means only that ATP has relatively weak bonds that require a relatively small amount of heat to break, thus leading to a larger release of heat when a strong new bond forms in a reaction. When a typical organic phosphate such as glycerol 3-phosphate reacts with water, for instance, only 9 kJ/mol of heat is released ($\Delta H = -9$ kJ/mol), but when ATP reacts with water, 30 kJ/mol of heat is released ($\Delta H = -30$ kJ/mol). The difference between the two reactions is due to the fact that the bond broken in ATP is substantially weaker than the bond broken in glycerol 3-phosphate. We’ll see the metabolic importance of this reaction in future chapters.

$$\Delta H^\circ = -9 \text{ kJ/mol}$$



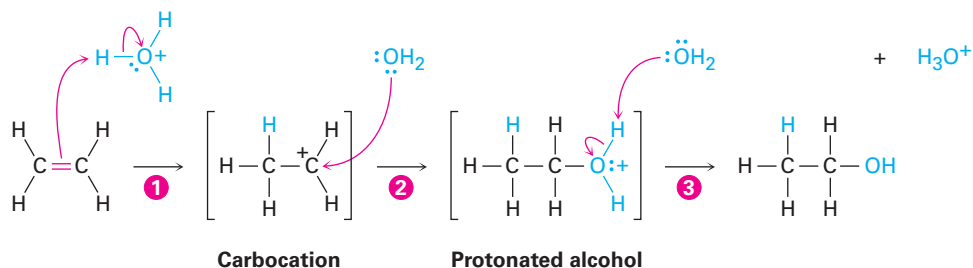
$$\Delta H^\circ = -30 \text{ kJ/mol}$$



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6-9 Describing a Reaction: Energy Diagrams and Transition States

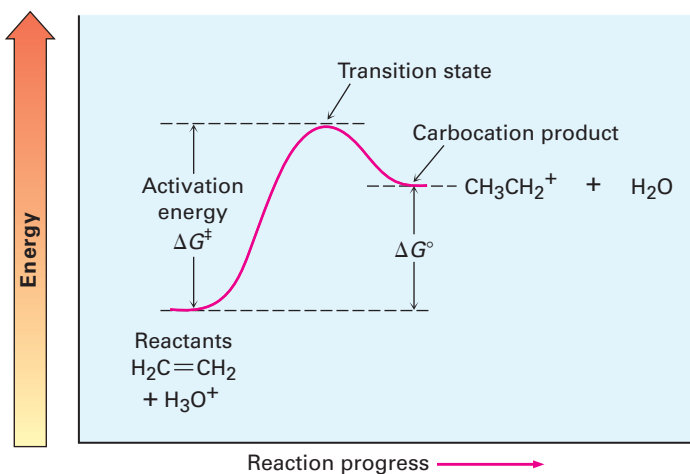
For a reaction to take place, reactant molecules must collide and reorganization of atoms and bonds must occur. Let's again look at the three-step addition reaction of H_2O and ethylene:



As the reaction proceeds, ethylene and H_3O^+ must approach each other, the ethylene π bond and an $\text{H}-\text{O}$ bond must break, a new $\text{C}-\text{H}$ bond must form in the first step, and a new $\text{C}-\text{O}$ bond must form in the second step.

To depict graphically the energy changes that occur during a reaction, chemists use energy diagrams, such as that shown in **FIGURE 6.4**. The vertical axis of the diagram represents the total energy of all reactants, and the horizontal axis, called the *reaction coordinate*, represents the progress of the reaction from beginning to end. Let's see how the addition of H_2O to ethylene can be described in an energy diagram.

FIGURE 6.4 Energy diagram for the first step in the reaction of ethylene with H_2O . The energy difference between reactants and transition state, ΔG^\ddagger , defines the reaction rate. The energy difference between reactants and carbocation product, ΔG° , defines the position of the equilibrium.



At the beginning of the reaction, ethylene and H_3O^+ have the total amount of energy indicated by the reactant level on the left side of the diagram in Figure 6.4. As the two reactants collide and reaction commences, their electron clouds repel each other, causing the energy level to rise. If the collision has occurred with enough force and proper orientation, however, the reactants continue to approach each other despite the rising repulsion until the new

C–H bond starts to form. At some point, a structure of maximum energy is reached, a structure called the *transition state*.

The **transition state** represents the highest-energy structure involved in this step of the reaction. It is unstable and can't be isolated, but we can nevertheless imagine it to be an activated complex of the two reactants in which both the C–C π bond and H–O bond are partially broken and the new C–H bond is partially formed (**FIGURE 6.5**).

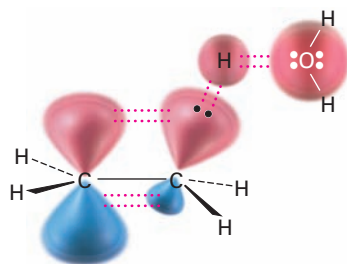


FIGURE 6.5 Hypothetical transition-state structure for the first step of the reaction of ethylene with H_3O^+ . The C=C π bond and O–H bond are just beginning to break, and the C–H bond is just beginning to form.

The energy difference between reactants and transition state is called the **activation energy**, ΔG^\ddagger , and determines how rapidly the reaction occurs at a given temperature. (The double-dagger superscript, \ddagger , always refers to the transition state.) A large activation energy results in a slow reaction because few collisions occur with enough energy for the reactants to reach the transition state. A small activation energy results in a rapid reaction because almost all collisions occur with enough energy for the reactants to reach the transition state.

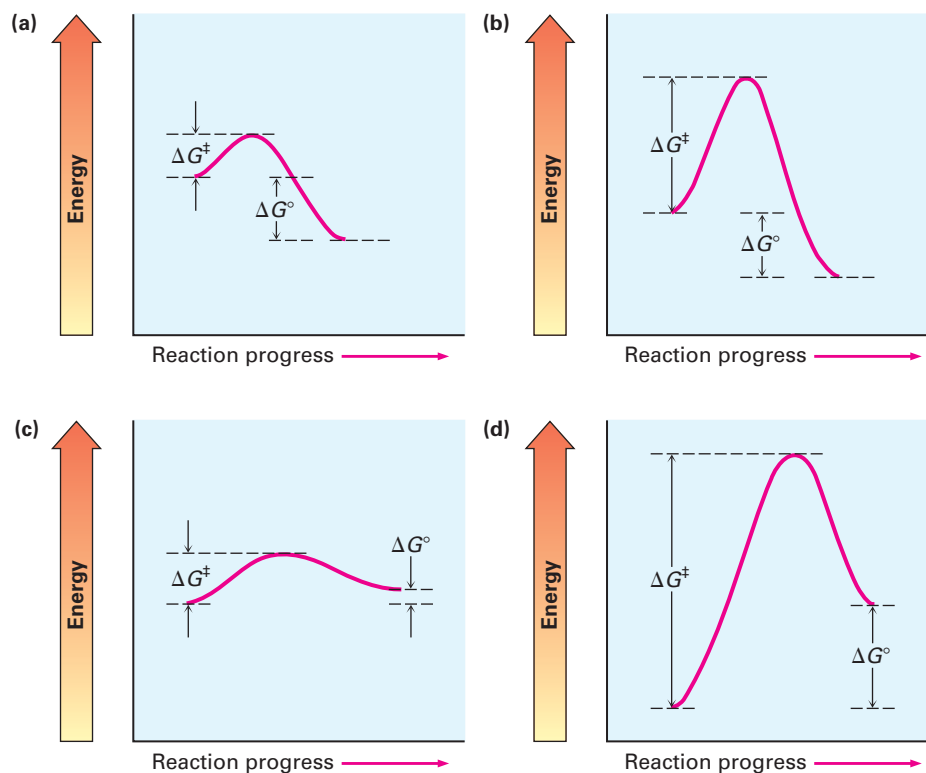
As an analogy, you might think of reactants that need enough energy to climb the activation barrier from reactant to transition state as similar to hikers who need enough energy to climb a mountain pass. If the pass is a high one, the hikers need a lot of energy and surmount the barrier with difficulty. If the pass is low, however, the hikers need less energy and reach the top easily.

As a rough generalization, many organic reactions have activation energies in the range 40 to 150 kJ/mol (10–35 kcal/mol). Reactions with activation energies less than 80 kJ/mol take place at or below room temperature, while reactions with higher activation energies normally require a higher temperature to give the reactants enough energy to climb the activation barrier.

Once the transition state is reached, the reaction can either continue on to give the carbocation product or revert back to reactants. When reversion to reactants occurs, the transition-state structure comes apart and an amount of free energy corresponding to $-\Delta G^\ddagger$ is released. When the reaction continues on to give the carbocation, the new C–H bond forms fully and an amount of energy corresponding to the difference between transition state and carbocation product is released. The net energy change for the step, ΔG° , is represented in the diagram as the difference in level between reactant and product. Since the carbocation is higher in energy than the starting alkene, the step is endergonic, has a positive value of ΔG° , and absorbs energy.

Not all energy diagrams are like that shown for the reaction of ethylene and H_3O^+ . Each reaction has its own energy profile. Some reactions are fast (small ΔG^\ddagger) and some are slow (large ΔG^\ddagger); some have a negative ΔG° , and some have a positive ΔG° . **FIGURE 6.6** illustrates some different possibilities.

FIGURE 6.6 Some hypothetical energy diagrams. (a) A fast exergonic reaction (small ΔG^\ddagger , negative ΔG°); (b) a slow exergonic reaction (large ΔG^\ddagger , negative ΔG°); (c) a fast endergonic reaction (small ΔG^\ddagger , small positive ΔG°); (d) a slow endergonic reaction (large ΔG^\ddagger , positive ΔG°).

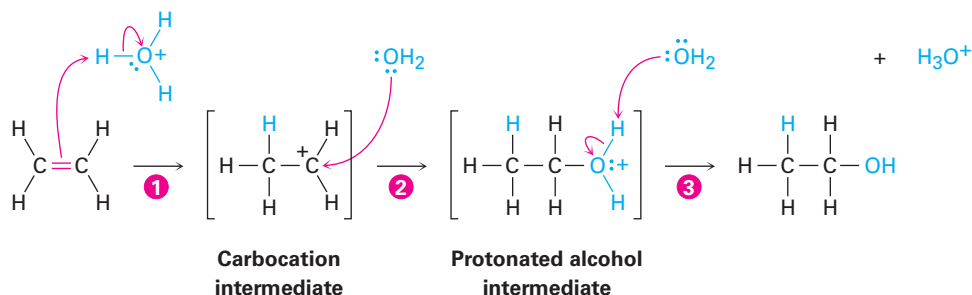


PROBLEM 6.12

Which reaction is faster, one with $\Delta G^\ddagger = +45$ kJ/mol or one with $\Delta G^\ddagger = +70$ kJ/mol?

6-10 Describing a Reaction: Intermediates

How can we describe the carbocation formed in the first step of the reaction of ethylene with water? The carbocation is clearly different from the reactants, yet it isn't a transition state and it isn't a final product.



We call the carbocation, which exists only transiently during the course of the multistep reaction, a **reaction intermediate**. As soon as the intermediate is formed in the first step by reaction of ethylene with H_3O^+ , it reacts further

with H_2O in the second step to give the protonated alcohol product. This second step has its own activation energy ΔG^\ddagger , its own transition state, and its own energy change ΔG° . We can picture the second transition state as an activated complex between the electrophilic carbocation intermediate and a nucleophilic water molecule, in which H_2O donates a pair of electrons to the positively charged carbon atom as the new C–O bond starts to form.

Just as the carbocation formed in the first step is a reaction intermediate, the protonated alcohol formed in the second step is also an intermediate. Only after this second intermediate is deprotonated by an acid–base reaction with water is the final product formed.

A complete energy diagram for the overall reaction of ethylene with water is shown in **FIGURE 6.7**. In essence, we draw a diagram for each of the individual steps and then join them so that the carbocation *product* of step 1 is the *reactant* for step 2 and the product of step 2 is the reactant for step 3. As indicated in Figure 6.7, the reaction intermediates lie at energy minima between steps. Because the energy level of each intermediate is higher than the level of either the reactant that formed it or the product it yields, intermediates can't normally be isolated. They are, however, more stable than the two transition states that neighbor them.

Each step in a multistep process can always be considered separately. Each step has its own ΔG^\ddagger and its own ΔG° . The overall ΔG° of the reaction, however, is the energy difference between initial reactants and final products.

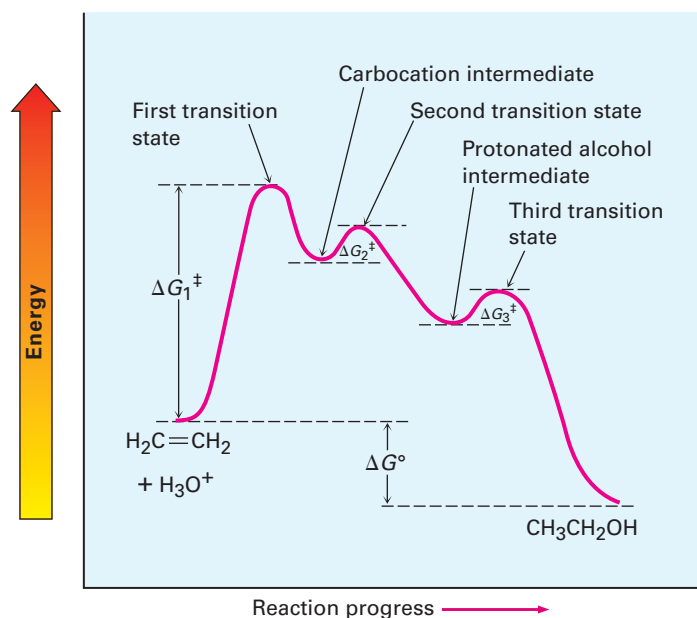


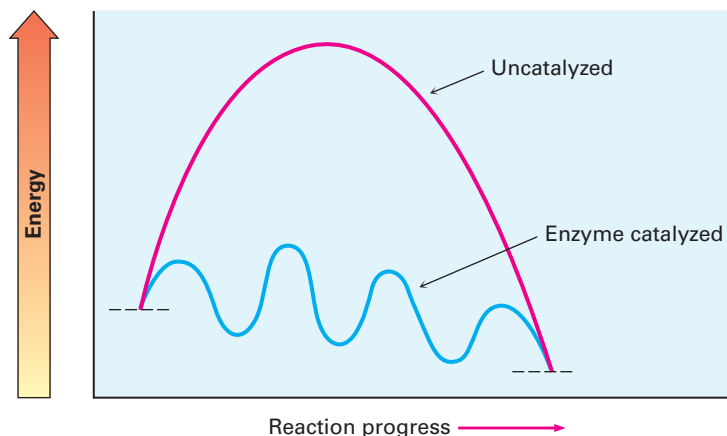
FIGURE 6.7 Overall energy diagram for the reaction of ethylene with water. Three steps are involved, each with its own transition state. The energy minimum between steps 1 and 2 represents the carbocation reaction intermediate, and the minimum between steps 2 and 3 represents the protonated alcohol intermediate.

The biological reactions that take place in living organisms have the same energy requirements as reactions that take place in the laboratory and can be described in similar ways. They are, however, constrained by the fact that they must have low enough activation energies to occur at moderate temperatures, and they must release energy in relatively small amounts to avoid overheating the organism. These constraints are generally met through the use of large, structurally complex, enzyme catalysts that change the mechanism of a reaction to an alternative pathway that proceeds through a series of small

steps rather than one or two large steps. Thus, a typical energy diagram for a biological reaction might look like that in **FIGURE 6.8**.

FIGURE 6.8 Energy diagrams for a typical enzyme-catalyzed biological reaction versus an uncatalyzed laboratory reaction.

The biological reaction involves many steps, each of which has a relatively small activation energy and small energy change. The end result is the same, however.



WORKED EXAMPLE 6.3

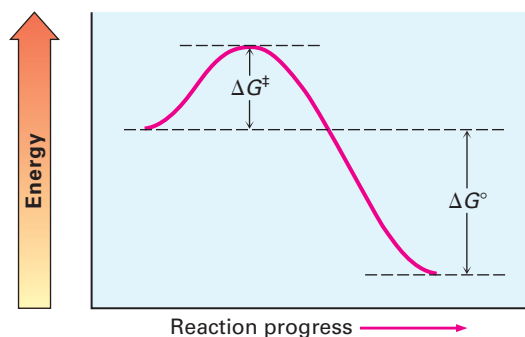
Drawing an Energy Diagram for a Reaction

Sketch an energy diagram for a one-step reaction that is fast and highly exergonic.

Strategy

A fast reaction has a small ΔG^\ddagger , and a highly exergonic reaction has a large negative ΔG° .

Solution



WORKED EXAMPLE 6.4

Drawing an Energy Diagram for a Reaction

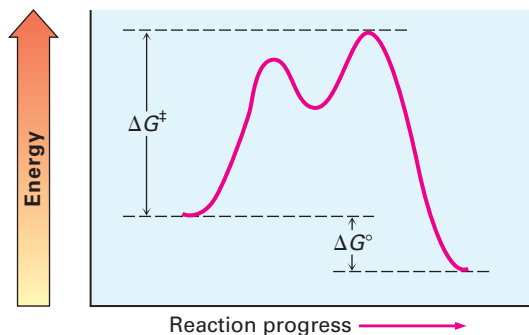
Sketch an energy diagram for a two-step exergonic reaction whose second step has a higher-energy transition state than its first step. Show ΔG^\ddagger and ΔG° for the overall reaction.

Strategy

A two-step reaction has two transition states and an intermediate between them. The ΔG^\ddagger for the overall reaction is the energy change between reactants

and the highest-energy transition state—the second one in this case. An exergonic reaction has a negative overall ΔG° .

Solution



PROBLEM 6.13

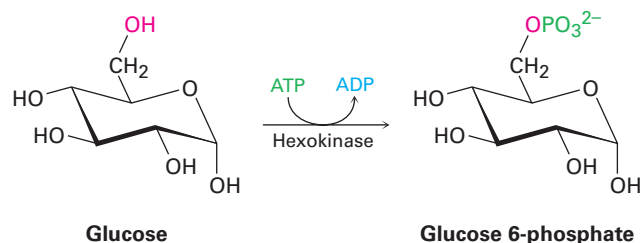
Sketch an energy diagram for a two-step reaction in which both steps are exergonic and in which the second step has a higher-energy transition state than the first. Label the parts of the diagram corresponding to reactant, product, intermediate, overall ΔG^\ddagger , and overall ΔG° .

6-11 A Comparison between Biological Reactions and Laboratory Reactions

Beginning in the next chapter, we'll be seeing a lot of reactions, some that are important in laboratory chemistry yet don't occur in nature and others that have counterparts in biological pathways. In comparing laboratory reactions with biological reactions, several differences are apparent. For one, laboratory reactions are usually carried out in an organic solvent such as diethyl ether or dichloromethane to dissolve the reactants and bring them into contact, whereas biological reactions occur in the aqueous medium inside cells. For another, laboratory reactions often take place over a wide range of temperatures without catalysts, while biological reactions take place at the temperature of the organism and are catalyzed by enzymes.

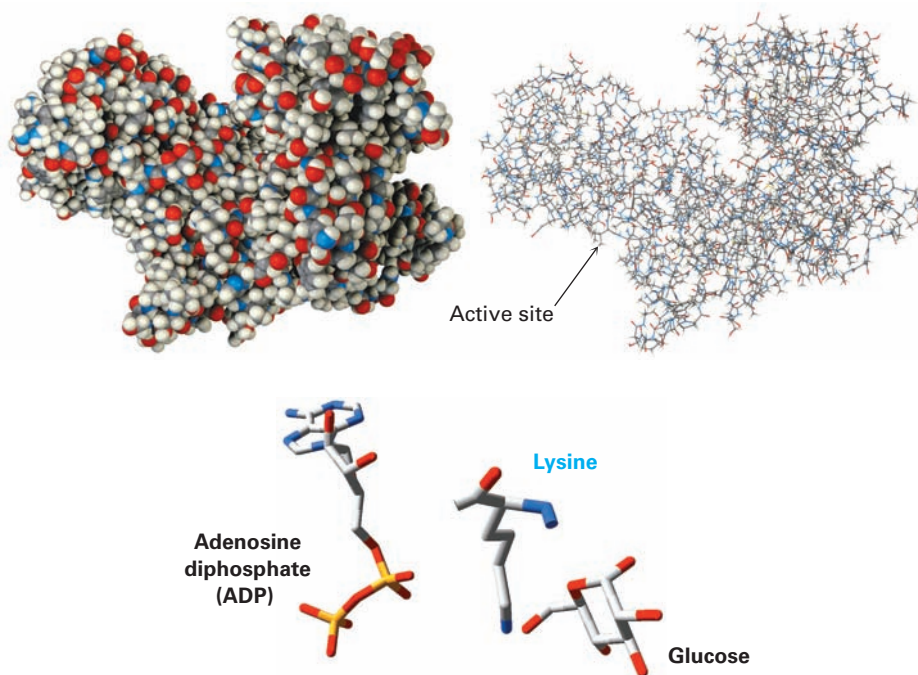
We'll be mentioning specific enzymes frequently throughout this book (all enzyme names end with the suffix *-ase*) and will look at them in more detail in Chapter 19. You may already be aware, however, that an **enzyme** is a large, globular, protein molecule that contains in its structure a protected pocket called its **active site**. The active site is lined by acidic or basic groups as needed for catalysis and has precisely the right shape to bind and hold a substrate molecule in the orientation necessary for reaction. **FIGURE 6.9** shows a molecular model of hexokinase, along with an X-ray crystal structure of the glucose substrate and adenosine diphosphate (ADP) bound in the active

site. Hexokinase is an enzyme that catalyzes the initial step of glucose metabolism—the transfer of a phosphate group from ATP to glucose, giving glucose 6-phosphate and ADP. The structures of ATP and ADP were shown at the end of Section 6-8.



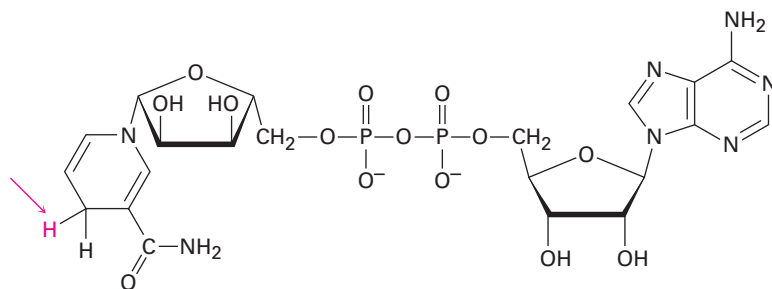
Note how the hexokinase-catalyzed phosphorylation reaction of glucose is shown. It's common when writing biological equations to show only the structure of the primary reactant and product, while abbreviating the structures of various biological “reagents” and by-products such as ATP and ADP. A curved arrow intersecting the straight reaction arrow indicates that ATP is also a reactant and ADP also a product.

FIGURE 6.9 Models of hexokinase in space-filling and wire-frame formats. The cleft that contains the active site where substrate binding and reaction catalysis occur is indicated. At the bottom is an X-ray crystal structure of the enzyme active site, showing the positions of both glucose and ADP as well as a lysine amino acid that acts as a base to deprotonate glucose.



Yet another difference between laboratory and biological reactions is that laboratory reactions are often done using relatively small, simple reagents such as Br_2 , HCl , NaBH_4 , CrO_3 , and so forth, while biological reactions usually

involve relatively complex “reagents” called *coenzymes*. In the hexokinase-catalyzed phosphorylation of glucose just shown, ATP is the coenzyme. As another example, compare the H_2 molecule, a laboratory reagent that adds to a carbon–carbon double bond to yield an alkane, with the reduced nicotinamide adenine dinucleotide (NADH) molecule, a coenzyme that effects an analogous addition of hydrogen to a double bond in many biological pathways. Of all the atoms in the entire coenzyme, only the one hydrogen atom shown in red is transferred to the double-bond substrate.



**Reduced nicotinamide adenine dinucleotide, NADH
(a coenzyme)**

Don't be intimidated by the size of the NADH molecule; most of the structure is there to provide an overall shape for binding to the enzyme and to provide appropriate solubility behavior. When looking at biological molecules, focus on the small part of the molecule where the chemical change takes place.

One final difference between laboratory and biological reactions is in their specificity. A catalyst such as sulfuric acid might be used in the laboratory to catalyze the addition of water to thousands of different alkenes (Section 6-5), but an enzyme, because it binds a specific substrate molecule having a very specific shape, will catalyze only a very specific reaction. It's this exquisite specificity that makes biological chemistry so remarkable and that makes life possible. **TABLE 6.4** summarizes some of the differences between laboratory and biological reactions.

TABLE 6.4 A Comparison of Typical Laboratory and Biological Reactions

	Laboratory reaction	Biological reaction
Solvent	Organic liquid, such as ether	Aqueous environment in cells
Temperature	Wide range; -80 to 150 °C	Temperature of organism
Catalyst	Either none or very simple	Large, complex enzymes needed
Reagent size	Usually small and simple	Relatively complex coenzymes
Specificity	Little specificity for substrate	Very high specificity for substrate

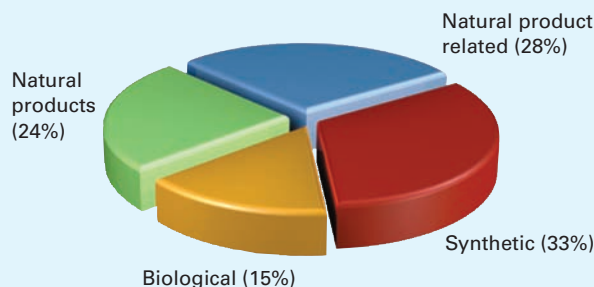
SOMETHING EXTRA

Where Do Drugs Come From?

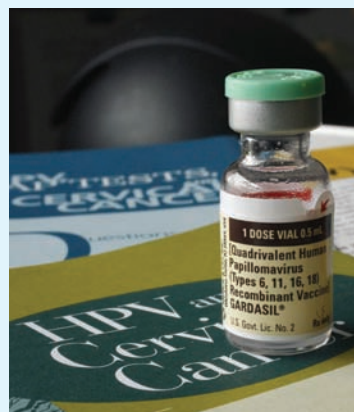
It has been estimated that major pharmaceutical companies in the United States spend some \$38 billion per year on drug research and development, while government agencies and private foundations spend another \$28 billion. What does this money buy? For the period 2001–2012, the money resulted in a total of 293 new molecular entities (NMEs)—new biologically active chemical substances approved for sale as drugs by the U.S. Food and Drug Administration (FDA). That's an average of only 24 new drugs each year, spread over all diseases and conditions.

Where do the new drugs come from? According to a study carried out at the U.S. National Cancer Institute, only about 33% of new drugs are entirely synthetic and completely unrelated to any naturally occurring substance. The remaining 67% take their lead, to a greater or lesser extent, from nature. Vaccines and genetically engineered proteins of biological origin account for 15% of NMEs, but most new drugs come from *natural products*, a catchall term generally taken to mean small molecules found in bacteria, plants, and other living organisms (see eChapter 25). Unmodified natural products isolated directly from the producing organism account for 24% of NMEs, while natural products that have been chemically modified in the laboratory account for the remaining 28%.

Origin of New Drugs 1981–2002



Many years of work go into screening many thousands of substances to identify a single compound that

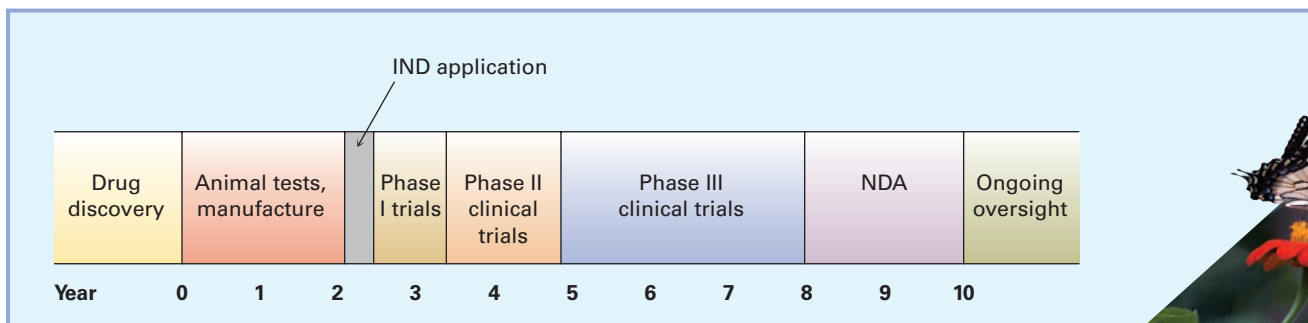


AP Images/Harry Cabluck, FILE

Introduced in June, 2006, Gardasil is the first vaccine ever approved for the prevention of cancer. Where do new drugs like this come from?

might ultimately gain approval as an NME. But after that single compound has been identified, the work has just begun because it takes an average of 9 to 10 years for a drug to make it through the approval process. First, the safety of the drug in animals must be demonstrated and an economical method of manufacture must be devised. With these preliminaries out of the way, an Investigational New Drug (IND) application is submitted to the FDA for permission to begin testing in humans.

Human testing takes 5 to 7 years and is divided into three phases. Phase I clinical trials are carried out on a small group of healthy volunteers to establish safety and look for side effects. Several months to a year are needed, and only about 70% of drugs pass at this point. Phase II clinical trials next test the drug for 1 to 2 years in several hundred patients with the target disease or condition, looking both for safety and for efficacy, and only about 33% of the original group pass. Finally, phase III trials are undertaken on a large sample of patients to document definitively the drug's safety, dosage, and efficacy. If the drug is one of the 25% of the original group that make it to the end of phase III, all the data are then gathered into a New Drug Application (NDA) and sent to the FDA for review and approval, which can take another 2 years. Ten years have elapsed and at least \$500 million has been spent, with only a 20% success rate for the drugs that began testing. Finally, though, the drug will begin to appear in medicine cabinets. The following timeline shows the process.

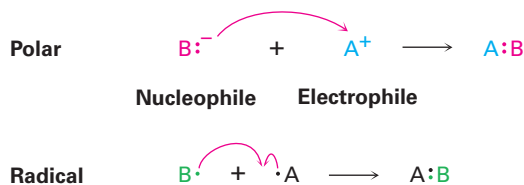


SUMMARY

All chemical reactions, whether in the laboratory or in living organisms, follow the same “rules.” To understand both organic and biological chemistry, it’s necessary to know not just *what* occurs but also *why* and *how* chemical reactions take place. In this chapter, we’ve taken a brief look at the fundamental kinds of organic reactions, we’ve seen why reactions occur, and we’ve seen how reactions can be described.

There are four common kinds of reactions: **addition reactions** take place when two reactants add together to give a single product; **elimination reactions** take place when one reactant splits apart to give two products; **substitution reactions** take place when two reactants exchange parts to give two new products; and **rearrangement reactions** take place when one reactant undergoes a reorganization of bonds and atoms to give an isomeric product.

A full description of how a reaction occurs is called its **mechanism**. There are two general kinds of mechanisms by which most reactions take place: **radical** mechanisms and **polar** mechanisms. Polar reactions, the more common type, occur because of an attractive interaction between a **nucleophilic** (electron-rich) site in one molecule and an **electrophilic** (electron-poor) site in another molecule. A bond is formed in a polar reaction when the nucleophile donates an electron pair to the electrophile. This movement of electrons is indicated by a curved arrow showing the direction of electron travel from the nucleophile to the electrophile. Radical reactions involve species that have an odd number of electrons. A bond is formed when each reactant donates one electron.



The energy changes that take place during reactions can be described by considering both rates (how fast the reactions occur) and equilibria (how much the reactions occur). The position of a chemical equilibrium is determined by the value of the **free-energy change (ΔG)** for the reaction, where $\Delta G = \Delta H - T\Delta S$. The **enthalpy** term (ΔH) corresponds to the net change in strength of chemical bonds broken and formed during reaction; the **entropy** term (ΔS) corresponds to the change in the amount of molecular randomness

KEY WORDS

- activation energy (ΔG^\ddagger), 169
- active site, 173
- addition reaction, 147
- bond dissociation energy (D), 166
- carbocation, 158
- electrophile, 154
- elimination reaction, 147
- endergonic, 163
- endothermic, 164
- enthalpy change (ΔH), 164
- entropy change (ΔS), 164
- enzyme, 173
- exergonic, 163
- exothermic, 164
- Gibbs free-energy change (ΔG), 163
- heat of reaction, 164
- nucleophile, 154
- polar reaction, 149
- radical, 149
- radical reaction, 149
- reaction intermediate, 170
- reaction mechanism, 148
- rearrangement reaction, 147
- substitution reaction, 147
- transition state, 169

during the reaction. Reactions that have negative values of ΔG release energy, are said to be **exergonic**, and have favorable equilibria. Reactions that have positive values of ΔG absorb energy, are said to be **endergonic**, and have unfavorable equilibria.

A reaction can be described pictorially using an energy diagram that follows the reaction course from reactant through transition state to product. The **transition state** is an activated complex occurring at the highest-energy point of a reaction. The amount of energy needed by reactants to reach this high point is the **activation energy**, ΔG^\ddagger . The higher the activation energy, the slower the reaction.

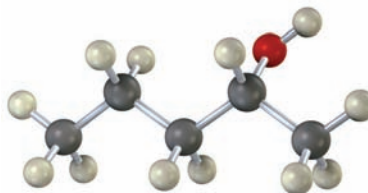
Many reactions take place in more than one step and involve the formation of a **reaction intermediate**. An intermediate is a species that lies at an energy minimum between steps on the reaction curve and is formed briefly during the course of a reaction.

EXERCISES

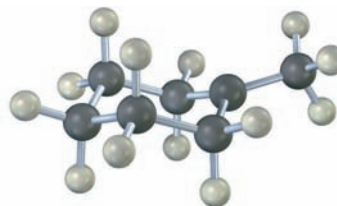
VISUALIZING CHEMISTRY

(Problems 6.1–6.13 appear within the chapter.)

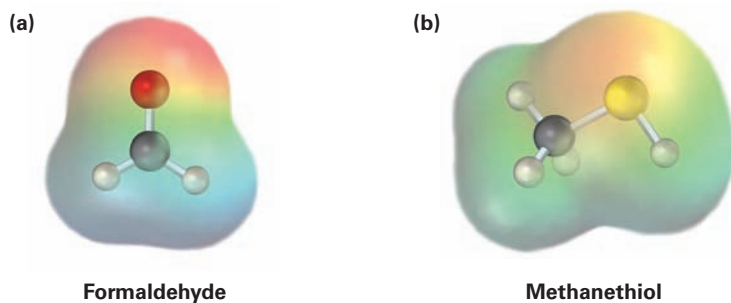
- 6.14 The following alcohol can be prepared by addition of H_2O to two different alkenes. Draw the structures of both (red = O).



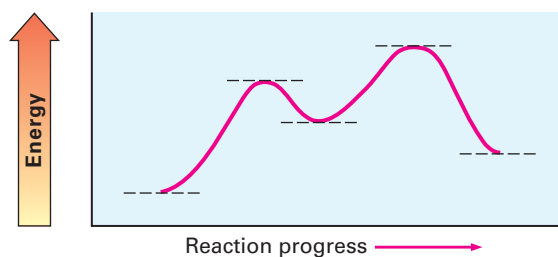
- 6.15 The following structure represents the carbocation intermediate formed in the addition reaction of HBr to two different alkenes to yield an alcohol. Draw the structures of both.



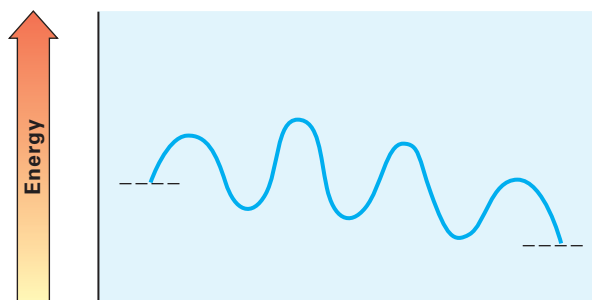
- 6.16 Electrostatic potential maps of (a) formaldehyde (CH_2O) and (b) methanethiol (CH_3SH) are shown. Is the formaldehyde carbon atom likely to be electrophilic or nucleophilic? What about the methanethiol sulfur atom? Explain.



- 6.17 Look at the following energy diagram:



- (a) Is ΔG° for the reaction positive or negative? Label it on the diagram.
- (b) How many steps are involved in the reaction?
- (c) How many transition states are there? Label them on the diagram.
- 6.18 Look at the following energy diagram for an enzyme-catalyzed reaction:

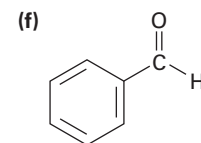
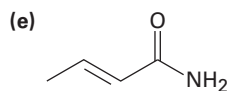
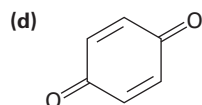
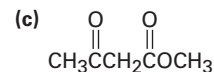
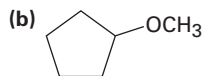
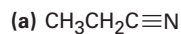


- (a) How many steps are involved?
- (b) Which step is most exergonic?
- (c) Which step is slowest?

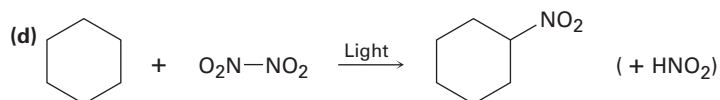
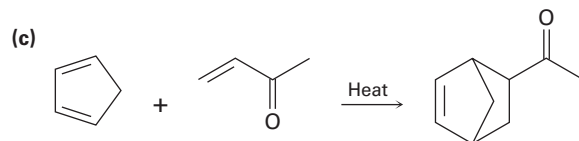
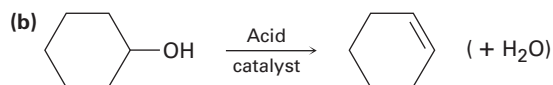
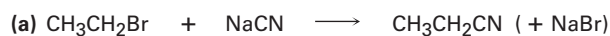
ADDITIONAL PROBLEMS

Polar Reactions

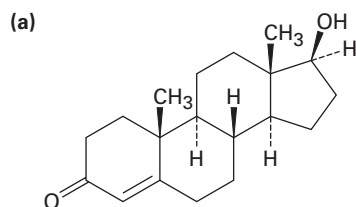
6.19 Identify the functional groups in the following molecules, and show the polarity of each:



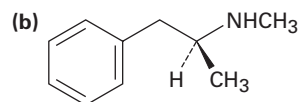
6.20 Identify the following reactions as additions, eliminations, substitutions, or rearrangements:



6.21 Identify the likely electrophilic and nucleophilic sites in each of the following molecules:

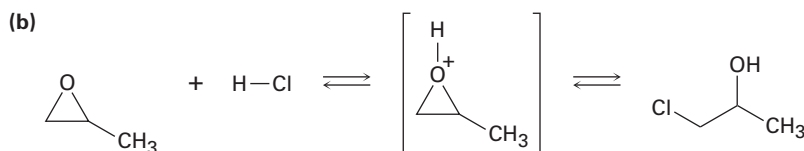
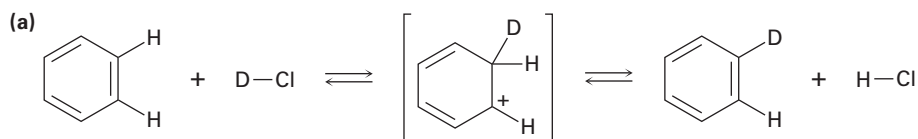


Testosterone

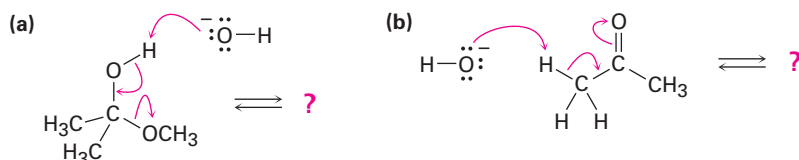


Methamphetamine

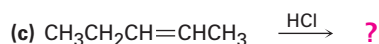
6.22 Add curved arrows to the following polar reactions to indicate the flow of electrons in each:



6.23 Follow the flow of electrons indicated by the curved arrows in each of the following polar reactions, and predict the products that result:



6.24 Alkenes undergo addition reactions when treated with HBr and HCl to give bromoalkanes and chloroalkanes, respectively. Draw the products you might expect from the following reactions:

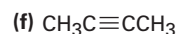
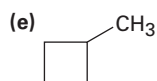
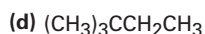
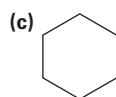
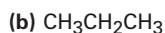


Radical Reactions

6.25 When a mixture of methane and chlorine is irradiated, reaction commences immediately. When irradiation is stopped, the reaction gradually slows down but does not stop immediately. Explain.

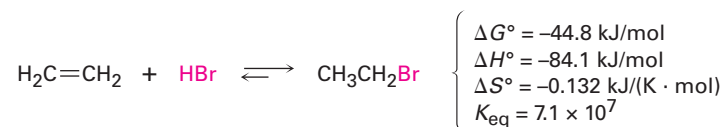
6.26 Radical chlorination of pentane is a poor way to prepare 1-chloropentane, but radical chlorination of neopentane, $(\text{CH}_3)_4\text{C}$, is a good way to prepare neopentyl chloride, $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$. Explain.

6.27 Despite the limitations of radical chlorination of alkanes, the reaction is still useful for synthesizing certain halogenated compounds. For which of the following compounds does radical chlorination give a single monochloro product?

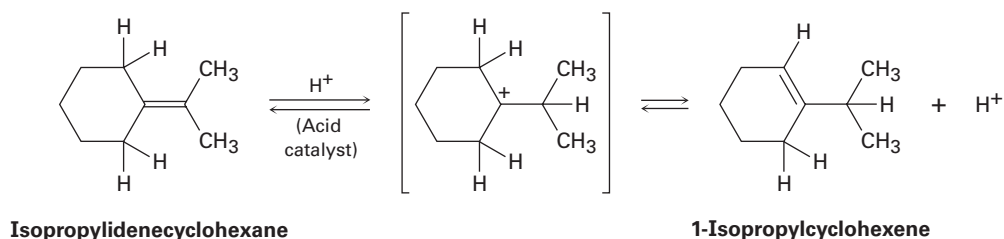


Energy Diagrams and Reaction Mechanisms

- 6.28** What is the difference between a transition state and an intermediate?
- 6.29** Draw an energy diagram for a one-step reaction with $K_{\text{eq}} < 1$. Label the parts of the diagram corresponding to reactants, products, transition state, ΔG° , and ΔG^\ddagger . Is ΔG° positive or negative?
- 6.30** Draw an energy diagram for a two-step reaction with $K_{\text{eq}} > 1$. Label the overall ΔG° , transition states, and intermediate. Is ΔG° positive or negative?
- 6.31** Draw an energy diagram for a two-step exergonic reaction whose second step is faster than its first step.
- 6.32** Draw an energy diagram for a reaction with $K_{\text{eq}} = 1$. What is the value of ΔG° in this reaction?
- 6.33** As noted in Problem 6.24, alkenes undergo addition reactions with HBr to yield bromoalkanes. The reaction of ethylene with HBr has the following thermodynamic parameters:



- (a) Is the reaction exothermic or endothermic?
- (b) Is the reaction favorable (spontaneous) or unfavorable (nonspontaneous) at room temperature (298 K)?
- 6.34** When isopropylidenecyclohexane is treated with strong acid at room temperature, isomerization occurs by the mechanism shown below to yield 1-isopropylcyclohexene:

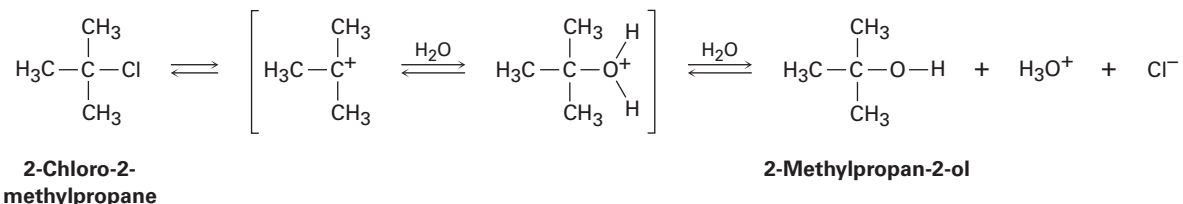


At equilibrium, the product mixture contains about 30% isopropylidenecyclohexane and about 70% 1-isopropylcyclohexene.

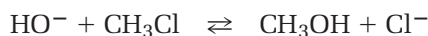
- (a) What is an approximate value of K_{eq} for the reaction?
- (b) Since the reaction occurs slowly at room temperature, what is its approximate ΔG^\ddagger ?
- (c) Draw an energy diagram for the reaction.
- 6.35** Add curved arrows to the mechanism shown in Problem 6.34 to indicate the electron movement in each step.

General Problems

- 6.36 2-Chloro-2-methylpropane reacts with water in three steps to yield 2-methylpropan-2-ol. The first step is slower than the second, which in turn is much slower than the third. The reaction takes place slowly at room temperature, and the equilibrium constant is near 1.

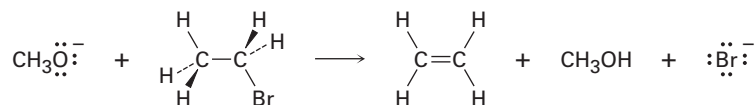


- (a) Give approximate values for ΔG^\ddagger and ΔG° that are consistent with the above information.
- (b) Draw an energy diagram for the reaction, labeling all points of interest and making sure that the relative energy levels on the diagram are consistent with the information given.
- 6.37 Add curved arrows to the mechanism shown in Problem 6.36 to indicate the electron movement in each step.
- 6.38 The reaction of hydroxide ion with chloromethane to yield methanol and chloride ion is an example of a general reaction type called a *nucleophilic substitution reaction*:



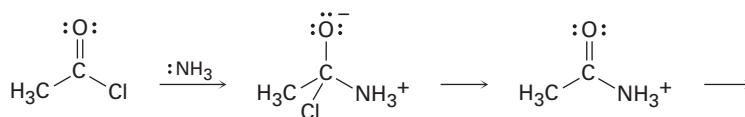
The value of ΔH° for the reaction is -75 kJ/mol , and the value of ΔS° is $+54 \text{ J/(K}\cdot\text{mol)}$. What is the value of ΔG° (in kJ/mol) at 298 K ? Is the reaction exothermic or endothermic? Is it exergonic or endergonic?

- 6.39 Methoxide ion (CH_3O^-) reacts with bromoethane in a single step according to the following equation:

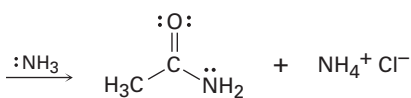


Identify the bonds broken and formed, and draw curved arrows to represent the flow of electrons during the reaction.

- 6.40 Ammonia reacts with acetyl chloride (CH_3COCl) to give acetamide (CH_3CONH_2). Identify the bonds broken and formed in each step of the reaction, and draw curved arrows to represent the flow of electrons in each step.

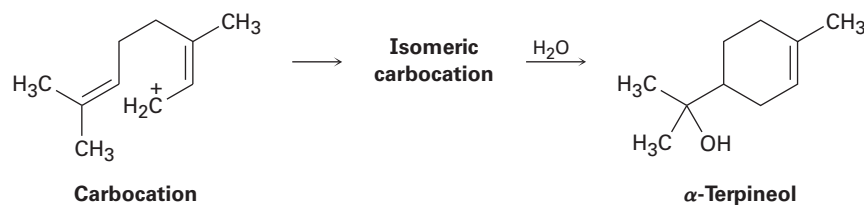


Acetyl chloride

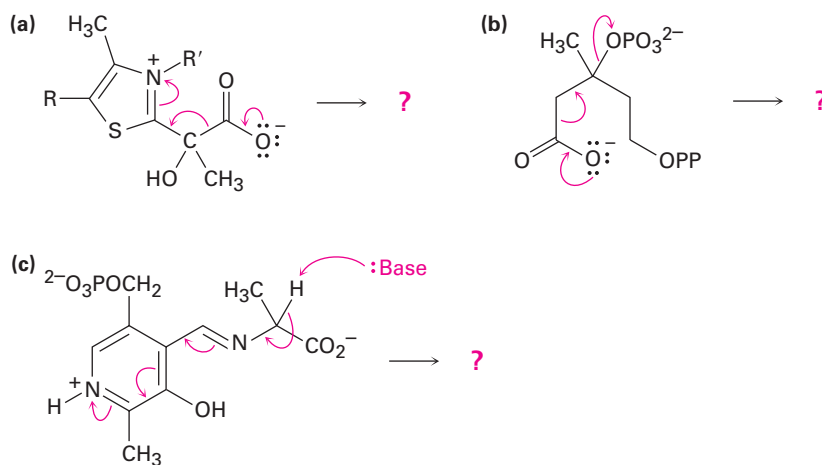


Acetamide

- 6.41 The naturally occurring molecule α -terpineol is biosynthesized by a route that includes the following step:



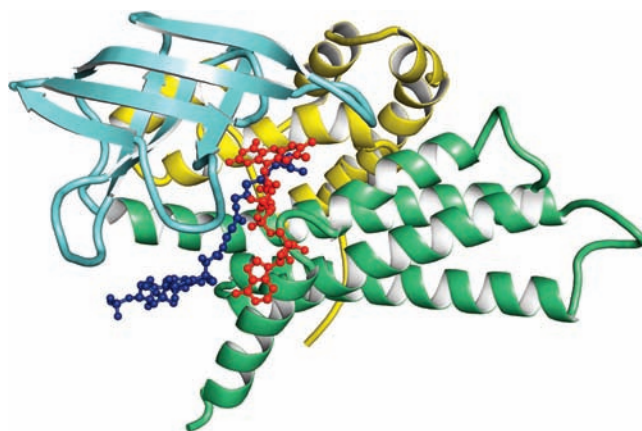
- (a) Propose a likely structure for the isomeric carbocation intermediate.
- (b) Show the mechanism of each step in the biosynthetic pathway, using curved arrows to indicate electron flow.
- 6.42 Predict the product(s) of each of the following biological reactions by interpreting the flow of electrons as indicated by the curved arrows:



- 6.43 Reaction of 2-methylpropene with H_3O^+ might, in principle, lead to a mixture of two alcohol addition products. Name them, and draw their structures.
- 6.44 Draw the structures of the two carbocation intermediates that might form during the reaction of 2-methylpropene with H_3O^+ (Problem 6.43). We'll see in the next chapter that the stability of carbocations depends on the number of alkyl substituents attached to the positively charged carbon—the more alkyl substituents there are, the more stable the cation. Which of the two carbocation intermediates you drew is more stable?

Alkenes and Alkynes

7

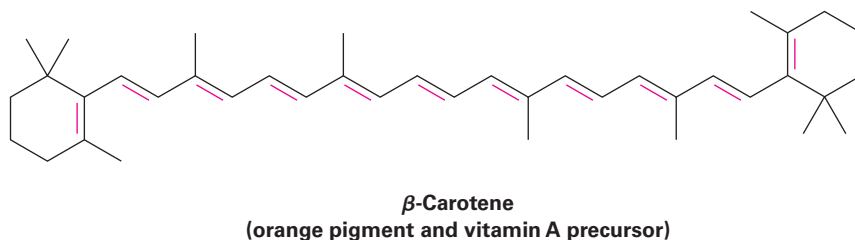
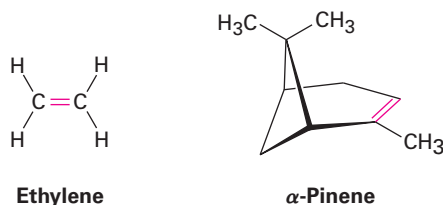


Acyl CoA dehydrogenase catalyzes the introduction of a C=C double bond into fatty acids during their metabolism.

WHY THIS CHAPTER?

Carbon-carbon double bonds are present in most organic and biological molecules, so a good understanding of their behavior is needed. In this chapter, we'll look at some consequences of alkene stereoisomerism and then focus in detail on the broadest and most general class of alkene reactions, the electrophilic addition reaction. Carbon-carbon *triple* bonds, by contrast, occur only rarely in biological molecules and pathways, so we'll not spend much time on their chemistry.

An **alkene**, sometimes called an *olefin*, is a hydrocarbon that contains a carbon-carbon double bond. An **alkyne** is a hydrocarbon that contains a carbon-carbon triple bond. Alkenes occur abundantly in nature, but alkynes are much less common. Ethylene, for instance, is a plant hormone that induces ripening in fruit, and α -pinene is the major component of turpentine. Life itself would be impossible without such polyalkenes as β -carotene, a compound that contains 11 double bonds. An orange pigment responsible for the color of carrots, β -carotene is an important dietary source of vitamin A and is thought to offer some protection against certain types of cancer.



CONTENTS

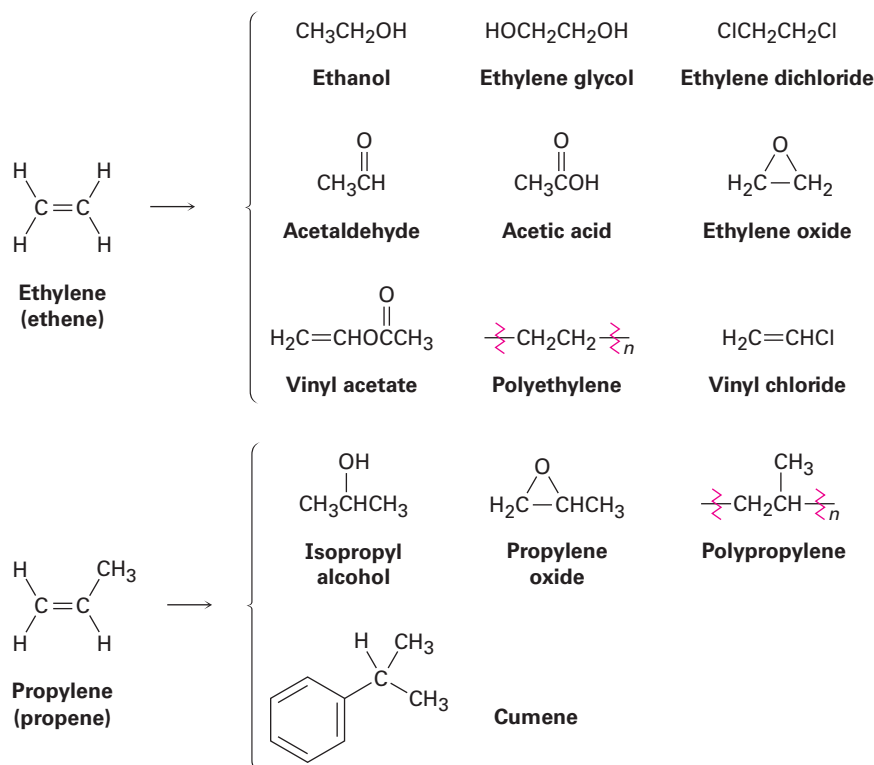
- 7-1** Calculating the Degree of Unsaturation
- 7-2** Naming Alkenes and Alkynes
- 7-3** Cis-Trans Isomerism in Alkenes
- 7-4** Alkene Stereochemistry and the *E,Z* Designation
- 7-5** Stability of Alkenes
- 7-6** Electrophilic Addition Reactions of Alkenes
- 7-7** Orientation of Electrophilic Addition: Markovnikov's Rule
- 7-8** Carbocation Structure and Stability
- 7-9** The Hammond Postulate
- 7-10** Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements

SOMETHING EXTRA

Terpenes: Naturally Occurring Alkenes

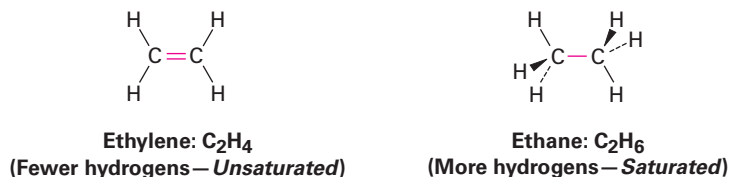


Ethylene and propylene, the simplest alkenes, are the two most important organic chemicals produced industrially. Approximately 127 million metric tons of ethylene and 54 million metric tons of propylene are produced worldwide each year (1 metric ton = 1000 kg = 2205 lb). Polyethylene, polypropylene, ethylene glycol, acetic acid, acetaldehyde, and a host of other substances are all prepared from ethylene and propylene. Both are synthesized industrially by the “cracking” of C_2 – C_8 alkanes on heating to temperatures up to 900 °C.



7-1 Calculating the Degree of Unsaturation

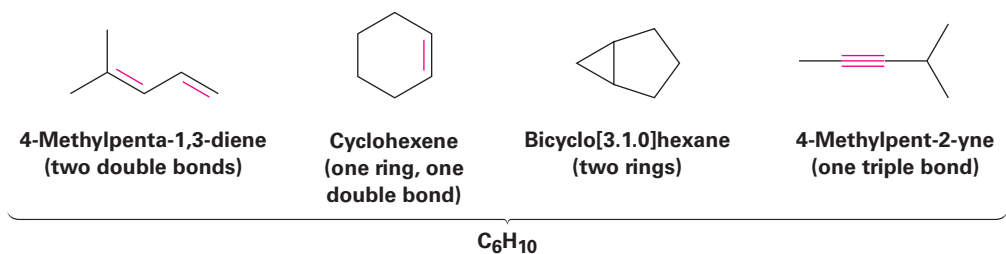
Because of its double bond, an alkene has two fewer hydrogens than an alkane with the same number of carbons— C_nH_{2n} for an alkene versus C_nH_{2n+2} for an alkane—and is therefore referred to as **unsaturated**. Ethylene, for example, has the formula C_2H_4 , whereas ethane has the formula C_2H_6 .



In general, each ring or double bond in a molecule corresponds to a loss of two hydrogens from the related alkane formula C_nH_{2n+2} . Knowing this relationship, it's possible to work backward from a molecular formula to calculate

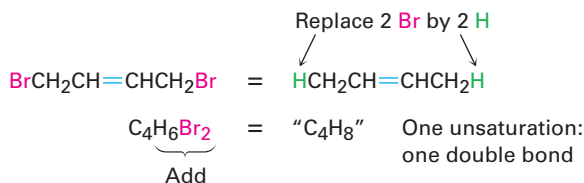
a molecule's **degree of unsaturation**—the number of rings and/or multiple bonds present in the molecule.

Let's assume that we want to find the structure of an unknown hydrocarbon. A molecular weight determination on the unknown yields a value of 82 u, which corresponds to a molecular formula of C_6H_{10} . Since the saturated C_6 alkane (hexane) has the formula C_6H_{14} , the unknown compound has two fewer pairs of hydrogens ($H_{14} - H_{10} = H_4 = 2 H_2$) so its degree of unsaturation is 2. The unknown therefore contains two double bonds, one ring and one double bond, two rings, or one triple bond. There's still a long way to go to establish structure, but the simple calculation has told us a lot about the molecule.

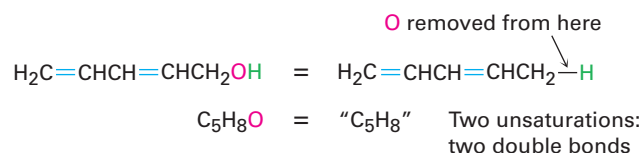


Similar calculations can be carried out for compounds containing elements other than just carbon and hydrogen:

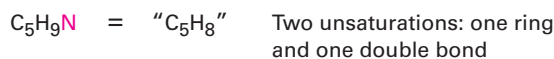
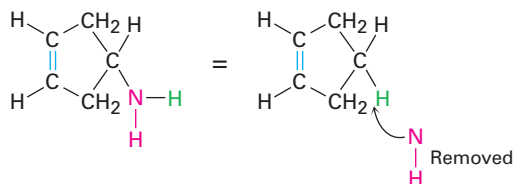
- **Organohalogen compounds (C, H, X, where X = F, Cl, Br, or I)** A halogen substituent forms one bond and acts as a replacement for hydrogen in an organic molecule, so we can add the number of halogens and hydrogens to arrive at an equivalent hydrocarbon formula from which the degree of unsaturation can be found. For example, the formula $C_4H_6Br_2$ is equivalent to the hydrocarbon formula C_4H_8 and thus corresponds to one degree of unsaturation.



- **Organooxygen compounds (C, H, O)** Oxygen forms two bonds, so it doesn't affect the formula of an equivalent hydrocarbon and can be ignored when calculating the degree of unsaturation. You can convince yourself of this by seeing what happens when an oxygen atom is inserted into an alkane bond: $C-C$ becomes $C-O-C$ or $C-H$ becomes $C-O-H$, and there is no change in the number of hydrogen atoms. For example, the formula C_5H_8O is equivalent to the hydrocarbon formula C_5H_8 and thus corresponds to two degrees of unsaturation.



- **Organonitrogen compounds (C, H, N)** Nitrogen forms three bonds, so an organonitrogen compound has one more hydrogen than a related hydrocarbon. We therefore subtract the number of nitrogens from the number of hydrogens to arrive at the equivalent hydrocarbon formula. Again, you can convince yourself of this by seeing what happens when a nitrogen atom is inserted into an alkane bond: C–C becomes C–NH–C or C–H becomes C–NH₂, meaning that one additional hydrogen atom has been added. We must therefore subtract this extra hydrogen atom to arrive at the equivalent hydrocarbon formula. For example, the formula C₅H₉N is equivalent to C₅H₈ and thus has two degrees of unsaturation.



To summarize:

- **Add** the number of halogens to the number of hydrogens.
- **Ignore** the number of oxygens.
- **Subtract** the number of nitrogens from the number of hydrogens.

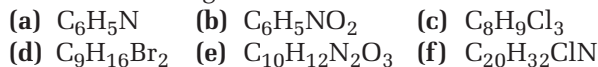
PROBLEM 7.1

Calculate the degree of unsaturation in each of the following formulas, and then draw as many structures as you can for each:



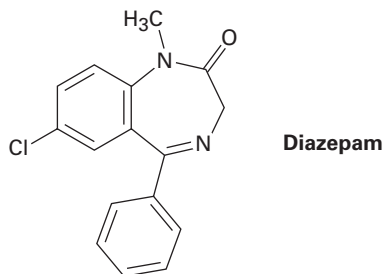
PROBLEM 7.2

Calculate the degree of unsaturation in each of the following formulas:



PROBLEM 7.3

Diazepam, marketed as an antianxiety medication under the name Valium, has three rings, eight double bonds, and the formula C₁₆H₇ClN₂O. How many hydrogens does diazepam have? (Calculate the answer; don't count hydrogens in the structure.)

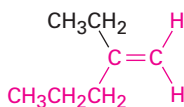


7-2 Naming Alkenes and Alkynes

Alkenes are named using a series of rules similar to those for alkanes (Section 3-4), with the suffix *-ene* used instead of *-ane* to identify the functional group. There are three steps:

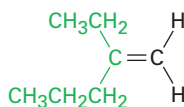
Step 1

Name the parent hydrocarbon. Find the longest carbon chain containing the double bond, and name the compound accordingly, using the suffix *-ene* in place of *-ane*.



Named as a *pentene*

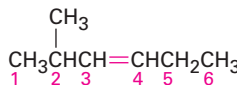
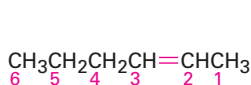
NOT



as a hexene, since the double bond is not contained in the six-carbon chain

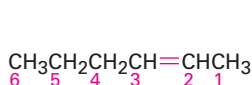
Step 2

Number the carbon atoms in the chain. Begin at the end nearer the double bond or, if the double bond is equidistant from the two ends, begin at the end nearer the first branch point. This rule ensures that the double-bond carbons receive the lowest possible numbers:

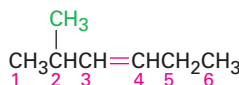


Step 3

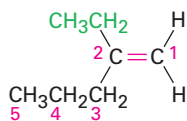
Write the full name. Number the substituents according to their positions in the chain, and list them alphabetically. Indicate the position of the double bond by giving the number of the first alkene carbon and placing that number directly before the *-ene* suffix. If more than one double bond is present, indicate the position of each and use one of the suffixes *-diene*, *-triene*, and so on.



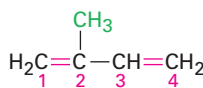
Hex-2-ene



2-Methylhex-3-ene



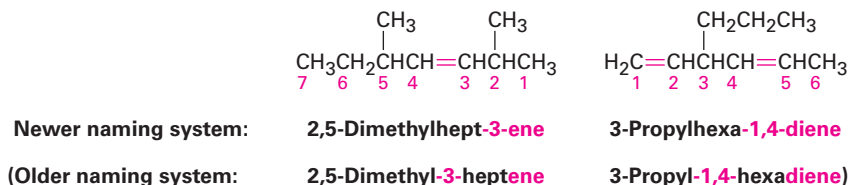
2-Ethylpent-1-ene



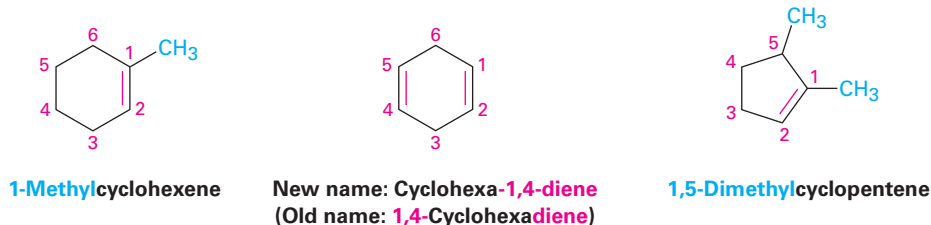
2-Methylbuta-1,3-diene

We should also note that IUPAC changed their naming recommendations in 1993. Prior to that time, the *locant*, or number locating the position of the double bond, was placed at the beginning of the name rather than before the

-ene suffix: 2-butene rather than but-2-ene, for instance. This change has not yet been fully accepted by the chemical community in the United States, however, and some texts have not yet been updated. We'll use the newer naming system in this book, although you will probably encounter the older system elsewhere. Fortunately, the difference between old and new is minor and rarely causes problems.



Cycloalkenes are named similarly, but because there is no chain end to begin from, we number the cycloalkene so that the double bond is between C1 and C2 and the first substituent has as low a number as possible. It's not necessary to indicate the position of the double bond in the name because it's always between C1 and C2.



For historical reasons, there are a few alkenes whose names are firmly entrenched in common usage but don't conform to the rules. For example, the alkene derived from ethane should be called *ethene*, but the name *ethylene* has been used so long that it is accepted by IUPAC. TABLE 7.1 lists several other common names that are often used and are recognized by IUPAC. Note also that a =CH₂ substituent is called a **methylene group**, a H₂C=CH- substituent is called a **vinyl group**, and a H₂C=CHCH₂- substituent is called an **allyl group**.

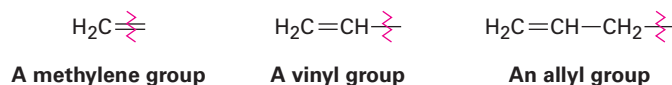


TABLE 7.1 Common Names of Some Alkenes

Compound	Systematic name	Common name
$\text{H}_2\text{C}=\text{CH}_2$	Ethene	Ethylene
$\text{CH}_3\text{CH}=\text{CH}_2$	Propene	Propylene
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{C}=\text{CH}_2 \end{array}$	2-Methylpropene	Isobutylene
$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{C}=\text{C}-\text{CH}=\text{CH}_2 \end{array}$	2-Methylbuta-1,3-diene	Isoprene

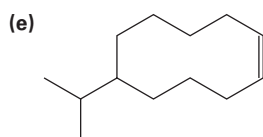
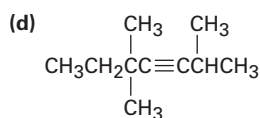
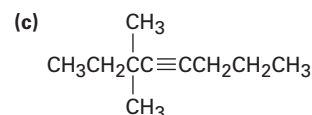
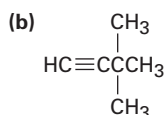
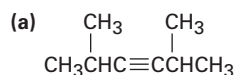
PROBLEM 7.5

Draw structures corresponding to the following IUPAC names:

- (a) 2-Methylhexa-1,5-diene
 (b) 3-Ethyl-2,2-dimethylhept-3-ene
 (c) 2,3,3-Trimethylocta-1,4,6-triene
 (d) 3,4-Diisopropyl-2,5-dimethylhex-3-ene

PROBLEM 7.6

Name the following alkynes:

**PROBLEM 7.7**

Change the following old names to new, post-1993 names, and draw the structure of each compound:

- (a) 2,5,5-Trimethyl-2-hexene (b) 2,2-Dimethyl-3-hexyne

7-3 Cis–Trans Isomerism in Alkenes

We saw in Chapter 1 that the carbon–carbon double bond can be described in two ways. In valence bond language (Section 1-8), the carbons are sp^2 -hybridized and have three equivalent hybrid orbitals that lie in a plane at angles of 120° to one another. The carbons form a σ bond by head-on overlap of sp^2 orbitals and a π bond by sideways overlap of unhybridized p orbitals oriented perpendicular to the sp^2 plane, as shown in Figure 1.15 on page 15.

In molecular orbital language (Section 1-11), interaction between the p orbitals leads to one bonding and one antibonding π molecular orbital. The π bonding MO has no node between nuclei and results from a combination of p orbital lobes with the same algebraic sign. The π antibonding MO has a node between nuclei and results from a combination of lobes with different algebraic signs, as shown in Figure 1.19 on page 21.

Although essentially free rotation is possible around single bonds (Section 3-6), the same is not true of double bonds. For rotation to occur around a double bond, the π bond must break and re-form (FIGURE 7.1). Thus, the barrier to double-bond rotation must be at least as great as the strength of the π bond itself, an estimated 350 kJ/mol (84 kcal/mol). Recall that the barrier to bond rotation in ethane is only 12 kJ/mol.

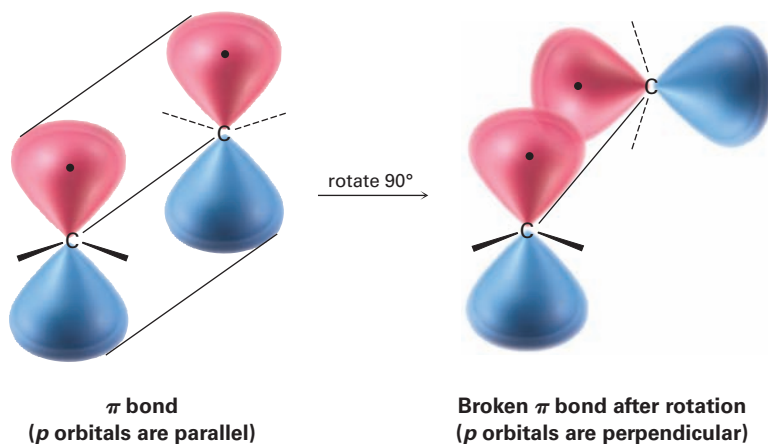


FIGURE 7.1 The lack of rotation in double bonds. The π bond must break for rotation to take place around a carbon-carbon double bond.

The lack of rotation around carbon-carbon double bonds has important chemical consequences. Imagine the situation for a disubstituted alkene such as but-2-ene, for instance. (*Disubstituted* means that two substituents other than hydrogen are attached to the double-bond carbons.) The two methyl groups in but-2-ene can be either on the same side of the double bond or on opposite sides, a situation reminiscent of disubstituted cycloalkanes (Section 4-2).

Because bond rotation can't occur, the two but-2-enes can't spontaneously interconvert; they are distinct, isolable compounds. As with disubstituted cycloalkanes, we call such compounds *cis-trans stereoisomers*. The compound with substituents on the same side of the double bond is called *cis-but-2-ene*, and the isomer with substituents on opposite sides is *trans-but-2-ene* (FIGURE 7.2).

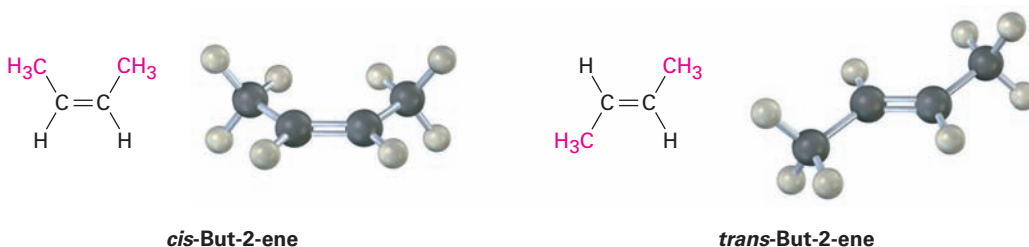
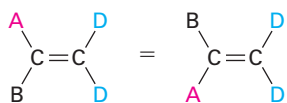
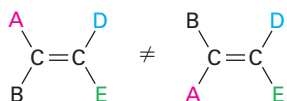


FIGURE 7.2 *Cis* and *trans* isomers of but-2-ene. The *cis* isomer has the two methyl groups on the same side of the double bond, and the *trans* isomer has the methyl groups on opposite sides.

Cis-trans isomerism is not limited to disubstituted alkenes. It can occur whenever both double-bond carbons are attached to two different groups. If one of the double-bond carbons is attached to two identical groups, however, *cis-trans* isomerism is not possible (FIGURE 7.3).



These two compounds are identical; they are not *cis-trans* isomers.



These two compounds are not identical; they are *cis-trans* isomers.

FIGURE 7.3 Requirement for *cis-trans* isomerism in alkenes. Compounds that have one of their carbons bonded to two identical groups can't exist as *cis-trans* isomers. Only when both carbons are bonded to two different groups is *cis-trans* isomerism possible.

PROBLEM 7.8

The sex attractant of the common housefly is an alkene named *cis*-tricos-9-ene. Draw its structure. (Tricosane is the straight-chain alkane $C_{23}H_{48}$.)

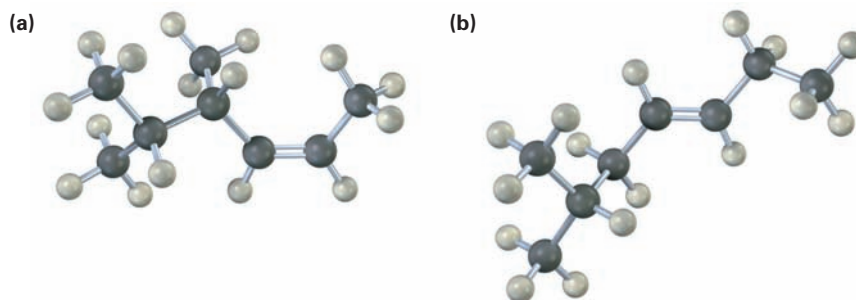
PROBLEM 7.9

Which of the following compounds can exist as pairs of *cis*–*trans* isomers? Draw each *cis*–*trans* pair, and indicate the geometry of each isomer.

- (a) $CH_3CH=CH_2$ (b) $(CH_3)_2C=CHCH_3$
 (c) $CH_3CH_2CH=CHCH_3$ (d) $(CH_3)_2C=C(CH_3)CH_2CH_3$
 (e) $ClCH=CHCl$ (f) $BrCH=CHCl$

PROBLEM 7.10

Name the following alkenes, including the *cis* or *trans* designation:



7-4 Alkene Stereochemistry and the *E,Z* Designation

The *cis*–*trans* naming system used in the previous section works only with disubstituted alkenes—compounds that have two substituents other than hydrogen on the double bond. With trisubstituted and tetrasubstituted double bonds, a more general method is needed for describing double-bond geometry. (*Trisubstituted* means three substituents other than hydrogen on the double bond; *tetrasubstituted* means four substituents other than hydrogen.)

The method used for describing alkene stereochemistry is called the ***E,Z* system** and employs the same Cahn–Ingold–Prelog sequence rules given in Section 5-5 for specifying the configuration of a chirality center. Let's briefly review the sequence rules and then see how they're used to specify double-bond geometry. For a more thorough review, you should reread Section 5-5.

Rule 1

Considering each of the double-bond carbons separately, look at the two attached substituents and rank them according to the atomic number of the first atom in each. An atom with higher atomic number ranks higher than an atom with lower atomic number.

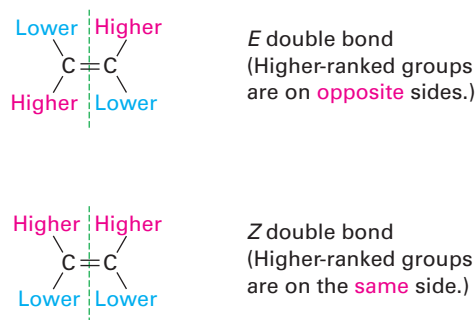
Rule 2

If a decision can't be reached by ranking the first atoms in the two substituents, look at the second, third, or fourth atoms away from the double-bond until the first difference is found.

Rule 3

Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.

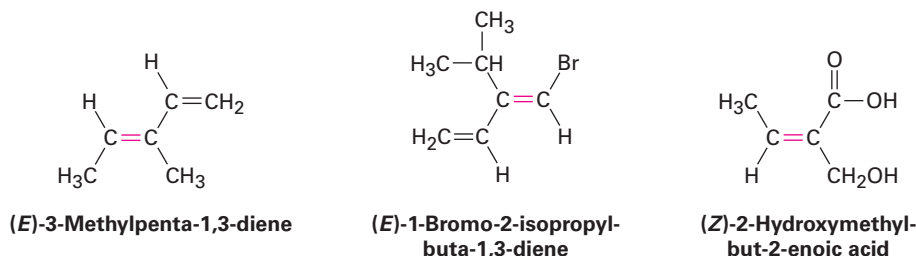
Once the two groups attached to each doubly bonded carbon atom have been ranked as either higher or lower, look at the entire molecule. If the higher-ranked groups on each carbon are on the same side of the double bond, the alkene is designated **Z**, for the German *zusammen*, meaning “together.” If the higher-ranked groups are on opposite sides, the alkene is designated **E**, for the German *entgegen*, meaning “opposite.” (A simple way to remember which is which is to note that the groups are on “ze zame zide” in the **Z** isomer.)



As an example, look at the following two isomers of 2-chlorobut-2-ene. Because chlorine has a higher atomic number than carbon, a $-\text{Cl}$ substituent is ranked higher than a $-\text{CH}_3$ group. Methyl is ranked higher than hydrogen, however, so isomer **(a)** is assigned **E** geometry because the higher-ranked groups are on opposite sides of the double bond. Isomer **(b)** has **Z** geometry because its higher-ranked groups are on ze zame zide of the double bond.



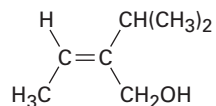
For further practice, work through each of the following examples to convince yourself that the assignments are correct:



WORKED EXAMPLE 7.1

Assigning *E* and *Z* Configurations to Substituted Alkenes

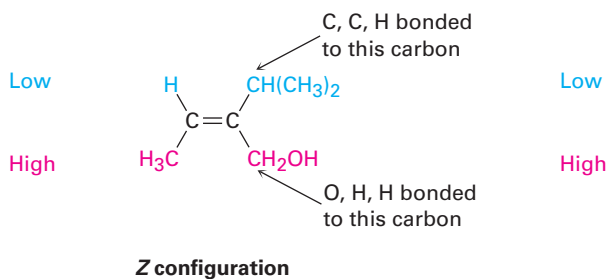
Assign *E* or *Z* configuration to the double bond in the following compound:

**Strategy**

Look at the two substituents connected to each double-bond carbon, and determine their ranking using the Cahn–Ingold–Prelog rules. Then see whether the two higher-ranked groups are on the same or opposite sides of the double bond.

Solution

The left-hand carbon has $-\text{H}$ and $-\text{CH}_3$ substituents, of which $-\text{CH}_3$ ranks higher by sequence rule 1. The right-hand carbon has $-\text{CH}(\text{CH}_3)_2$ and $-\text{CH}_2\text{OH}$ substituents, which are equivalent by rule 1. By rule 2, however, $-\text{CH}_2\text{OH}$ ranks higher than $-\text{CH}(\text{CH}_3)_2$ because the substituent $-\text{CH}_2\text{OH}$ has an *oxygen* as its highest second atom, but $-\text{CH}(\text{CH}_3)_2$ has a *carbon* as its highest second atom. The two higher-ranked groups are on the same side of the double bond, so we assign *Z* configuration.

**PROBLEM 7.11**

Which member in each of the following sets ranks higher?

- (a) $-\text{H}$ or $-\text{CH}_3$ (b) $-\text{Cl}$ or $-\text{CH}_2\text{Cl}$
 (c) $-\text{CH}_2\text{CH}_2\text{Br}$ or $-\text{CH}=\text{CH}_2$ (d) $-\text{NHCH}_3$ or $-\text{OCH}_3$
 (e) $-\text{CH}_2\text{OH}$ or $-\text{CH}=\text{O}$ (f) $-\text{CH}_2\text{OCH}_3$ or $-\text{CH}=\text{O}$

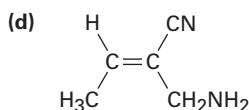
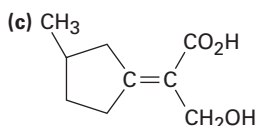
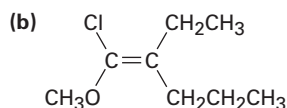
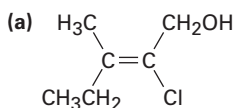
PROBLEM 7.12

Rank the substituents in each of the following sets according to the sequence rules:

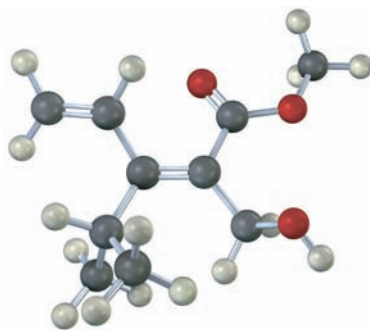
- (a) $-\text{CH}_3$, $-\text{OH}$, $-\text{H}$, $-\text{Cl}$
 (b) $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{OH}$
 (c) $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{OH}$, $-\text{C}\equiv\text{N}$, $-\text{CH}_2\text{NH}_2$
 (d) $-\text{CH}_2\text{CH}_3$, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{N}$, $-\text{CH}_2\text{OCH}_3$

PROBLEM 7.13

Assign *E* or *Z* configuration to the double bonds in the following compounds:

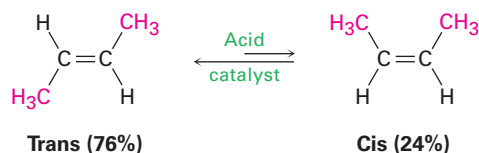
**PROBLEM 7.14**

Assign *E* or *Z* configuration to the double bond in the following compound, and convert the drawing into a skeletal structure (red = O):



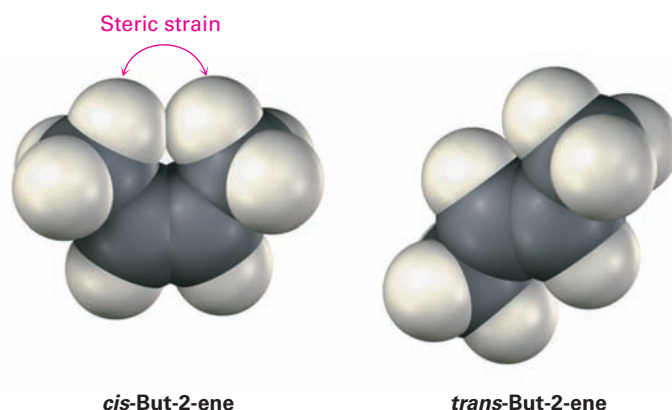
7-5 Stability of Alkenes

Although the *cis*–*trans* interconversion of alkene isomers does not occur spontaneously, it can often be brought about by treating the alkene with a strong acid catalyst. If we interconvert *cis*-but-2-ene with *trans*-but-2-ene and allow them to reach equilibrium, we find that they aren't of equal stability. The *trans* isomer is more stable than the *cis* isomer by 2.8 kJ/mol (0.66 kcal/mol) at room temperature, corresponding to a 76 : 24 ratio.

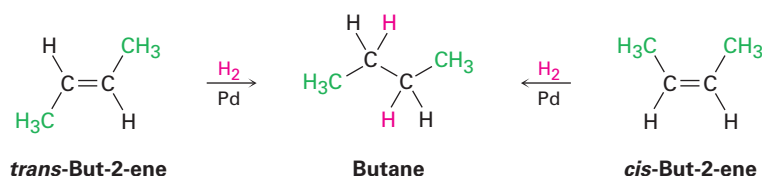


Cis alkenes are less stable than their *trans* isomers because of steric strain between the two larger substituents on the same side of the double bond. This

is the same kind of steric interference that we saw previously in the axial conformation of methylcyclohexane (Section 4-7).

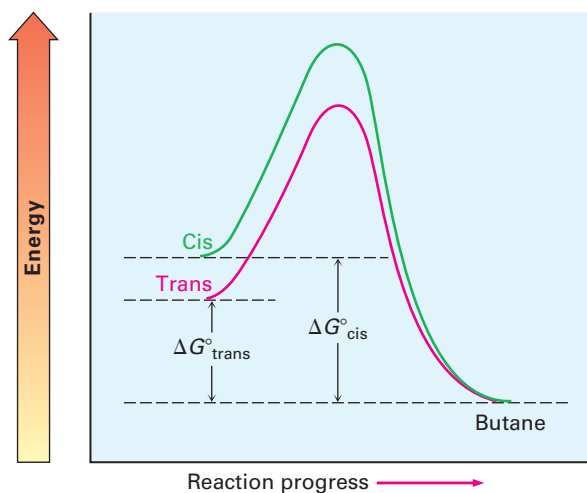


Although it's sometimes possible to find relative stabilities of alkene isomers by establishing a cis–trans equilibrium through treatment with strong acid, a more general method is to take advantage of the fact that alkenes undergo a *hydrogenation* reaction to give the corresponding alkane on treatment with H₂ gas in the presence of a catalyst such as palladium or platinum:



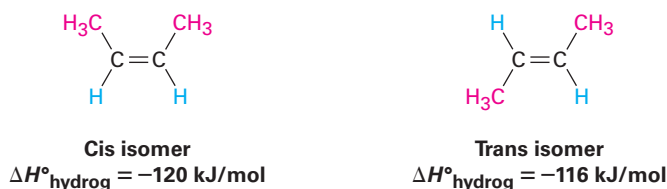
Energy diagrams for the hydrogenation reactions of *cis*- and *trans*-but-2-ene are shown in **FIGURE 7.4**. Because *cis*-but-2-ene is less stable than *trans*-but-2-ene by 2.8 kJ/mol, the energy diagram shows the *cis* alkene at a higher energy level. After reaction, however, both curves are at the same energy level (butane). It therefore follows that ΔG° for reaction of the *cis* isomer must be larger than ΔG° for reaction of the *trans* isomer by 2.8 kJ/mol. In other words, more energy is released in the hydrogenation of the *cis* isomer than the *trans* isomer because the *cis* isomer is higher in energy to begin with.

FIGURE 7.4 Energy diagrams for hydrogenation of *cis*- and *trans*-but-2-ene. The *cis* isomer is higher in energy than the *trans* isomer by about 2.8 kJ/mol and therefore releases more energy in the reaction.



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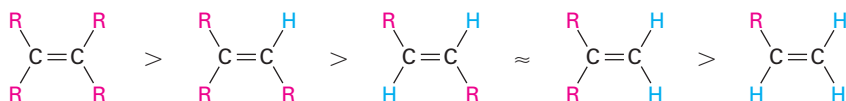
If we were to measure the so-called heats of hydrogenation ($\Delta H^\circ_{\text{hydrog}}$) for two double-bond isomers and find their difference, we could determine the relative stabilities of *cis* and *trans* isomers without having to measure an equilibrium position. *cis*-But-2-ene, for instance, has $\Delta H^\circ_{\text{hydrog}} = -120$ kJ/mol (-28.6 kcal/mol), while *trans*-but-2-ene has $\Delta H^\circ_{\text{hydrog}} = -116$ kJ/mol (-27.6 kcal/mol)—a difference of 4 kJ/mol.



The 4 kJ/mol energy difference between the but-2-ene isomers calculated from heats of hydrogenation agrees reasonably well with the 2.8 kJ/mol energy difference calculated from equilibrium data, but the numbers aren't exactly the same for two reasons. First, there is probably some experimental error because heats of hydrogenation are difficult to measure accurately. Second, heats of reaction and equilibrium constants don't measure exactly the same thing. Heats of reaction measure enthalpy changes, ΔH° , whereas equilibrium constants measure free-energy changes, ΔG° , so we might expect a small difference between the two.

TABLE 7.2 lists some representative data for the hydrogenation of different alkenes and shows that alkenes become more stable with increasing substitution. That is, alkenes follow the stability order:

Tetrasubstituted > Trisubstituted > Disubstituted > Monosubstituted



We'll see some consequences of this stability order in later chapters.

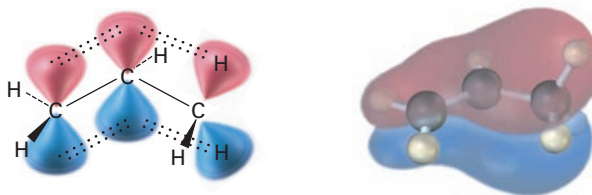
TABLE 7.2 Heats of Hydrogenation of Some Alkenes

Substitution	Alkene	$\Delta H^\circ_{\text{hydrog}}$	
		(kJ/mol)	(kcal/mol)
Ethylene	$\text{H}_2\text{C}=\text{CH}_2$	-137	-32.8
Monosubstituted	$\text{CH}_3\text{CH}=\text{CH}_2$	-126	-30.1
Disubstituted	$\text{CH}_3\text{CH}=\text{CHCH}_3$ (<i>cis</i>)	-120	-28.6
	$\text{CH}_3\text{CH}=\text{CHCH}_3$ (<i>trans</i>)	-116	-27.6
	$(\text{CH}_3)_2\text{C}=\text{CH}_2$	-119	-28.4
Trisubstituted	$(\text{CH}_3)_2\text{C}=\text{CHCH}_3$	-113	-26.9
Tetrasubstituted	$(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)_2$	-111	-26.6

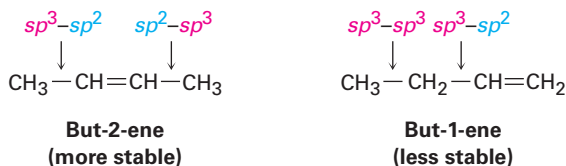
The stability order of substituted alkenes is due to a combination of two factors. One is a stabilizing interaction between the C=C π bond and adjacent C–H σ bonds on substituents. In valence-bond language, the interaction is called **hyperconjugation**. In a molecular orbital description, there is a bonding MO that extends over the four-atom C=C–C–H grouping, as shown in **FIGURE 7.5**. The more substituents that are present on the double bond, the more hyperconjugation there is and the more stable the alkene.

FIGURE 7.5 Hyperconjugation.

Hyperconjugation is a stabilizing interaction between the C=C π bond and adjacent C–H σ bonds on substituents. The more substituents there are, the greater the stabilization of the alkene.

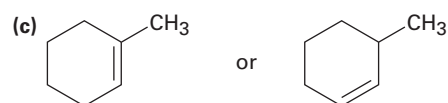
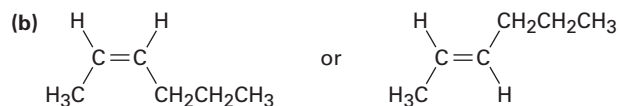
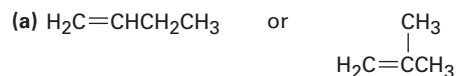


A second factor that contributes to alkene stability involves bond strengths. A bond between an sp^2 carbon and an sp^3 carbon is somewhat stronger than a bond between two sp^3 carbons. Thus, in comparing but-1-ene and but-2-ene, the monosubstituted isomer has one sp^3 – sp^3 bond and one sp^3 – sp^2 bond, while the disubstituted isomer has two sp^3 – sp^2 bonds. More highly substituted alkenes always have a higher ratio of sp^3 – sp^2 bonds to sp^3 – sp^3 bonds than less highly substituted alkenes and are therefore more stable.



PROBLEM 7.15

Name the following alkenes, and tell which compound in each pair is more stable:



7-6 Electrophilic Addition Reactions of Alkenes

Before beginning a detailed discussion of alkene reactions, let's review briefly some conclusions from the previous chapter. We said in Section 6-5 that alkenes behave as nucleophiles (Lewis bases) in polar reactions, donating a pair of electrons from their electron-rich C=C bond to an electrophile (Lewis acid). For example, acid-catalyzed reaction of 2-methylpropene with H₂O yields 2-methylpropan-2-ol, where the *-ol* name ending on the product indicates an alcohol. A careful study of this and similar reactions has led to the generally accepted mechanism shown in **FIGURE 7.6** for the **electrophilic addition reaction**.

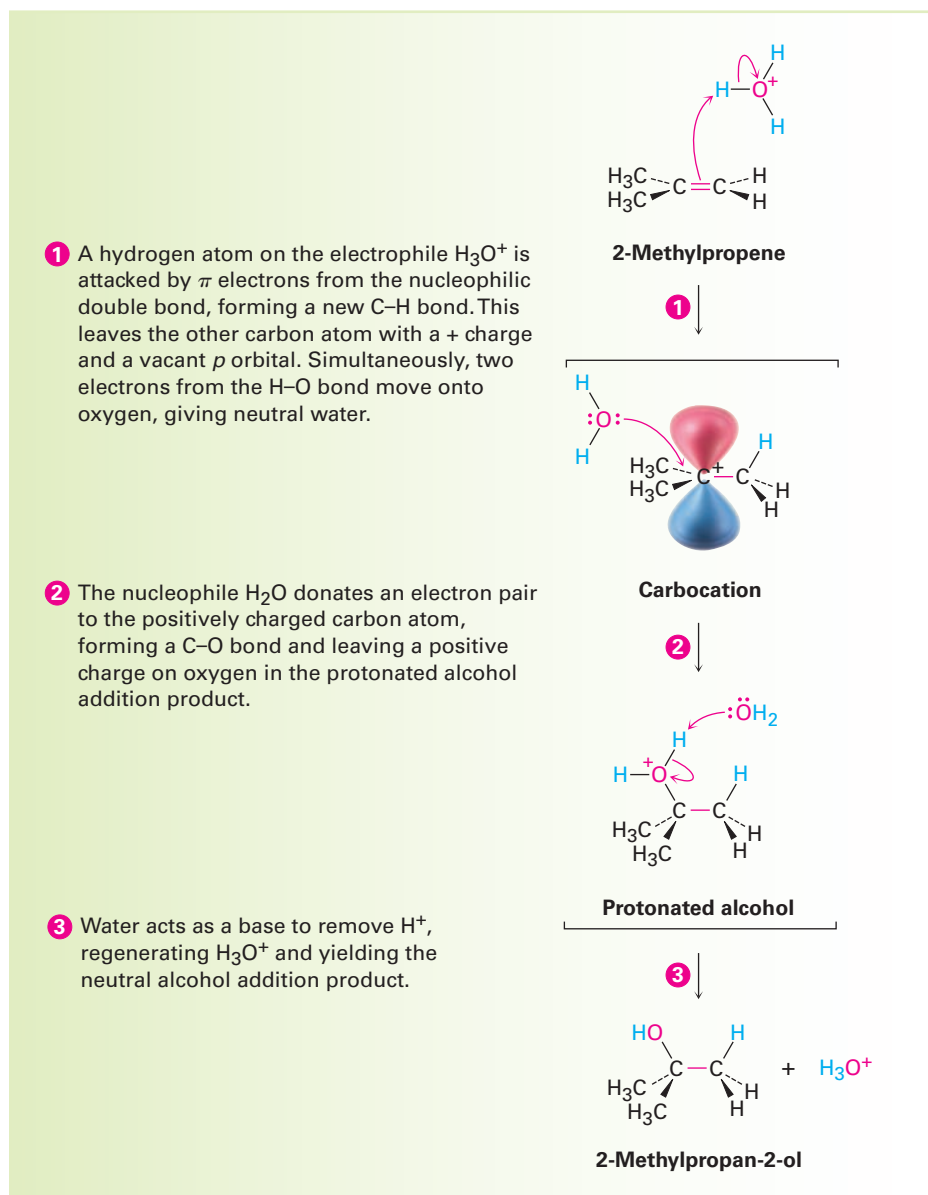
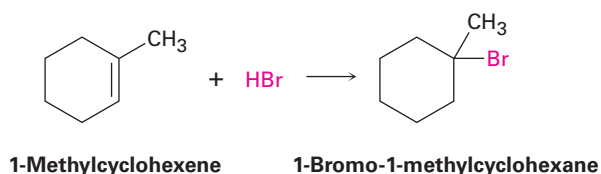
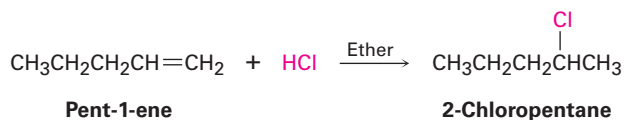


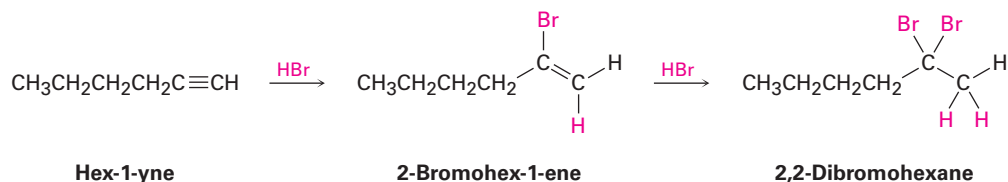
FIGURE 7.6 Mechanism of the acid-catalyzed electrophilic addition of H₂O to 2-methylpropene. The reaction involves a carbocation intermediate.

The reaction begins with an attack on a hydrogen of the electrophile H_3O^+ by the electrons of the nucleophilic π bond. Two electrons from the π bond form a new σ bond between the entering hydrogen and an alkene carbon, as shown by the curved arrow at the top of Figure 7.6. The carbocation intermediate that results is itself an electrophile, which can accept an electron pair from nucleophilic H_2O to form a C–O bond and yield a protonated alcohol addition product. Removal of H^+ by acid–base reaction with water then gives the alcohol addition product and regenerates the acid catalyst.

Electrophilic addition to alkenes is successful not only with H_2O but with HBr , HCl , and HI as well, although the addition of halogen acids is not common in living organisms.

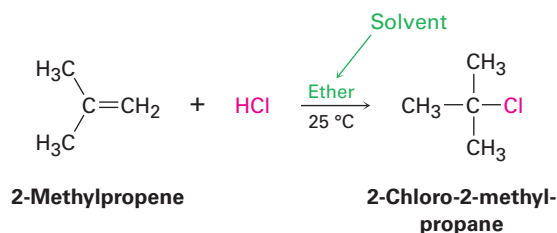


Alkynes, too, undergo electrophilic addition reactions, although their reactivity is substantially less than that of alkenes. Hex-1-yne, for instance, reacts with 1 molar equivalent of HBr to give 2-bromohex-1-ene and with 2 molar equivalents of HBr to give 2,2-dibromohexane.



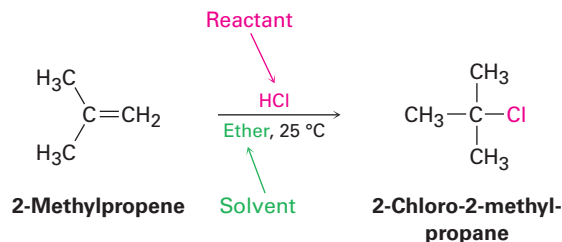
WRITING ORGANIC REACTIONS

This is a good time to mention that equations for organic reactions are sometimes written in different ways to emphasize different points. In describing a laboratory process, for instance, the reaction of 2-methylpropene with HCl might be written in the format $\text{A} + \text{B} \rightarrow \text{C}$ to emphasize that both reactants are equally important for the purposes of the discussion. The solvent and notes about other reaction conditions, such as temperature, are written either above or below the reaction arrow:

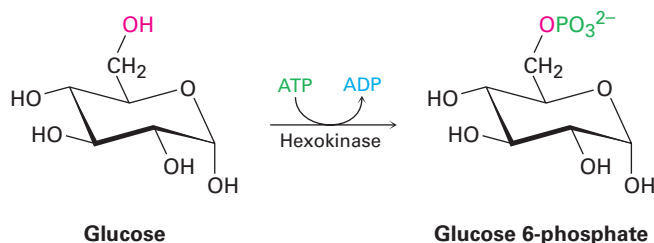


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Alternatively, we might write the same reaction in a format to emphasize that 2-methylpropene is the reactant whose chemistry is of greater interest. The second reactant, HCl, is placed above the reaction arrow together with notes about solvent and reaction conditions:

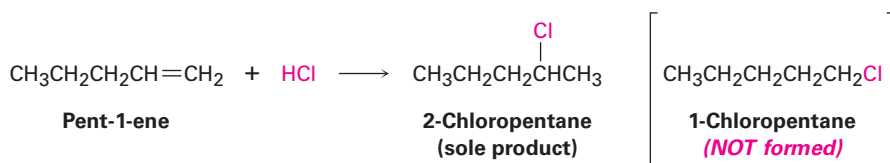


In describing a biological process, the reaction is usually written to show only the structure of the primary reactant and product, while abbreviating the structures of various biological “reagents” and by-products by using a curved arrow that intersects the straight reaction arrow. As discussed in Section 6-11, the reaction of glucose with ATP to give glucose 6-phosphate plus ADP would be written as



7-7 Orientation of Electrophilic Addition: Markovnikov's Rule

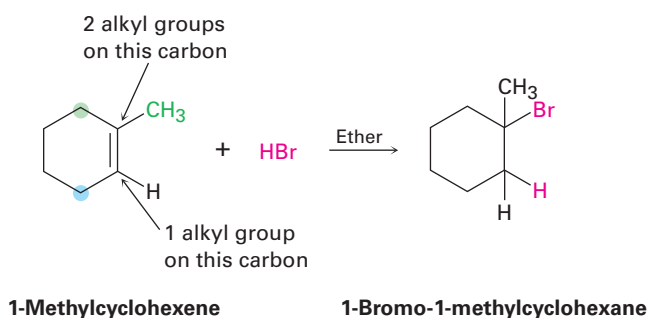
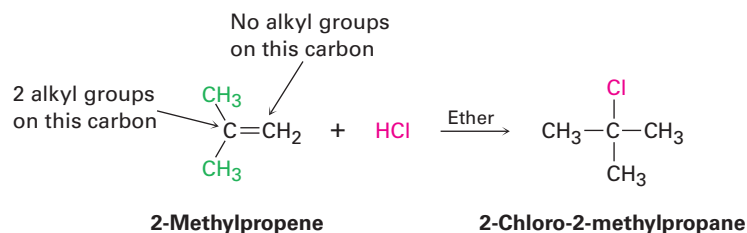
Look carefully at the electrophilic addition reactions shown in the previous section. In each case, an unsymmetrically substituted alkene gives a single addition product rather than the mixture that might be expected. For example, pent-1-ene *might* react with HCl to give both 1-chloropentane and 2-chloropentane, but it doesn't. It gives only 2-chloropentane as the sole product. Similarly, it's invariably the case in biological alkene addition reactions that only a single product is formed. We say that such reactions are **regiospecific** (**ree-jee-oh-specific**) when only one of two possible orientations of addition occurs.



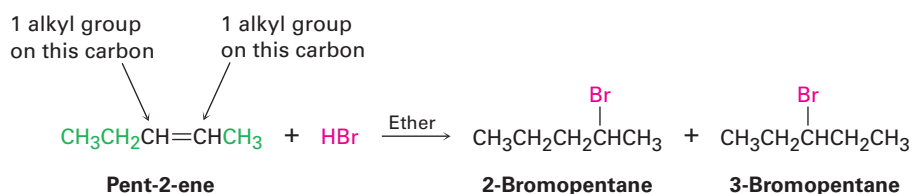
After looking at the results of many such reactions, the Russian chemist Vladimir Markovnikov proposed in 1869 what has become known as **Markovnikov's rule**:

Markovnikov's rule

In the addition of HX to an alkene, the H attaches to the carbon with fewer alkyl substituents and the X attaches to the carbon with more alkyl substituents.



When both double-bond carbon atoms have the same degree of substitution, a mixture of addition products results:

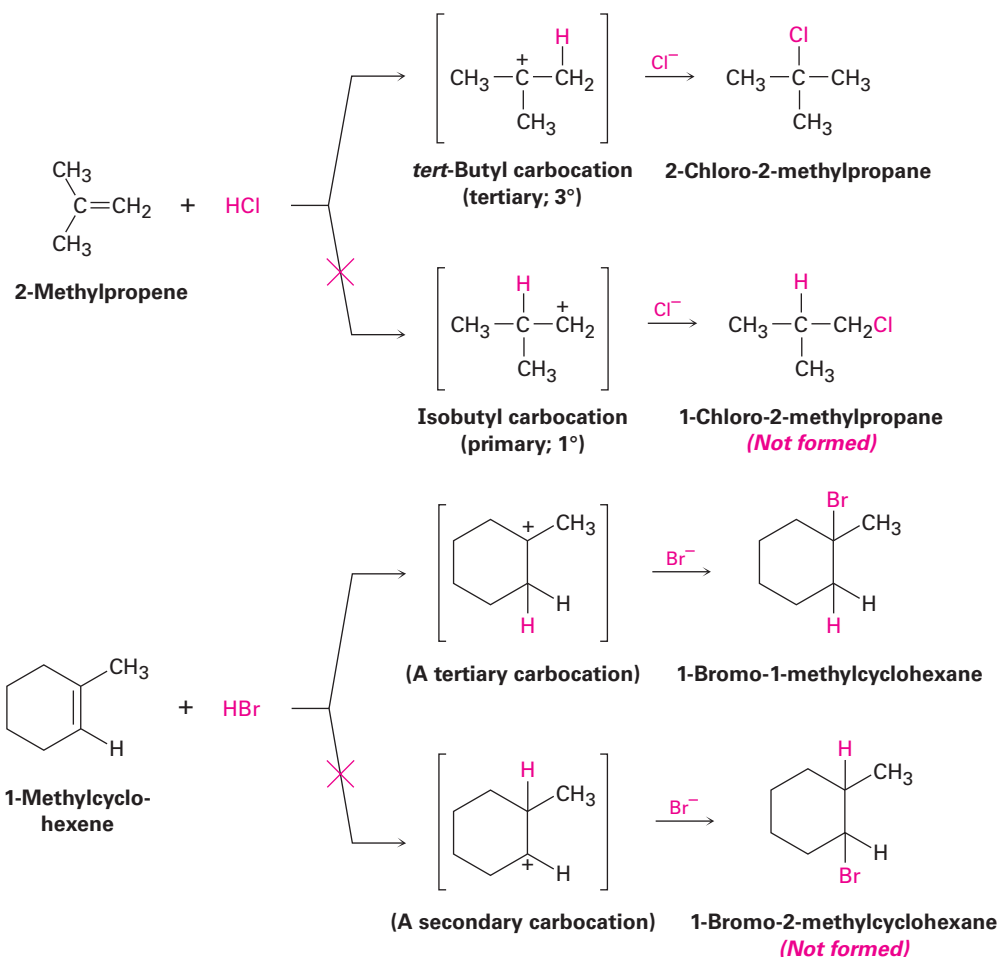


Because carbocations are involved as intermediates in these electrophilic addition reactions, Markovnikov's rule can be restated in the following way:

Markovnikov's rule restated

In the addition of HX to an alkene, the more highly substituted carbocation is formed as the intermediate rather than the less highly substituted one.

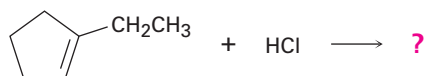
For example, addition of H⁺ to 2-methylpropene yields the intermediate *tertiary* carbocation rather than the alternative primary carbocation, and addition to 1-methylcyclohexene yields a tertiary cation rather than a secondary one. Why should this be?



Predicting the Product of an Electrophilic Addition Reaction

WORKED EXAMPLE 7.2

What product would you expect from reaction of HCl with 1-ethylcyclopentene?

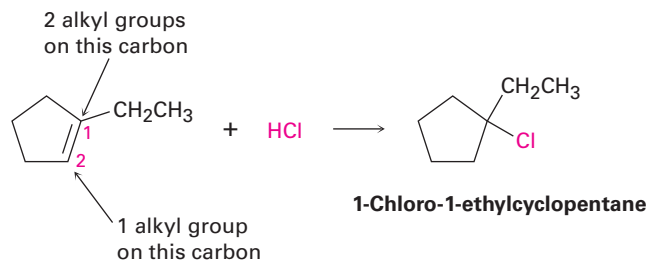


Strategy

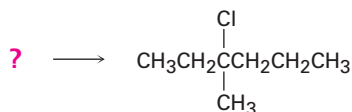
When solving a problem that asks you to predict a reaction product, begin by looking at the functional group(s) in the reactants and deciding what kind of reaction is likely to occur. In the present instance, the reactant is an alkene that will probably undergo an electrophilic addition reaction with HCl. Next, recall what you know about electrophilic addition reactions and use your knowledge to predict the product. You know that electrophilic addition reactions follow Markovnikov's rule, so H⁺ will add to the double-bond carbon that has one alkyl group (C2 on the ring) and the Cl will add to the double-bond carbon that has two alkyl groups (C1 on the ring).

Solution

The expected product is 1-chloro-1-ethylcyclopentane.

**WORKED EXAMPLE 7.3****Synthesizing a Target Compound**

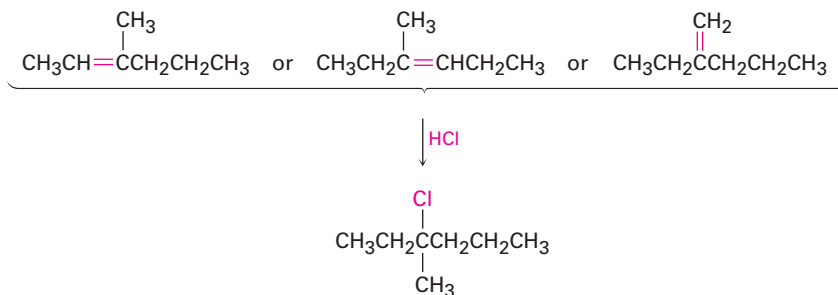
What alkene would you start with to prepare the following alkyl halide? There may be more than one possibility.

**Strategy**

When solving a problem that asks how to prepare a given product, *always work backward*. Look at the product, identify the functional group(s) it contains, and ask yourself, “How can I prepare that functional group?” In the present instance, the product is a tertiary alkyl chloride, which can be prepared by reaction of an alkene with HCl. The carbon atom bearing the –Cl atom in the product must be one of the double-bond carbons in the reactant. Draw and evaluate all possibilities.

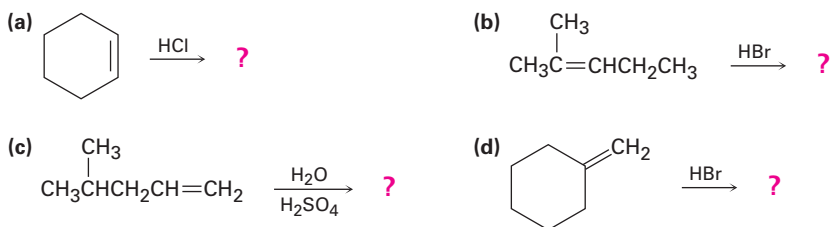
Solution

There are three possibilities, any one of which could give the desired product according to Markovnikov’s rule.

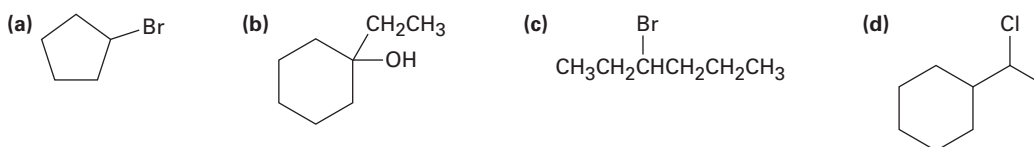


PROBLEM 7.16

Predict the products of the following reactions:

**PROBLEM 7.17**

What alkenes would you start with to prepare the following products?



7-8 Carbocation Structure and Stability

To understand why Markovnikov's rule works, we need to learn more about the structure and stability of carbocations and about the general nature of reactions and transition states. The first point to explore involves structure.

A great deal of experimental evidence has shown that carbocations are planar. The trivalent carbon is sp^2 -hybridized, and the three substituents are oriented toward the corners of an equilateral triangle, as indicated in **FIGURE 7.7**. Because there are only six valence electrons on carbon and all six are used in the three σ bonds, the p orbital extending above and below the plane is unoccupied.

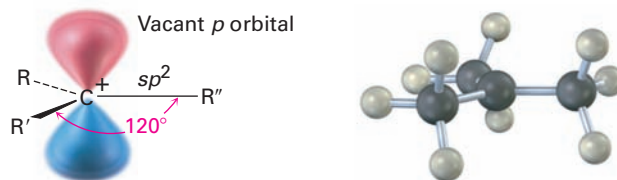
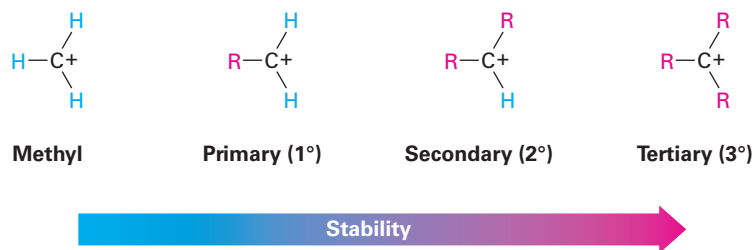


FIGURE 7.7 The structure of a carbocation. The trivalent carbon is sp^2 -hybridized and has a vacant p orbital perpendicular to the plane of the carbon and three attached groups.

The second point to explore involves carbocation stability. 2-Methylpropene might react with H^+ to form a carbocation having three alkyl substituents (a tertiary ion, 3°), or it might react to form a carbocation having one alkyl substituent (a primary ion, 1°). Since the tertiary alkyl chloride, 2-chloro-2-methylpropane, is the only product observed, formation of the tertiary cation is evidently favored over formation of the primary cation. Thermodynamic measurements show that, indeed, the stability of

carbocations increases with increasing substitution so that the stability order is tertiary > secondary > primary > methyl.



Why are more highly substituted carbocations more stable than less highly substituted ones? There are at least two reasons. Part of the answer has to do with inductive effects, and part has to do with hyperconjugation. Inductive effects, discussed in Section 2-1 in connection with polar covalent bonds, result from the shifting of electrons in a σ bond in response to the electronegativity of nearby atoms. In the present instance, electrons from a relatively larger and more polarizable alkyl group can shift toward a neighboring positive charge more easily than the electron from a hydrogen. Thus, the more alkyl groups there are attached to the positively charged carbon, the more electron density shifts toward the charge and the more inductive stabilization of the cation occurs (FIGURE 7.8).

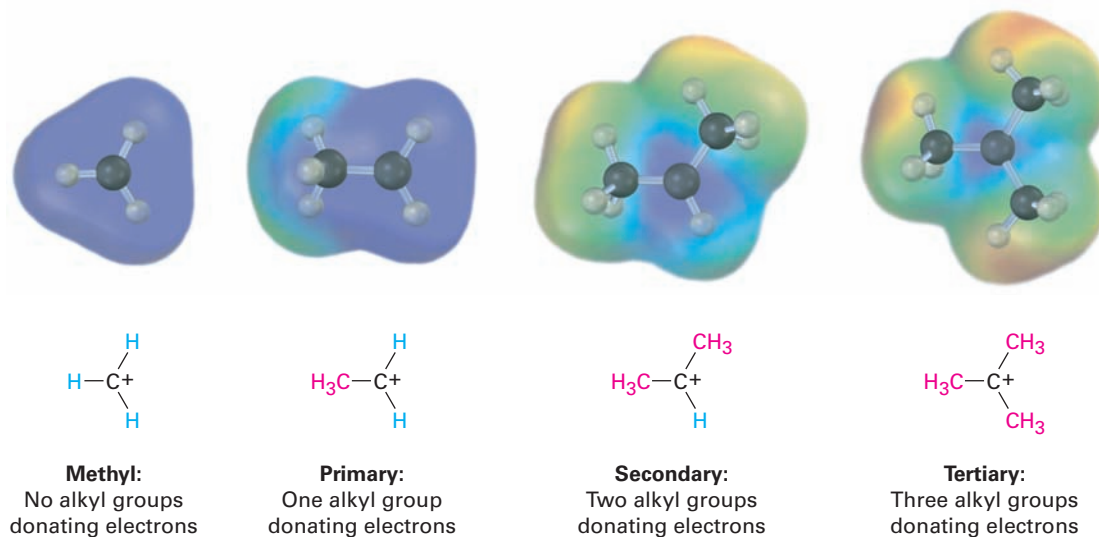


FIGURE 7.8 Comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups that are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron poor (blue in electrostatic potential maps).

Hyperconjugation, discussed in Section 7-5 in connection with the stabilities of substituted alkenes, is the stabilizing interaction between a p orbital and C-H σ bonds on neighboring carbons that are roughly parallel to the p orbital (FIGURE 7.9). The more alkyl groups there are on the carbocation, the more stable the carbocation.

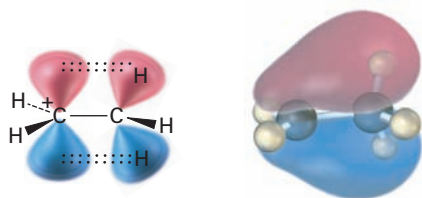


FIGURE 7.9 The ethyl carbocation, CH_3CH_2^+ . There is a stabilizing interaction between the carbocation p orbital and adjacent C–H σ bonds on the methyl substituent, as indicated by this molecular orbital. The more substituents there are, the greater the stabilization of the cation. Only the C–H bonds that are roughly parallel to the neighboring p orbital are oriented properly to take part in hyperconjugation.

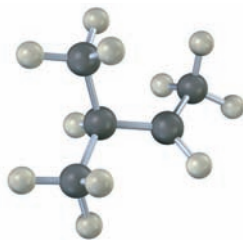
PROBLEM 7.18

Show the structures of the carbocation intermediates you would expect in the following reactions:



PROBLEM 7.19

Draw a skeletal structure of the following carbocation. Identify it as primary, secondary, or tertiary, and identify the hydrogen atoms that have the proper orientation for hyperconjugation in the conformation shown.



7-9 The Hammond Postulate

Let's summarize our knowledge of electrophilic addition reactions to this point:

- **Electrophilic addition to an unsymmetrically substituted alkene gives the more highly substituted carbocation intermediate.** A more highly substituted carbocation forms faster than a less highly substituted one and, once formed, rapidly goes on to give the final product.
- **A more highly substituted carbocation is more stable than a less highly substituted one.** That is, the stability order of carbocations is tertiary > secondary > primary > methyl.

What we have not yet seen is how these two points are related. Why does the *stability* of the carbocation intermediate affect the *rate* at which it's formed and thereby determine the structure of the final product? After all, carbocation stability is determined by the free-energy change ΔG° , but reaction rate is determined by the activation energy ΔG^\ddagger . The two quantities aren't directly related.

Although there is no simple quantitative relationship between the stability of a carbocation intermediate and the rate of its formation, there *is* an intuitive relationship. It's generally true when comparing two similar reactions that the

more stable intermediate forms faster than the less stable one. The situation is shown graphically in **FIGURE 7.10**, where the energy profile in part **(a)** represents the typical situation rather than the profile in **(b)**. That is, the curves for two similar reactions don't cross one another.

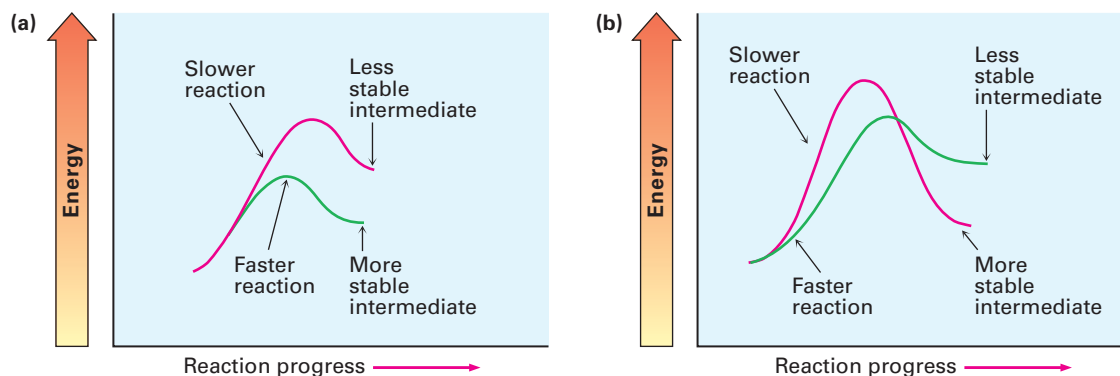


FIGURE 7.10 Energy diagrams for two similar competing reactions. In **(a)**, the faster reaction yields the more stable intermediate. In **(b)**, the slower reaction yields the more stable intermediate. The curves shown in **(a)** represent the typical situation.

Called the **Hammond postulate**, the explanation of the relationship between reaction rate and intermediate stability goes like this: Transition states represent energy maxima. They are high-energy activated complexes that occur transiently during the course of a reaction and immediately go on to a more stable species. Although we can't actually *observe* transition states, because they have no finite lifetime, the Hammond postulate says that we can get an idea of a particular transition state's structure by looking at the structure of the nearest stable species. Imagine the two cases shown in **FIGURE 7.11**, for example. The reaction profile in part **(a)** shows the energy curve for an endergonic reaction step, and the profile in part **(b)** shows the curve for an exergonic step.

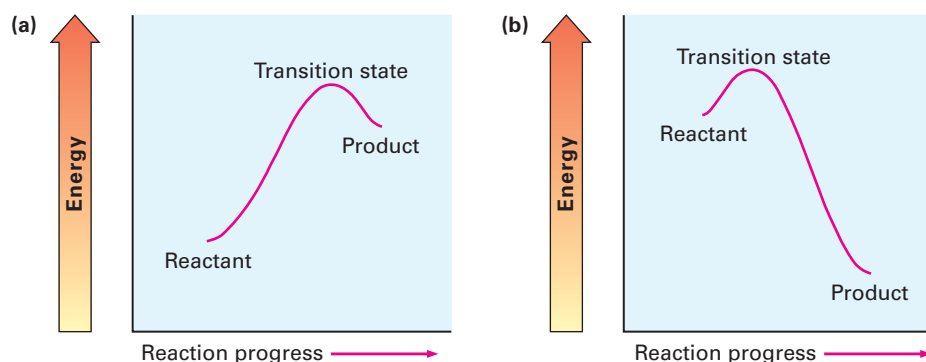


FIGURE 7.11 Energy diagrams for endergonic and exergonic steps. **(a)** In an endergonic step, the energy levels of transition state and *product* are closer. **(b)** In an exergonic step, the energy levels of transition state and *reactant* are closer.

In an endergonic reaction (Figure 7.11a), the energy level of the transition state is closer to that of the product than to that of the reactant. Since the

transition state is closer energetically to the product, we make the assumption that it's also closer structurally. In other words, *the transition state for an endergonic reaction step structurally resembles the product of that step*. Conversely, the transition state for an exergonic reaction (Figure 7.11b) is closer energetically, and thus structurally, to the reactant than to the product. We therefore say that *the transition state for an exergonic reaction step structurally resembles the reactant for that step*.

Hammond postulate

The structure of a transition state resembles the structure of the nearest stable species. Transition states for endergonic steps structurally resemble products, and transition states for exergonic steps structurally resemble reactants.

How does the Hammond postulate apply to electrophilic addition reactions? The formation of a carbocation by protonation of an alkene is an endergonic step. Thus, the transition state for alkene protonation structurally resembles the carbocation intermediate, and any factor that stabilizes the carbocation will also stabilize the nearby transition state. Since increasing alkyl substitution stabilizes carbocations, it also stabilizes the transition states leading to those ions, thus resulting in faster reaction. More stable carbocations form faster because their greater stability is reflected in the lower-energy transition state leading to them (FIGURE 7.12).

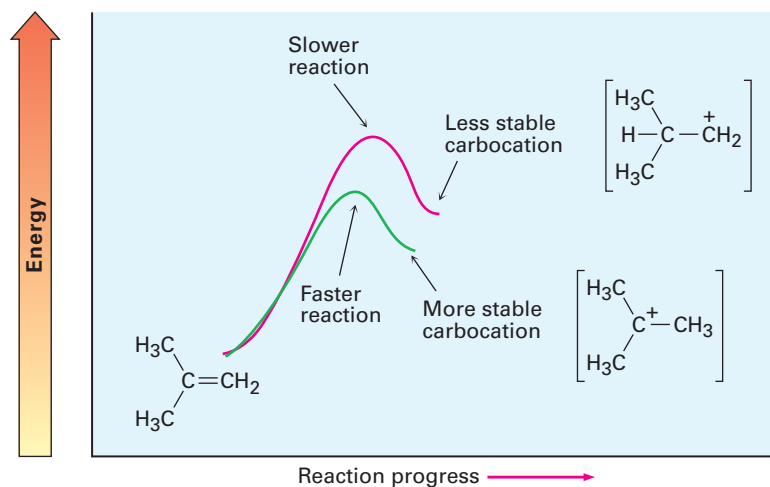


FIGURE 7.12 Energy diagrams for carbocation formation. The more stable tertiary carbocation is formed faster (green curve) because its increased stability lowers the energy of the transition state leading to it.

We can imagine the transition state for alkene protonation to be a structure in which one of the alkene carbon atoms has almost completely rehybridized from sp^2 to sp^3 and the remaining alkene carbon bears much of the positive charge (FIGURE 7.13). This transition state is stabilized by hyperconjugation and inductive effects in the same way as the product carbocation. The more alkyl groups that are present, the greater the extent of stabilization and the faster the transition state forms.

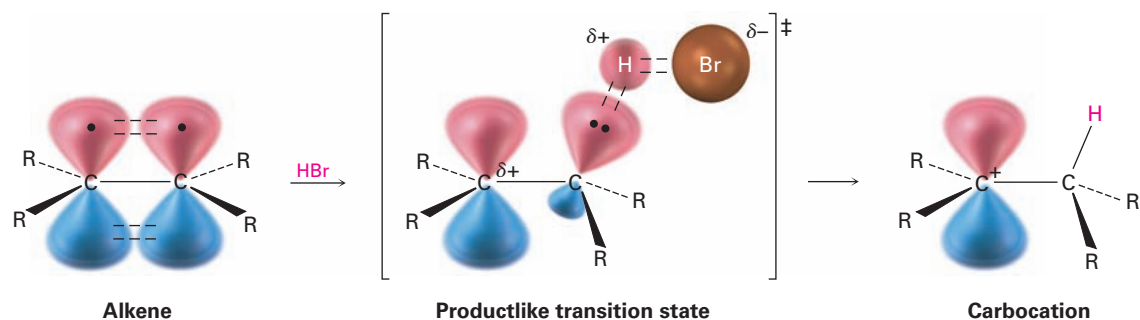


FIGURE 7.13 Hypothetical structure of a transition state for alkene protonation. The transition state is closer in both energy and structure to the carbocation than to the alkene. Thus, an increase in carbocation stability (lower ΔG°) also causes an increase in transition-state stability (lower ΔG^\ddagger), thereby increasing the rate of its formation.

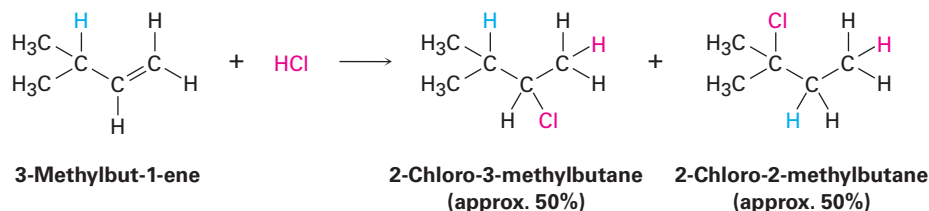
PROBLEM 7.20

What about the second step in the electrophilic addition of HCl to an alkene—the reaction of chloride ion with the carbocation intermediate? Is this step exergonic or endergonic? Does the transition state for this second step resemble the reactant (carbocation) or product (alkyl chloride)? Make a rough drawing of what the transition-state structure might look like.

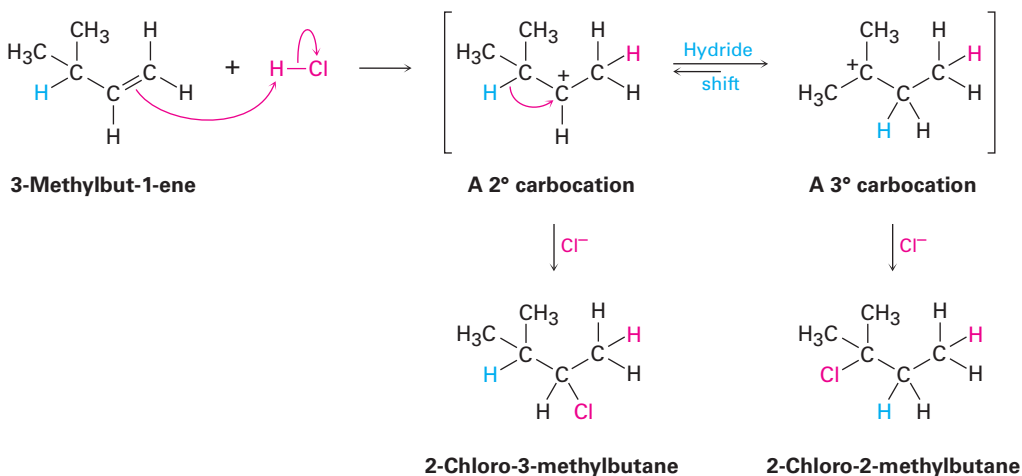
7-10 Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements

How do we know that the carbocation mechanism for electrophilic addition reactions of alkenes is correct? The answer is that we *don't* know it's correct; at least we don't know with complete certainty. Although an incorrect reaction mechanism can be disproved by demonstrating that it doesn't account for observed data, a correct reaction mechanism can never be entirely proved. The best we can do is to show that a proposed mechanism is consistent with all known facts. If enough facts are accounted for, the mechanism is probably correct.

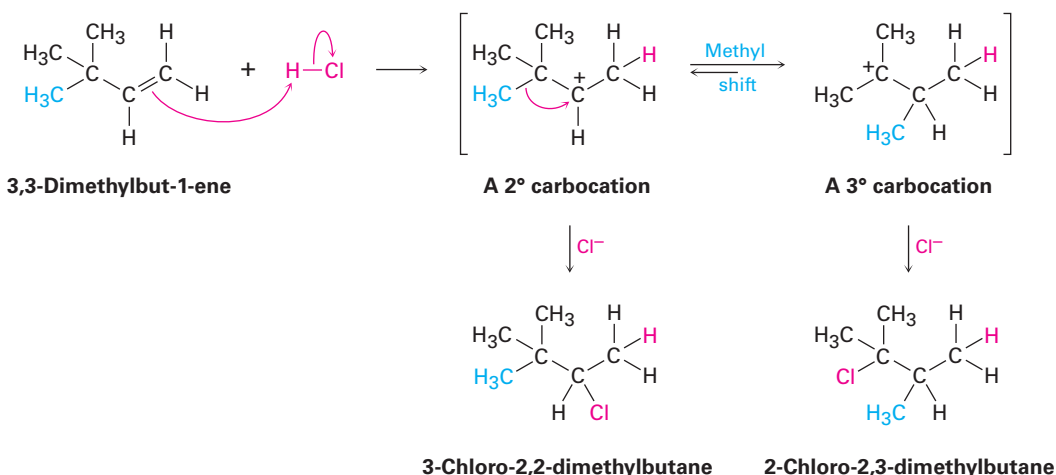
One of the best pieces of evidence supporting the carbocation mechanism proposed for the electrophilic addition reaction of alkenes is that structural *rearrangements* often occur during the reaction of HX with an alkene. For example, reaction of HCl with 3-methylbut-1-ene yields a substantial amount of 2-chloro-2-methylbutane in addition to the “expected” product, 2-chloro-3-methylbutane:



If the reaction takes place in a single step, it would be difficult to account for rearrangement, but if the reaction takes place in several steps, rearrangement is more easily explained. What evidently happens is that the secondary carbocation formed by protonation of 3-methylbut-1-ene rearranges in an intermediate step to give a more stable tertiary carbocation, which then reacts with chloride ion. The rearrangement occurs by a **hydride shift**—the shift of a hydrogen atom and its electron pair (a hydride ion, :H^-) between neighboring carbons.

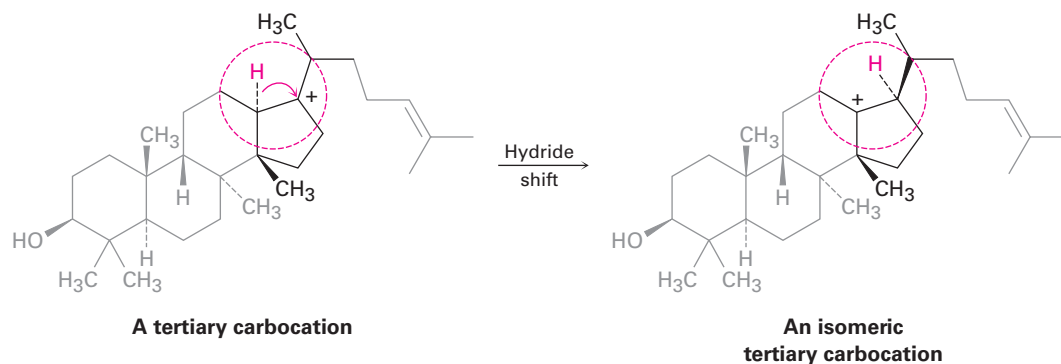


Carbocation rearrangements can also occur by the shift of an alkyl group with its electron pair. For example, reaction of 3,3-dimethylbut-1-ene with HCl leads to an equal mixture of unrearranged 3-chloro-2,2-dimethylbutane and rearranged 2-chloro-2,3-dimethylbutane. In this instance, a secondary carbocation rearranges to a more stable tertiary carbocation by the shift of a methyl group:



Note the similarities between the two carbocation rearrangements: in both cases, a group (:H^- or :CH_3^-) moves to an adjacent positively charged carbon,

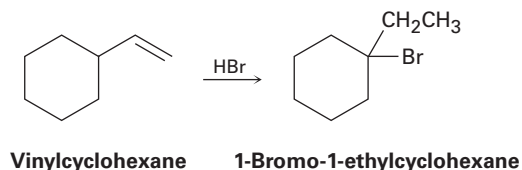
taking its bonding electron pair with it. Also in both cases, a less stable carbocation rearranges to a more stable ion. Rearrangements of this kind are a common feature of carbocation chemistry and are particularly important in the biological pathways by which steroids and related substances are synthesized. An example is the following hydride shift that occurs during the biosynthesis of cholesterol in the liver. Sections 23-9 and 23-10 show many others.



A word of advice that we've noted before and will repeat on occasion: biological molecules are often larger and more complex in appearance than the molecules chemists work with in the laboratory, but don't be intimidated. When looking at *any* chemical transformation, whether biochemical or not, focus on the part of the molecule where the change is occurring and don't worry about the rest. The tertiary carbocation just pictured looks complicated, but all the chemistry is taking place in the small part of the molecule inside the red circle.

PROBLEM 7.21

On treatment with HBr, vinylcyclohexane undergoes addition and rearrangement to yield 1-bromo-1-ethylcyclohexane. Using curved arrows, propose a mechanism to account for this result.

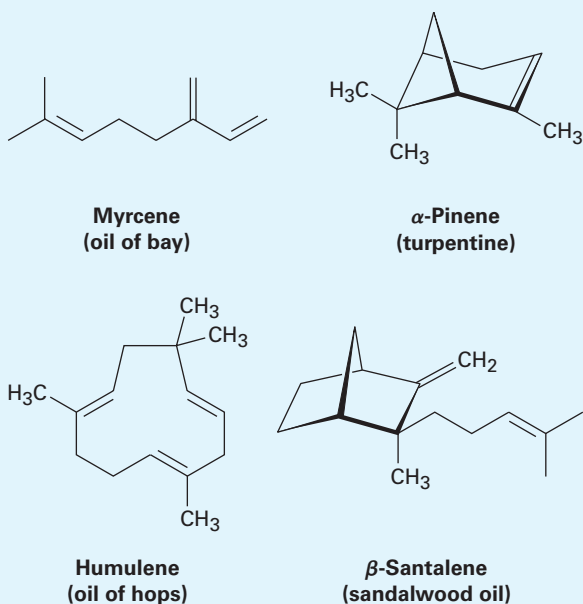


SOMETHING EXTRA

Terpenes: Naturally Occurring Alkenes

Ever since its discovery in Persia around 1000 A.D., it has been known that *steam distillation*, the codistillation of plant materials with water, produces a fragrant mixture of liquids called *essential oils*. The resulting oils have long been used as medicines, spices, and perfumes, and their investigation played a major role in the emergence of organic chemistry as a science during the 19th century.

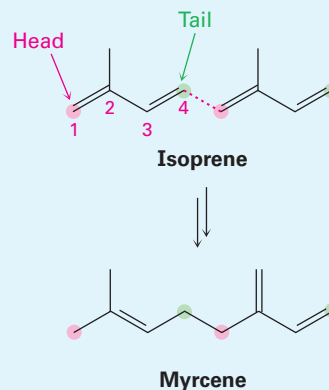
Chemically, plant essential oils consist largely of mixtures of compounds called *terpenoids*—small organic molecules with an immense diversity of structure. More than 35,000 different terpenoids are known. Some are open-chain molecules, and others contain rings; some are hydrocarbons, and others contain oxygen. Hydrocarbon terpenoids, in particular, are known as *terpenes*, and all contain double bonds. For example:



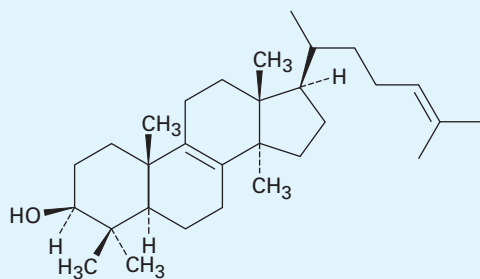
iStockphoto.com/Stephen Shankland

The wonderful fragrance of leaves from the California bay laurel is due primarily to myrcene, a simple terpene.

Regardless of their apparent structural differences, all terpenoids are related. According to a formalism called the *isoprene rule*, they can be thought of as arising from head-to-tail joining of 5-carbon isoprene units (2-methylbuta-1,3-diene). Carbon 1 is the head of the isoprene unit, and carbon 4 is the tail. For example, myrcene contains two isoprene units joined head to tail, forming an 8-carbon chain with two 1-carbon branches. α -Pinene similarly contains two isoprene units assembled into a more complex cyclic structure, and humulene and β -santalene contain three isoprene units. See if you can identify the isoprene units in α -pinene, humulene, and β -santalene.

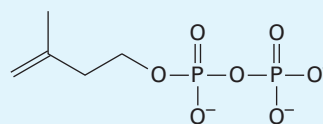


Terpenes (and terpenoids) are further classified according to the number of 5-carbon units they contain. Thus, *monoterpenes* are 10-carbon substances derived from two isoprene units, *sesquiterpenes* are 15-carbon molecules derived from three isoprene units, *diterpenes* are 20-carbon substances derived from four isoprene units, and so on. Monoterpenes and sesquiterpenes are found primarily in plants, but the higher terpenoids occur in both plants and animals, and many have important biological roles. The triterpenoid lanosterol, for example, is the precursor from which all steroid hormones are made.

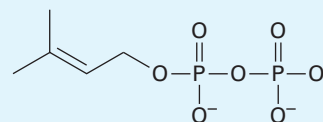


Lanosterol
(a triterpene, C₃₀)

Isoprene itself is not the true biological precursor of terpenoids. Nature instead uses two “isoprene equivalents”—isopentenyl diphosphate and dimethylallyl diphosphate—which are themselves made by two different routes depending on the organism. Lanosterol, in particular, is biosynthesized from acetic acid by a complex pathway that has been worked out in great detail. We’ll look at the subject more closely in Section 23-7.



Isopentenyl diphosphate



Dimethylallyl diphosphate

KEY WORDS

- alkene (R₂C=CR₂), 179
- alkyne (RC≡CR), 179
- allyl group, 184
- degree of unsaturation, 181
- E* geometry, 189
- electrophilic addition reaction, 195
- Hammond postulate, 204
- hydride shift, 207
- hyperconjugation, 194
- Markovnikov’s rule, 198
- methylene group, 184
- regiospecific, 197
- unsaturated, 180
- vinyl group, 184
- Z* geometry, 189

SUMMARY

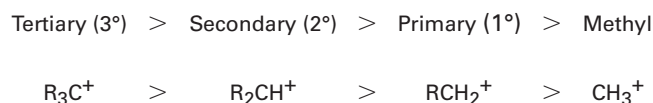
Carbon–carbon double bonds are present in most organic and biological molecules, so a good understanding of their behavior is needed. In this chapter, we’ve looked at some consequences of alkene stereoisomerism and at the details of the broadest and most general class of alkene reactions—the electrophilic addition reaction.

An **alkene** is a hydrocarbon that contains a carbon–carbon double bond, and an **alkyne** is a hydrocarbon that contains a triple bond. Because they contain fewer hydrogens than alkanes with the same number of carbons, alkenes and alkynes are said to be **unsaturated**.

Because rotation around the double bond can’t occur, substituted alkenes can exist as *cis*–*trans* stereoisomers. The geometry of a double bond can be specified by application of the Cahn–Ingold–Prelog sequence rules, which rank the substituents on each double-bond carbon. If the higher-ranking groups on each carbon are on the same side of the double bond, the geometry is **Z** (*zusammen*, “together”); if the higher-ranking groups on each carbon are on opposite sides of the double bond, the geometry is **E** (*entgegen*, “apart”).

Alkene chemistry is dominated by **electrophilic addition reactions**. When HX reacts with an unsymmetrically substituted alkene, **Markovnikov’s rule** predicts that the H will add to the carbon having fewer alkyl substituents and the X group will add to the carbon having more alkyl substituents. Electrophilic additions to alkenes take place through carbocation intermediates

formed by reaction of the nucleophilic alkene π bond with electrophilic H^+ . Carbocation stability follows the order



Markovnikov's rule can be restated by saying that, in the addition of HX to an alkene, the more stable carbocation intermediate is formed. This result is explained by the **Hammond postulate**, which says that the transition state of an exergonic reaction step structurally resembles the reactant, whereas the transition state of an endergonic reaction step structurally resembles the product. Since an alkene protonation step is endergonic, the stability of the more highly substituted carbocation is reflected in the stability of the transition state leading to its formation.

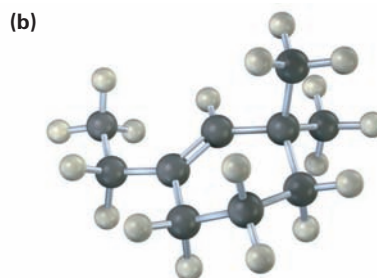
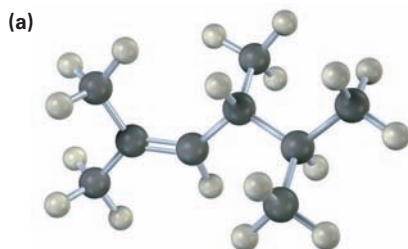
Evidence in support of a carbocation mechanism for electrophilic additions comes from the observation that structural rearrangements often take place during reaction. Rearrangements occur by shift of either a hydride ion, $:H^-$ (a **hydride shift**), or an alkyl anion, $:R^-$, from a carbon atom to the adjacent positively charged carbon. The result is isomerization of a less stable carbocation to a more stable one.

EXERCISES

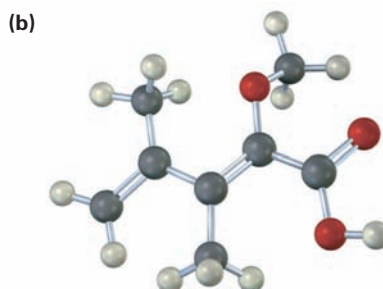
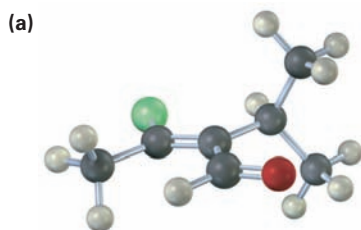
VISUALIZING CHEMISTRY

(Problems 7.1–7.21 appear within the chapter.)

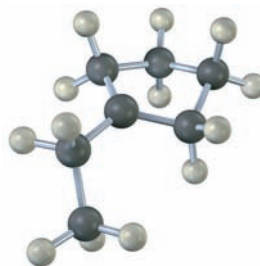
- 7.22** Name the following alkenes, and convert each drawing into a skeletal structure:



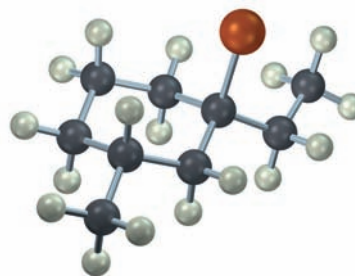
- 7.23** Assign *E* or *Z* stereochemistry to the double bonds in each of the following alkenes, and convert each drawing into a skeletal structure (red = O, green = Cl):



- 7.24 The following carbocation is an intermediate in the electrophilic addition reaction of HCl with two different alkenes. Identify both, and tell which C–H bonds in the carbocation are aligned for hyperconjugation with the vacant p orbital on the positively charged carbon.



- 7.25 The following alkyl bromide can be made by HBr addition to three different alkenes. Show their structures.

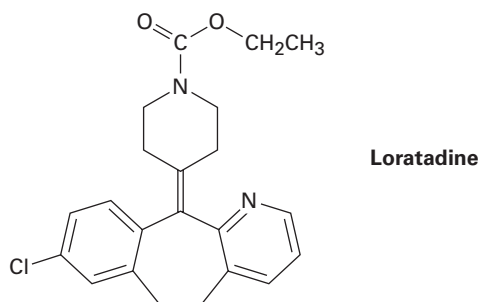


ADDITIONAL PROBLEMS

Calculating a Degree of Unsaturation

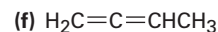
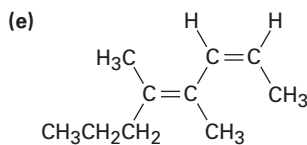
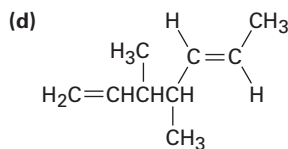
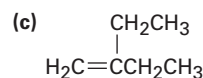
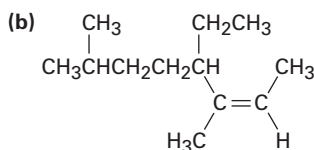
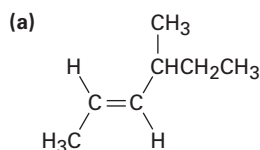
- 7.26 Calculate the degree of unsaturation in the following formulas, and draw five possible structures for each:
- (a) $C_{10}H_{16}$ (b) C_8H_8O (c) $C_7H_{10}Cl_2$
 (d) $C_{10}H_{16}O_2$ (e) $C_5H_9NO_2$ (f) $C_8H_{10}ClNO$
- 7.27 How many hydrogens does each of the following compounds have?
- (a) $C_8H_?O_2$, has two rings and one double bond
 (b) $C_7H_?N$, has two double bonds
 (c) $C_9H_?NO$, has one ring and three double bonds

- 7.28** Loratadine, marketed as an antiallergy medication under the name Claritin, has four rings, eight double bonds, and the formula $C_{22}H_{27}ClN_2O_2$. How many hydrogens does loratadine have? (Calculate your answer; don't count hydrogens in the structure.)



Naming Alkenes

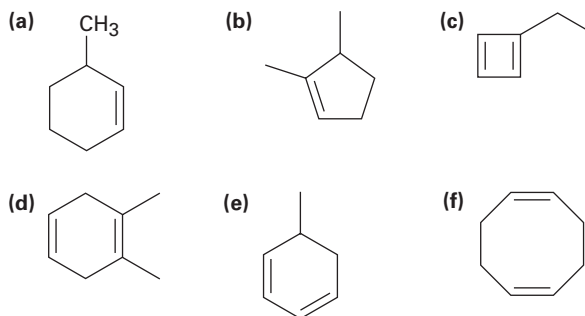
- 7.29** Name the following alkenes:



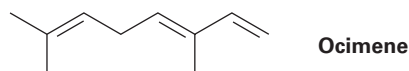
- 7.30** Draw structures corresponding to the following systematic names:

- (a) (4*E*)-2,4-Dimethylhexa-1,4-diene
 (b) *cis*-3,3-Dimethyl-4-propylocta-1,5-diene
 (c) 4-Methylpenta-1,2-diene
 (d) (3*E*,5*Z*)-2,6-Dimethylocta-1,3,5,7-tetraene
 (e) 3-Butylhept-2-ene
 (f) *trans*-2,2,5,5-Tetramethylhex-3-ene

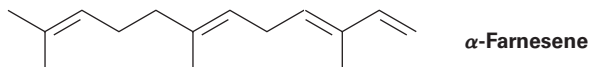
7.31 Name the following cycloalkenes:



7.32 Ocimene is a triene found in the essential oils of many plants. What is its IUPAC name, including stereochemistry?



7.33 α -Farnesene is a constituent of the natural wax found on apples. What is its IUPAC name, including stereochemistry?



7.34 Menthene, a hydrocarbon found in mint plants, has the systematic name 1-isopropyl-4-methylcyclohexene. Draw its structure.

7.35 Draw and name the six alkene isomers, C_5H_{10} , including *E,Z* isomers.

7.36 There are seven isomeric alkynes with the formula C_6H_{10} . Draw and name them.

7.37 Draw and name the 17 alkene isomers, C_6H_{12} , including *E,Z* isomers.

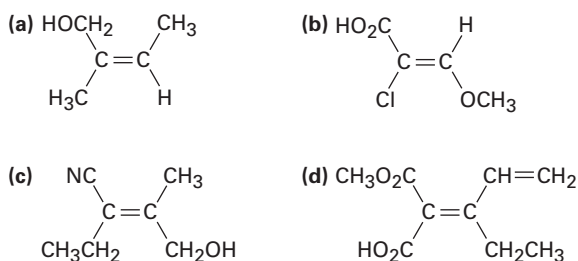
7.38 Tridec-1-ene-3,5,7,9,11-pentayne is a hydrocarbon isolated from sunflowers. Draw its structure. (Tridecane is the straight-chain alkane $C_{13}H_{28}$.)

Alkene Isomers and Their Stability

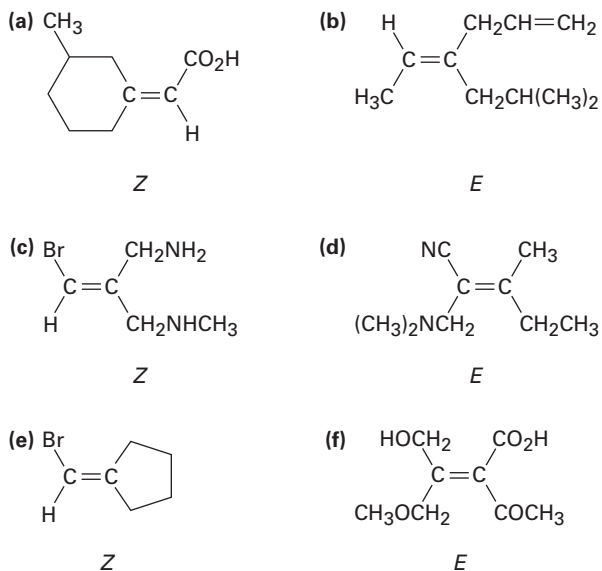
7.39 Rank the substituents in each of the following sets according to the Cahn–Ingold–Prelog sequence rules:

- (a) $-\text{CH}_3$, $-\text{Br}$, $-\text{H}$, $-\text{I}$
 (b) $-\text{OH}$, $-\text{OCH}_3$, $-\text{H}$, $-\text{CO}_2\text{H}$
 (c) $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$
 (d) $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\overset{\text{O}}{\parallel}\text{CCH}_3$
 (e) $-\text{CH}=\text{CH}_2$, $-\text{CN}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{Br}$
 (f) $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OH}$

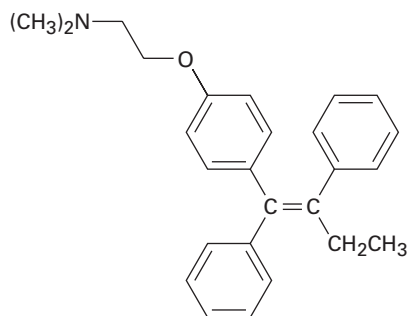
7.40 Assign *E* or *Z* configuration to the double bonds in each of the following compounds:



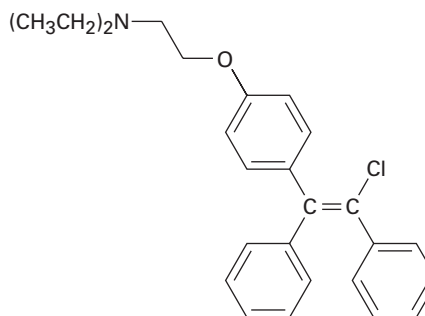
7.41 Which of the following *E,Z* designations are correct, and which are incorrect?



- 7.42 *trans*-But-2-ene is more stable than *cis*-but-2-ene by only 4 kJ/mol, but *trans*-2,2,5,5-tetramethylhex-3-ene is more stable than its *cis* isomer by 39 kJ/mol. Explain.
- 7.43 Cyclodecene can exist in both *cis* and *trans* forms, but cyclohexene cannot. Explain. (Making molecular models is helpful.)
- 7.44 Normally, a *trans* alkene is *more* stable than its *cis* isomer. *trans*-Cyclooctene, however, is *less* stable than *cis*-cyclooctene by 38.5 kJ/mol. Explain.
- 7.45 *trans*-Cyclooctene is less stable than *cis*-cyclooctene by 38.5 kJ/mol, but *trans*-cyclononene is less stable than *cis*-cyclononene by only 12.2 kJ/mol. Explain.
- 7.46 Tamoxifen, a drug used in the treatment of breast cancer, and clomiphene, a drug used as a fertility treatment, have similar structures but very different effects. Assign *E* or *Z* configuration to the double bonds in both compounds.



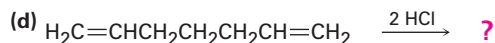
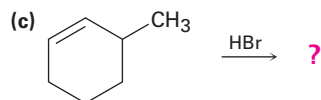
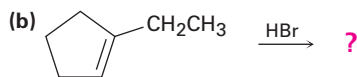
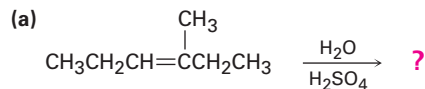
Tamoxifen
(anticancer)



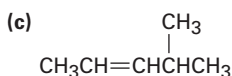
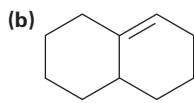
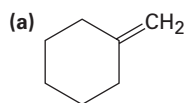
Clomiphene
(fertility treatment)

Carbocations and Electrophilic Addition Reactions

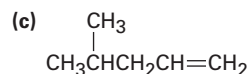
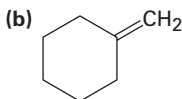
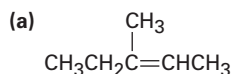
7.47 Predict the major product in each of the following reactions:



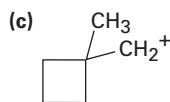
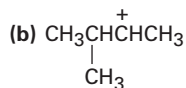
- 7.48 Predict the major product from addition of HBr to each of the following alkenes:



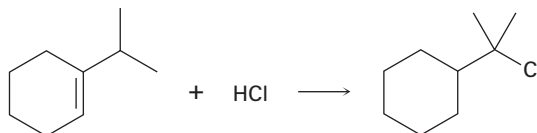
- 7.49 Predict the major alcohol product from acid-catalyzed addition of water to each of the following alkenes.



- 7.50 Each of the following carbocations can rearrange to a more stable ion. Propose structures for the likely rearrangement products.

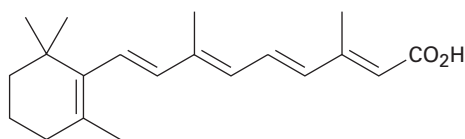


- 7.51 Addition of HCl to 1-isopropylcyclohexene yields a rearranged product. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.



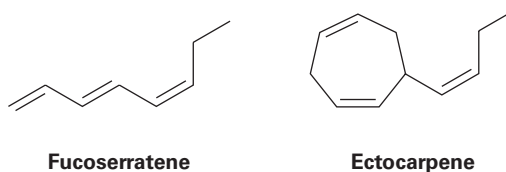
General Problems

- 7.52 Allene (propa-1,2-diene), $\text{H}_2\text{C}=\text{C}=\text{CH}_2$, has two adjacent double bonds. What kind of hybridization must the central carbon have? Sketch the bonding π orbitals in allene. What shape do you predict for allene?
- 7.53 The heat of hydrogenation for allene (Problem 7.52) to yield propane is -295 kJ/mol, and the heat of hydrogenation for a typical monosubstituted alkene such as propene is -126 kJ/mol. Is allene more stable or less stable than you might expect for a diene? Explain.
- 7.54 Retin A, or retinoic acid, is a medication commonly used to reduce wrinkles and treat severe acne. How many different isomers arising from double-bond isomerizations are possible?

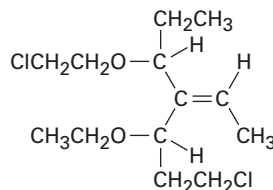


Retin A (retinoic acid)

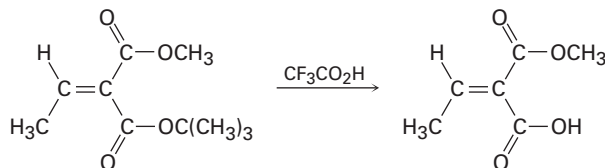
- 7.55 Fucoserratene and ectocarpene are sex pheromones produced by marine brown algae. What are their systematic names? (Ectocarpene is a bit difficult; make your best guess, and then check your answer in the *Study Guide and Solutions Manual*.)



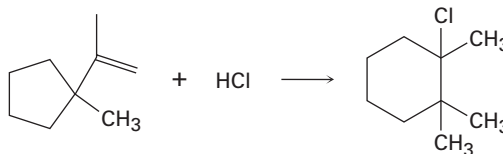
- 7.56 Assign *E* or *Z* configuration to the double bond in the following compound. (It's a bit difficult, so check your answer in the *Study Guide and Solutions Manual*.)



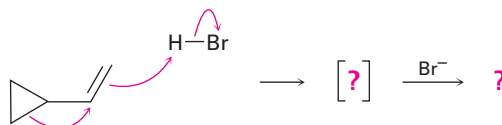
- 7.57 *tert*-Butyl esters [RCO₂C(CH₃)₃] are converted into carboxylic acids (RCO₂H) by reaction with trifluoroacetic acid, a reaction useful in protein synthesis (Section 19-7). Assign *E,Z* designation to the double bonds of both reactant and product in the following scheme, and explain why there is an apparent change of double-bond stereochemistry:



- 7.58 Addition of HCl to 1-isopropenyl-1-methylcyclopentane yields 1-chloro-1,2,2-trimethylcyclohexane. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.

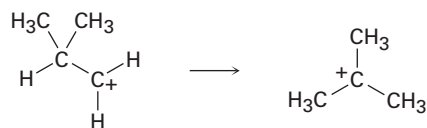


- 7.59 Vinylcyclopropane reacts with HBr to yield a rearranged alkyl bromide. Follow the flow of electrons as represented by the curved arrows, show the structure of the carbocation intermediate in brackets, and show the structure of the final product.



Vinylcyclopropane

- 7.60 Calculate the degree of unsaturation in each of the following compounds:
- (a) Cholesterol, $C_{27}H_{46}O$ (b) DDT, $C_{14}H_9Cl_5$
 (c) Prostaglandin E_1 , $C_{20}H_{34}O_5$ (d) Caffeine, $C_8H_{10}N_4O_2$
 (e) Cortisone, $C_{21}H_{28}O_5$ (f) Atropine, $C_{17}H_{23}NO_3$
- 7.61 The isobutyl cation spontaneously rearranges to the *tert*-butyl cation by a hydride shift. Is the rearrangement exergonic or endergonic? Draw what you think the transition state for the hydride shift might look like according to the Hammond postulate.

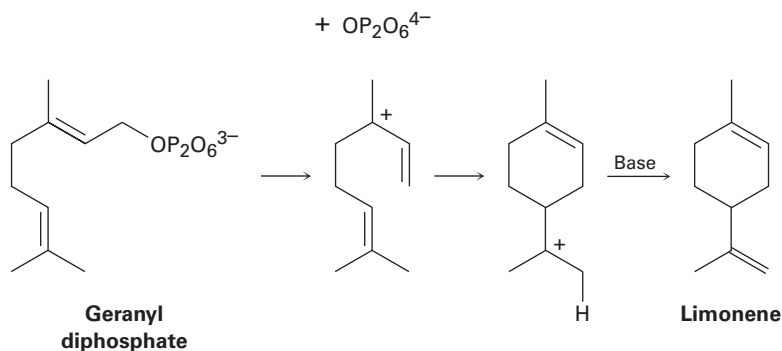


Isobutyl cation

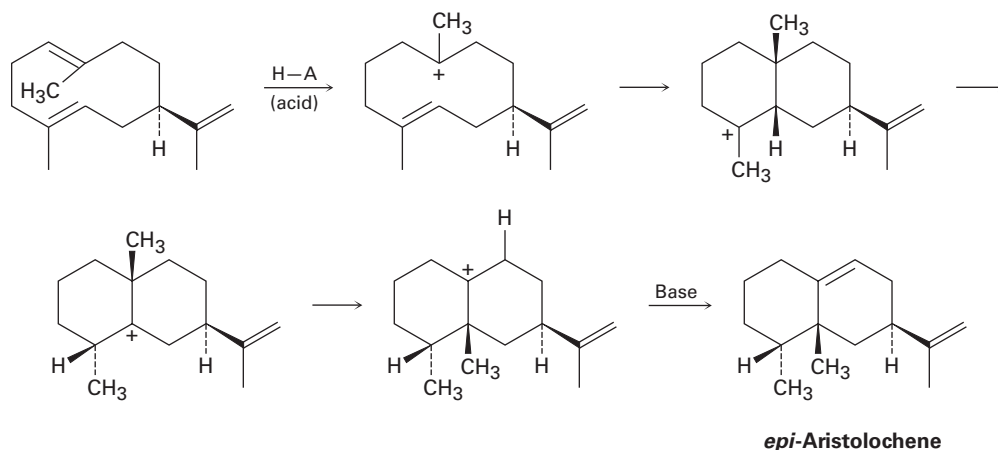
tert-Butyl cation

- 7.62 Draw an energy diagram for the addition of HBr to pent-1-ene. Let one curve on your diagram show the formation of 1-bromopentane product and another curve on the same diagram show the formation of 2-bromopentane product. Label the positions for all reactants, intermediates, and products. Which curve has the higher-energy carbocation intermediate? Which curve has the higher-energy first transition state?
- 7.63 Make sketches of the transition-state structures involved in the reaction of HBr with pent-1-ene (Problem 7.62). Tell whether each structure resembles reactant or product.

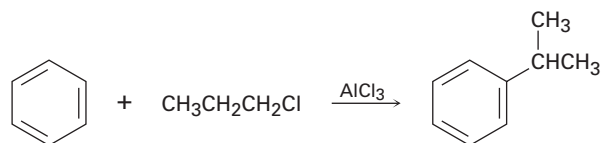
- 7.64 Limonene, a fragrant hydrocarbon found in lemons and oranges, is biosynthesized from geranyl diphosphate by the following pathway. Add curved arrows to show the mechanism of each step. Which step involves an alkene electrophilic addition? (The ion $\text{OP}_2\text{O}_6^{4-}$ is the diphosphate ion, and “Base” is an unspecified base in the enzyme that catalyzes the reaction.)



- 7.65 *epi*-Aristolochene, a hydrocarbon found in both pepper and tobacco, is biosynthesized by the following pathway. Add curved arrows to show the mechanism of each step. Which steps involve alkene electrophilic addition(s), and which involve carbocation rearrangement(s)? (The abbreviation H–A stands for an unspecified acid, and “Base” is an unspecified base in the enzyme.)



- 7.66** Aromatic compounds such as benzene react with alkyl chlorides in the presence of AlCl_3 catalyst to yield alkylbenzenes. The reaction occurs through a carbocation intermediate, formed by reaction of the alkyl chloride with AlCl_3 ($\text{R-Cl} + \text{AlCl}_3 \rightarrow \text{R}^+ + \text{AlCl}_4^-$). How can you explain the observation that reaction of benzene with 1-chloropropane yields isopropylbenzene as the major product?



- 7.67** Reaction of 2,3-dimethylbut-1-ene with HBr leads to an alkyl bromide, $\text{C}_6\text{H}_{13}\text{Br}$. On treatment of this alkyl bromide with KOH in methanol, elimination of HBr occurs and a hydrocarbon that is isomeric with the starting alkene is formed. What is the structure of this hydrocarbon, and how do you think it is formed from the alkyl bromide?

8

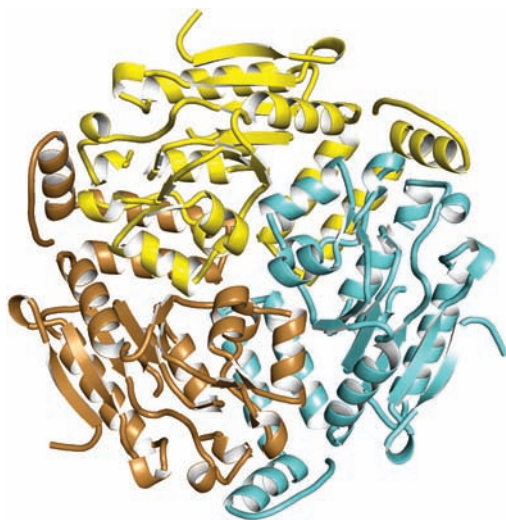
Reactions of Alkenes and Alkynes

CONTENTS

- 8-1 Preparing Alkenes:
A Preview of Elimination
Reactions
- 8-2 Halogenation of Alkenes
- 8-3 Halohydrins from Alkenes
- 8-4 Hydration of Alkenes
- 8-5 Reduction of Alkenes:
Hydrogenation
- 8-6 Oxidation of Alkenes:
Epoxidation
- 8-7 Oxidation of Alkenes:
Hydroxylation
- 8-8 Oxidation of Alkenes:
Cleavage to Carbonyl
Compounds
- 8-9 Addition of Carbenes
to Alkenes: Cyclopropane
Synthesis
- 8-10 Radical Additions
to Alkenes: Chain-Growth
Polymers
- 8-11 Biological Additions
of Radicals to Alkenes
- 8-12 Conjugated Dienes
- 8-13 Reactions of Conjugated
Dienes
- 8-14 The Diels–Alder
Cycloaddition Reaction
- 8-15 Reactions of Alkynes

SOMETHING EXTRA

Natural Rubber



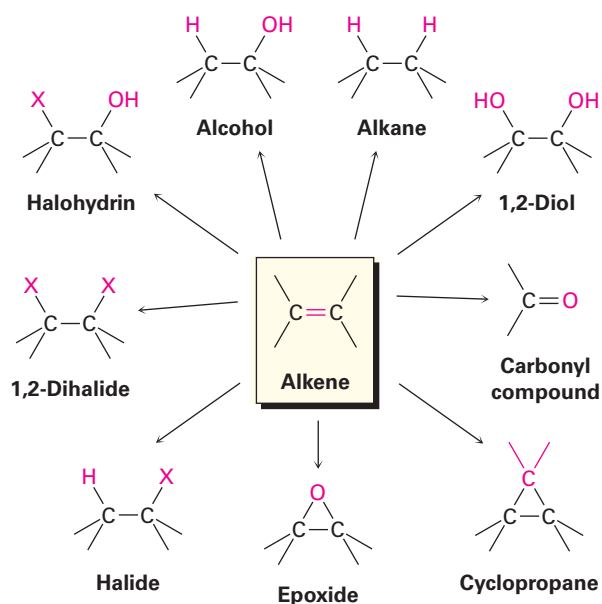
Enoyl CoA hydratase catalyzes the addition of water to a C=C double bond during fatty-acid metabolism.

WHY THIS CHAPTER?

Much of the background needed to understand organic reactions has now been covered, and it's time to begin a systematic description of the major functional groups. Both in this chapter on alkenes and in future chapters on other functional groups, we'll discuss a variety of reactions but try to focus on those that have direct or indirect counterparts in biological pathways. There are no shortcuts: you have to know the reactions to understand organic and biological chemistry.

Alkene addition reactions occur widely, both in the laboratory and in living organisms. Although we've studied only the addition of H₂O and HX thus far, many closely related reactions also take place. In this chapter, we'll see

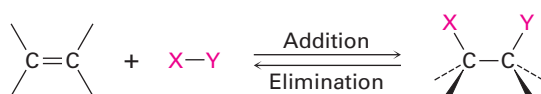
briefly how alkenes are prepared and we'll discuss further examples of alkene addition reactions. Particularly important are the addition of a halogen to give a 1,2-dihalide, addition of a hypohalous acid to give a halohydrin, addition of water to give an alcohol, addition of hydrogen to give an alkane, addition of a single oxygen to give a three-membered cyclic ether called an *epoxide*, and addition of two hydroxyl groups to give a 1,2-diol.



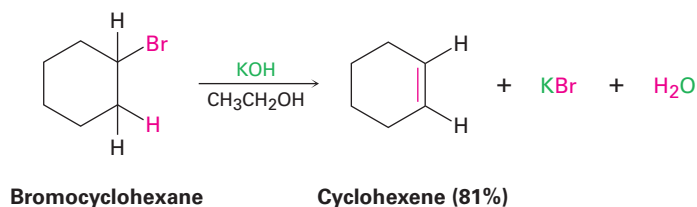
8-1 Preparing Alkenes: A Preview of Elimination Reactions

Before getting to the main subject of this chapter—the reactions of alkenes—let's take a brief look at how alkenes are prepared. The subject is a bit complex, though, so we'll return in Chapter 12 for a more detailed study. For the present, it's enough to realize that alkenes are readily available from simple precursors—usually alcohols in biological systems and either alcohols or alkyl halides in the laboratory.

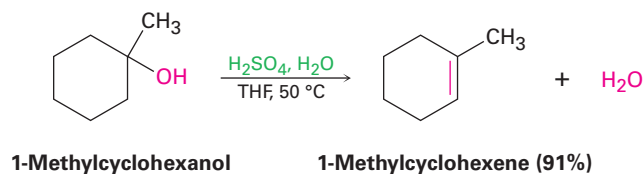
Just as the chemistry of alkenes is dominated by addition reactions, the preparation of alkenes is dominated by elimination reactions. Additions and eliminations are, in many respects, two sides of the same coin. That is, an addition reaction might involve the addition of HBr or H₂O to an alkene to form an alkyl halide or alcohol, whereas an elimination reaction might involve the loss of HBr or H₂O from an alkyl halide or alcohol to form an alkene.



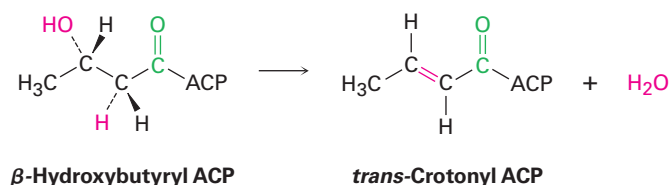
The two most common elimination reactions are **dehydrohalogenation**—the loss of HX from an alkyl halide—and **dehydration**—the loss of water from an alcohol. Dehydrohalogenation usually occurs by reaction of an alkyl halide with a strong base, such as potassium hydroxide. For example, bromocyclohexane yields cyclohexene when treated with KOH in ethanol solution:



Dehydration is often carried out in the laboratory by treatment of an alcohol with a strong acid. For example, when 1-methylcyclohexanol is warmed with aqueous sulfuric acid in tetrahydrofuran (THF) solvent, loss of water occurs and 1-methylcyclohexene is formed.



In biological pathways, dehydrations rarely occur with isolated alcohols. Instead, they normally take place on substrates in which the -OH is positioned two carbons away from a carbonyl group. In the biosynthesis of fats, for instance, β -hydroxybutyryl ACP is converted by dehydration to *trans*-crotonyl ACP, where ACP is an abbreviation for *acyl carrier protein*. We'll see the reason for this requirement in Section 12-13.

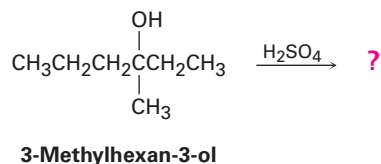


PROBLEM 8.1

One problem with elimination reactions is that mixtures of products are often formed. For example, treatment of 2-bromo-2-methylbutane with KOH in ethanol yields a mixture of two alkene products. What are their likely structures?

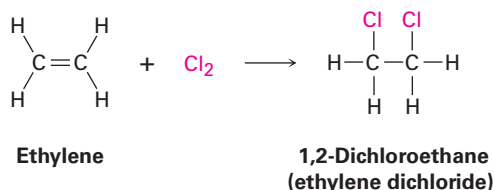
PROBLEM 8.2

How many alkene products, including *E,Z* isomers, might be obtained by dehydration of 3-methylhexan-3-ol with aqueous sulfuric acid?

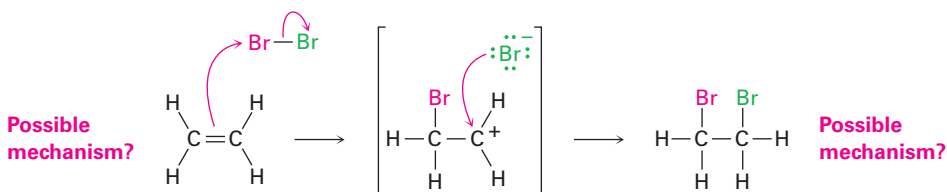


8-2 Halogenation of Alkenes

Bromine and chlorine add to alkenes to yield 1,2-dihalides, a process called **halogenation**. For example, more than 17 million metric tons of 1,2-dichloroethane (ethylene dichloride) is synthesized worldwide each year, much of it by addition of Cl_2 to ethylene. The product is used both as a solvent and as starting material for the manufacture of poly(vinyl chloride), PVC. Fluorine is too reactive and difficult to control for most applications, and iodine does not react with most alkenes.

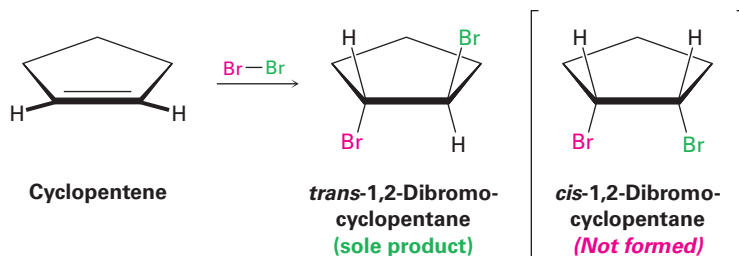


Based on what we've learned thus far about electrophilic addition reactions, a possible mechanism for the reaction of bromine with alkenes might involve addition of Br^+ to the alkene, giving a carbocation intermediate that could undergo further reaction with Br^- to yield the dibromo addition product.

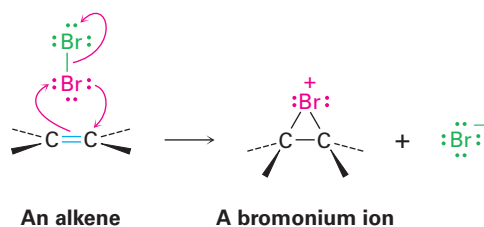


Although this mechanism seems plausible, it's not fully consistent with known facts. In particular, it doesn't explain the *stereochemistry* of the addition reaction. That is, the mechanism doesn't tell which product stereoisomer is formed.

When the halogenation reaction is carried out on a cycloalkene, such as cyclopentene, only the *trans* stereoisomer of the dihalide addition product is formed rather than the mixture of *cis* and *trans* isomers that might have been expected if a planar carbocation intermediate were involved. We say that the reaction occurs with **anti stereochemistry**, meaning that the two bromine atoms come from opposite faces of the double bond—one from the top face and one from the bottom face.

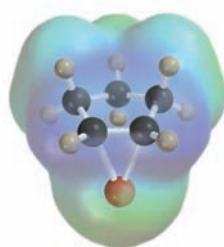
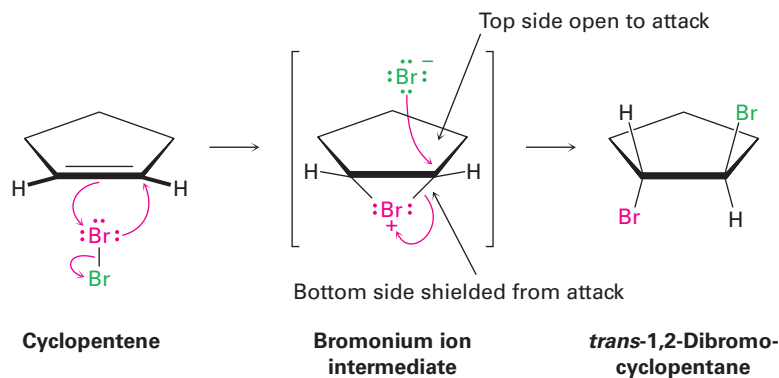


An explanation for the observed stereochemistry of addition came in 1937 with the suggestion that the reaction intermediate is not a carbocation but is instead a **bromonium ion** (R_2Br^+), formed by electrophilic addition of Br^+ to the alkene. (Similarly, a *chloronium ion* contains a positively charged, divalent chlorine, R_2Cl^+ .) The bromonium ion is formed in a single step by interaction of the alkene with Br_2 and simultaneous loss of Br^- .

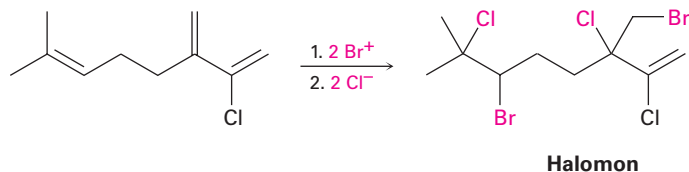


How does the formation of a bromonium ion account for the observed anti stereochemistry of addition to cyclopentene? If a bromonium ion is formed as an intermediate, we can imagine that the large bromine atom might “shield”

one side of the molecule. Reaction with Br^- ion in the second step can then occur only from the opposite, unshielded side to give the trans product.



Alkene halogenation reactions occur in nature just as they do in the laboratory but are limited primarily to marine organisms, which live in a halide-rich environment. The biological halogenation reactions are carried out by enzymes called *haloperoxidases*, which use H_2O_2 to oxidize Br^- or Cl^- ions to a biological equivalent of Br^+ or Cl^+ . Electrophilic addition to the double bond of a substrate molecule then yields a bromonium or chloronium ion intermediate just as in the laboratory, and reaction with another halide ion completes the process. Halomon, for example, an anticancer pentahalide isolated from red alga, is thought to arise by a route that involves twofold addition of BrCl through the corresponding bromonium ions.



PROBLEM 8.3

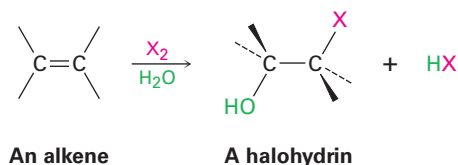
What product would you expect to obtain from addition of Cl_2 to 1,2-dimethylcyclohexene? Show the stereochemistry of the product.

PROBLEM 8.4

Addition of HCl to 1,2-dimethylcyclohexene yields a mixture of two products. Show the stereochemistry of each, and explain why a mixture is formed.

8-3 Halohydrins from Alkenes

Another example of an electrophilic addition is the reaction of alkenes with the hypohalous acids HO–Cl or HO–Br to yield 1,2-halo alcohols, called **halohydrins**. Halohydrin formation doesn't take place by direct reaction of an alkene with HOBr or HOCl, however. Rather, the addition is done indirectly by reaction of the alkene with either Br₂ or Cl₂ in the presence of water.



We saw in the previous section that when Br₂ reacts with an alkene, the cyclic bromonium ion intermediate reacts with the only nucleophile present, Br[−] ion, to give a dibromide. If the reaction is carried out in the presence of an *additional* nucleophile, however, the intermediate bromonium ion can be intercepted and diverted to a different product. In the presence of a high concentration of water, for instance, water competes with Br[−] ion as nucleophile and reacts with the bromonium ion intermediate to yield a bromohydrin. The net effect is addition of HOBr to the alkene by the pathway shown in **FIGURE 8.1**.

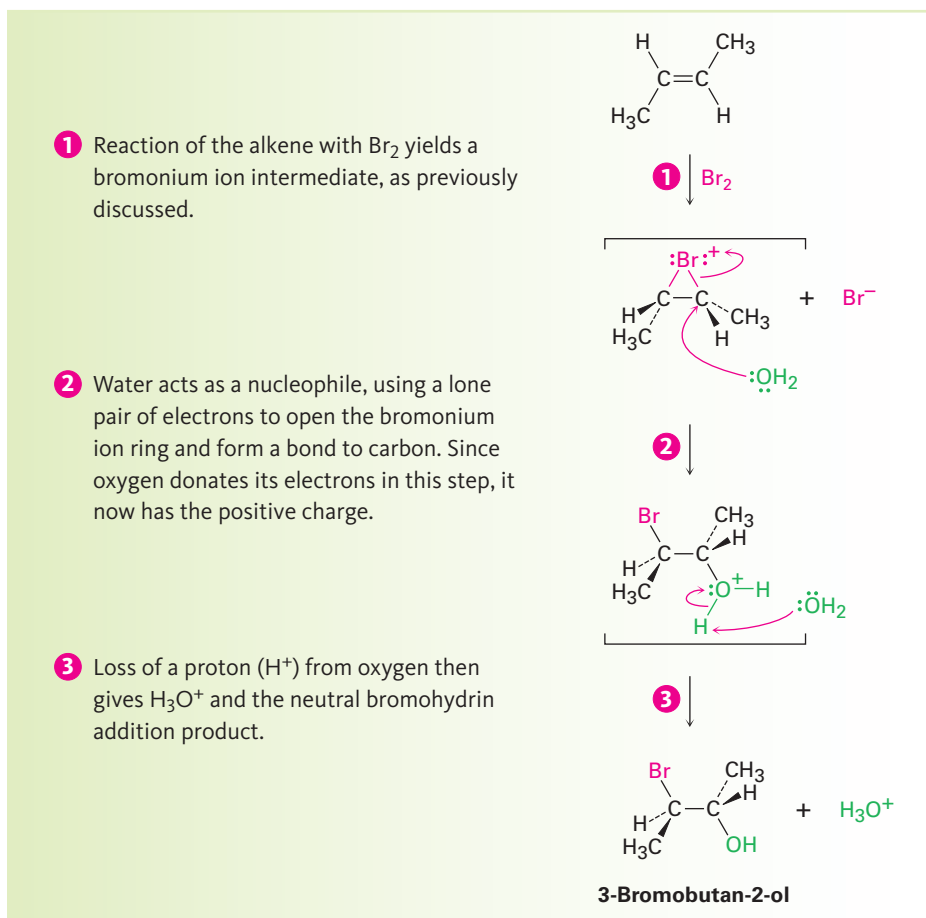
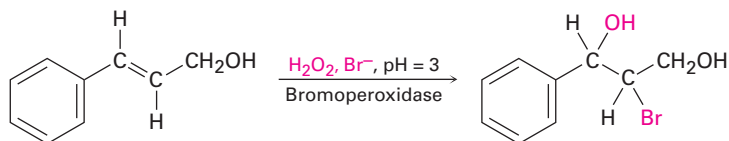


FIGURE 8.1 Mechanism of bromohydrin formation by reaction of an alkene with Br₂ in the presence of water. Water acts as a nucleophile to react with the intermediate bromonium ion.

There are a number of biological examples of halohydrin formation, particularly in marine organisms. As with halogenation (Section 8-2), halohydrin formation is carried out by haloperoxidases, which function by oxidizing Br^- or Cl^- ions to the corresponding HOBr or HOCl bonded to a metal atom in the enzyme. Electrophilic addition to the double bond of a substrate molecule then yields a bromonium or chloronium ion intermediate, and reaction with water gives the halohydrin. For example:

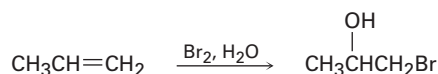


PROBLEM 8.5

What product would you expect from the reaction of cyclopentene with Br_2 and water? Show the stereochemistry.

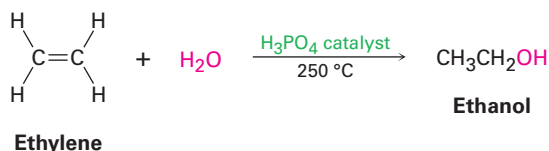
PROBLEM 8.6

When an unsymmetrically substituted alkene such as propene is treated with Br_2 and water, the major product has the bromine atom bonded to the less highly substituted carbon atom. Is this Markovnikov or non-Markovnikov orientation? Explain.



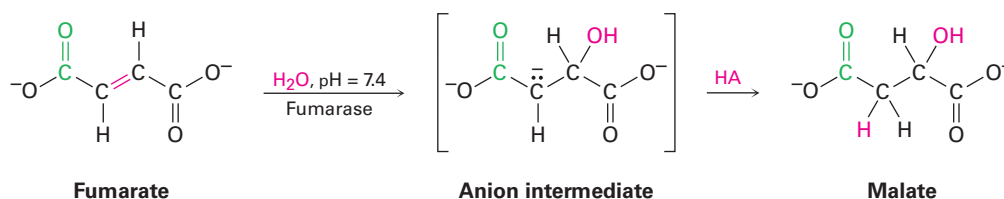
8-4 Hydration of Alkenes

We saw in Section 7-6 that alkenes undergo an acid-catalyzed addition reaction with water to yield alcohols. The process is particularly suited to large-scale industrial procedures, and approximately 300,000 metric tons of ethanol is manufactured each year in the United States by hydration of ethylene. Unfortunately, the reaction is not of much use in the laboratory because of the strongly acidic conditions and high temperatures needed—250 °C in the case of ethylene.



Acid-catalyzed hydration of isolated double bonds is also uncommon in biological pathways. More frequently, biological hydrations require that the double bond be adjacent to a carbonyl group for reaction to proceed. Fumarate,

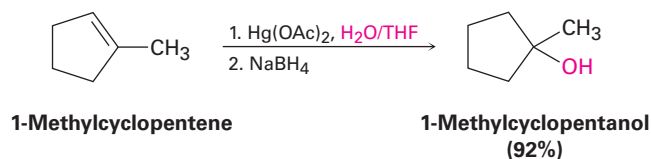
for instance, is hydrated to give malate as one step in the citric acid cycle of food metabolism. Note that the requirement for an adjacent carbonyl group in the addition of water is the same as that we saw in Section 8-1 for the elimination of water. We'll see the reason for the requirement in Section 14-11, but might note for now that the reaction is not an electrophilic addition but instead occurs through a mechanism that involves formation of an anion intermediate followed by protonation by an acid HA.



When it comes to circumventing problems like those with acid-catalyzed alkene hydrations, laboratory chemists have a great advantage over the cellular “chemists” in living organisms. Laboratory chemists are not constrained to carry out their reactions in water solution; they can choose from any of a large number of solvents. Laboratory reactions don't need to be carried out at a fixed temperature; they can take place over a wide range of temperatures. And laboratory reagents aren't limited to containing carbon, oxygen, nitrogen, and a few other elements; they can contain any element in the periodic table.

The general theme of this text is to focus on reactions that have a direct relevance to the chemistry of living organisms. Every so often, though, we'll discuss a particularly useful laboratory reaction that has no biological counterpart. In the present instance, alkenes are often hydrated in the laboratory by two nonbiological procedures, *oxymercuration–demercuration* and *hydroboration–oxidation*, which give complementary results.

Oxymercuration involves electrophilic addition of Hg^{2+} to the alkene on treatment with mercury(II) acetate $[(\text{CH}_3\text{CO}_2)_2\text{Hg}]$, often abbreviated $\text{Hg}(\text{OAc})_2$ in aqueous tetrahydrofuran (THF) solvent. The intermediate organomercury compound is then treated with sodium borohydride, NaBH_4 , and demercuration occurs to produce an alcohol. For example:



Alkene oxymercuration is closely analogous to halohydrin formation. The reaction is initiated by electrophilic addition of Hg^{2+} (mercuric ion) to the alkene to give an intermediate *mercurinium ion*, whose structure resembles that of a bromonium ion (FIGURE 8.2). Nucleophilic addition of water as in halohydrin formation, followed by loss of a proton, then yields a stable organomercury product. The final step, demercuration with sodium borohydride, involves radicals. Note that the regiochemistry of the reaction corresponds to Markovnikov addition of water; that is, the $-\text{OH}$ group attaches to the more

highly substituted carbon atom and the $-H$ attaches to the less highly substituted carbon.

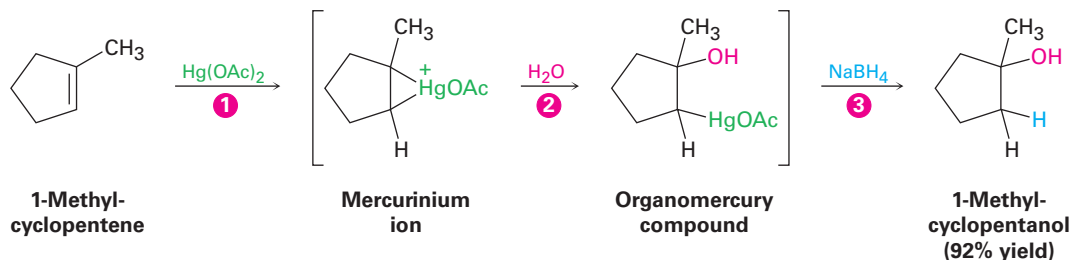
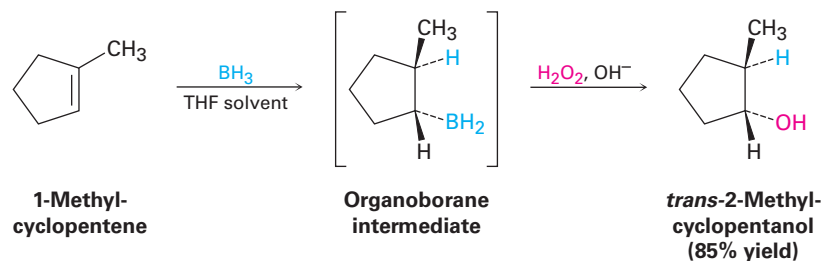


FIGURE 8.2 Mechanism of the oxymercuration of an alkene to yield an alcohol. The reaction proceeds by a mechanism similar to that of halohydrin formation. (1) Electrophilic addition of Hg^{2+} gives a mercurinium ion, which (2) reacts with water as in halohydrin formation. Loss of a proton gives an organomercury product, and (3) reaction with NaBH_4 removes the mercury. The product of the reaction is the more highly substituted alcohol, corresponding to Markovnikov regiochemistry.

In addition to the oxymercuration method, which yields the Markovnikov product, a complementary hydroboration–oxidation method that yields the non-Markovnikov product is also used in the laboratory. Hydroboration involves addition of a B–H bond of borane, BH_3 , to an alkene to yield an organoborane intermediate, RBH_2 . Oxidation of the organoborane by reaction with basic hydrogen peroxide, H_2O_2 , then gives the alcohol. For example:



Note that during the initial addition step, both boron and hydrogen add to the alkene from the same face of the double bond—that is, with **syn stereochemistry**, the opposite of anti. In this step, boron attaches to the less highly substituted carbon. During the subsequent oxidation, the boron is replaced by an $-\text{OH}$ with the same stereochemistry, resulting in an overall syn, non-Markovnikov addition of water.

Why does hydroboration–oxidation take place with syn, non-Markovnikov regiochemistry to yield the less highly substituted alcohol? Hydroboration differs from many other alkene addition reactions in that it occurs in a single step without a carbocation intermediate. Because both C–H and C–B bonds form at the same time and from the same face of the alkene, syn stereochemistry results. Non-Markovnikov regiochemistry is found because attachment of boron is favored at the less sterically crowded carbon atom of the alkene rather than at the more crowded carbon (**FIGURE 8.3**).

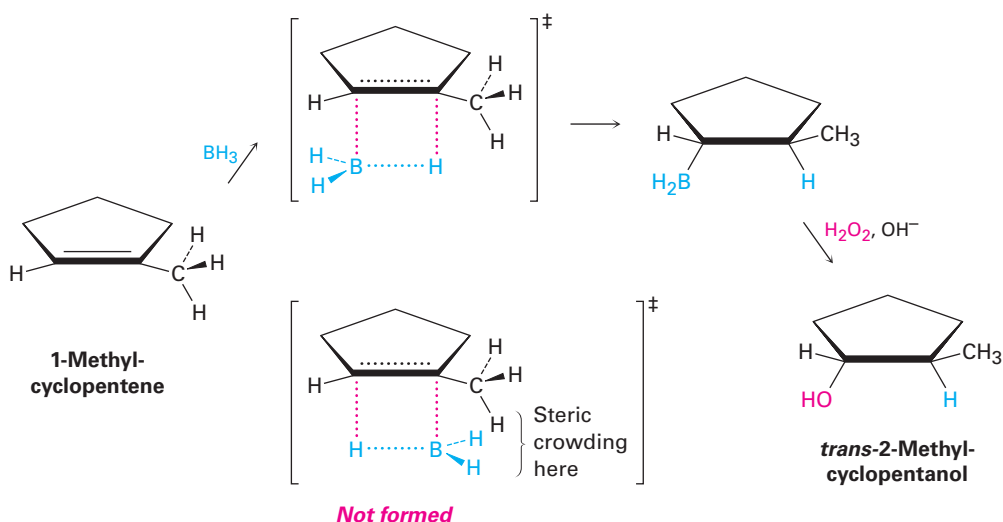


FIGURE 8.3 Mechanism of alkene hydroboration.

The reaction occurs in a single step in which both C–H and C–B bonds form at the same time and on the same face of the double bond. The lower energy, more rapidly formed transition state is the one with less steric crowding, leading to non-Markovnikov regiochemistry.

Predicting the Products of a Hydration Reaction

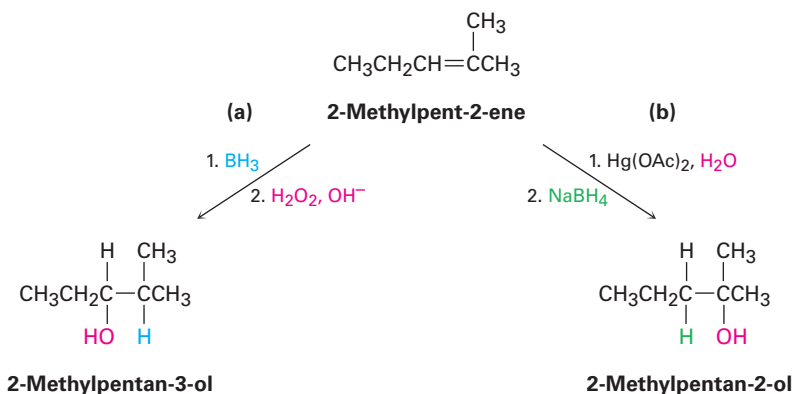
WORKED EXAMPLE 8.1

What products would you obtain from reaction of 2-methylpent-2-ene with: **(a)** BH_3 , followed by $\text{H}_2\text{O}_2, \text{OH}^-$ **(b)** $\text{Hg}(\text{OAc})_2$, followed by NaBH_4

Strategy

When predicting the product of a reaction, you have to recall what you know about the kind of reaction being carried out and then apply that knowledge to the specific case you're dealing with. In the present instance, recall that the two methods of hydration, hydroboration–oxidation and oxymercuration–demercuration, give complementary products. Hydroboration–oxidation occurs with syn stereochemistry and gives the non-Markovnikov addition product; oxymercuration–demercuration gives the Markovnikov product.

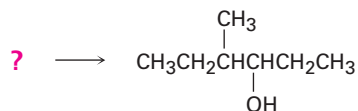
Solution



WORKED EXAMPLE 8.2

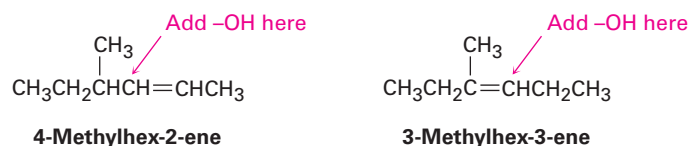
Synthesizing an Alcohol

How might you prepare the following alcohol?



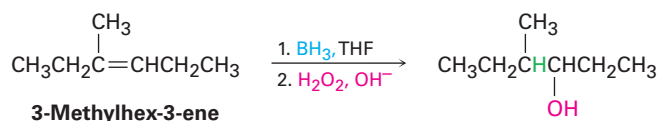
Strategy

Problems that require the synthesis of a specific target molecule should always be worked backward. Look at the target, identify its functional group(s), and ask yourself, “What are the methods for preparing that functional group?” In the present instance, the target molecule is a secondary alcohol (R_2CHOH), and we’ve seen that alcohols can be prepared from alkenes by either hydroboration–oxidation or oxymercuration–demercuration. The $-\text{OH}$ bearing carbon in the product must have been a double-bond carbon in the alkene reactant, so there are two possibilities: 4-methylhex-2-ene and 3-methylhex-3-ene.



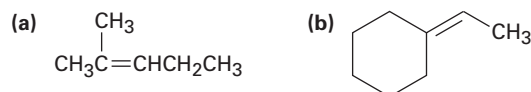
4-Methylhex-2-ene has a disubstituted double bond, $\text{RCH}=\text{CHR}'$, and will probably give a mixture of two alcohols with either hydration method since Markovnikov’s rule does not apply to symmetrically substituted alkenes. 3-Methylhex-3-ene, however, has a trisubstituted double bond and should give only the desired product on non-Markovnikov hydration using the hydroboration–oxidation method.

Solution



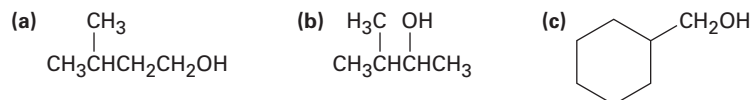
PROBLEM 8.7

What products would you expect from oxymercuration–demercuration of the following alkenes? From hydroboration–oxidation?



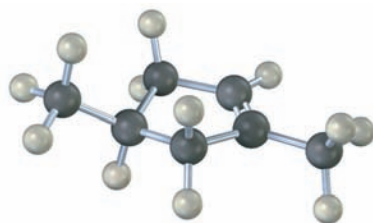
PROBLEM 8.8

What alkenes might the following alcohols have been prepared from?



PROBLEM 8.9

The following cycloalkene gives a mixture of two alcohols on hydroboration–oxidation. Draw the structures of both, and explain the result.

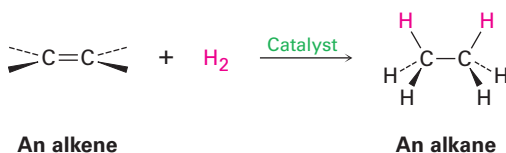
**8-5 Reduction of Alkenes: Hydrogenation**

Alkenes react with H_2 in the presence of a metal catalyst such as palladium or platinum to yield the corresponding saturated alkane addition products. We describe the result by saying that the double bond has been **hydrogenated**, or *reduced*. Note that the word *reduction* is used somewhat differently in organic chemistry than what you might have learned previously. In general chemistry, a reduction is defined as the gain of one or more electrons by an atom. In organic chemistry, however, a **reduction** is a reaction that results in a gain of electron density by carbon, caused either by bond-making between carbon and a less electronegative atom—usually hydrogen—or by bond-breaking between carbon and a more electronegative atom—usually oxygen, nitrogen, or a halogen.

Reduction Increases electron density on carbon by:

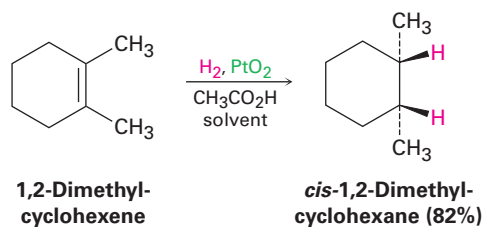
- forming this: C–H
- or breaking one of these: C–O C–N C–Hal

A reduction:



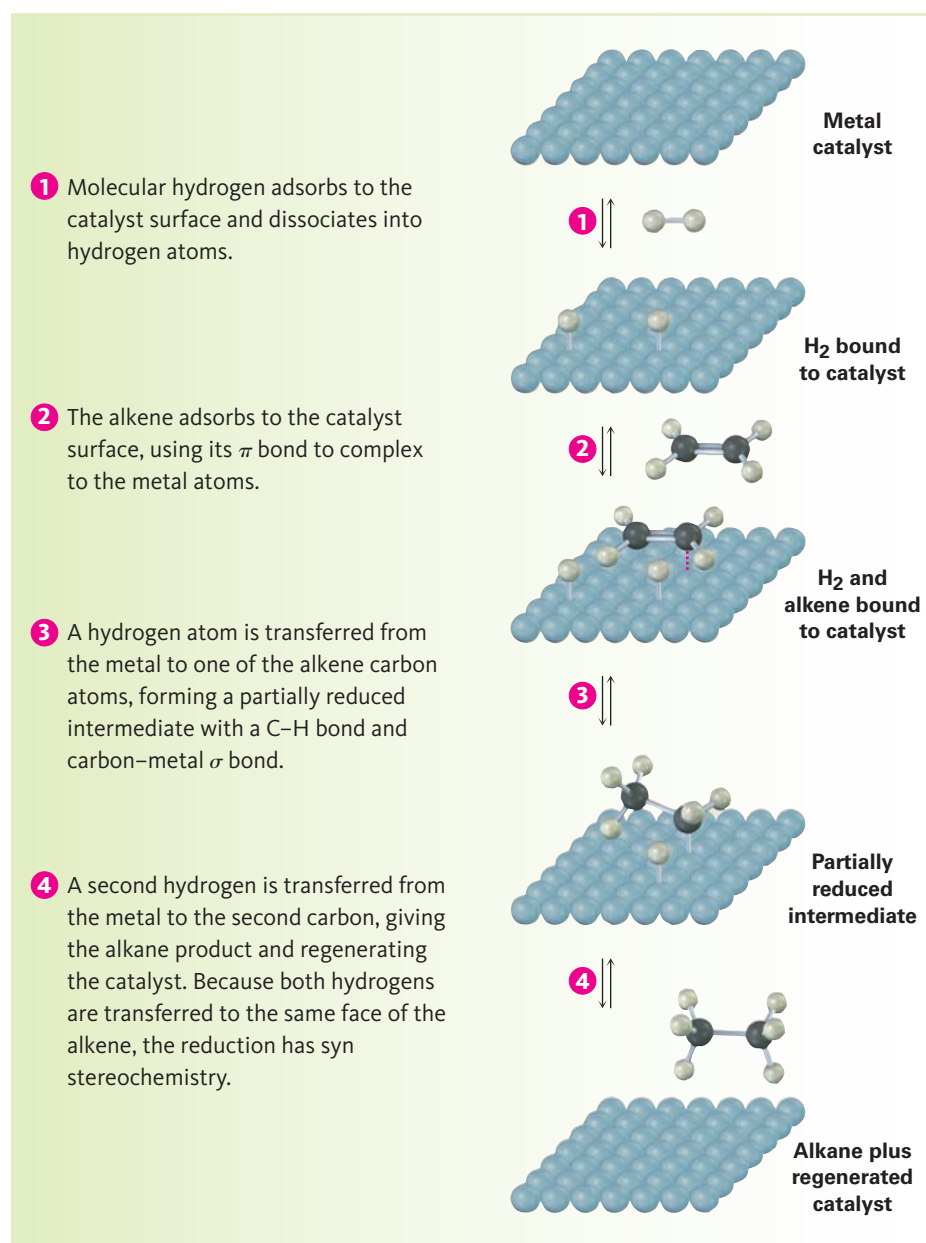
Platinum and palladium are the most common laboratory catalysts for alkene hydrogenations. Palladium is normally used as a very fine powder “supported” on an inert material such as charcoal (Pd/C) to maximize surface area. Platinum is normally used as PtO_2 , a reagent known as Adams’ catalyst after its discoverer, Roger Adams.

Catalytic hydrogenation, unlike most other organic reactions, is a heterogeneous process rather than a homogeneous one. That is, the hydrogenation reaction does not occur in a homogeneous solution but instead takes place on the surface of insoluble catalyst particles. Hydrogenation usually occurs with syn stereochemistry—both hydrogens add to the double bond from the same face.



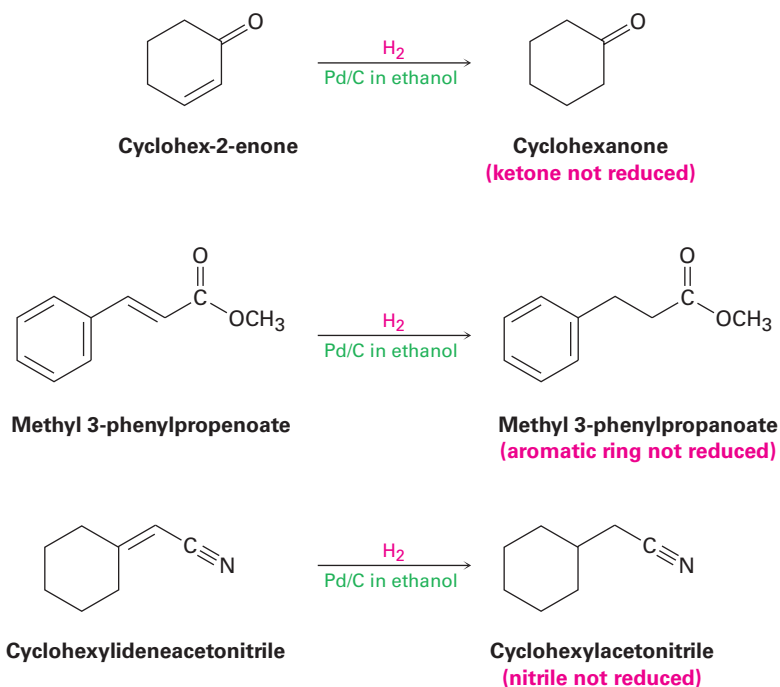
As shown in **FIGURE 8.4**, hydrogenation begins with adsorption of H_2 onto the catalyst surface. Complexation between catalyst and alkene then occurs as a vacant orbital on the metal interacts with the filled alkene π orbital. In the final steps, hydrogen is inserted into the double bond and the saturated

FIGURE 8.4 Mechanism of alkene hydrogenation. The reaction takes place with syn stereochemistry on the surface of insoluble catalyst particles.



product diffuses away from the catalyst. The stereochemistry of hydrogenation is syn because both hydrogens add to the double bond from the same catalyst surface.

Alkenes are much more reactive than most other unsaturated functional groups toward catalytic hydrogenation, and the reaction is therefore quite selective. Other functional groups such as aldehydes, ketones, and esters often survive alkene hydrogenation conditions unchanged, although reaction with these groups does occur under more vigorous conditions. Note particularly in the hydrogenation of methyl 3-phenylpropenoate shown below that the aromatic ring is not reduced by hydrogen and palladium even though it contains apparent double bonds.



In addition to its usefulness in the laboratory, catalytic hydrogenation is also important in the food industry, where unsaturated vegetable oils are reduced on a large scale to produce the saturated fats used in margarine and cooking products (FIGURE 8.5). As we'll see in Section 23-1, vegetable oils are triesters of glycerol, HOCH₂CH(OH)CH₂OH, with three long-chain carboxylic acids called fatty acids. The fatty acids are generally polyunsaturated, and their double bonds have cis stereochemistry. Complete hydrogenation yields the corresponding saturated fatty acids, but incomplete hydrogenation often results in partial cis–trans isomerization of a remaining double bond. When eaten and digested, the free trans fatty acids are released, raising blood cholesterol levels and contributing to potential coronary problems.

Double-bond reductions are extremely common in biological pathways, although the mechanism of the process is completely different from that of laboratory catalytic hydrogenation over palladium. As with biological

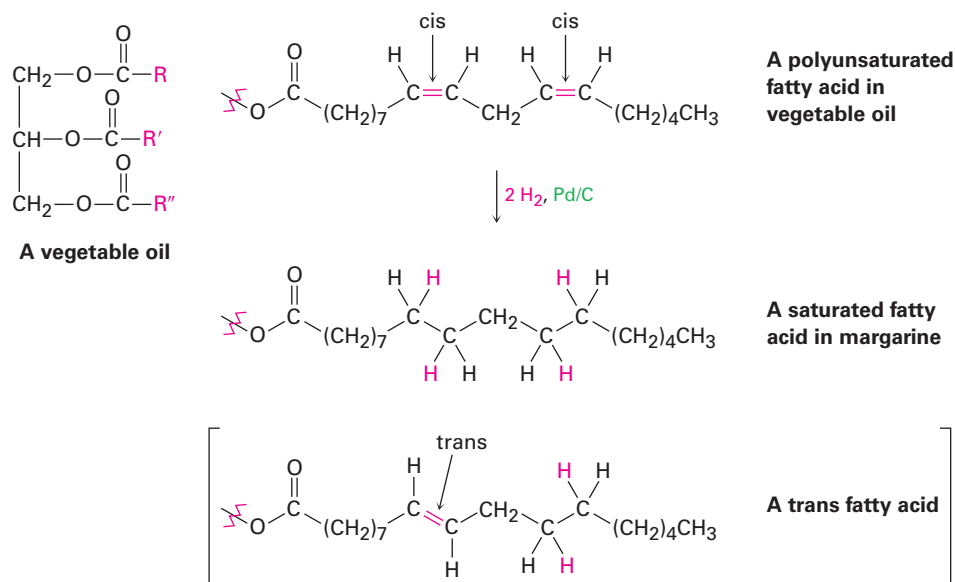
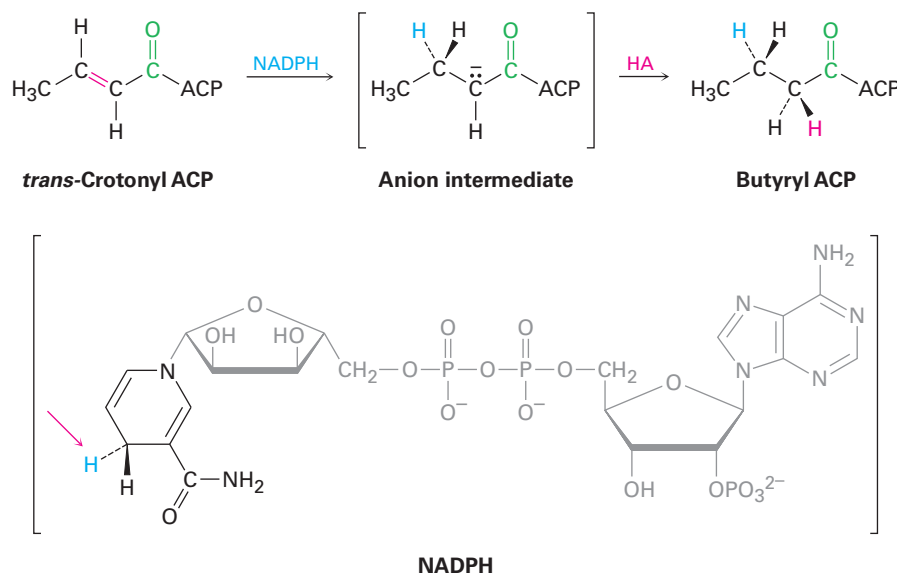


FIGURE 8.5 Catalytic hydrogenation of polyunsaturated fats. Saturated products are produced by hydrogenation, along with a small amount of isomerized *trans* fats.

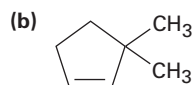
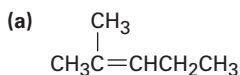
hydrations (Section 8-4), biological reductions usually occur in two steps and require that the double bond be adjacent to a carbonyl group. In the first step, the biological reducing agent NADPH (reduced nicotinamide adenine dinucleotide phosphate), adds a hydride ion (H^-) to the double bond to give an anion. In the second, the anion is protonated by acid HA, leading to overall addition of H_2 . An example is the reduction of *trans*-crotonyl ACP to yield butyryl ACP, a step in the biosynthesis pathway for fatty acids (FIGURE 8.6).

FIGURE 8.6 Reduction of the carbon–carbon double bond in *trans*-crotonyl ACP. In this step in fatty-acid biosynthesis, **one hydrogen** is delivered from NADPH as a hydride ion, H^- ; **the other hydrogen** is delivered by protonation of the anion intermediate with an acid, HA. As is often the case in biological reactions, the structure of the biochemical reagent, NADPH in this case, is relatively complex considering the apparent simplicity of the transformation itself.



PROBLEM 8.10

What product would you obtain from catalytic hydrogenation of the following alkenes?



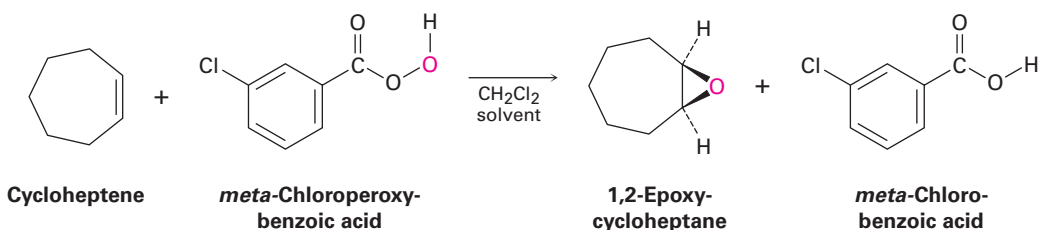
8-6 Oxidation of Alkenes: Epoxidation

Like the word *reduction* used in the previous section for the addition of hydrogen to a double bond, the word *oxidation* has a slightly different meaning in organic chemistry from what you might have previously learned. In general chemistry, an oxidation is defined as the loss of one or more electrons by an atom. In organic chemistry, however, an **oxidation** is a reaction that results in a loss of electron density by carbon, caused either by bond-making between carbon and a more electronegative atom—usually oxygen, nitrogen, or a halogen—or by bond-breaking between carbon and a less electronegative atom—usually hydrogen. Note that an oxidation often adds oxygen, while a reduction often adds hydrogen.

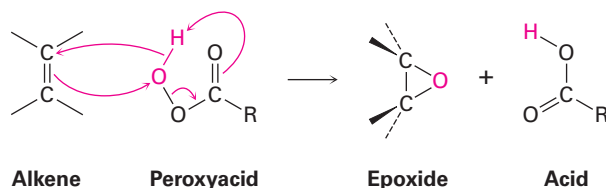
Oxidation Decreases electron density on carbon by:

- forming one of these: C–O C–N C–Hal
- or breaking this: C–H

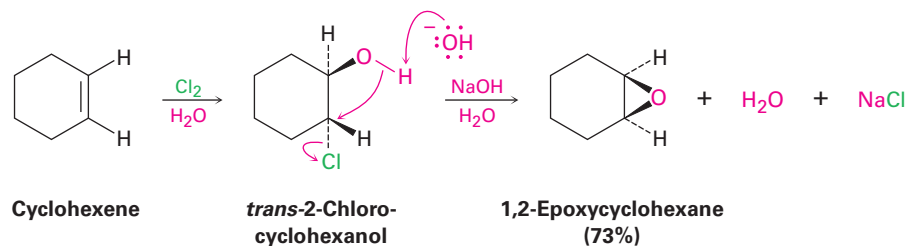
In the laboratory, alkenes are oxidized to give *epoxides* on treatment with a peroxyacid, RCO_3H , such as *meta*-chloroperoxybenzoic acid. An **epoxide**, also called an *oxirane*, is a cyclic ether with an oxygen atom in a three-membered ring. For example:



Peroxyacids transfer an oxygen atom to the alkene with syn stereochemistry—both C–O bonds form on the same face of the double bond—through a one-step mechanism without intermediates. The oxygen atom farthest from the carbonyl group is the one transferred.



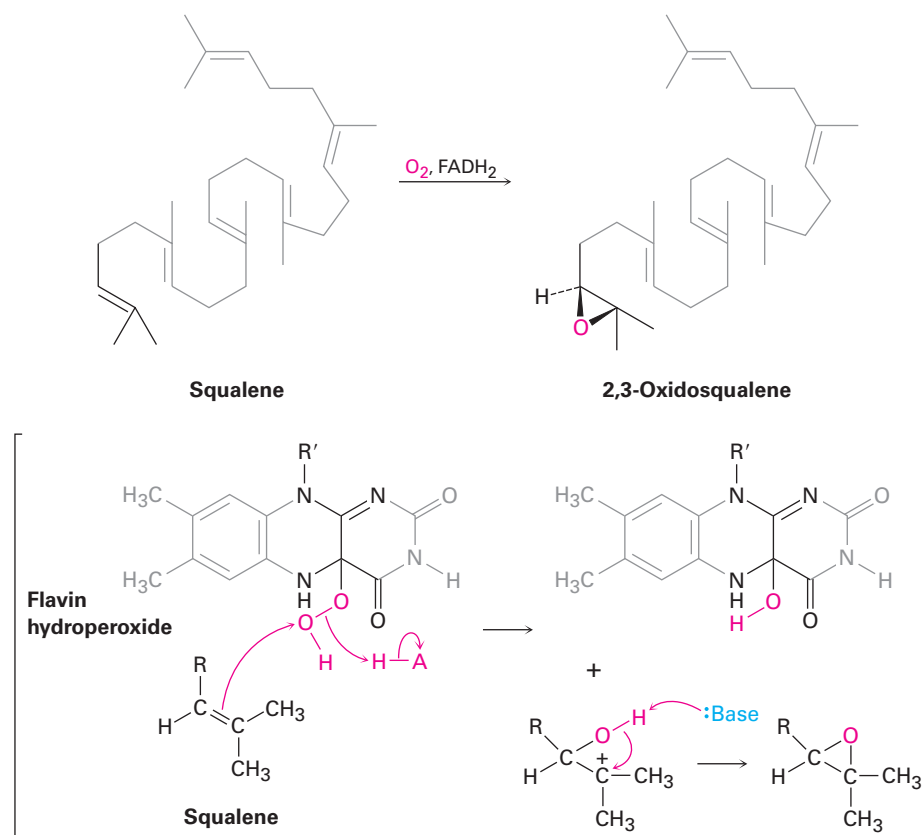
Another method for the synthesis of epoxides is through the use of halohydrins, prepared by electrophilic addition of HO–X to alkenes (Section 8-3). When a halohydrin is treated with base, HX is eliminated and an epoxide is produced.



Epoxides are also produced from alkenes as intermediates in various biological pathways, although peroxyacids are not involved. An example is the conversion of squalene into 2,3-oxidosqualene, a key step in the biosynthesis of steroids. The reaction is carried out by a flavin hydroperoxide, which is formed by reaction of O₂ with the coenzyme reduced flavin adenine dinucleotide, abbreviated FADH₂. Note the specificity of the reaction in which only one double bond out of six in the substrate molecule undergoes reaction. Note also that, once again, the structure of the biochemical reagent, flavin hydroperoxide, is relatively complex given the apparent simplicity of the transformation (FIGURE 8.7).

FIGURE 8.7 Biological epoxidation reaction of squalene.

The squalene epoxidation reaction occurs in steroid biosynthesis and is effected by a flavin hydroperoxide, formed by reaction of O₂ with the coenzyme reduced flavin adenine dinucleotide, FADH₂.



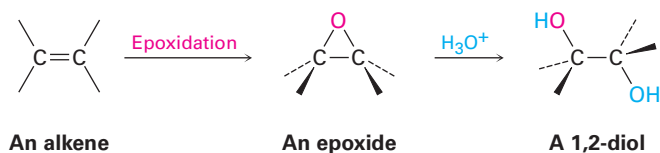
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PROBLEM 8.11

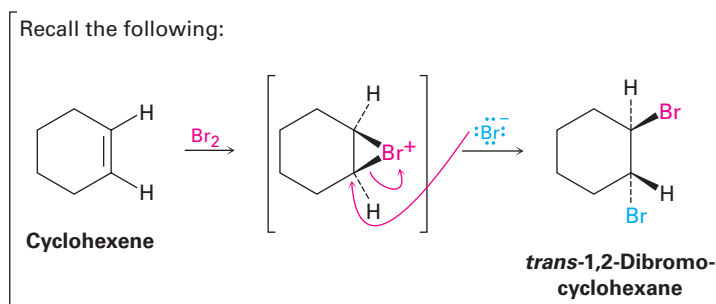
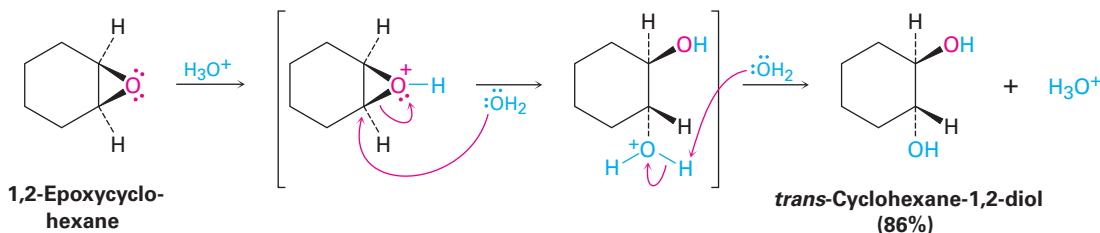
What product would you expect from reaction of *cis*-but-2-ene with *meta*-chloroperoxybenzoic acid? Show the stereochemistry.

8-7 Oxidation of Alkenes: Hydroxylation

Both in the laboratory and in living organisms, epoxides undergo an acid-catalyzed ring-opening reaction with water (a *hydrolysis*) to give the corresponding 1,2-dialcohol, or *diol*, also called a **glycol**. Thus, the net result of the two-step alkene epoxidation–hydrolysis is **hydroxylation**—the addition of an –OH group to each of the two double-bond carbons. In fact, approximately 18 million metric tons of ethylene glycol, HOCH₂CH₂OH, most of it used for automobile antifreeze, is produced worldwide each year by epoxidation of ethylene followed by hydrolysis.

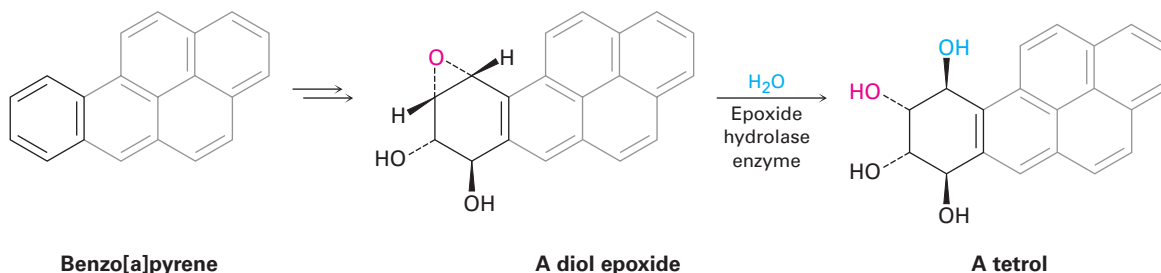


Acid-catalyzed epoxide opening takes place by protonation of the epoxide to increase its reactivity, followed by nucleophilic addition of water. This nucleophilic addition is analogous to the final step of alkene bromination, in which a cyclic bromonium ion is opened by a nucleophile (Section 8-2). That is, a *trans*-1,2-diol results when an epoxycycloalkane is opened by aqueous acid, just as a *trans*-1,2-dibromide results when a cycloalkene is brominated.

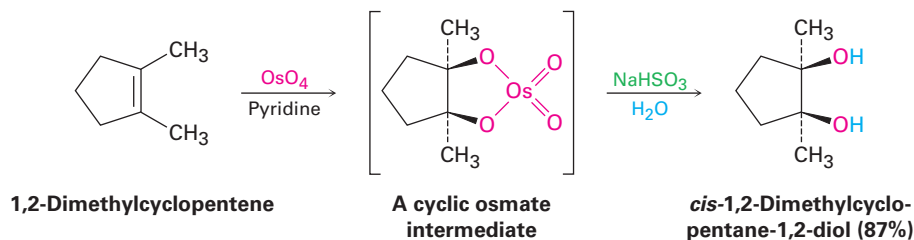


Biological examples of epoxide hydrolysis are common, particularly in the pathways that animals use to detoxify harmful substances. The cancer-causing

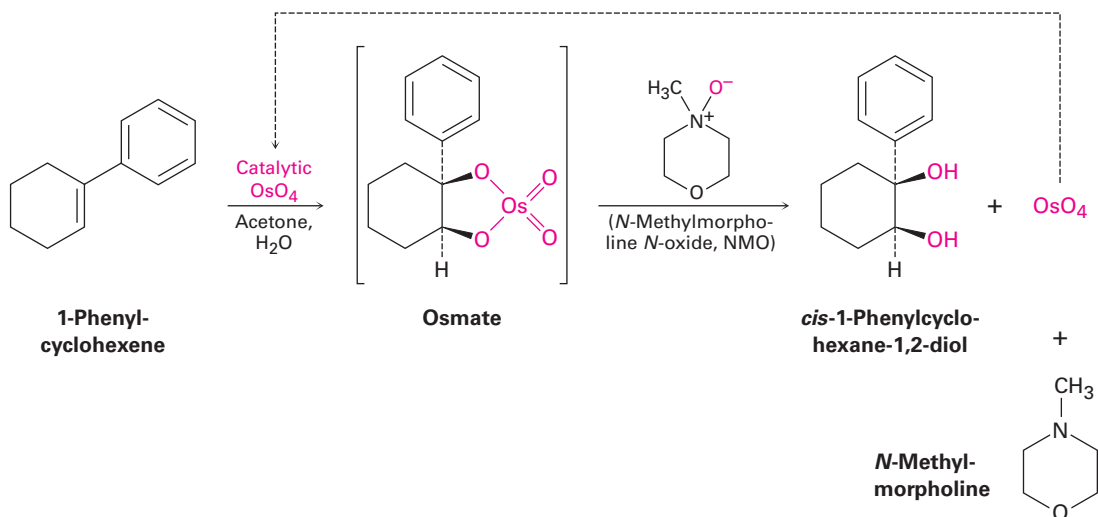
(*carcinogenic*) substance benzo[a]pyrene, for instance, is found in cigarette smoke, chimney soot, and barbecued meat. In the human liver, benzo[a]pyrene is detoxified by conversion to a diol epoxide, which then undergoes enzyme-catalyzed hydrolysis to give a soluble tetrol that is excreted.



In the laboratory, hydroxylation can also be carried out directly without going through an intermediate epoxide by treating an alkene with osmium tetroxide, OsO_4 . The reaction occurs with *syn* stereochemistry and does not involve a carbocation intermediate. Instead, it takes place through an intermediate cyclic *osmate*, which is formed in a single step by addition of OsO_4 to the alkene. This cyclic osmate is then cleaved using aqueous sodium bisulfite, NaHSO_3 .



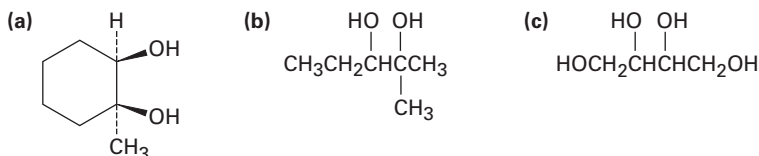
Because OsO_4 is both very expensive and *very* toxic, the reaction is usually carried out using only a small, catalytic amount of OsO_4 in the presence of a stoichiometric amount of a safe and inexpensive co-oxidant such as *N*-methylmorpholine *N*-oxide, abbreviated NMO. The initially formed osmate intermediate reacts rapidly with NMO to yield the product diol plus *N*-methylmorpholine and reoxidized OsO_4 . The OsO_4 then reacts with more alkene in a catalytic cycle.



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PROBLEM 8.12

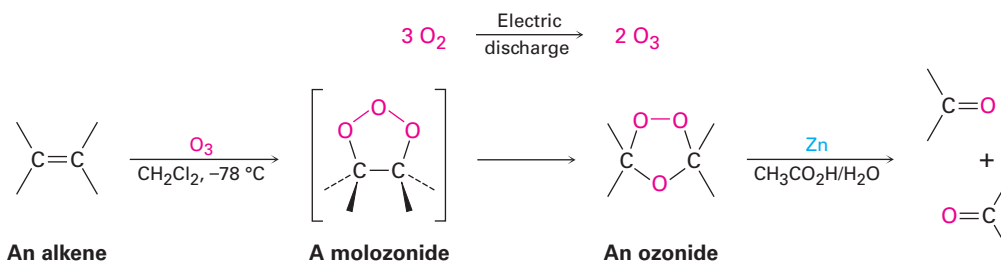
How would you prepare each of the following compounds starting with an alkene?



8-8 Oxidation of Alkenes: Cleavage to Carbonyl Compounds

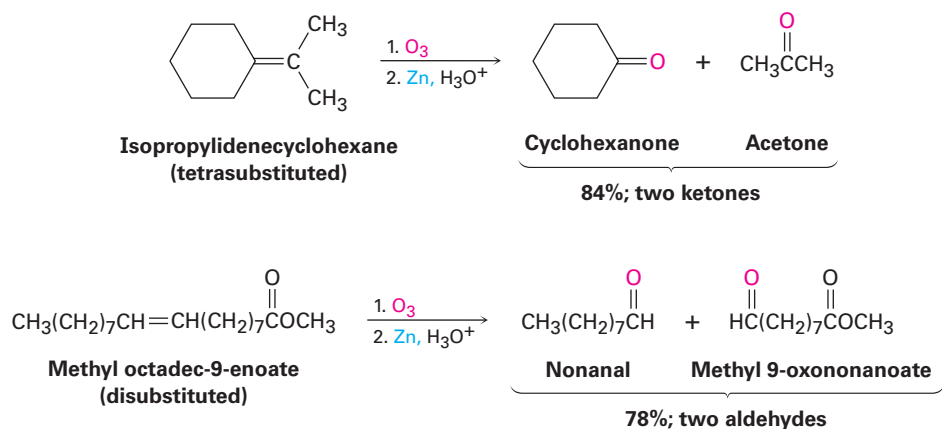
In all the alkene addition reactions we've seen thus far, the carbon-carbon double bond has been converted into a single bond but the carbon skeleton has been unchanged. There are, however, powerful oxidizing reagents that will cleave C=C bonds and produce two carbonyl-containing fragments.

Ozone (O_3) is perhaps the most useful double-bond cleavage reagent in the laboratory. Prepared by passing a stream of oxygen through a high-voltage electrical discharge, ozone adds rapidly to a C=C bond at low temperature to give a cyclic intermediate called a *molozonide*. Once formed, the molozonide then spontaneously rearranges to form an *ozonide*. Although we won't study the mechanism of this rearrangement in detail, it involves the molozonide coming apart into two fragments, which then recombine in a different way.

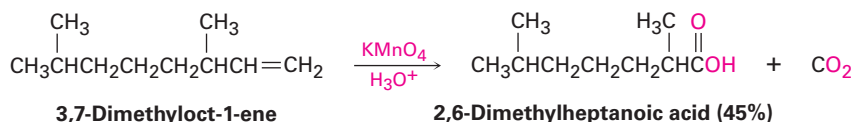


Low-molecular-weight ozonides are explosive and are therefore not isolated. Instead, a solution of the ozonide is immediately treated with a reducing agent such as zinc metal in acetic acid to convert it to carbonyl compounds. The net result of the ozonolysis-reduction sequence is that the C=C bond is cleaved and an oxygen atom becomes doubly bonded to each of the original alkene carbons. If an alkene with a tetrasubstituted double bond is ozonized,

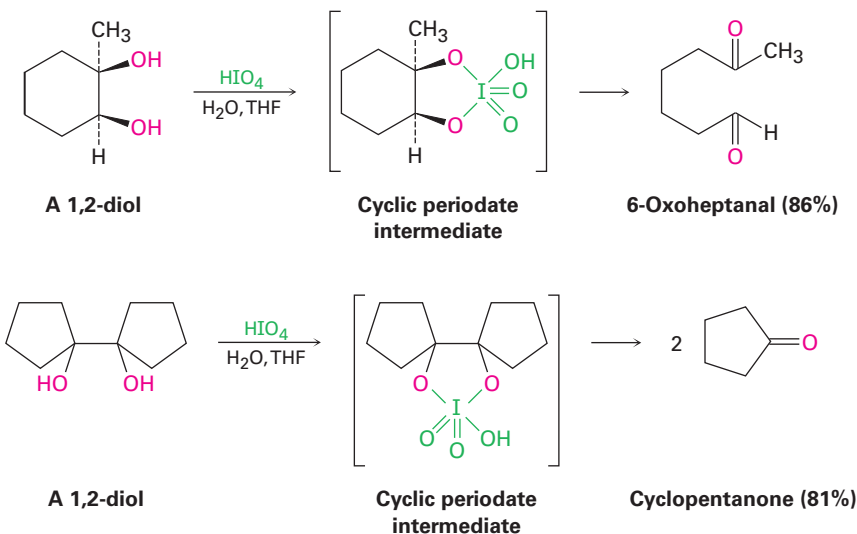
two ketone fragments result; if an alkene with a trisubstituted double bond is ozonized, one ketone and one aldehyde result; and so on.



Several oxidizing reagents other than ozone also cause double-bond cleavage, although the reaction is not often used. For example, potassium permanganate (KMnO_4) in neutral or acidic solution cleaves alkenes to give carbonyl-containing products. If hydrogens are present on the double bond, carboxylic acids are produced; if two hydrogens are present on one carbon, CO_2 is formed.



In addition to direct cleavage with ozone or KMnO_4 , an alkene can also be cleaved in a two-step process by hydroxylation to a 1,2-diol, as discussed in the previous section, followed by treatment of the diol with periodic acid, HIO_4 . If the two $-\text{OH}$ groups are in an open chain, two carbonyl compounds result. If the two $-\text{OH}$ groups are on a ring, a single, open-chain dicarbonyl compound is formed. As indicated in the following examples, the cleavage reaction takes place through a cyclic periodate intermediate.

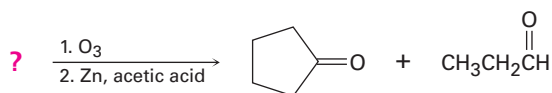


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Predicting the Reactant in an Ozonolysis Reaction

WORKED EXAMPLE 8.3

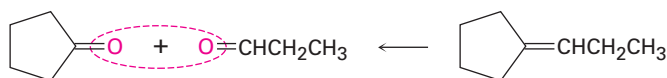
What alkene would yield a mixture of cyclopentanone and propanal on treatment with ozone followed by reduction with zinc?



Strategy

Reaction of an alkene with ozone, followed by reduction with zinc, cleaves the C=C bond and gives two carbonyl-containing fragments. That is, the C=C bond becomes two C=O bonds. Working backward from the carbonyl-containing products, the alkene precursor can be found by removing the oxygen from each product and joining the two carbon atoms to form a double bond.

Solution



PROBLEM 8.13

What products would you expect from reaction of 1-methylcyclohexene with the following reagents?

(a) Aqueous acidic KMnO_4 (b) O_3 , followed by Zn , $\text{CH}_3\text{CO}_2\text{H}$

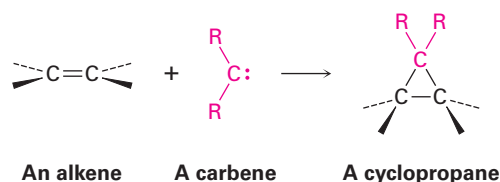
PROBLEM 8.14

Propose structures for alkenes that yield the following products on reaction with ozone followed by treatment with Zn :

(a) $(\text{CH}_3)_2\text{C}=\text{O} + \text{H}_2\text{C}=\text{O}$ (b) 2 equiv $\text{CH}_3\text{CH}_2\text{CH}=\text{O}$

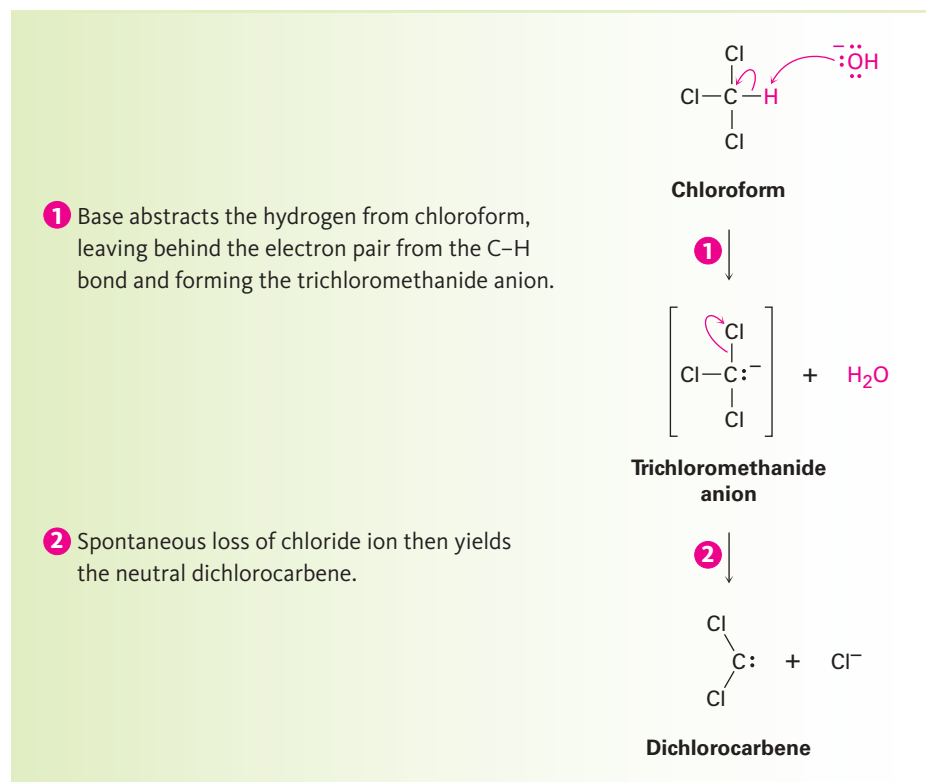
8-9 Addition of Carbenes to Alkenes: Cyclopropane Synthesis

Yet another kind of alkene addition is the reaction with a *carbene* to yield a cyclopropane. A **carbene**, $\text{R}_2\text{C}:$, is a neutral molecule containing a divalent carbon with only six electrons in its valence shell. It is therefore highly reactive and is generated only as a reaction intermediate, rather than as an isolable molecule. Because they're electron-deficient, carbenes behave as electrophiles and react with nucleophilic C=C bonds. The reaction occurs in a single step without intermediates.



One of the simplest methods for generating a substituted carbene is by treatment of chloroform, CHCl_3 , with a strong base such as KOH . Loss of a proton from CHCl_3 gives the trichloromethanide anion, $^-\text{:CCl}_3$, which spontaneously expels a Cl^- ion to yield dichlorocarbene, $:\text{CCl}_2$ (FIGURE 8.8).

FIGURE 8.8 Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base. Deprotonation of CHCl_3 gives the trichloromethanide anion, $^-\text{:CCl}_3$, which spontaneously expels a Cl^- ion.



The dichlorocarbene carbon atom is sp^2 -hybridized, with a vacant p orbital extending above and below the plane of the three atoms and with an unshared pair of electrons occupying the third sp^2 lobe. Note that this electronic description of dichlorocarbene is similar to that of a carbocation (Section 7-8) with respect to both the sp^2 hybridization of carbon and the vacant p orbital. Electrostatic potential maps further show this similarity (FIGURE 8.9).

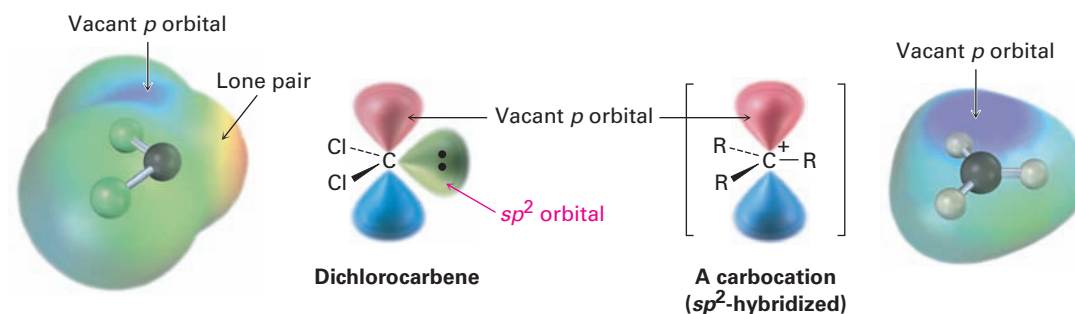
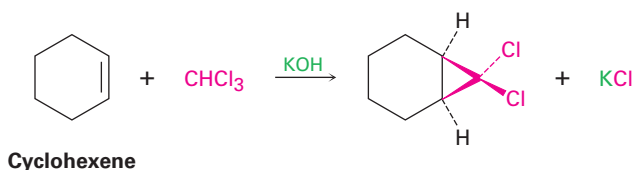
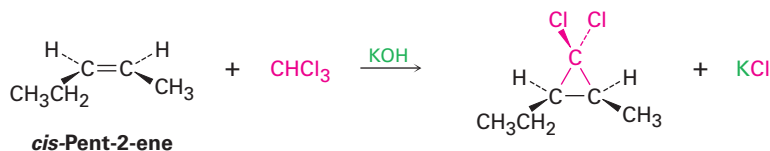


FIGURE 8.9 The structure of dichlorocarbene. Electrostatic potential maps show how the positive region coincides with the empty p orbital in both dichlorocarbene and a carbocation (CH_3^+). The negative region in the dichlorocarbene map coincides with the lone-pair electrons.

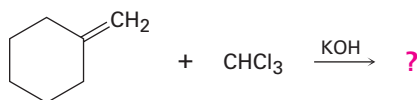
If dichlorocarbene is generated in the presence of an alkene, addition to the double bond occurs and a dichlorocyclopropane is formed. As the reaction of dichlorocarbene with *cis*-pent-2-ene demonstrates, the addition is **stereospecific**, meaning that only a single stereoisomer is formed as product. Starting from a *cis* alkene, for instance, only *cis*-disubstituted cyclopropane is produced; starting from a *trans* alkene, only *trans*-disubstituted cyclopropane is produced.



Although interesting from a mechanistic point of view, these carbene addition reactions are limited to the laboratory and do not occur in biological processes.

PROBLEM 8.15

What product would you expect from the following reaction?



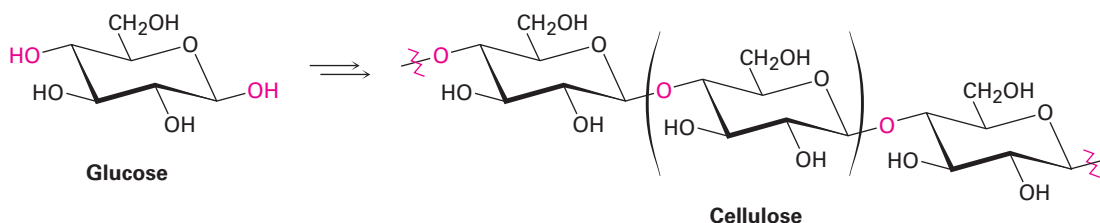
8-10 Radical Additions to Alkenes: Chain-Growth Polymers

In the brief introduction to radical reactions in Section 6-3, we said that radicals can add to $\text{C}=\text{C}$ bonds, taking one electron from the double bond and leaving one behind to yield a new radical. Let's now look at the process in more detail, focusing on the industrial synthesis of alkene polymers. A **polymer** is simply a large—sometimes *very* large—molecule built up by repetitive bonding together of many smaller molecules, called **monomers**.

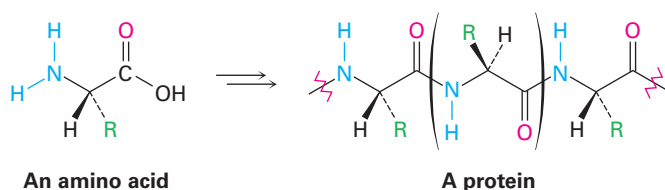
Nature makes wide use of biological polymers. Cellulose, for instance, is a polymer built of repeating glucose monomer units; proteins are polymers

built of repeating amino acid monomers; and nucleic acids are polymers built of repeating nucleotide monomers.

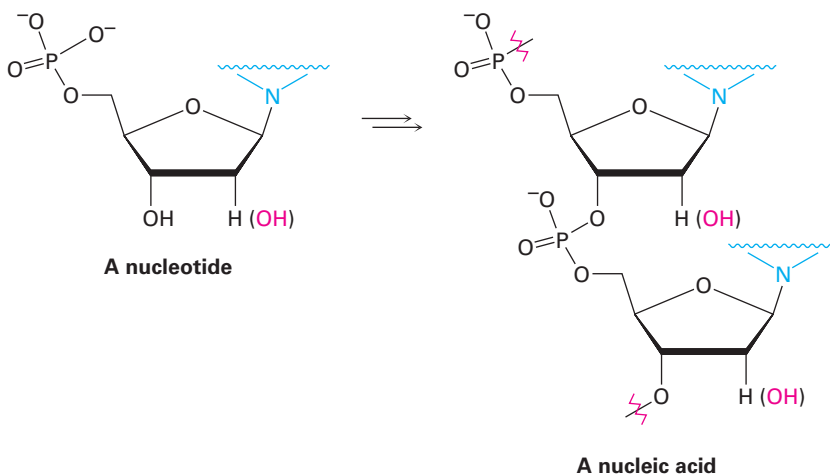
Cellulose—a glucose polymer



Protein—an amino acid polymer



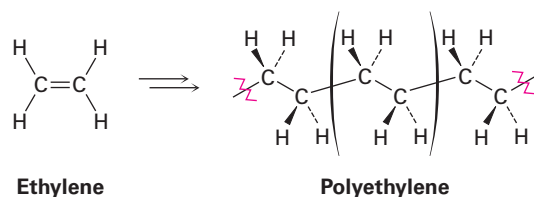
Nucleic acid—a nucleotide polymer



Synthetic polymers, such as polyethylene, are chemically much simpler than biopolymers, but there is still a great diversity to their structures and properties, depending on the identity of the monomers and on the reaction conditions used for polymerization. The simplest synthetic polymers are those that result when an alkene is treated with a small amount of a suitable catalyst. Ethylene, for example, yields polyethylene, an enormous alkane that may have a molecular weight up to *6 million* and may contain as many as 200,000 monomer units incorporated into a gigantic hydrocarbon chain.

Worldwide production of polyethylene is approximately 80 million metric tons per year.

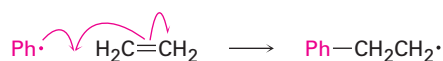
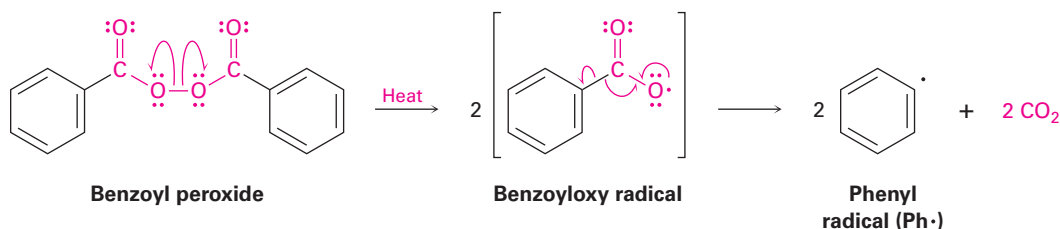
Polyethylene—a synthetic alkene polymer



Polyethylene and other simple alkene polymers are called **chain-growth polymers** because they are formed in a chain reaction process in which an initiator adds to a carbon–carbon double bond to yield a reactive intermediate. The intermediate then reacts with a second molecule of monomer to yield a new intermediate, which reacts with a third monomer unit, and so on.

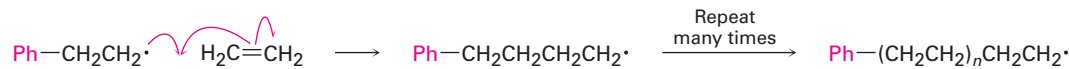
Historically, ethylene polymerization was carried out at high pressure (1000–3000 atm) and high temperature (100–250 °C) in the presence of a radical initiator such as benzoyl peroxide, although other reaction conditions and catalysts are now used. The key step is the addition of a radical to the ethylene double bond, a reaction similar in many respects to what takes place in the addition of an electrophile. In writing the mechanism, recall that a curved half-arrow, or “fishhook” \frown , is used to show the movement of a single electron, as opposed to the full curved arrow used to show the movement of an electron pair in a polar reaction.

- **Initiation** The polymerization reaction is initiated when a few radicals are generated on heating a small amount of benzoyl peroxide catalyst to break the weak O–O bond. The initially formed benzoyloxy radical loses CO_2 and gives a phenyl radical ($\text{Ph}\cdot$), which adds to the C=C bond of ethylene to start the polymerization process. One electron from the C=C bond pairs up with the odd electron on the phenyl radical to form a C–C bond, and the other electron remains on carbon.



- **Propagation** Polymerization occurs when the carbon radical formed in the initiation step adds to another ethylene molecule to yield another

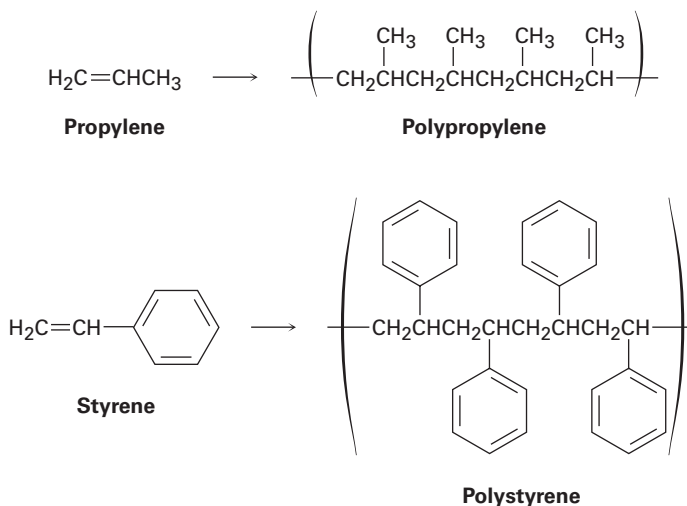
radical. Repetition of the process for hundreds or thousands of times builds the polymer chain.



- **Termination** The chain process is eventually ended by a reaction that consumes the radical. Combination of two growing chains is one possible chain-terminating reaction:



Ethylene is not unique in its ability to form a polymer. Many substituted ethylenes, called *vinyl monomers*, also undergo polymerization to yield polymers with substituent groups regularly spaced on alternating carbon atoms along the chain. Propylene, for example, yields polypropylene, and styrene yields polystyrene.



When an unsymmetrically substituted vinyl monomer such as propylene or styrene is polymerized, the radical addition steps can take place at either end of the double bond to yield either a primary radical intermediate ($\text{RCH}_2\cdot$) or a secondary radical ($\text{R}_2\text{CH}\cdot$). Just as in electrophilic addition reactions, however, we find that only the more highly substituted, secondary radical is formed.

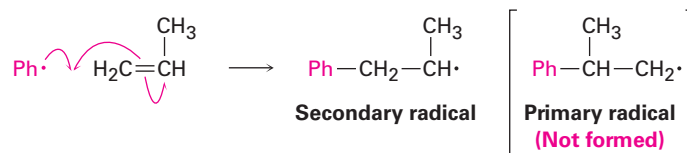


TABLE 8.1 shows some commercially important alkene polymers, their uses, and the vinyl monomers from which they're made.

TABLE 8.1 Some Alkene Polymers and Their Uses

Monomer	Formula	Trade or common name of polymer	Uses
Ethylene	$\text{H}_2\text{C}=\text{CH}_2$	Polyethylene	Packaging, bottles
Propene (propylene)	$\text{H}_2\text{C}=\text{CHCH}_3$	Polypropylene	Moldings, rope, carpets
Chloroethylene (vinyl chloride)	$\text{H}_2\text{C}=\text{CHCl}$	Poly(vinyl chloride)	Insulation, films, pipes
Styrene	$\text{H}_2\text{C}=\text{CHC}_6\text{H}_5$	Polystyrene	Foam, moldings
Tetrafluoroethylene	$\text{F}_2\text{C}=\text{CF}_2$	Teflon	Gaskets, nonstick coatings
Acrylonitrile	$\text{H}_2\text{C}=\text{CHCN}$	Orlon, Acrilan	Fibers
Methyl methacrylate	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{C}=\text{CCO}_2\text{CH}_3 \end{array}$	Plexiglas, Lucite	Paint, sheets, moldings
Vinyl acetate	$\text{H}_2\text{C}=\text{CHOCOCH}_3$	Poly(vinyl acetate)	Paint, adhesives, foams

Predicting the Structure of a Polymer

WORKED EXAMPLE 8.4

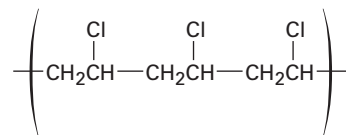
Show the structure of poly(vinyl chloride), a polymer made from $\text{H}_2\text{C}=\text{CHCl}$, by drawing several repeating units.

Strategy

Mentally break the carbon-carbon double bond in the monomer unit, and form single bonds by connecting numerous units together.

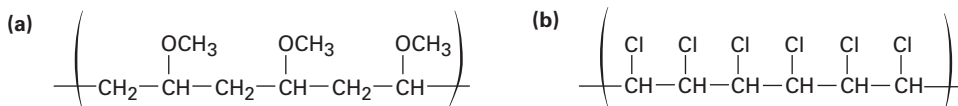
Solution

The general structure of poly(vinyl chloride) is



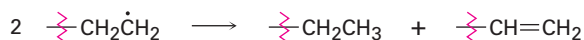
PROBLEM 8.16

What monomer units would you use to prepare the following polymers?



PROBLEM 8.17

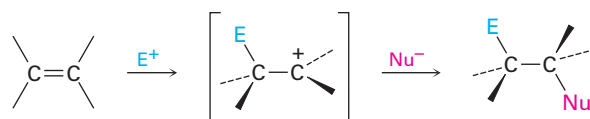
One of the chain-termination steps that sometimes occurs to interrupt polymerization is the following reaction between two radicals. Propose a mechanism for the reaction, using fishhook arrows to indicate electron flow.



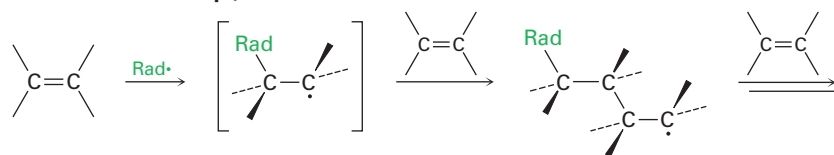
8-11 Biological Additions of Radicals to Alkenes

The same high reactivity of radicals that makes possible alkene polymerization also makes it difficult to carry out controlled radical reactions on complex molecules. As a result, there are severe limitations on the usefulness of radical addition reactions in the laboratory. In contrast to an electrophilic addition, where reaction occurs once and the reactive cation intermediate is rapidly quenched by a nucleophile, the reactive intermediate in a radical reaction is not usually quenched, so it reacts again and again in a largely uncontrollable way.

Electrophilic addition
(Intermediate is quenched,
so reaction stops.)



Radical addition
(Intermediate is not quenched,
so reaction does not stop.)



In biological reactions, the situation is different from that in the laboratory. Only one substrate molecule at a time is present in the active site of the enzyme where reaction takes place, and that molecule is held in a precise position, with other necessary reacting groups nearby. As a result, biological radical reactions are both more controlled and more common than laboratory or industrial radical reactions. A particularly impressive example occurs in the biosynthesis of prostaglandins from arachidonic acid, where a sequence of four radical additions takes place. The reaction mechanism was discussed briefly in Section 6-3.

Prostaglandin biosynthesis begins with abstraction of a hydrogen atom from C13 of arachidonic acid by an iron–oxy radical (FIGURE 8.10), 1 to give a carbon radical that reacts with O_2 at C11 through a resonance form 2. The oxygen radical that results adds to the C8–C9 double bond 3 to give a carbon radical at C8, which then adds to the C12–C13 double bond and gives a carbon radical at C13 4. A resonance form of this carbon radical adds at C15 to a second O_2 molecule 5, completing the prostaglandin skeleton, and reduction of the O–O bond then gives prostaglandin H_2 6. The pathway looks complicated, but the entire process is catalyzed with exquisite control by a single enzyme.

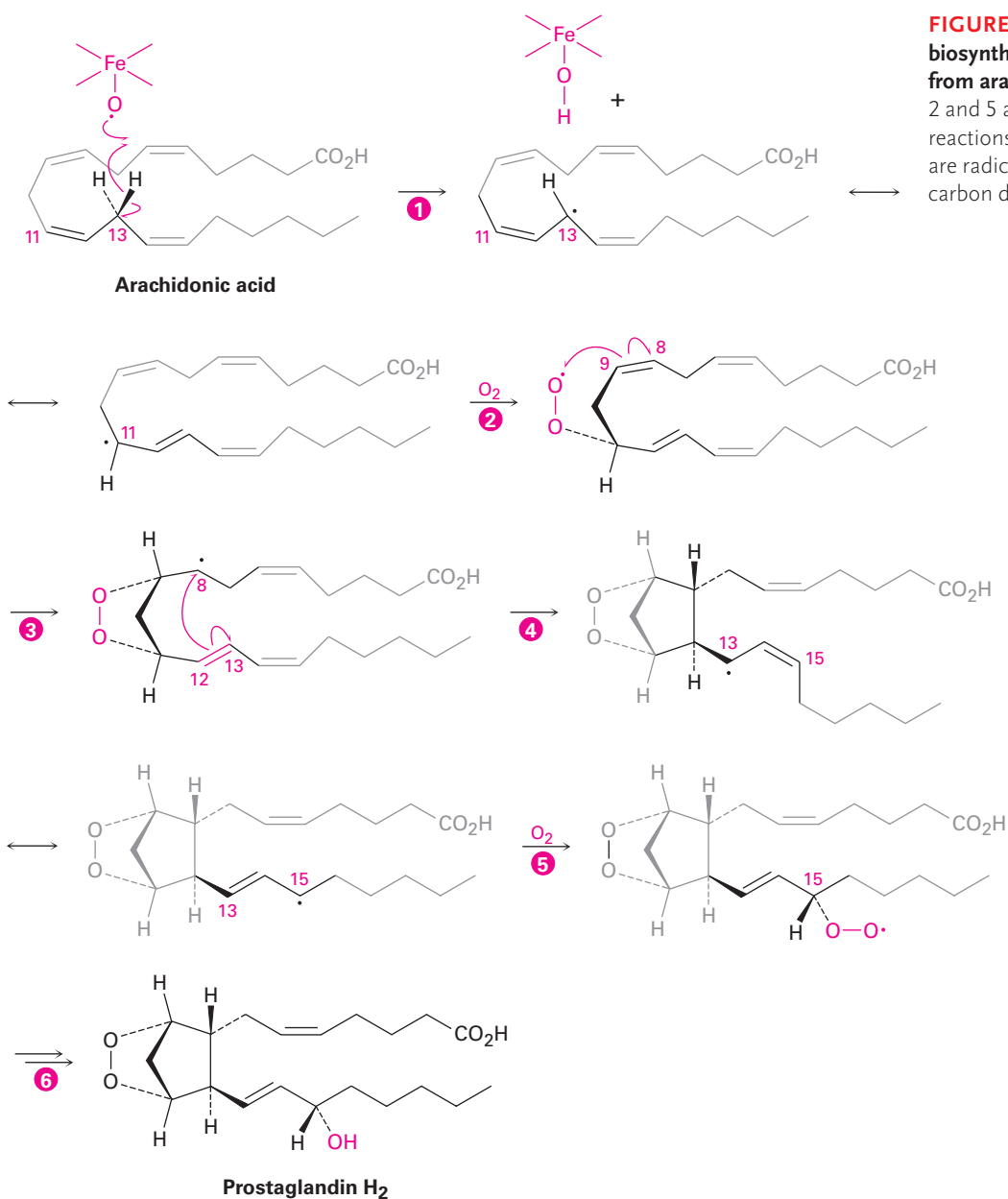
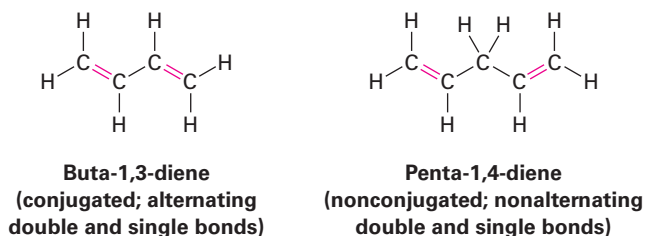


FIGURE 8.10 Pathway for the biosynthesis of prostaglandins from arachidonic acid. Steps 2 and 5 are radical addition reactions to O₂; steps 3 and 4 are radical additions to carbon-carbon double bonds.

8-12 Conjugated Dienes

Thus far, we've looked primarily at compounds with just one double bond, but many compounds have numerous sites of unsaturation. If the different unsaturations are well separated in a molecule, they react independently, but if they're close together, they may interact with one another. In particular, double bonds that alternate with single bonds—so-called **conjugated** double bonds—have some distinctive characteristics. The conjugated diene

buta-1,3-diene, for instance, has some properties quite different from those of the nonconjugated penta-1,4-diene.



One difference is that conjugated dienes are somewhat more stable than nonconjugated dienes, as evidenced by their heats of hydrogenation (TABLE 8.2). We saw in Section 7-5 that monosubstituted alkenes, such as but-1-ene, have $\Delta H^\circ_{\text{hydrog}}$ near -126 kJ/mol (-30.1 kcal/mol), whereas disubstituted alkenes, such as 2-methylpropene, have $\Delta H^\circ_{\text{hydrog}}$ near -119 kJ/mol (-28.4 kcal/mol). We concluded from these data that more highly substituted alkenes are more stable than less substituted ones. That is, more highly substituted alkenes release less heat on hydrogenation because they contain less energy to start with. A similar conclusion can be drawn for conjugated dienes.

TABLE 8.2 Heats of Hydrogenation for Some Alkenes and Dienes

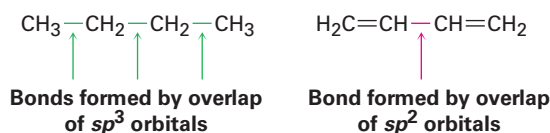
Alkene or diene	Product	$\Delta H^\circ_{\text{hydrog}}$	
		(kJ/mol)	(kcal/mol)
$\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$	-126	-30.1
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{C}=\text{CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHCH}_3 \end{array}$	-119	-28.4
$\text{H}_2\text{C}=\text{CHCH}_2\text{CH}=\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	-253	-60.5
$\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$	-236	-56.4
$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{C}=\text{CH}-\text{C}=\text{CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2\text{CHCH}_3 \end{array}$	-229	-54.7

Because a monosubstituted alkene has a $\Delta H^\circ_{\text{hydrog}}$ of approximately -126 kJ/mol, we might expect that a compound with two monosubstituted double bonds would have a $\Delta H^\circ_{\text{hydrog}}$ approximately twice that value, or -252 kJ/mol. Nonconjugated dienes, such as penta-1,4-diene ($\Delta H^\circ_{\text{hydrog}} = -253$ kJ/mol), meet this expectation, but the conjugated diene buta-1,3-diene ($\Delta H^\circ_{\text{hydrog}} = -236$ kJ/mol) does not. Buta-1,3-diene is approximately 16 kJ/mol (3.8 kcal/mol) more stable than expected.

	$\Delta H^\circ_{\text{hydrog}}$ (kJ/mol)	
$\text{H}_2\text{C}=\text{CHCH}_2\text{CH}=\text{CH}_2$	$-126 + (-126) = -252$	Expected
Penta-1,4-diene	-253	Observed
	1	Difference
$\text{H}_2\text{C}=\text{CHCH}=\text{CH}_2$	$-126 + (-126) = -252$	Expected
Buta-1,3-diene	-236	Observed
	-16	Difference

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What accounts for the stability of conjugated dienes? According to valence bond theory (Sections 1-5 and 1-8), the stability is due to orbital hybridization. Typical C–C single bonds like those in alkanes result from σ overlap of sp^3 orbitals on both carbons, but in a conjugated diene, the central C–C single bond results from σ overlap of sp^2 orbitals on both carbons. Since sp^2 orbitals have more s character (33% s) than sp^3 orbitals (25% s), the electrons in sp^2 orbitals are closer to the nucleus and the bonds they form are somewhat shorter and stronger. Thus, the “extra” stability of a conjugated diene results in part from the greater amount of s character in the orbitals forming the C–C single bond.



According to molecular orbital theory (Section 1-11), the stability of a conjugated diene arises because of an interaction between the π orbitals of the two double bonds. To review briefly, when two p atomic orbitals combine to form a π bond, two π molecular orbitals (MOs) result. One is lower in energy than the starting p orbitals and is therefore bonding; the other is higher in energy, has a node between nuclei, and is antibonding. The two π electrons occupy the low-energy, bonding orbital, resulting in formation of a stable bond between atoms (FIGURE 8.11).

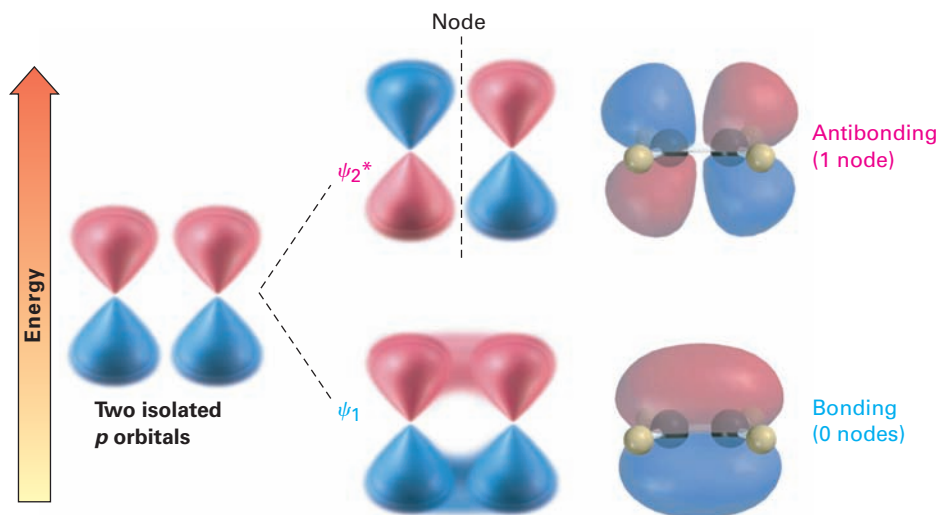
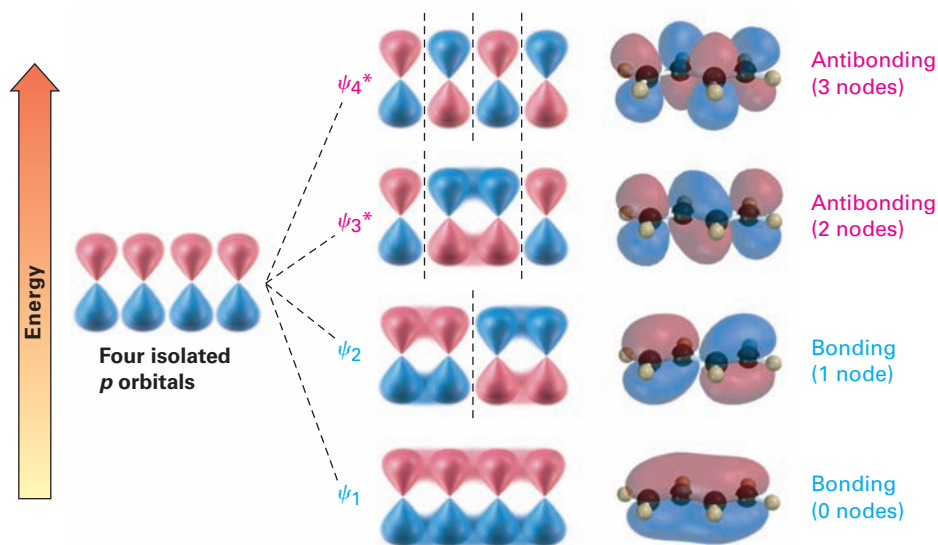


FIGURE 8.11 Formation of two π molecular orbitals by combination of two p orbitals. Both electrons occupy the low-energy, bonding orbital, leading to a net lowering of energy and formation of a stable bond. The asterisk on ψ_2^* indicates an antibonding orbital.

Now let’s combine four adjacent p atomic orbitals, as occurs in a conjugated diene. In so doing, we generate a set of four π molecular orbitals, two of which are bonding and two of which are antibonding (FIGURE 8.12). The four π electrons occupy the two bonding orbitals, leaving the antibonding orbitals vacant.

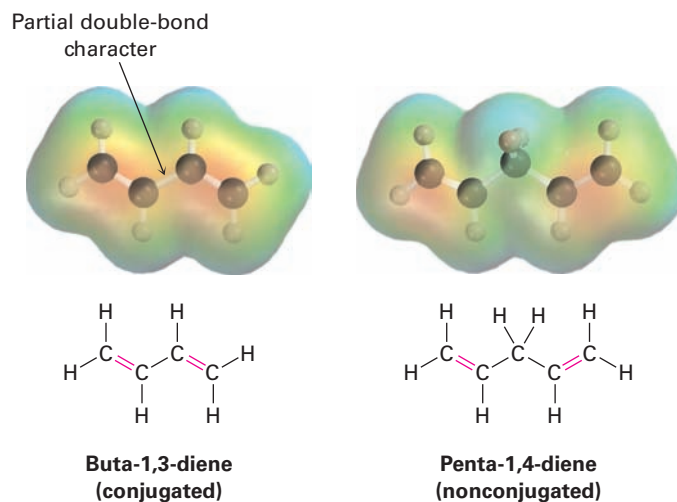
FIGURE 8.12 The four π molecular orbitals in buta-1,3-diene. Note that the number of nodes between nuclei increases as the energy level of the orbital increases.



The lowest-energy π molecular orbital (denoted ψ_1 , Greek psi) has no nodes between the nuclei and is therefore bonding. The π MO of next lowest energy, ψ_2 , has one node between nuclei and is also bonding. Above ψ_1 and ψ_2 in energy are the two antibonding π MOs, ψ_3^* and ψ_4^* . (The asterisks indicate antibonding orbitals.) Note that the number of nodes between nuclei increases as the energy level of the orbital increases. The ψ_3^* orbital has two nodes between nuclei, and ψ_4^* , the highest-energy MO, has three nodes between nuclei.

Comparing the π molecular orbitals of buta-1,3-diene (two conjugated double bonds) with those of penta-1,4-diene (two isolated double bonds) shows why the conjugated diene is more stable. In a conjugated diene, the lowest-energy π MO (ψ_1) has a favorable bonding interaction between C2 and C3 that is absent in a nonconjugated diene. As a result, there is a certain amount of double-bond character to the C2–C3 bond, making that bond both stronger and shorter than a typical single bond. Electrostatic potential maps show clearly the additional electron density in the central bond of buta-1,3-diene, corresponding to partial double-bond character (FIGURE 8.13).

FIGURE 8.13 Electrostatic potential maps of buta-1,3-diene (conjugated) and penta-1,4-diene (nonconjugated). Additional electron density is present in the central C–C bond of buta-1,3-diene, corresponding to partial double-bond character.

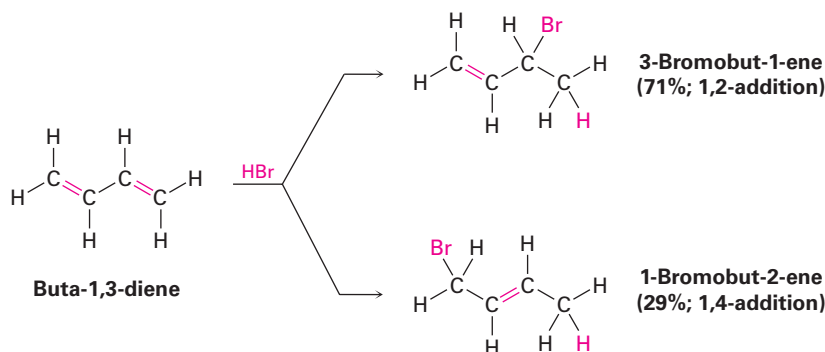


In describing buta-1,3-diene, we say that the π electrons are spread out, or *delocalized*, over the entire π framework rather than localized between two

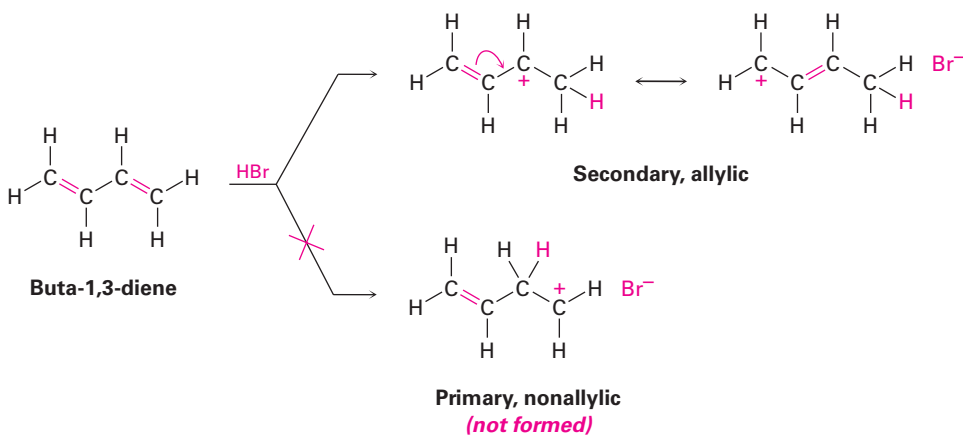
specific nuclei. Delocalization allows the bonding electrons to be closer to more nuclei, thus leading to lower energy and greater stability.

8-13 Reactions of Conjugated Dienes

One of the most striking differences between conjugated and isolated double bonds is their behavior in electrophilic addition reactions. Conjugated dienes undergo electrophilic addition reactions readily, but mixtures of products are invariably obtained. Addition of HBr to buta-1,3-diene, for instance, yields a mixture of two products (not counting *cis-trans* isomers). 3-Bromobut-1-ene is the typical Markovnikov product of *1,2-addition* to a double bond, but 1-bromobut-2-ene appears unusual. The double bond in this product has moved to a position between carbons 2 and 3, and HBr has added to carbons 1 and 4, a result described as *1,4-addition*.

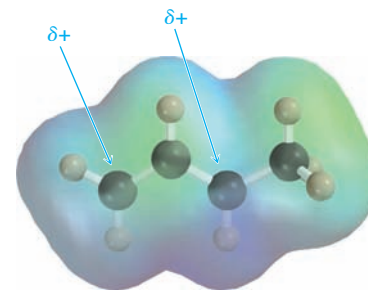
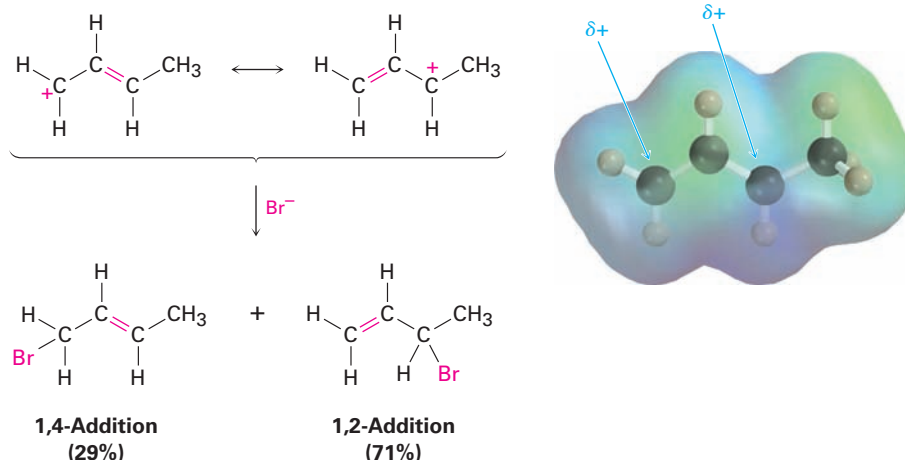


How can we account for the formation of the 1,4-addition product? The answer is that an allylic carbocation is involved as an intermediate, where the word **allylic** means “next to a double bond.” When buta-1,3-diene reacts with an electrophile such as H^+ , two carbocation intermediates are possible—a primary carbocation and a secondary allylic cation. Because an allylic cation is stabilized by resonance between two forms (Section 2-4), it is more stable and forms faster than a nonallylic carbocation.



When the allylic cation reacts with Br^- to complete the electrophilic addition, reaction can occur either at C1 or at C3 because both carbons share the positive charge (FIGURE 8.14). Thus, a mixture of 1,2- and 1,4-addition products results.

FIGURE 8.14 Electrostatic potential map of the carbocation produced by protonation of buta-1,3-diene. The positive charge is shared by carbons 1 and 3. Reaction of Br^- with the more positive carbon (C3) gives predominantly the 1,2-addition product.



WORKED EXAMPLE 8.5 Predicting the Product of Electrophilic Addition to a Conjugated Diene

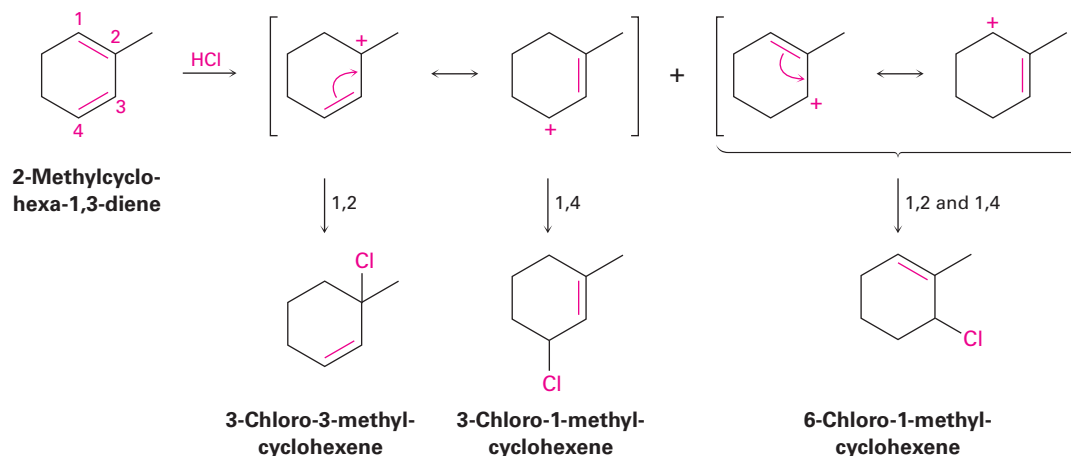
Give the structures of the likely products from reaction of 1 equivalent of HCl with 2-methylcyclohexa-1,3-diene. Show both 1,2- and 1,4-adducts.

Strategy

Electrophilic addition of HCl to a conjugated diene involves the formation of an allylic carbocation intermediate. Thus, the first step is to protonate the two ends of the diene and draw the resonance forms of the two allylic carbocations that result. Then allow each resonance form to react with Cl^- , generating a maximum of four possible products.

In the present instance, protonation of the C1–C2 double bond gives a carbocation that can react further to give the 1,2-adduct 3-chloro-3-methylcyclohexene and the 1,4-adduct 3-chloro-1-methylcyclohexene. Protonation of the C3–C4 double bond gives a symmetrical carbocation, whose two resonance forms are equivalent. Thus, the 1,2-adduct and the 1,4-adduct have the same structure: 6-chloro-1-methylcyclohexene. Of the two possible modes of protonation, the first is more likely because it yields a tertiary allylic cation rather than a secondary allylic cation.

Solution



PROBLEM 8.18

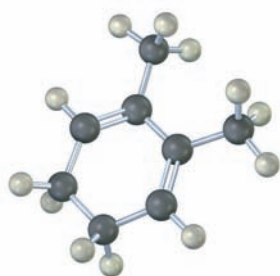
Give the structures of both 1,2- and 1,4-adducts resulting from reaction of 1 equivalent of HCl with penta-1,3-diene.

PROBLEM 8.19

Look at the possible carbocation intermediates produced during addition of HCl to penta-1,3-diene (Problem 8.18), and predict which 1,2 adduct predominates. Which 1,4 adduct predominates?

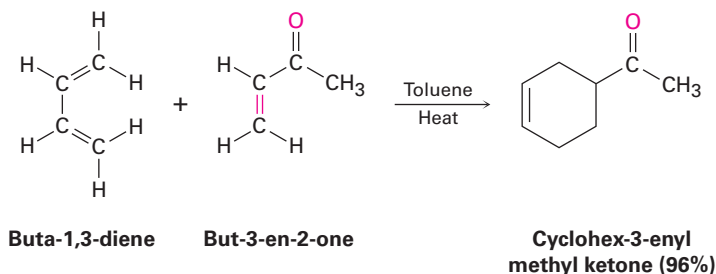
PROBLEM 8.20

Give the structures of both 1,2- and 1,4-adducts resulting from reaction of 1 equivalent of HBr with the following compound:



8-14 The Diels–Alder Cycloaddition Reaction

Perhaps the most striking difference between conjugated and nonconjugated dienes is that a conjugated diene can undergo an addition reaction with an alkene to yield a substituted cyclohexene product. For example, buta-1,3-diene and but-3-en-2-one give cyclohex-3-enyl methyl ketone.



This process, named the **Diels–Alder cycloaddition reaction** after its discoverers, is extremely useful in the laboratory because it forms two carbon–carbon bonds in a single step and is one of the few general methods available for making cyclic molecules. (As the name implies, a *cycloaddition* reaction is one in which two reactants add together to give a cyclic product.) The 1950 Nobel Prize in Chemistry was awarded to Diels and Alder in recognition of their discovery.

The mechanism of the Diels–Alder cycloaddition is different from that of other reactions we’ve studied because it is neither polar nor radical. Rather, the Diels–Alder reaction is a so-called pericyclic process. **Pericyclic reactions**, which are less common than either polar or radical reactions, take place in a single step by a cyclic redistribution of bonding electrons. The two reactants simply join together through a cyclic transition state in which the two new carbon–carbon bonds form at the same time.

We can picture a Diels–Alder addition as occurring by head-on (σ) overlap of the two alkene p orbitals with the two p orbitals on carbons 1 and 4 of the diene (FIGURE 8.15), a cyclic orientation of the reactants.

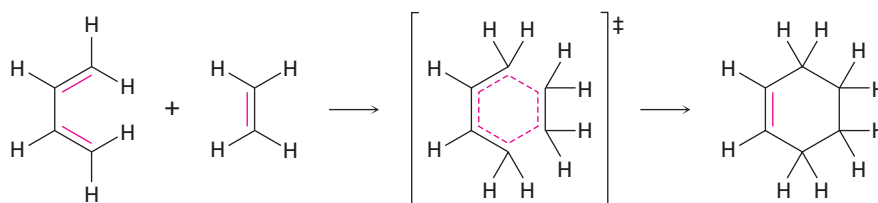
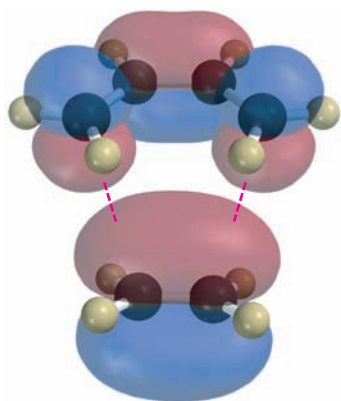
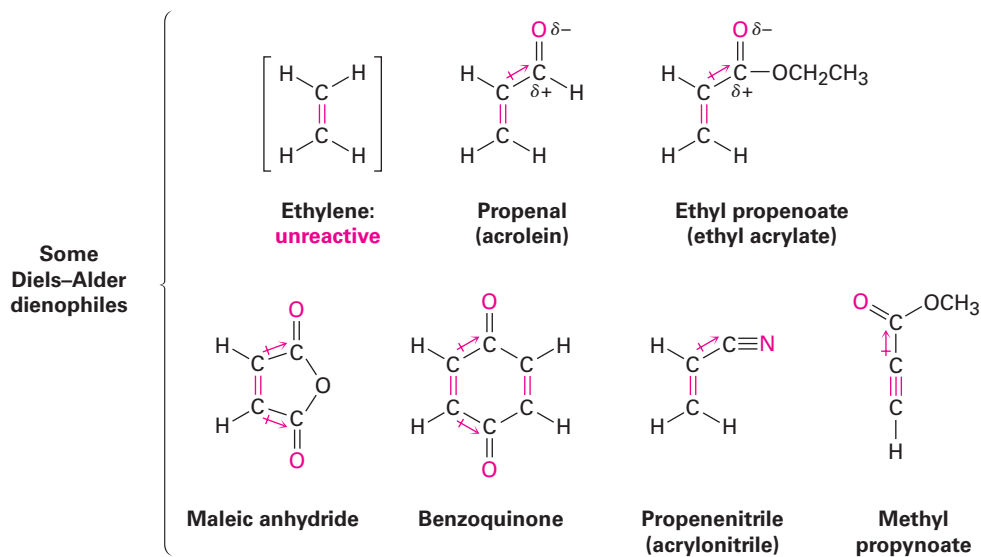


FIGURE 8.15 Mechanism of the Diels–Alder cycloaddition reaction. The reaction occurs in a single step through a cyclic transition state in which the two new carbon–carbon bonds form simultaneously.

In the Diels–Alder transition state, the two alkene carbons and carbons 1 and 4 of the diene rehybridize from sp^2 to sp^3 to form two new single bonds, while carbons 2 and 3 of the diene remain sp^2 hybridized to form the new double bond in the cyclohexene product.

The Diels–Alder cycloaddition reaction occurs most rapidly if the alkene component, or **dienophile** (“diene lover”), has an electron-withdrawing substituent group. Thus, ethylene itself reacts sluggishly, but propenal, ethyl propenoate, maleic anhydride, benzoquinone, propenenitrile, and similar compounds are highly reactive. Note also that alkynes, such as methyl propynoate, can act as Diels–Alder dienophiles.



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In all cases, the double or triple bond of the dienophile is adjacent to the positively polarized carbon of an electron-withdrawing substituent. As a result, the double-bond carbons in these substances are substantially less electron-rich than the carbons in ethylene, as indicated by the electrostatic potential maps in **FIGURE 8.16**.

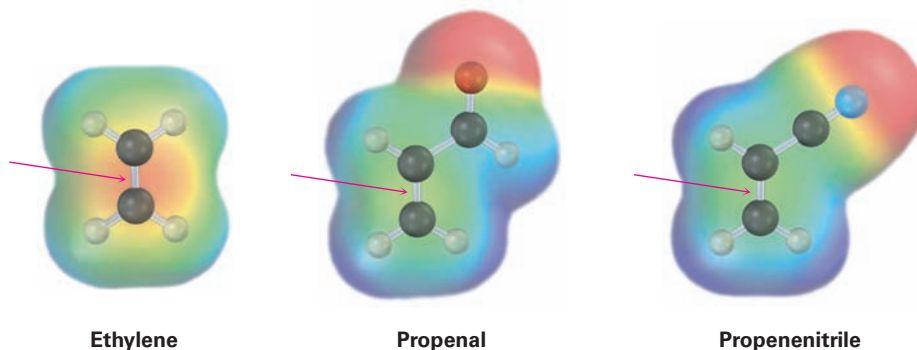
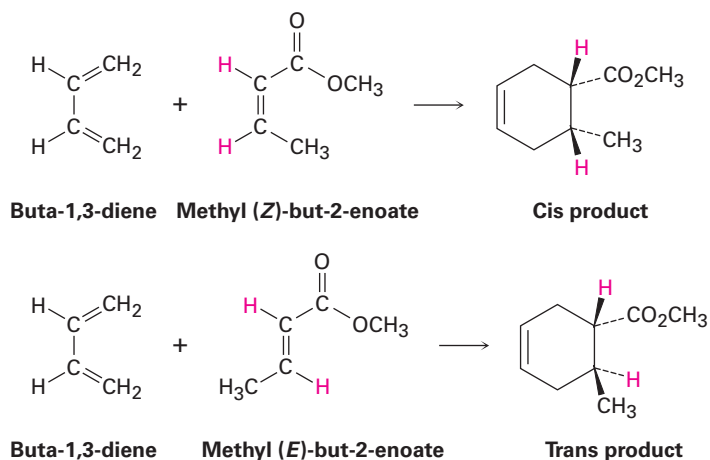


FIGURE 8.16 Electrostatic potential maps of ethylene, propenal, and propenenitrile.

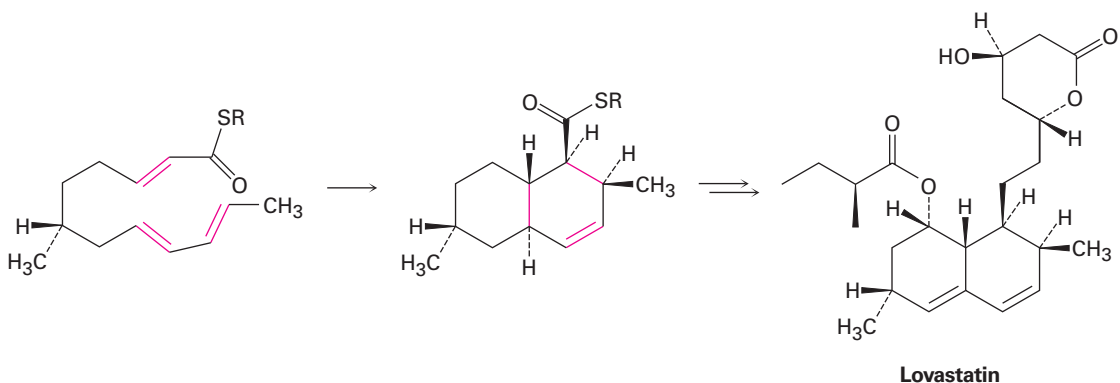
Electron-withdrawing groups make the double-bond carbons **less electron-rich**.

One of the most useful features of the Diels–Alder reaction is that it is *stereospecific*, meaning that a single product stereoisomer is formed (Section 8-9). Furthermore, the stereochemistry of the dienophile is retained. If we carry out the cycloaddition with methyl *cis*-but-2-enoate, only the *cis*-substituted cyclohexene product is formed. With methyl *trans*-but-2-enoate, only the *trans*-substituted cyclohexene product is formed.



Just as the dienophile component has certain constraints that affect its reactivity, so too with the conjugated diene component. The diene must adopt what is called an *s-cis conformation*, meaning “*cis*-like” about the single bond, to undergo a Diels–Alder reaction. Only in the *s-cis* conformation are carbons 1 and 4 of the diene close enough to react through a cyclic transition

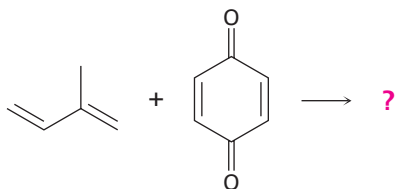
Biological Diels–Alder reactions are known but uncommon. One example occurs in the biosynthesis of the cholesterol-lowering drug lovastatin (Chapter 1 Introduction) isolated from the bacterium *Aspergillus terreus*. The key step is the *internal* Diels–Alder reaction of a triene in which the diene and dienophile components are within the same molecule.



Predicting the Product of a Diels–Alder Reaction

WORKED EXAMPLE 8.6

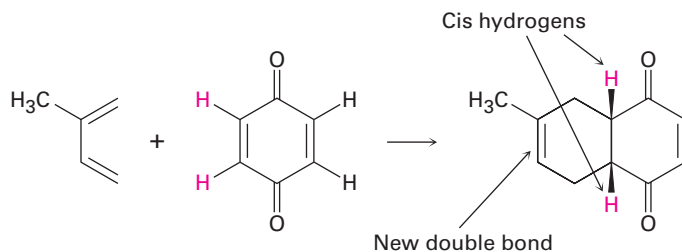
Predict the product of the following Diels–Alder reaction:



Strategy

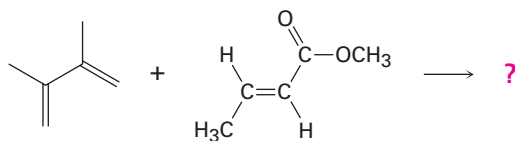
Draw the diene so that the ends of its two double bonds are near the dienophile double bond. Then form two single bonds between the partners, convert the three double bonds into single bonds, and convert the former single bond of the diene into a double bond. Because the dienophile double bond is *cis* to begin with, the two attached hydrogens must remain *cis* in the product.

Solution

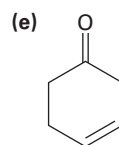
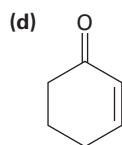
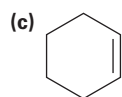
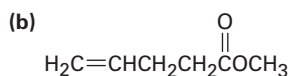
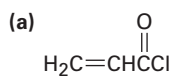


PROBLEM 8.21

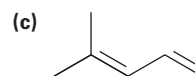
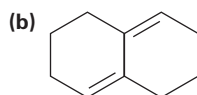
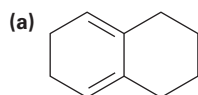
Predict the product of the following Diels–Alder reaction:

**PROBLEM 8.22**

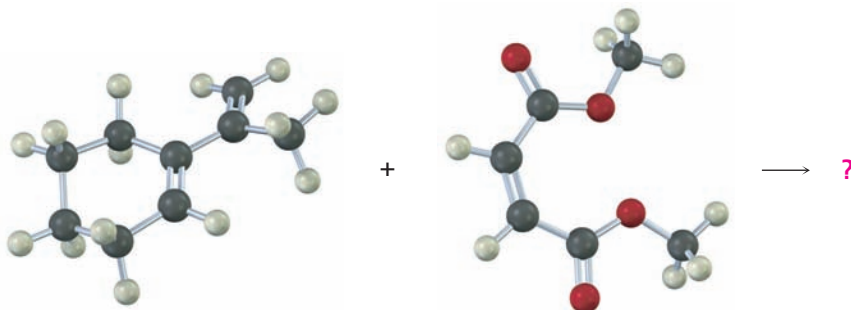
Which of the following alkenes would you expect to be good Diels–Alder dienophiles?

**PROBLEM 8.23**

Which of the following dienes have an *s-cis* conformation, and which have an *s-trans* conformation? Of the *s-trans* dienes, which can readily rotate to *s-cis*?

**PROBLEM 8.24**

Predict the product of the following Diels–Alder reaction:

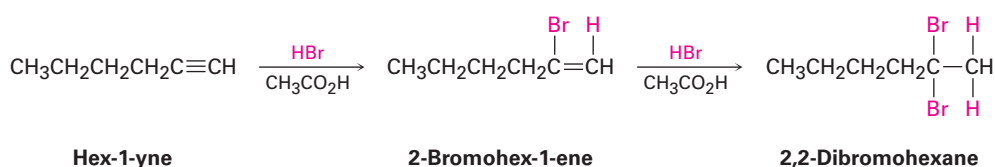


8-15 Reactions of Alkynes

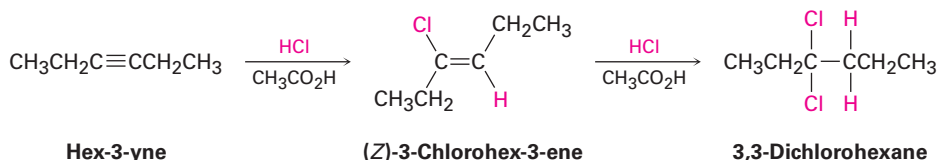
Alkyne Addition Reactions

We mentioned briefly in Section 7-6 that alkynes behave similarly to alkenes in much of their chemistry. Thus, they undergo many addition reactions just as alkenes do. As a general rule, however, alkynes are somewhat less reactive than alkenes, so the various reactions can often be stopped at the monoaddition stage if only one molar equivalent of reagent is used. The additions typically show Markovnikov regiochemistry. Note that for the addition of 1 molar equivalent of H_2 to an alkyne to give an alkene, a special hydrogenation catalyst called the *Lindlar catalyst* is needed. The alkene that results has *cis* stereochemistry.

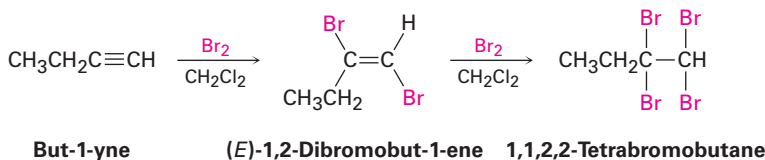
HBr addition



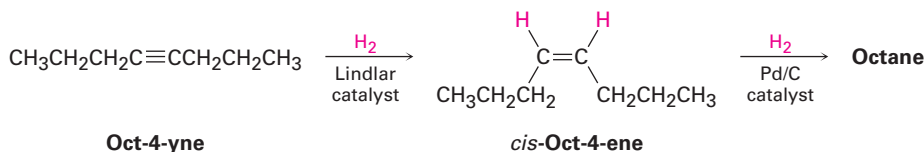
HCl addition



Br_2 addition

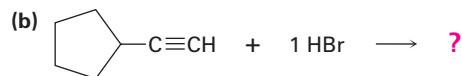


H_2 addition

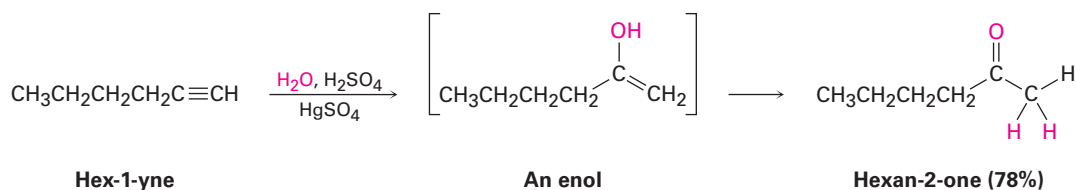


PROBLEM 8.25

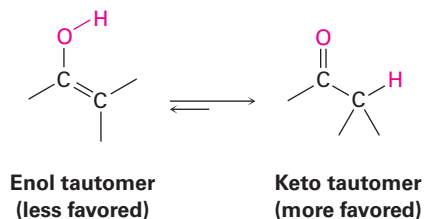
What products would you expect from the following reactions?

**Mercury(II)-Catalyzed Hydration of Alkynes**

Alkynes don't react directly with aqueous acid as alkenes do but will undergo hydration readily in the presence of mercury(II) sulfate as a Lewis acid catalyst. The reaction occurs with Markovnikov regiochemistry, so the $-\text{OH}$ group adds to the more highly substituted carbon and the $-\text{H}$ attaches to the less highly substituted one.



Interestingly, the product actually isolated from alkyne hydration is not the vinylic alcohol, or *enol* (*ene* + *ol*), but is instead a ketone. Although the enol is an intermediate in the reaction, it immediately rearranges to a ketone by a process called *keto-enol tautomerism*. The individual keto and enol forms are said to be *tautomers*, a word used to describe two isomers that undergo spontaneous interconversion accompanied by the change in position of a hydrogen. With few exceptions, the keto-enol tautomeric equilibrium lies on the side of the ketone; enols are almost never isolated. We'll look more closely at this equilibrium in Section 17-1.



As shown in **FIGURE 8.18**, the mechanism of the mercury(II)-catalyzed alkyne hydration reaction is analogous to the oxymercuration reaction of

alkenes (Section 8-4). Electrophilic addition of mercury(II) ion to the alkyne gives a carbocation, which reacts with water and loses a proton to yield a mercury-containing enol intermediate. In contrast with alkene oxymercuration, however, no treatment with NaBH_4 is necessary to remove the mercury. The acidic reaction conditions alone are sufficient to effect replacement of mercury by hydrogen. Tautomerization then gives the ketone.

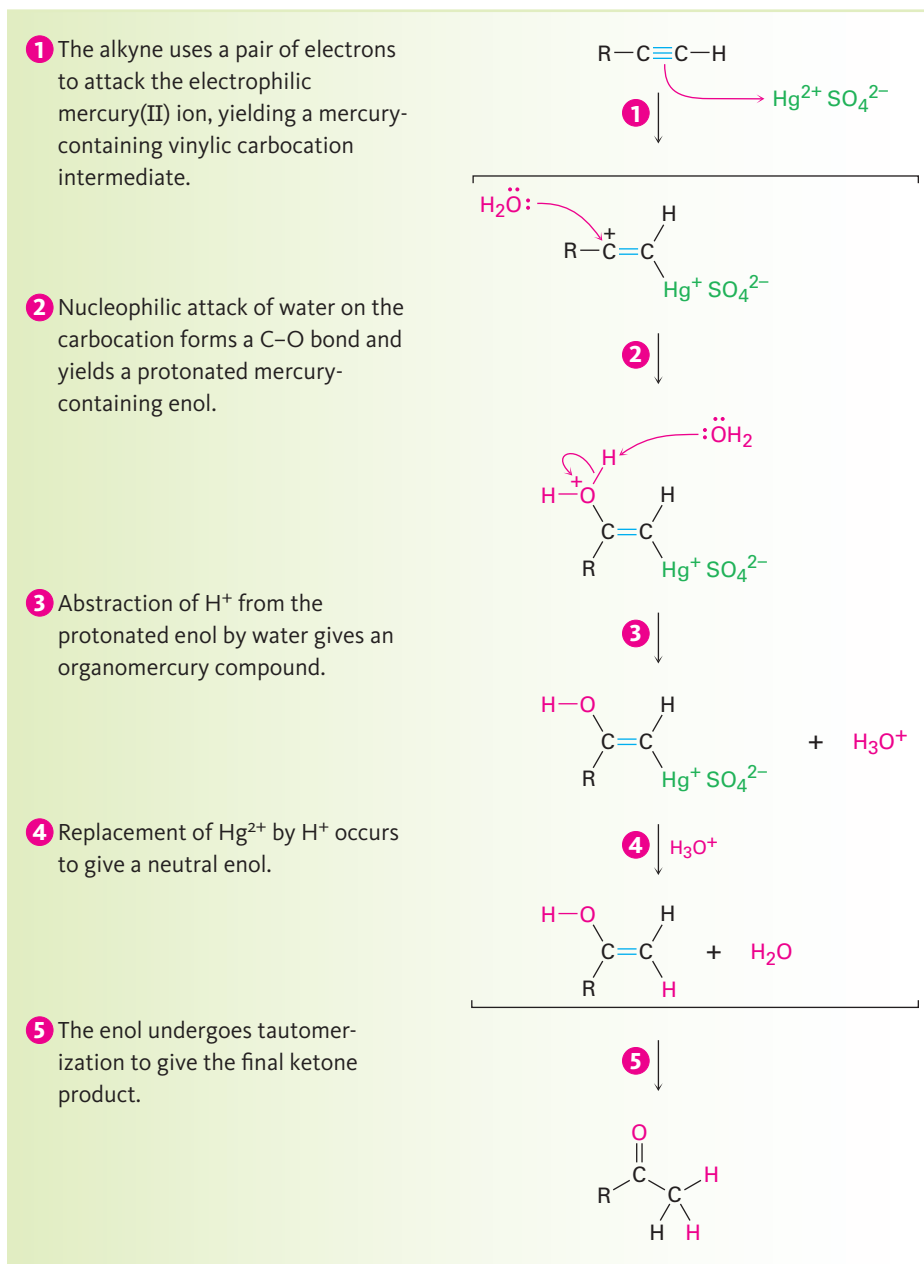


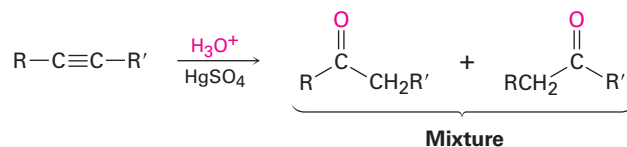
FIGURE 8.18 Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone.

The reaction occurs through initial formation of an intermediate enol, which tautomerizes to the ketone.

A mixture of both possible ketones results when an unsymmetrically substituted internal alkyne ($\text{RC}\equiv\text{CR}'$) is hydrated. The reaction is therefore most

useful when applied to a terminal alkyne ($\text{RC}\equiv\text{CH}$) because only a methyl ketone is formed.

An internal alkyne

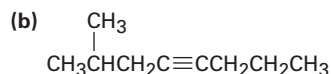
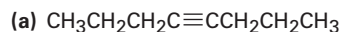


A terminal alkyne



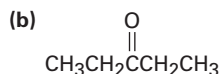
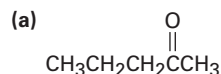
PROBLEM 8.26

What product would you obtain by hydration of the following alkynes?



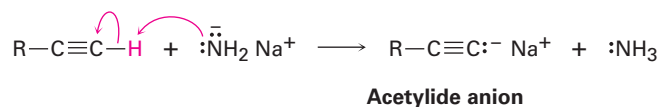
PROBLEM 8.27

What alkynes would you start with to prepare the following ketones?



Alkyne Acidity

The most striking difference in properties between alkenes and alkynes is that terminal alkynes ($\text{RC}\equiv\text{CH}$) are relatively acidic. When a terminal alkyne is treated with a strong base, such as sodium amide, $\text{Na}^+ \text{NH}_2^-$, the terminal hydrogen is removed and the corresponding **acetylide anion** is formed:



According to the Brønsted–Lowry definition (Section 2-7), an acid is a substance that donates H^+ . Although we usually think of oxyacids (H_2SO_4 , HNO_3) or halogen acids (HCl , HBr) in this context, any compound containing a hydrogen atom can be an acid under the right circumstances. By measuring dissociation

constants of different acids and expressing the results as pK_a values, an acidity order can be established. Recall from Section 2-8 that a lower pK_a corresponds to a stronger acid and a higher pK_a corresponds to a weaker acid.

Where do hydrocarbons lie on the acidity scale? As the data in **TABLE 8.3** show, both methane ($pK_a \approx 60$) and ethylene ($pK_a = 44$) are very weak acids and thus do not react with any of the common bases. Acetylene, however, has $pK_a = 25$ and can be deprotonated by the conjugate base of any acid whose pK_a is greater than 25. Amide ion (NH_2^-), for example, the conjugate base of ammonia ($pK_a = 35$), is often used to deprotonate terminal alkynes.

TABLE 8.3 Acidity of Simple Hydrocarbons

Family	Example	K_a	pK_a	
Alkyne	$\text{HC}\equiv\text{CH}$	10^{-25}	25	<p>Stronger acid</p> <p>Weaker acid</p>
Alkene	$\text{H}_2\text{C}=\text{CH}_2$	10^{-44}	44	
Alkane	CH_4	10^{-60}	60	

Why are terminal alkynes more acidic than alkenes or alkanes? In other words, why are acetylide anions more stable than vinylic (alkenyl) or alkyl anions? The simplest explanation involves the hybridization of the negatively charged carbon atom. An acetylide anion has an sp -hybridized carbon, so the negative charge resides in an orbital that has 50% s character. A vinylic anion has an sp^2 -hybridized carbon with 33% s character, and an alkyl anion (sp^3) has only 25% s character. Because s orbitals are nearer the positive nucleus and lower in energy than p orbitals, the negative charge is stabilized to a greater extent in an orbital with higher s character (**FIGURE 8.19**).

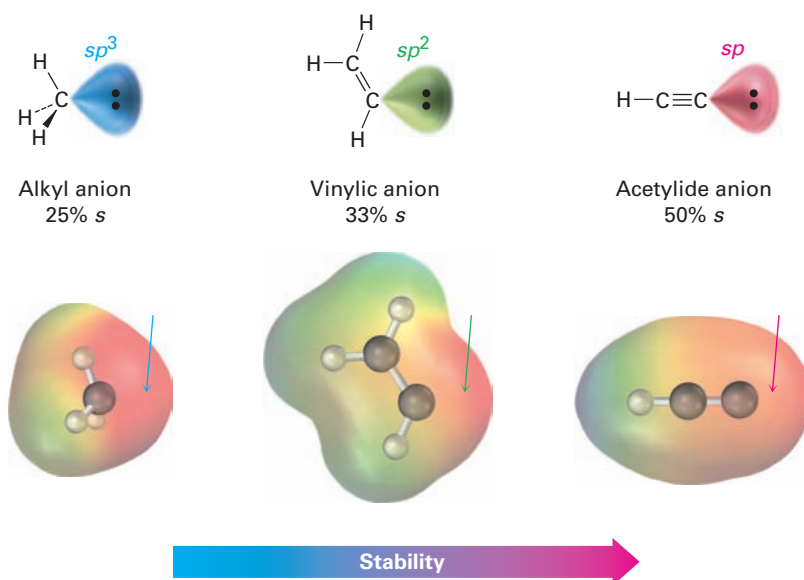
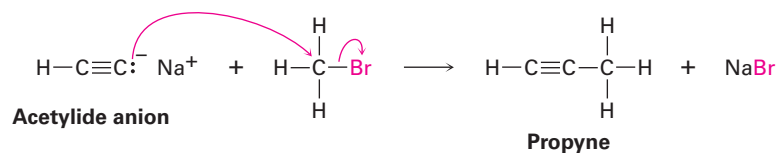
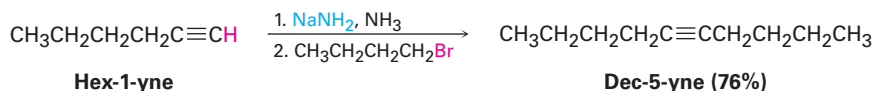


FIGURE 8.19 Comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with sp hybridization, has more s character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear **less negative**.

The presence of a negative charge and an unshared electron pair on carbon makes acetylide anions strongly nucleophilic. As a result, they react with many different kinds of electrophiles, such as alkyl halides, in a process that replaces the halide and yields a new alkyne product.



We'll study the details of this substitution reaction in Section 12-6 but might note for now that the reaction is not limited to acetylene itself. Any terminal alkyne can be converted by base into its corresponding anion and then allowed to react with an alkyl halide to give an internal alkyne product. Hex-1-yne, for instance, gives dec-5-yne when treated first with NaNH_2 and then with 1-bromobutane.



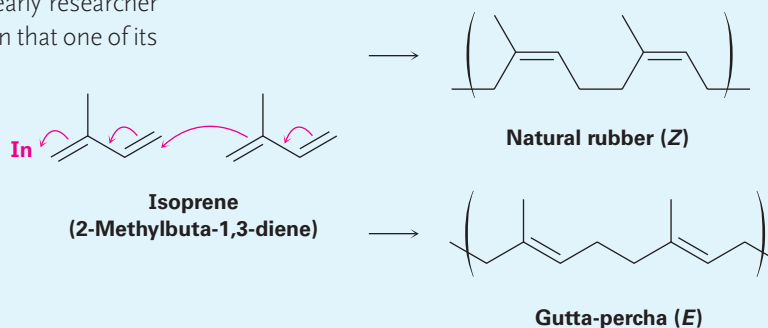
SOMETHING EXTRA

Natural Rubber

Rubber—an unusual name for an unusual substance—is a naturally occurring polymer produced by more than 400 different plants. The major source is the so-called rubber tree, *Hevea brasiliensis*, from which the crude material is harvested as it drips from a slice made through the bark. The name *rubber* was coined by Joseph Priestley, the discoverer of oxygen and early researcher of rubber chemistry, for the simple reason that one of its early uses was to rub out pencil marks on paper.

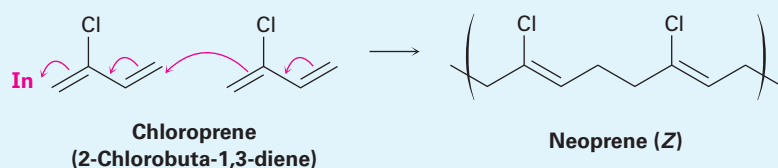
Unlike polyethylene and other simple alkene polymers, natural rubber is a polymer of a conjugated diene, 2-methylbuta-1,3-diene, commonly called isoprene. The polymerization takes place by 1,4-addition of isoprene

monomer units to the growing chain, leading to formation of a polymer that still contains double bonds spaced regularly at four-carbon intervals. The double bonds of rubber have *Z* stereochemistry, but gutta-percha, the *E* isomer of rubber, also occurs naturally. Harder and more brittle than rubber, gutta-percha has a variety of minor applications, including occasional use in dentistry and as the covering on golf balls.



Crude rubber, called *latex*, is collected from the tree as an aqueous dispersion that is washed, dried, and coagulated by warming in air. The resultant polymer has chains that average about 5000 monomer units in length and have molecular weights of 200,000 to 500,000. This crude coagulate is too soft and tacky to be useful until it is hardened by heating with elemental sulfur, a process called *vulcanization*. Vulcanization cross-links the rubber chains together by forming carbon–sulfur bonds between them, thereby hardening and stiffening the polymer. The exact degree of hardening can be varied, yielding material soft enough for automobile tires or hard enough for bowling balls (*ebonite*).

A number of different synthetic rubbers are produced commercially by diene polymerization. Both *cis*- and *trans*-polyisoprene can be made, and the synthetic rubber thus produced is similar to the natural material. Chloroprene (2-chlorobuta-1,3-diene) is polymerized to yield neoprene, an excellent, although expensive, synthetic rubber with good weather resistance. Neoprene is used in the production of industrial hoses and gloves, among other things.



The remarkable ability of rubber to stretch and then contract to its original shape is due to the irregular shapes of the polymer chains caused by the double



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Natural rubber is obtained from the bark of the rubber tree, *Hevea brasiliensis*, grown on enormous plantations in Southeast Asia.

bonds. These double bonds introduce bends and kinks into the polymer chains, thereby preventing neighboring chains from nestling together. When stretched, the randomly coiled chains straighten out and orient along the direction of the pull but are kept from sliding over

one another by the cross-links. When the stretch is released, the polymer reverts to its original random state.



SUMMARY

With the background needed to understand organic reactions now covered, this chapter has begun the systematic description of major functional groups. A large variety of reactions have been covered, but we've focused on those reactions that have direct or indirect counterparts in biological pathways.

KEY WORDS

acetylide anion, 256
 allylic, 245
 anti stereochemistry, 215

bromonium ion (R_2Br^+),	215
carbene ($R_2C:$),	233
chain-growth polymer,	237
conjugation,	241
dehydration,	213
dehydrohalogenation,	213
Diels–Alder cycloaddition reaction,	247
dienophile,	248
epoxide,	227
glycol,	229
halogenation,	214
halohydrin,	217
hydrogenation,	223
hydroxylation,	229
monomer,	235
oxidation,	227
pericyclic reaction,	248
polymer,	235
reduction,	223
stereospecific,	235
syn stereochemistry,	220

Methods for the preparation of alkenes generally involve *elimination reactions*, such as **dehydrohalogenation**—the elimination of HX from an alkyl halide—and **dehydration**—the elimination of water from an alcohol. The flip side of that elimination reaction to prepare alkenes is the addition of various substances to the alkene double bond to give saturated products.

The hydrohalic acids HCl and HBr add to alkenes by a two-step electrophilic addition mechanism. Initial reaction of the nucleophilic double bond with H^+ gives a carbocation intermediate, which then reacts with halide ion. Bromine and chlorine add to alkenes via three-membered-ring **bromonium ion** or **chloronium ion** intermediates to give addition products having **anti stereochemistry**. If water is present during halogen addition reactions, a **halohydrin** is formed.

Hydration of an alkene—the addition of water—is carried out in the laboratory by either of two complementary procedures, depending on the product desired. Oxymercuration–demercuration gives the product of Markovnikov addition, whereas hydroboration–oxidation gives the product with non-Markovnikov **syn stereochemistry**.

Alkenes are reduced by addition of H_2 in the presence of a catalyst such as platinum or palladium to yield alkanes, a process called catalytic **hydrogenation**. Alkenes are also converted into **epoxides** by reaction with a peroxyacid and thence into trans-1,2-diols by acid-catalyzed epoxide hydrolysis. The corresponding cis-1,2-diols can be made directly from alkenes by **hydroxylation** with OsO_4 , and the diol can be cleaved to produce two carbonyl compounds by treatment with HIO_4 . Alkenes can also be cleaved to produce carbonyl compounds directly by reaction with ozone followed by treatment with zinc metal. In addition, alkenes react with divalent substances called **carbenes** to yield cyclopropanes.

Alkene **polymers**—large molecules resulting from repetitive bonding together of many hundreds or thousands of small **monomer** units—are formed by reaction of simple alkenes with a radical initiator at high temperature and pressure. Polyethylene, polypropylene, and polystyrene are examples. As a general rule, radical addition reactions are not common in the laboratory but occur much more frequently in biological pathways.

A **conjugated diene** is one that contains alternating double and single bonds. One characteristic of conjugated dienes is that they are more stable than their nonconjugated counterparts. This stability can be explained by a molecular orbital description in which four p atomic orbitals combine to form four π molecular orbitals. A π bonding interaction in the lowest-energy MO introduces some partial double-bond character between carbons 2 and 3, thereby strengthening the C2–C3 bond and stabilizing the molecule. When a conjugated diene is treated with an electrophile such as HCl, a resonance-stabilized **allylic** carbocation intermediate is formed, from which both 1,2-addition and 1,4-addition products result.

Another reaction unique to conjugated dienes is the **Diels–Alder cycloaddition**. Conjugated dienes react with electron-poor alkenes (**dienophiles**) in a single step through a cyclic transition state to yield a cyclohexene product. The reaction is **stereospecific**, meaning that only a single product stereoisomer is formed, and can occur only if the diene is able to adopt an *s-cis* conformation.

Alkynes undergo addition reactions in much the same way that alkenes do, although their reactivity is typically less than that of alkenes. In addition,

terminal alkynes ($\text{RC}\equiv\text{CH}$) are weakly acidic and can be converted into their corresponding **acetylide anions** by treatment with a sufficiently strong base.

LEARNING REACTIONS

What's seven times nine? Sixty-three, of course. You didn't have to stop and figure it out; you knew the answer immediately because you long ago learned the multiplication tables. Learning the reactions of organic chemistry requires the same approach: reactions have to be learned for immediate recall if they are to be useful.

Different people take different approaches to learning reactions. Some people make flashcards; others find studying with friends to be helpful. To help guide your study, most chapters in this book end with a summary of the reactions just presented. In addition, the accompanying *Study Guide and Solutions Manual* has several appendixes that organize organic reactions from other viewpoints. Fundamentally, though, there are no shortcuts. Learning organic chemistry does take effort.

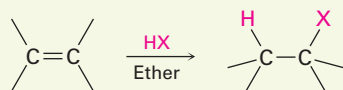
SUMMARY OF REACTIONS

Note: No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.

1. Addition reactions of alkenes

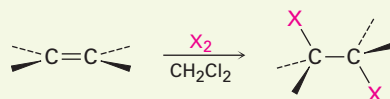
(a) Addition of HCl and HBr (Sections 7-6 and 7-7)

Markovnikov regiochemistry occurs, with H adding to the less highly substituted alkene carbon and halogen adding to the more highly substituted carbon.



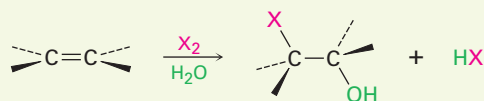
(b) Addition of halogens Cl_2 and Br_2 (Section 8-2)

Anti addition is observed through a halonium ion intermediate.



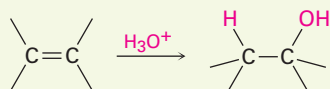
(c) Halohydrin formation (Section 8-3)

Markovnikov regiochemistry and anti stereochemistry occur.



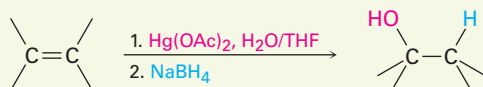
- (d) Addition of water by acid-catalyzed reaction (Sections 7-6 and 7-7)

Markovnikov regiochemistry occurs.



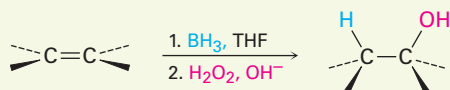
- (e) Addition of water by oxymercuration–demercuration (Section 8-4)

Markovnikov regiochemistry occurs.



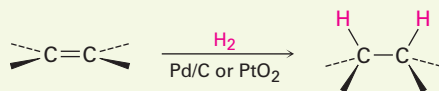
- (f) Addition of water by hydroboration–oxidation (Section 8-4)

Non-Markovnikov syn addition occurs.



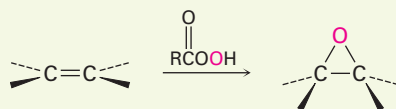
- (g) Catalytic hydrogenation (Section 8-5)

Syn addition occurs.



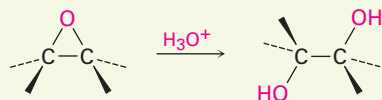
- (h) Epoxidation with a peroxyacid (Section 8-6)

Syn addition occurs.



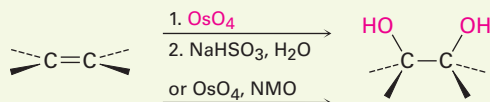
- (i) Hydroxylation by acid-catalyzed epoxide hydrolysis (Section 8-7)

Anti stereochemistry occurs.

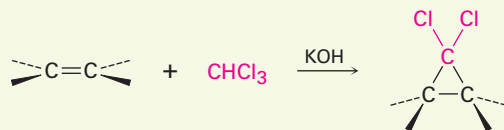


- (j) Hydroxylation with OsO_4 (Section 8-7)

Syn addition occurs.



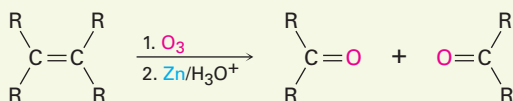
(k) Addition of carbenes to give cyclopropanes (Section 8-9)



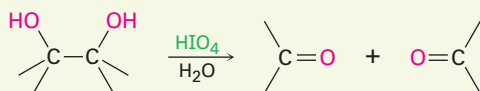
(l) Radical polymerization (Section 8-10)



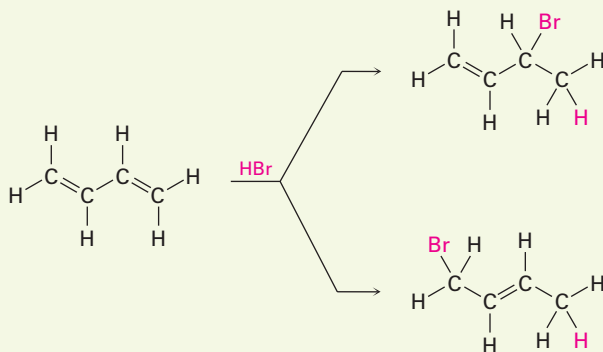
2. Oxidative cleavage of alkenes by ozonolysis (Section 8-8)



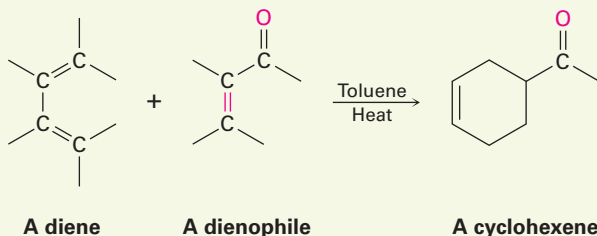
3. Cleavage of 1,2-diols with HIO_4 (Section 8-8)



4. Addition reactions of conjugated dienes (Section 8-13)

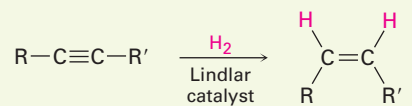
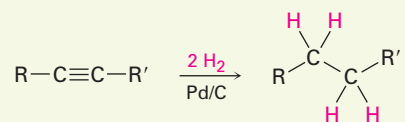


5. Diels–Alder cycloaddition reaction (Section 8-14)

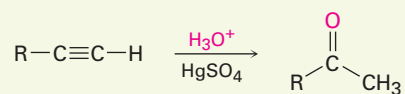


6. Reactions of alkynes (Section 8-15)

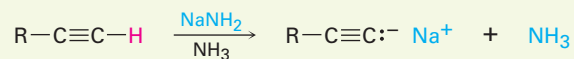
(a) Catalytic hydrogenation

**A cis alkene**

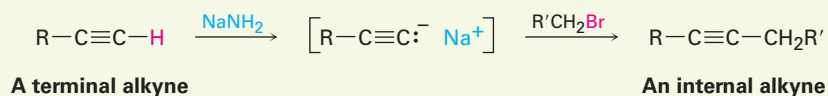
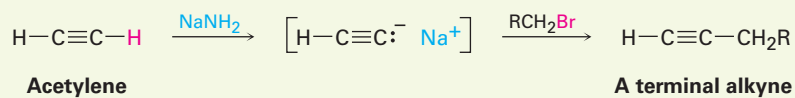
(b) Mercury(II)-catalyzed hydration



(c) Conversion into acetylide anions



(d) Reaction of acetylide anions with alkyl halides



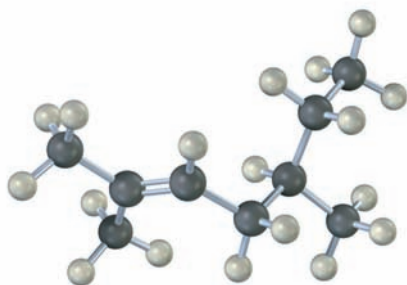
EXERCISES

VISUALIZING CHEMISTRY

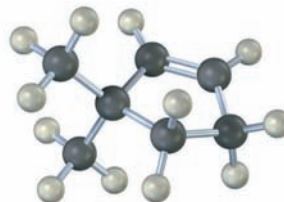
(Problems 8.1–8.27 appear within the chapter.)

- 8.28** Name the following alkenes, and predict the products of their reaction with (i) *meta*-chloroperoxybenzoic acid, (ii) KMnO_4 in aqueous acid, and (iii) O_3 followed by Zn in acetic acid:

(a)

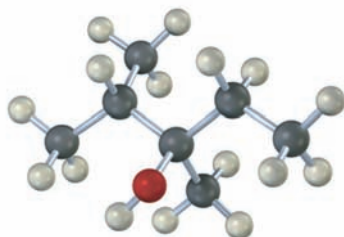


(b)

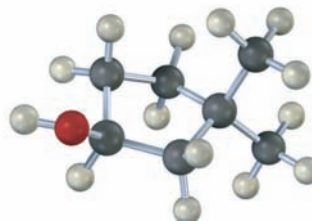


- 8.29** Draw the structures of alkenes that would yield the following alcohols on hydration (red = O). Tell in each case whether you would use hydroboration–oxidation or oxymercuration–demercuration.

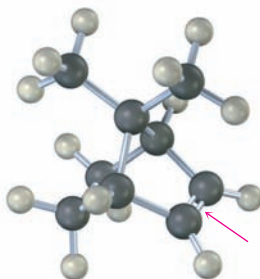
(a)



(b)

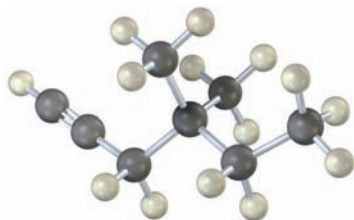


- 8.30** The following alkene undergoes hydroboration–oxidation to yield a single product rather than a mixture. Explain the result, and draw the product showing its stereochemistry.

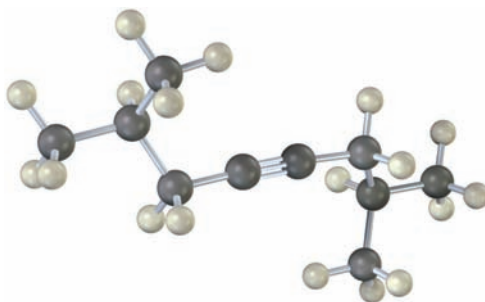


8.31 Name the following alkynes, and predict the product of their reactions with (i) 1 molar equivalent of H_2 in the presence of Lindlar catalyst, (ii) 1 molar equivalent of Br_2 , and (iii) aqueous acid and $HgSO_4$ catalyst:

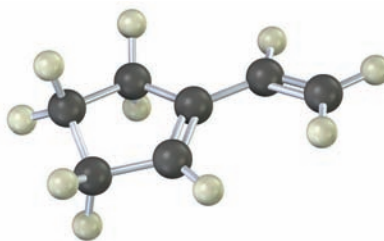
(a)



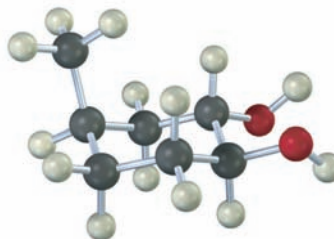
(b)



8.32 Write the structures of the possible products from reaction of the following diene with 1 molar equivalent of HCl :



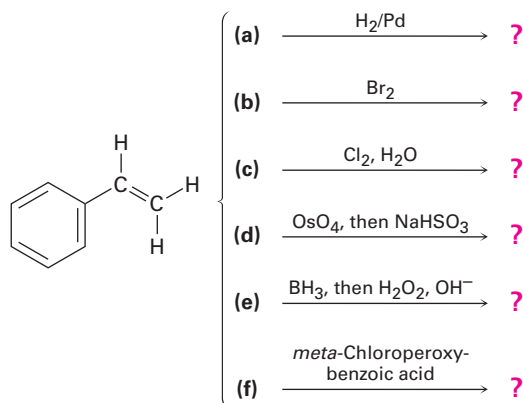
8.33 From what alkene was the following 1,2-diol made, and what method was used, epoxide hydrolysis or OsO_4 ?



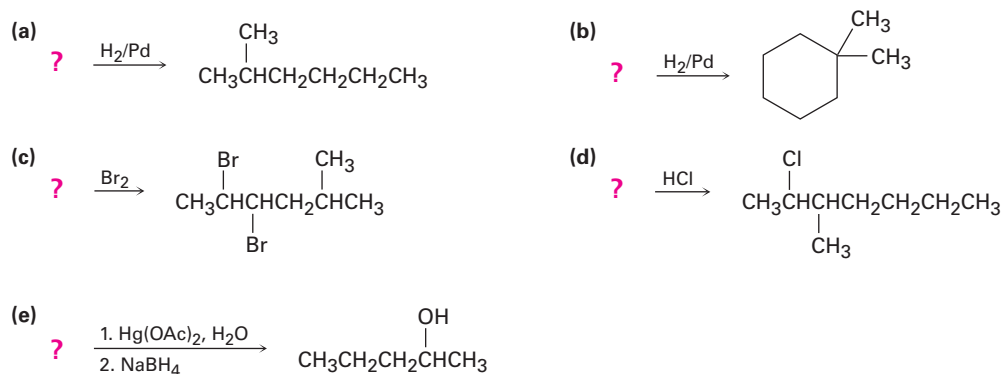
ADDITIONAL PROBLEMS

Reactions of Alkenes and Alkynes

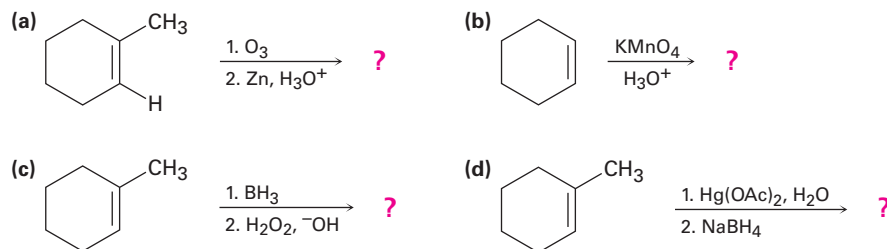
8.34 Predict the products of the following reactions (the aromatic ring is unreactive in all cases). Indicate regiochemistry when relevant.



8.35 Suggest structures for alkenes that give the following reaction products. There may be more than one answer for some cases.

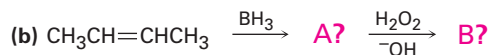


8.36 Predict the products of the following reactions, showing both regiochemistry (orientation) and stereochemistry where appropriate:

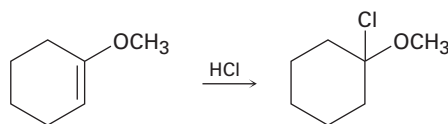


8.37 Which reaction would you expect to be faster, addition of HBr to cyclohexene or to 1-methylcyclohexene? Explain.

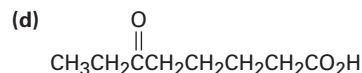
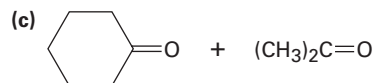
- 8.38** What product will result from hydroboration–oxidation of 1-methylcyclopentene with deuterated borane, BD_3 ? Show both the stereochemistry and the regiochemistry of the product.
- 8.39** The *cis* and *trans* isomers of but-2-ene give different dichlorocyclopropane products when treated with CHCl_3 and KOH . Show the structure of each, and explain the difference.
- 8.40** Predict the products of the following reactions, and indicate regiochemistry if relevant:



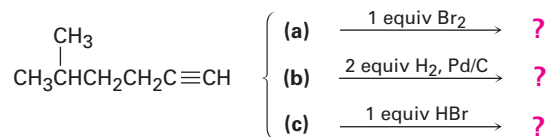
- 8.41** Reaction of 2-methylpropene with CH_3OH in the presence of H_2SO_4 catalyst yields methyl *tert*-butyl ether, $\text{CH}_3\text{OC}(\text{CH}_3)_3$, by a mechanism analogous to that of acid-catalyzed alkene hydration. Write the mechanism, using curved arrows for each step.
- 8.42** Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as the sole product. Use resonance structures to explain why none of the other regioisomer is formed.



- 8.43** Draw the structure of an alkene that yields only acetone, $(\text{CH}_3)_2\text{C}=\text{O}$, on ozonolysis followed by treatment with Zn .
- 8.44** Show the structures of alkenes that give the following products on oxidative cleavage with KMnO_4 in acidic solution:



- 8.45** As we've seen, alkynes undergo many of the same addition reactions that alkenes do. What product might you expect from each of the following reactions?

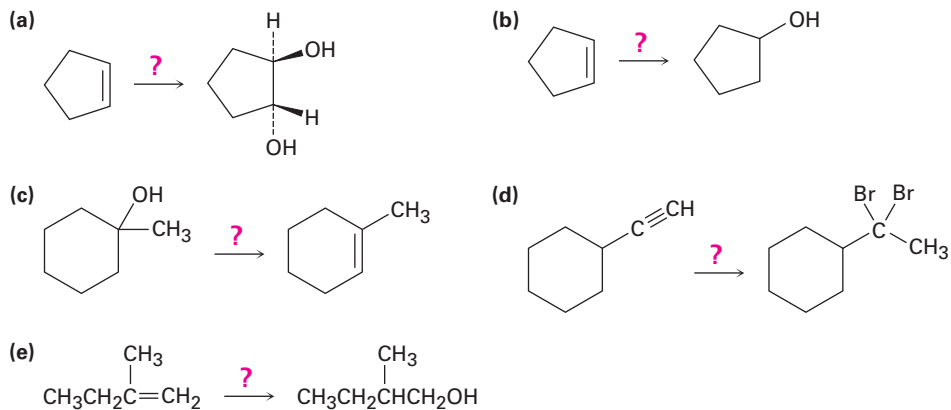


- 8.46** Predict the products of the following reactions on dec-5-yne:

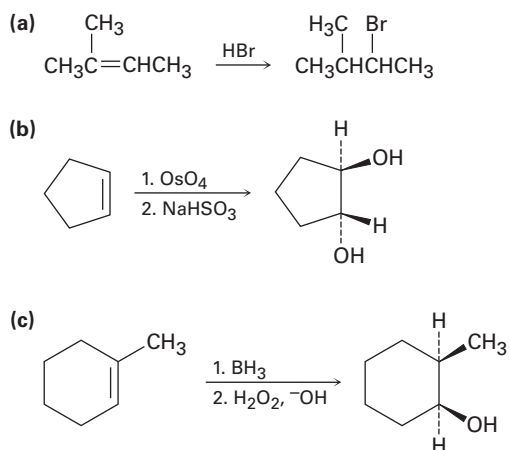


Synthesizing Compounds from Alkenes

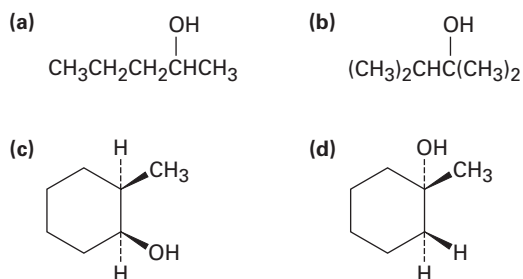
8.47 How would you carry out the following transformations? Indicate the reagents you would use in each case.



8.48 In planning the synthesis of one compound from another, it's just as important to know what *not* to do as to know what to do. The following reactions all have serious drawbacks to them. Explain the potential problems of each.



8.49 Which of the following alcohols could *not* be made selectively by hydroboration–oxidation of an alkene? Explain.

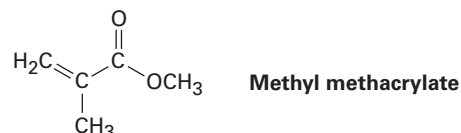


8.50 Using but-1-yne as the only organic starting material, along with any inorganic reagents needed, how would you synthesize the following compounds? More than one step may be needed.

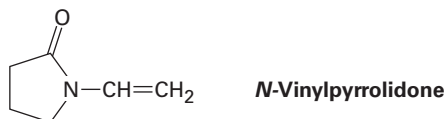
- (a) Butane (b) 1,1,2,2-Tetrachlorobutane
 (c) 2-Bromobutane (d) Butan-2-one ($\text{CH}_3\text{CH}_2\text{COCH}_3$)

Polymers

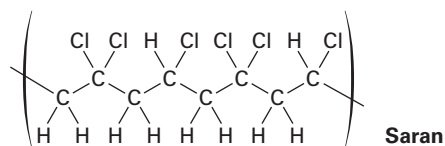
8.51 Plexiglas, a clear plastic used to make many molded articles, is made by polymerization of methyl methacrylate. Draw a representative segment of Plexiglas.



8.52 Poly(vinyl pyrrolidone), prepared from *N*-vinylpyrrolidone, is used both in cosmetics and as a synthetic blood substitute. Draw a representative segment of the polymer.



8.53 When a single alkene monomer, such as ethylene, is polymerized, the product is a *homopolymer*. If a mixture of two alkene monomers is polymerized, however, a *copolymer* often results. The following structure represents a segment of a copolymer called *Saran*. What two monomers were copolymerized to make *Saran*?

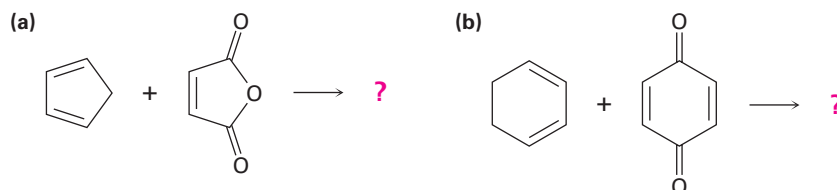


Conjugated Dienes

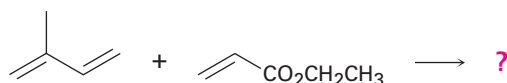
8.54 Draw and name the six diene isomers of formula C_5H_8 . Which of the six are conjugated dienes?

8.55 Propose a structure for a conjugated diene that gives the same product from both 1,2- and 1,4-addition of HCl.

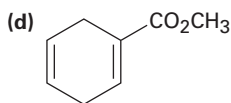
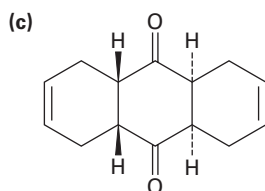
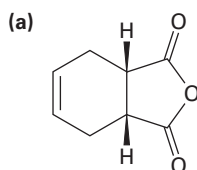
8.56 Predict the products of the following Diels–Alder reactions:



- 8.57 How can you account for the fact that *cis*-penta-1,3-diene is much less reactive than *trans*-penta-1,3-diene in the Diels–Alder reaction?
- 8.58 Would you expect a conjugated diyne such as buta-1,3-diyne to undergo Diels–Alder reaction with a dienophile? Explain.
- 8.59 Reaction of isoprene (2-methylbuta-1,3-diene) with ethyl propenoate gives a mixture of two Diels–Alder adducts. Show the structure of each, and explain why a mixture is formed.

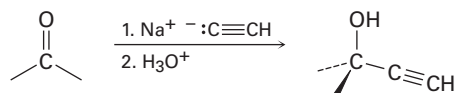


- 8.60 How could you use Diels–Alder reactions to prepare the following products? Show the starting diene and dienophile in each case.

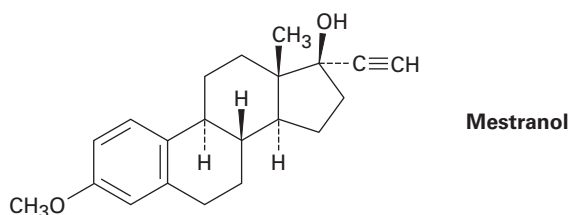


General Problems

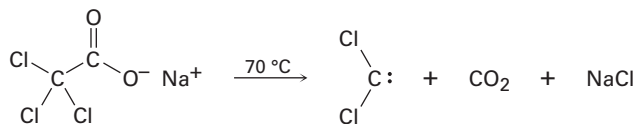
- 8.61 Acetylide anions react with aldehydes and ketones to give alcohol addition products. How might you use this reaction as part of a scheme to prepare 2-methylbuta-1,3-diene, the starting material used in the manufacture of synthetic rubber?



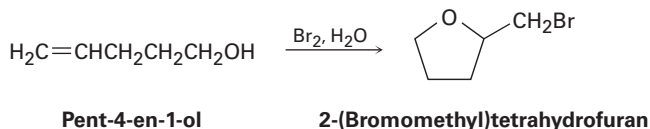
- 8.62 The oral contraceptive agent Mestranol is synthesized using a carbonyl addition reaction like that shown in Problem 8.61. Draw the structure of the ketone needed.



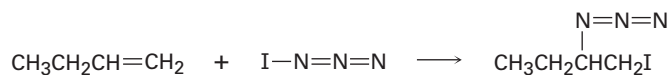
- 8.63** The sex attractant of the common housefly is a hydrocarbon with the formula $C_{23}H_{46}$. On treatment with aqueous acidic $KMnO_4$, two products are obtained, $CH_3(CH_2)_{12}CO_2H$ and $CH_3(CH_2)_7CO_2H$. Propose a structure.
- 8.64** Dichlorocarbene can be generated by heating sodium trichloroacetate. Propose a mechanism for the reaction, and use curved arrows to indicate the movement of electrons in each step. What relationship does your mechanism bear to the base-induced elimination of HCl from chloroform?



- 8.65** Compound **A** has the formula $C_{10}H_{16}$. On catalytic hydrogenation over palladium, it reacts with only 1 molar equivalent of H_2 . Compound **A** also undergoes reaction with ozone, followed by zinc treatment, to yield a symmetrical diketone, **B** ($C_{10}H_{16}O_2$).
- (a) How many rings does **A** have?
- (b) What are the structures of **A** and **B**?
- (c) Write the reactions.
- 8.66** An unknown hydrocarbon **A** with the formula C_6H_{12} reacts with 1 molar equivalent of H_2 over a palladium catalyst. Hydrocarbon **A** also reacts with OsO_4 to give diol **B**. When oxidized with $KMnO_4$ in acidic solution, **A** gives two fragments. One fragment is propanoic acid, $CH_3CH_2CO_2H$, and the other fragment is ketone **C**. What are the structures of **A**, **B**, and **C**? Write all reactions, and show your reasoning.
- 8.67** When pent-4-en-1-ol is treated with aqueous Br_2 , a cyclic bromo ether is formed, rather than the expected bromohydrin. Propose a mechanism, using curved arrows to show electron movement.



- 8.68** Iodine azide, IN_3 , adds to alkenes by an electrophilic mechanism similar to that of bromine. If a monosubstituted alkene such as but-1-ene is used, only one product results:

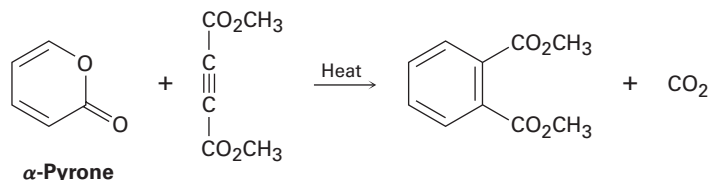


- (a) Add lone-pair electrons to the structure shown for IN_3 , and draw a second resonance form for the molecule.

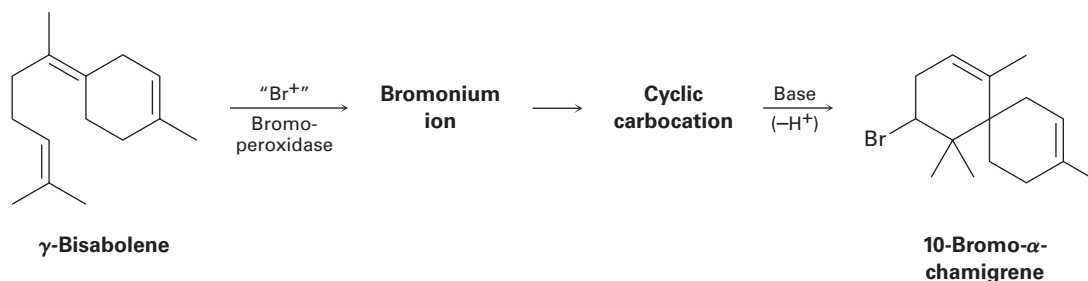
(b) Calculate formal charges for the atoms in both resonance structures you drew for IN_3 in part (a).

(c) In light of the result observed when IN_3 adds to but-1-ene, what is the polarity of the $\text{I}-\text{N}_3$ bond? Propose a mechanism for the reaction using curved arrows to show the electron flow in each step.

8.69 The Diels–Alder reaction is reversible and can go either forward, from diene plus dienophile to a cyclohexene, or backward, from a cyclohexene to diene plus dienophile. In light of that information, propose a mechanism for the following reaction:

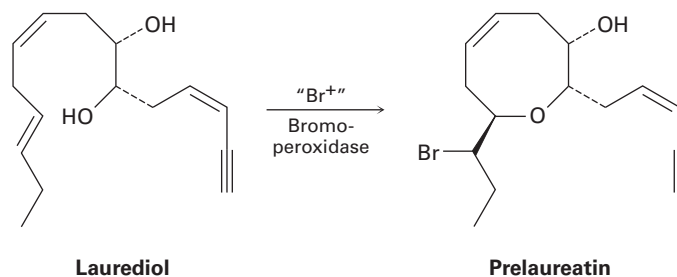


8.70 10-Bromo- α -chamigrene, a compound isolated from marine algae, is thought to be biosynthesized from γ -bisabolene by the following route:

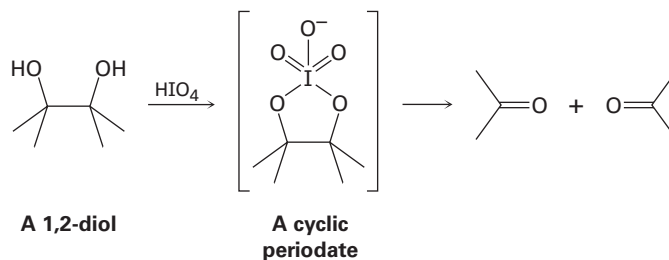


Draw the structures of the intermediate bromonium ion and cyclic carbocation, and propose mechanisms for all three steps.

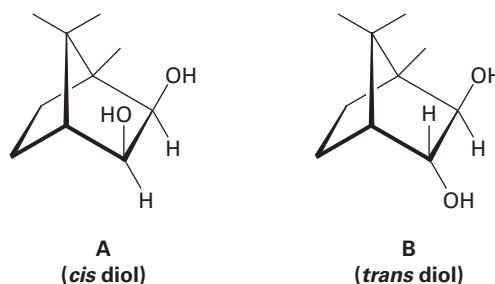
8.71 Prelaureatin, a compound isolated from marine algae, is thought to be biosynthesized from laurediol by the following route. Propose a mechanism. (See Problem 8.70.)



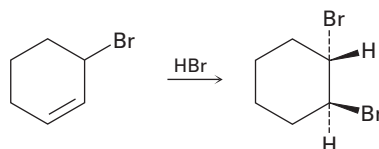
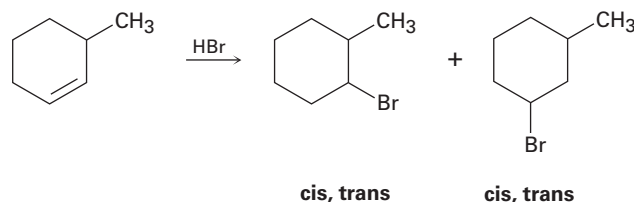
- 8.72 As we saw in Section 8-8, 1,2-diols undergo a cleavage reaction to give carbonyl-containing products on treatment with periodic acid, HIO_4 . The reaction occurs through a five-membered cyclic periodate intermediate:



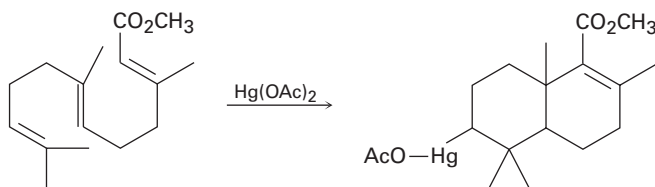
When diols **A** and **B** were prepared and the rates of their reaction with HIO_4 were measured, it was found that diol **A** cleaved approximately 1 million times faster than diol **B**. Make molecular models of **A** and **B** and of the potential periodate intermediates, and explain the results.



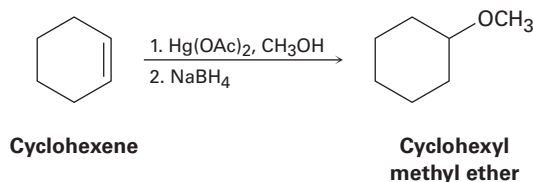
- 8.73 Reaction of HBr with 3-methylcyclohexene yields a mixture of four products: *cis*- and *trans*-1-bromo-3-methylcyclohexane and *cis*- and *trans*-1-bromo-2-methylcyclohexane. The analogous reaction of HBr with 3-bromocyclohexene yields *trans*-1,2-dibromocyclohexane as the sole product. Draw structures of the possible intermediates, and explain why only a single product is formed in the reaction of HBr with 3-bromocyclohexene.



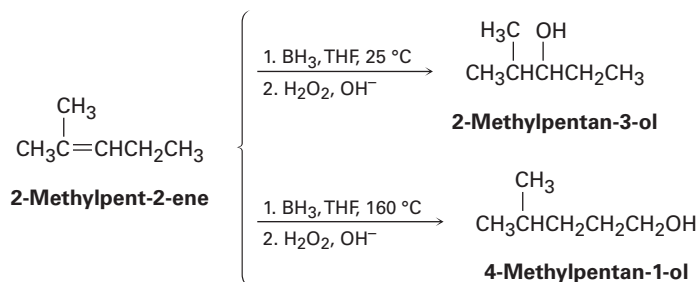
- 8.74 The following reaction takes place in high yield. Use your general knowledge of alkene electrophilic additions to propose a mechanism, even though you've never seen the exact reaction before.



- 8.75 Reaction of cyclohexene with mercury(II) acetate in CH₃OH rather than H₂O, followed by treatment with NaBH₄, yields cyclohexyl methyl ether rather than cyclohexanol. Suggest a mechanism.

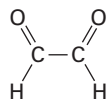
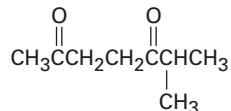


- 8.76 Addition of BH₃ to a double bond is reversible under some conditions. Explain why hydroboration of 2-methylpent-2-ene at 25 °C followed by oxidation with alkaline H₂O₂ yields 2-methylpentan-3-ol, but hydroboration at 160 °C followed by oxidation yields 4-methylpentan-1-ol.



- 8.77 Compound **A**, C₁₁H₁₆O, was found to be an optically active alcohol. Despite its apparent unsaturation, no hydrogen was absorbed on catalytic reduction over a palladium catalyst. On treatment of **A** with dilute sulfuric acid, dehydration occurred and an optically inactive alkene **B**, C₁₁H₁₄, was produced as the major product. Alkene **B**, on ozonolysis, gave two products. One product was identified as propanal, CH₃CH₂CHO. Compound **C**, the other product, was shown to be a ketone, C₈H₈O. How many degrees of unsaturation does **A** have? Write the reactions, and identify **A**, **B**, and **C**.

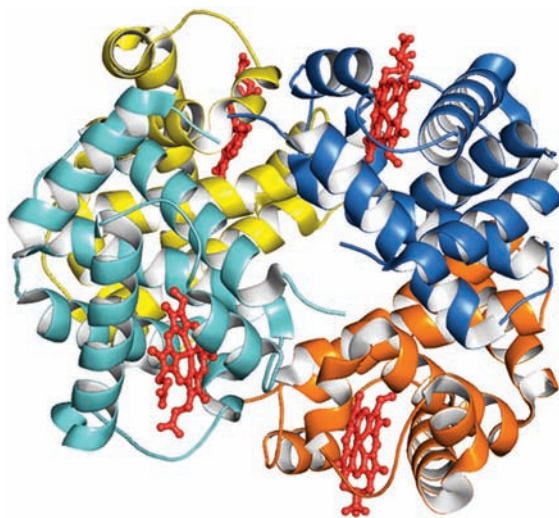
- 8.78** α -Terpinene, $C_{10}H_{16}$, is a pleasant-smelling hydrocarbon that has been isolated from oil of marjoram. On hydrogenation over a palladium catalyst, α -terpinene reacts with 2 molar equivalents of H_2 to yield a hydrocarbon, $C_{10}H_{20}$. On ozonolysis, followed by reduction with zinc and acetic acid, α -terpinene yields two products, glyoxal and 6-methylheptane-2,5-dione.

**Glyoxal****6-Methylheptane-2,5-dione**

- (a) How many degrees of unsaturation does α -terpinene have?
- (b) How many double bonds and how many rings does it have?
- (c) Propose a structure for α -terpinene.

Aromatic Compounds

9



Hemoglobin, the oxygen-carrying protein in blood, contains a large aromatic cofactor called heme.

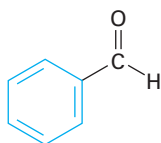
WHY THIS CHAPTER?

Aromatic rings are a common part of many biological structures and are particularly important in the chemistry of nucleic acids and several amino acids. In this chapter, we'll find out how and why aromatic compounds are different from such apparently related compounds as alkenes. As usual, we'll focus primarily on those reactions that occur in both the laboratory and living organisms.

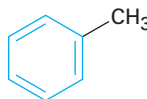
In the early days of organic chemistry, the word *aromatic* was used to describe such fragrant substances as benzene (from coal distillate), benzaldehyde (from cherries, peaches, and almonds), and toluene (from Tolu balsam). It was soon realized, however, that substances classed as aromatic differed from most other organic compounds in their chemical behavior.



Benzene



Benzaldehyde



Toluene

Today, the association of aromaticity with fragrance has long been lost, and we now use the word **aromatic** to refer to the class of compounds that contain six-membered benzene-like rings with three double bonds. Many naturally occurring compounds are aromatic in part, including steroids such as estrone and well-known pharmaceuticals such as the cholesterol-lowering drug atorvastatin, marketed as Lipitor. Benzene itself was once used as a common laboratory solvent but was subsequently found to cause

CONTENTS

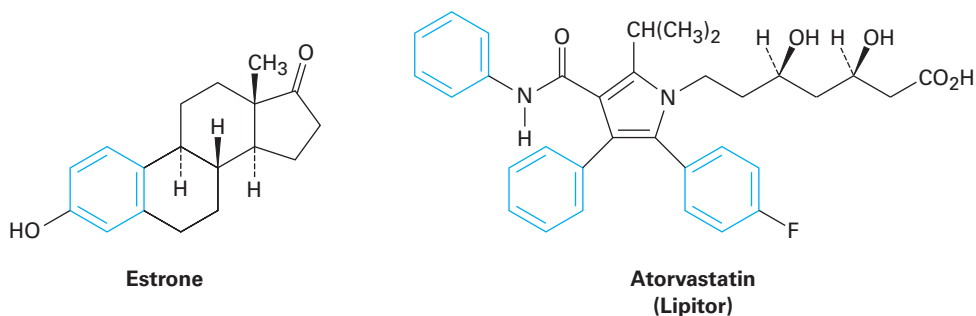
- 9-1 Naming Aromatic Compounds
- 9-2 Structure and Stability of Benzene
- 9-3 Aromaticity and the Hückel $4n + 2$ Rule
- 9-4 Aromatic Ions and Aromatic Heterocycles
- 9-5 Polycyclic Aromatic Compounds
- 9-6 Reactions of Aromatic Compounds: Electrophilic Substitution
- 9-7 Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction
- 9-8 Substituent Effects in Electrophilic Substitutions
- 9-9 Nucleophilic Aromatic Substitution
- 9-10 Oxidation and Reduction of Aromatic Compounds
- 9-11 An Introduction to Organic Synthesis: Polysubstituted Benzenes

SOMETHING EXTRA

Aspirin, NSAIDs, and COX-2 Inhibitors



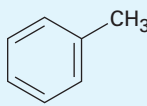
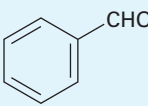
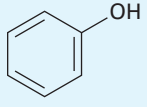
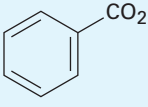
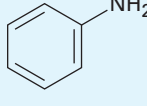
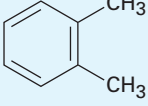
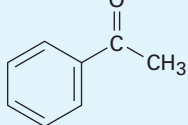
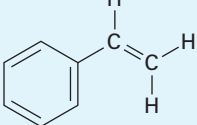
a lowered white blood cell count (leukopenia) on prolonged exposure and is best avoided.



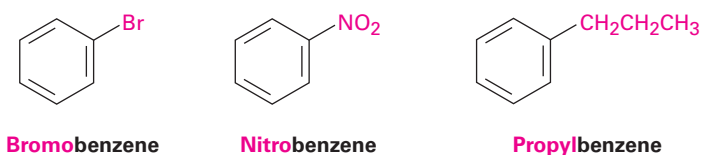
9-1 Naming Aromatic Compounds

Aromatic substances, more than any other class of organic compounds, have acquired a large number of nonsystematic names. IUPAC rules discourage the use of most such names but do allow for some of the more widely used ones to be retained (TABLE 9.1). Thus, methylbenzene is known commonly as *toluene*, hydroxybenzene as *phenol*, aminobenzene as *aniline*, and so on.

TABLE 9.1 Common Names of Some Aromatic Compounds

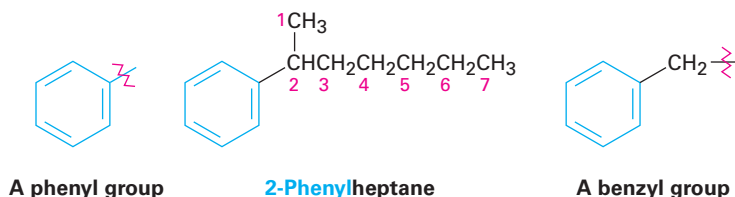
Structure	Name	Structure	Name
	Toluene (bp 111 °C)		Benzaldehyde (bp 178 °C)
	Phenol (mp 43 °C)		Benzoic acid (mp 122 °C)
	Aniline (bp 184 °C)		<i>ortho</i> -Xylene (bp 144 °C)
	Acetophenone (mp 21 °C)		Styrene (bp 145 °C)

Monosubstituted benzenes are named systematically in the same manner as other hydrocarbons, with *-benzene* as the parent name. Thus, C_6H_5Br is bromobenzene, $C_6H_5NO_2$ is nitrobenzene, and $C_6H_5CH_2CH_2CH_3$ is propylbenzene.

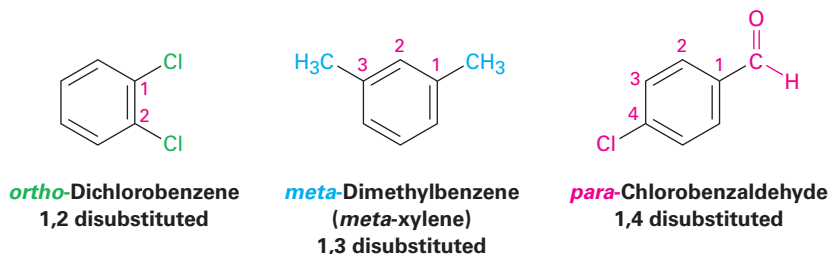


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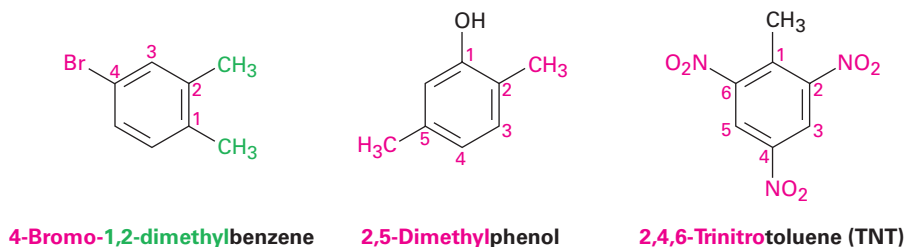
Alkyl-substituted benzenes are sometimes referred to as **arenes** and are named in different ways depending on the size of the alkyl group. If the alkyl substituent is smaller than the ring (six or fewer carbons), the arene is named as an alkyl-substituted benzene. If the alkyl substituent is larger than the ring (seven or more carbons), the compound is named as a phenyl-substituted alkane. The name **phenyl**, pronounced **fen-nil** and sometimes abbreviated as Ph or Φ (Greek phi), is used for the $-\text{C}_6\text{H}_5$ unit when the benzene ring is considered as a substituent. The word is derived from the Greek *pheno* (“I bear light”), commemorating the discovery of benzene by Michael Faraday in 1825 from the oily residue left by the illuminating gas used in London street lamps. In addition, the name **benzyl** is used for the $\text{C}_6\text{H}_5\text{CH}_2-$ group.



Disubstituted benzenes are named using one of the prefixes **ortho (o)**, **meta (m)**, or **para (p)**. An ortho-disubstituted benzene has its two substituents in a 1,2 relationship on the ring, a meta-disubstituted benzene has its two substituents in a 1,3 relationship, and a para-disubstituted benzene has its substituents in a 1,4 relationship.



As with cycloalkanes (Section 4-1), benzenes with more than two substituents are named by choosing a point of attachment as carbon 1 and numbering the substituents on the ring so that the second substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found. The substituents are listed alphabetically when writing the name.

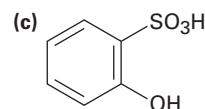
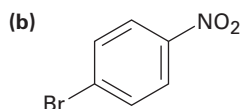
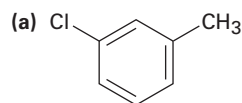


Note in the second and third examples shown that *-phenol* and *-toluene* are used as the parent names rather than *-benzene*. Any of the monosubstituted

aromatic compounds shown in Table 9.1 can be used as a parent name, with the principal substituent ($-\text{OH}$ in phenol or $-\text{CH}_3$ in toluene) attached to C1 on the ring.

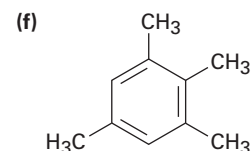
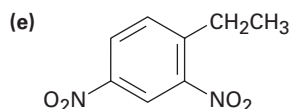
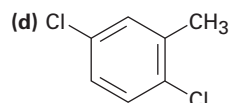
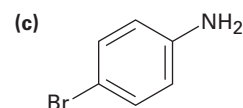
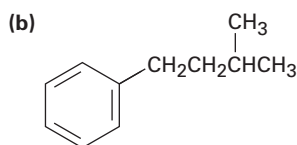
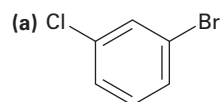
PROBLEM 9.1

Tell whether the following compounds are ortho-, meta-, or para-disubstituted:



PROBLEM 9.2

Give IUPAC names for the following compounds:



PROBLEM 9.3

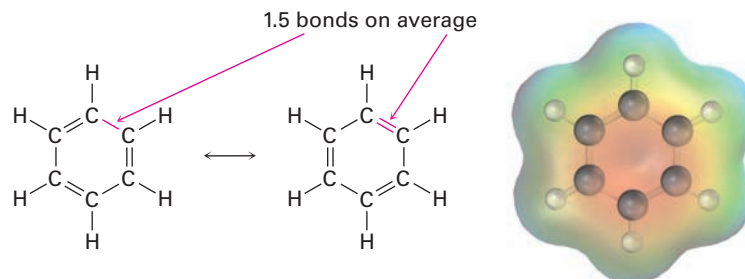
Draw structures corresponding to the following IUPAC names:

- (a) *p*-Bromochlorobenzene (b) *p*-Bromotoluene
 (c) *m*-Chloroaniline (d) 1-Chloro-3,5-dimethylbenzene

9-2 Structure and Stability of Benzene

Benzene (C_6H_6) has six fewer hydrogens than the corresponding six-carbon cycloalkane (C_6H_{12}) and is clearly unsaturated, usually being represented as a six-membered ring with alternating double and single bonds. Yet it has been known since the mid-1800s that benzene is much less reactive than typical alkenes and fails to undergo typical alkene addition reactions. Cyclohexene, for instance, reacts rapidly with Br_2 and gives the addition product

sp^2 -hybridized, and each carbon has a p orbital perpendicular to the plane of the six-membered ring.



Because all six carbon atoms and all six p orbitals in benzene are equivalent, it's not possible to define three localized π bonds in which a given p orbital overlaps only one neighboring p orbital. Rather, each p orbital overlaps equally well with both neighboring p orbitals, leading to a picture of benzene in which all six π electrons are free to move about the entire ring (FIGURE 9.2). In resonance terms (Sections 2-4 and 2-5), benzene is a hybrid of two equivalent forms. Neither form is correct by itself; the true structure of benzene is somewhere in between the two resonance forms but is impossible to draw with our usual conventions. Because of this resonance, benzene is more stable and less reactive than a typical alkene.

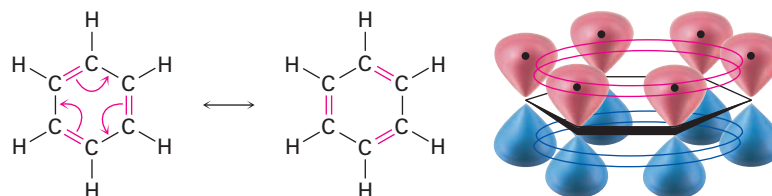
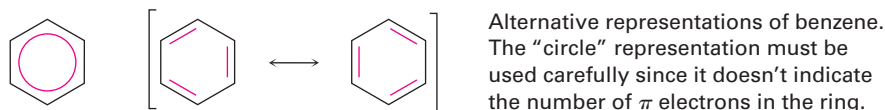


FIGURE 9.2 An orbital picture of benzene. Each of the six carbon atoms has a p orbital that can overlap equally well with neighboring p orbitals on both sides. As a result, all C–C bonds are equivalent and benzene must be represented as a hybrid of two resonance forms.

Chemists sometimes represent the two benzene resonance forms by using a circle to indicate the equivalence of the carbon–carbon bonds. This kind of representation has to be used carefully, however, because it doesn't indicate the number of π electrons in the ring. (How many electrons does a circle represent?) In this book, benzene and other aromatic compounds will be represented by a single line-bond structure. We'll be able to keep count of π electrons this way but must be aware of the limitations of the drawings.



Having just seen a resonance description of benzene, let's now look at the alternative molecular orbital description. We can construct π molecular

orbitals for benzene just as we did for buta-1,3-diene in Section 8-12. If six p atomic orbitals combine in a cyclic manner, six benzene molecular orbitals result, as shown in **FIGURE 9.3**. The three lower-energy molecular orbitals, denoted ψ_1 , ψ_2 , and ψ_3 , are bonding combinations, and the three higher-energy orbitals are antibonding.

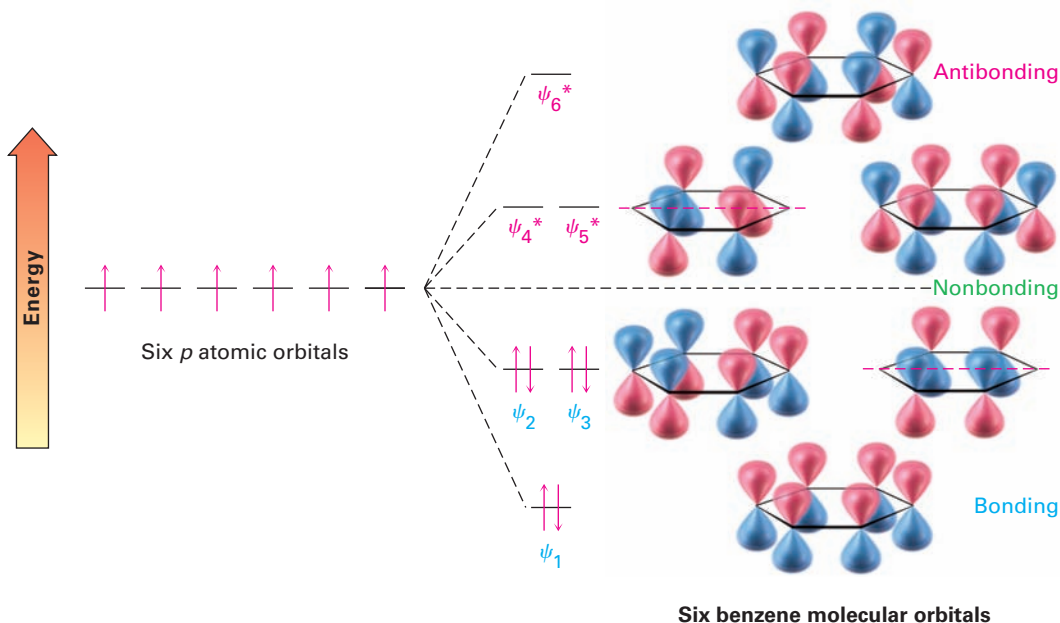
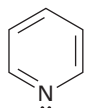


FIGURE 9.3 The six benzene π molecular orbitals. The bonding orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate, as are the antibonding orbitals ψ_4^* and ψ_5^* . The orbitals ψ_3 and ψ_4^* have no π electron density on two carbons because of a node passing through the atoms.

Note that the two bonding orbitals ψ_2 and ψ_3 have the same energy, as do the two antibonding orbitals ψ_4^* and ψ_5^* . Such orbitals with the same energy are said to be *degenerate*. Note also that the two orbitals ψ_3 and ψ_4^* have nodes passing through ring carbon atoms, thereby leaving no π electron density on these carbons. The six p electrons of benzene occupy the three bonding molecular orbitals and are delocalized over the entire conjugated system, leading to the observed 150 kJ/mol stabilization of benzene.

PROBLEM 9.4

Pyridine is a flat, hexagonal molecule with bond angles of 120° . It undergoes substitution rather than addition and generally behaves like benzene. Draw a picture of the π orbitals of pyridine to explain its properties. Check your answer by looking ahead to Section 9-4.



Pyridine

9-3 Aromaticity and the Hückel $4n + 2$ Rule

Let's list what we've said thus far about benzene and, by extension, about other benzene-like aromatic molecules:

- Benzene is cyclic and conjugated.
- Benzene is unusually stable, having a heat of hydrogenation 150 kJ/mol less negative than we might expect for a conjugated cyclic triene.
- Benzene is planar and has the shape of a regular hexagon. All bond angles are 120° , all carbon atoms are sp^2 -hybridized, and all carbon-carbon bond lengths are 139 pm.
- Benzene undergoes substitution reactions that retain the cyclic conjugation rather than electrophilic addition reactions that would destroy the conjugation.
- Benzene can be described as a resonance hybrid whose structure is intermediate between two line-bond structures.

This list would seem to be a good description of benzene and other aromatic molecules, but it isn't enough. Something else, called the **Hückel $4n + 2$ rule**, is needed to complete a description of aromaticity. According to a theory devised in 1931 by the German physicist Erich Hückel, a molecule is aromatic only if it has a planar, monocyclic system of conjugation and contains a total of $4n + 2 \pi$ electrons, where n is an integer ($n = 0, 1, 2, 3, \dots$). In other words, only molecules with 2, 6, 10, 14, 18, $\dots \pi$ electrons can be aromatic. Molecules with $4n \pi$ electrons (4, 8, 12, 16, \dots) can't be aromatic, even though they may be cyclic, planar, and apparently conjugated. In fact, planar, conjugated molecules with $4n \pi$ electrons are said to be *antiaromatic* because delocalization of their π electrons would lead to their destabilization.

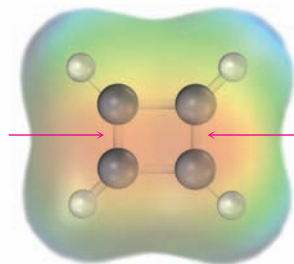
Let's look at several examples to see how the Hückel $4n + 2$ rule works.

- **Cyclobutadiene** has four π electrons and is antiaromatic. The π electrons are localized in two double bonds rather than delocalized around the ring, as indicated by an electrostatic potential map. Cyclobutadiene is highly reactive and shows none of the properties associated with aromaticity. In fact, it was not even prepared until 1965.



Cyclobutadiene

Two double bonds;
four π electrons



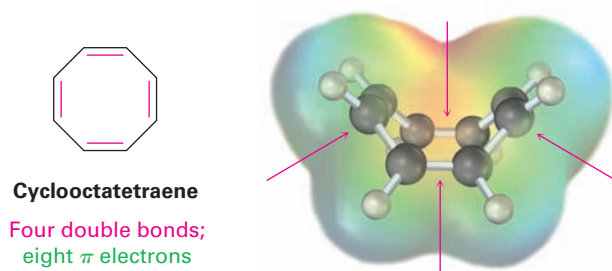
- **Benzene** has six π electrons ($4n + 2 = 6$ when $n = 1$) and is aromatic:



Benzene

Three double bonds;
six π electrons

- **Cyclooctatetraene** has eight π electrons and is not aromatic. The π electrons are localized into four double bonds rather than delocalized around the ring, and the molecule is tub-shaped rather than planar. It has no cyclic conjugation because neighboring p orbitals don't have the necessary parallel alignment for overlap, and it resembles an open-chain polyene in its reactivity.

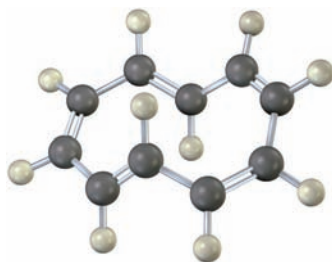


What's so special about $4n + 2$ π electrons? Why do 2, 6, 10, 14 . . . π electrons lead to aromatic stability, while other numbers of electrons do not? The answer comes from molecular orbital theory. When the energy levels of molecular orbitals for cyclic conjugated molecules are calculated, it turns out that there is always a single lowest-lying MO, above which the MOs come in degenerate pairs. Thus, when electrons fill the various molecular orbitals, it takes two electrons, or one pair, to fill the lowest-lying orbital and four electrons, or two pairs, to fill each of n successive energy levels—a total of $4n + 2$. Any other number would leave a bonding energy level partially unfilled.

As shown previously in Figure 9.3 for benzene, the lowest-energy MO, ψ_1 , occurs singly and contains two electrons. The next two lowest-energy orbitals, ψ_2 and ψ_3 , are degenerate, and it therefore takes four electrons to fill them. The result is a stable six- π -electron aromatic molecule with filled bonding orbitals.

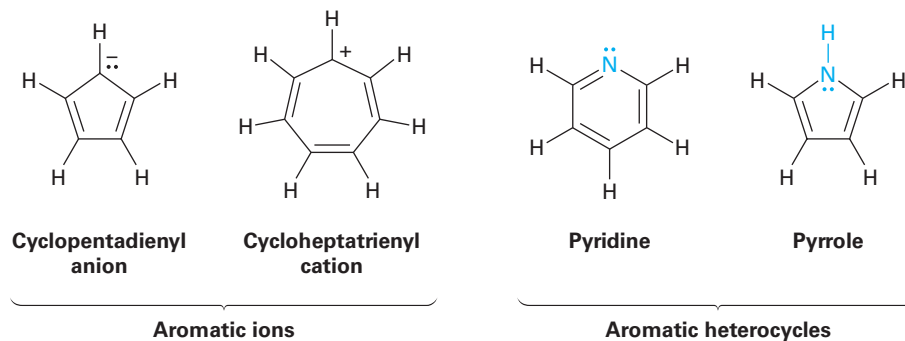
PROBLEM 9.5

To be aromatic, a molecule must have $4n + 2$ π electrons and must be planar for cyclic conjugation. Cyclodecapentaene fulfills one of these criteria but not the other and has resisted all attempts at synthesis. Explain.



9-4 Aromatic Ions and Aromatic Heterocycles

According to the Hückel criteria for aromaticity described in the previous section, a molecule must be cyclic, conjugated (nearly planar with a p orbital on each atom), and have $4n + 2 \pi$ electrons. Nothing in this definition says that the number of π electrons must be the same as the number of atoms in the ring, that the compound must be neutral, or that all the atoms in the ring must be carbon. In fact, the number of π electrons can be different from the number of atoms in the ring, the compounds can be *ions*, and they can also be *heterocycles*, which contain atoms of different elements in their ring. The cyclopentadienyl anion and the cycloheptatrienyl cation are perhaps the best known aromatic ions, while pyridine and pyrrole are common aromatic heterocycles.



Aromatic Ions

To see why the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic, imagine starting from the related neutral hydrocarbons, cyclopenta-1,3-diene and cyclohepta-1,3,5-triene, and removing one hydrogen from the saturated CH_2 carbon in each. If that carbon then rehybridizes from sp^3 to sp^2 , the resultant products would be fully conjugated and have a p orbital on every carbon. There are three ways in which the hydrogen might be removed.

- The hydrogen can be removed with *both* electrons (H^-) from the C–H bond, leaving a carbocation as product.
- The hydrogen can be removed with *one* electron ($\text{H}\cdot$) from the C–H bond, leaving a carbon radical as product.
- The hydrogen can be removed with *no* electrons (H^+) from the C–H bond, leaving a carbon anion, or *carbanion*, as product.

All the potential products formed by removing a hydrogen from cyclopenta-1,3-diene and from cyclohepta-1,3,5-triene can be drawn with numerous resonance structures, but only the six- π -electron cyclopentadienyl anion and cycloheptatrienyl cation obey the $4n + 2$ rule and are aromatic (FIGURE 9.4).

In practice, both the four- π -electron cyclopentadienyl cation and the five- π -electron cyclopentadienyl radical are highly reactive and difficult to prepare. Neither shows any sign of the stability expected for an aromatic system. The six- π -electron cyclopentadienyl anion, by contrast, is easily prepared and remarkably stable (FIGURE 9.5a). In fact, the anion is so stable and easily formed

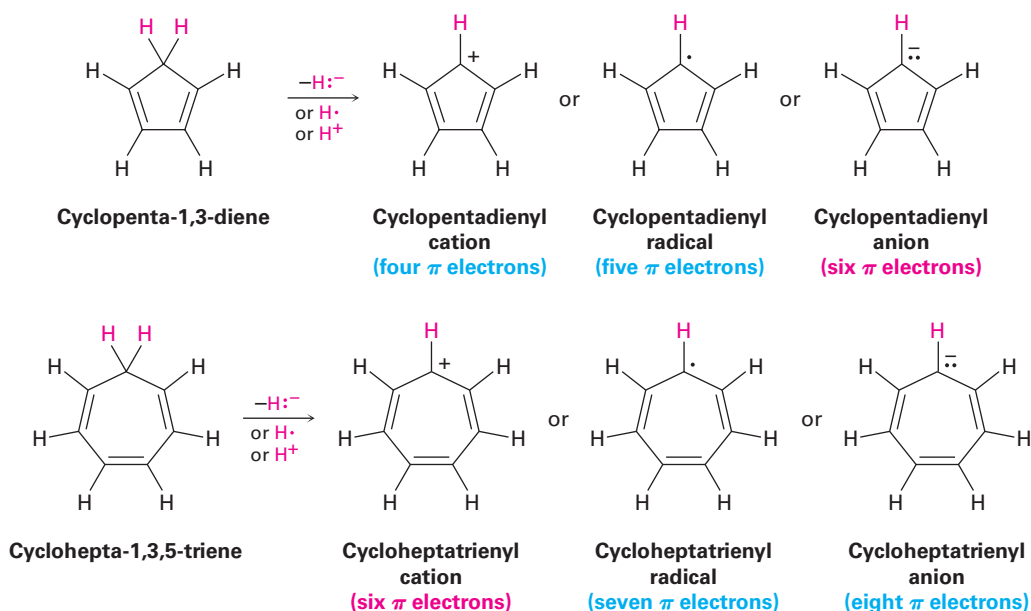


FIGURE 9.4 The aromatic six- π -electron cyclopentadienyl anion and the six- π -electron cycloheptatrienyl cation. The anion can be formed by removing a hydrogen ion (H^+) from the CH_2 group of cyclopenta-1,3-diene. The cation can be generated by removing a hydride ion (H^-) from the CH_2 group of cyclohepta-1,3,5-triene.

that cyclopenta-1,3-diene is one of the most acidic hydrocarbons known, with $\text{p}K_{\text{a}} = 16$, a value comparable to that of water!

In the same way, the seven- π -electron cycloheptatrienyl radical and eight- π -electron anion are reactive and difficult to prepare, while the six- π -electron cycloheptatrienyl cation is extraordinarily stable (FIGURE 9.5b). In fact, the cycloheptatrienyl cation was first prepared more than a century ago by reaction of cyclohepta-1,3,5-triene with Br_2 , although its structure was not recognized at the time.

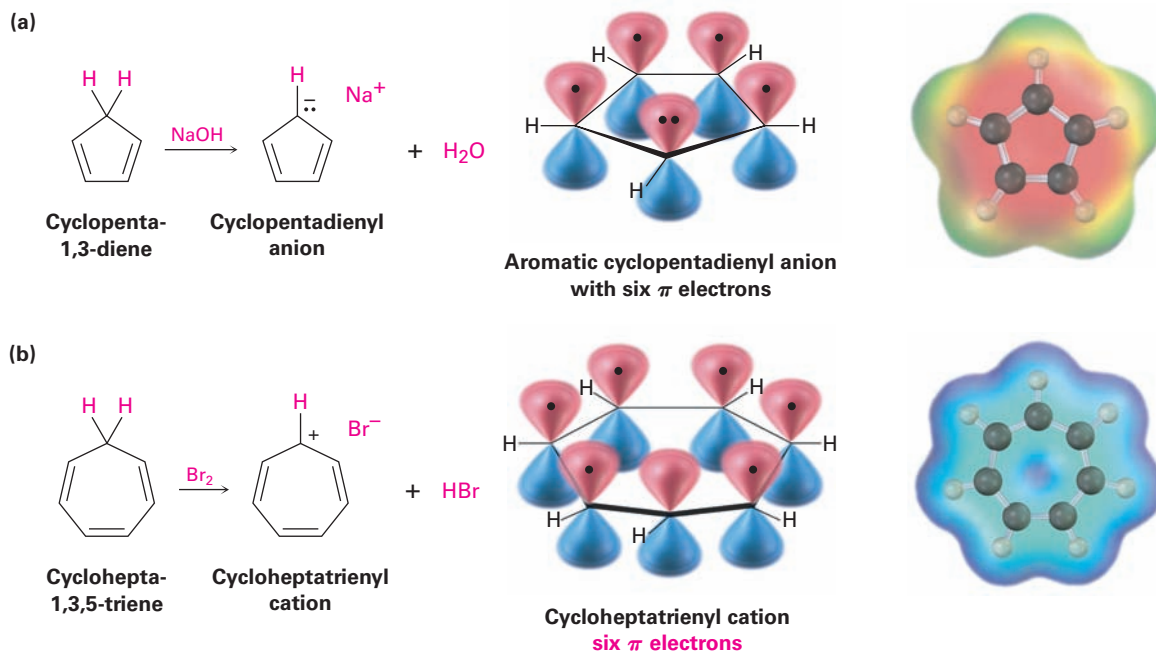
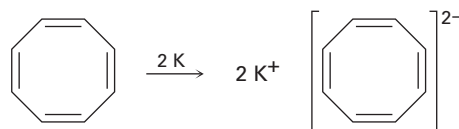


FIGURE 9.5 (a) The aromatic cyclopentadienyl anion, with six π electrons in five p orbitals, and (b) the aromatic cycloheptatrienyl cation, with six π electrons in seven p orbitals. Electrostatic potential maps indicate that both ions are symmetrical, with the charge equally shared among all atoms in each ring.

PROBLEM 9.6

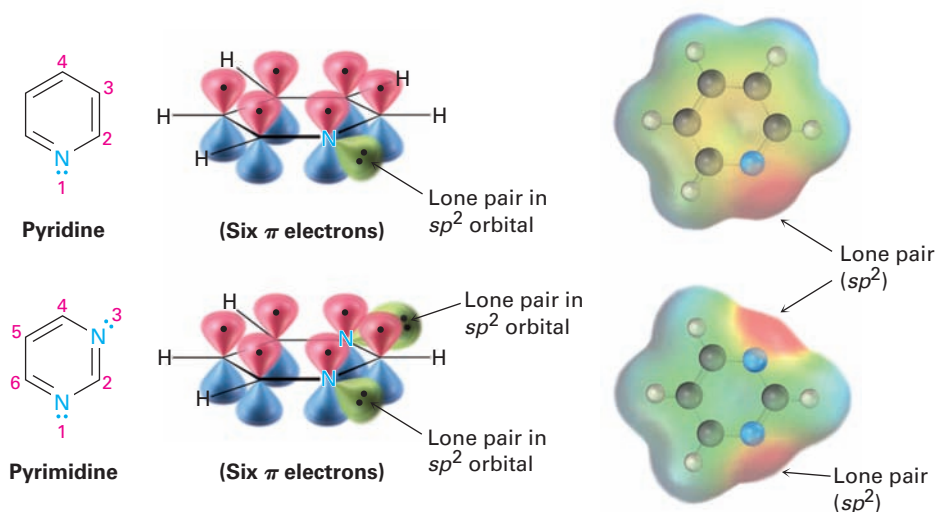
Cycloocta-1,3,5,7-tetraene readily reacts with potassium metal to form the stable cyclooctatetraene dianion, $C_8H_8^{2-}$. Why do you suppose this reaction occurs so easily? What geometry do you think the cyclooctatetraene dianion might have?

**Aromatic Heterocycles**

A **heterocycle**, as noted earlier in this section, is a cyclic compound that contains atoms of two or more elements in its ring, usually carbon along with nitrogen, oxygen, or sulfur. Pyridine and pyrimidine, for example, are six-membered heterocycles with carbon and nitrogen in their rings.

Pyridine is much like benzene in its π electron structure. Each of the five sp^2 -hybridized carbons has a p orbital perpendicular to the plane of the ring, and each p orbital contains one π electron. The nitrogen atom is also sp^2 -hybridized and has one electron in a p orbital, bringing the total to six π electrons. The nitrogen lone-pair electrons (red in an electrostatic potential map) are in an sp^2 orbital in the plane of the ring and are not part of the aromatic π system (FIGURE 9.6). Pyrimidine, also shown in Figure 9.6, is a benzene analog that has two nitrogen atoms in a six-membered, unsaturated ring. Both nitrogens are sp^2 -hybridized, and each contributes one electron to the aromatic π system.

FIGURE 9.6 Structures of pyridine and pyrimidine. Both are nitrogen-containing aromatic heterocycles with π electron arrangements like that of benzene, and both have a lone pair of electrons on nitrogen in an sp^2 orbital in the plane of the ring.



Pyrrole (spelled with two *r*'s and one *l*) and imidazole are *five*-membered heterocycles, yet both have *six* π electrons and are aromatic. In pyrrole,

each of the four sp^2 -hybridized carbons contributes one π electron, and the sp^2 -hybridized nitrogen atom contributes the two from its lone pair, which occupies a p orbital (FIGURE 9.7). Imidazole, also shown in Figure 9.7, is an analog of pyrrole that has two nitrogen atoms in a five-membered, unsaturated ring. Both nitrogens are sp^2 -hybridized, but one is in a double bond and contributes only one electron to the aromatic π system, while the other is not in a double bond and contributes two from its lone pair.

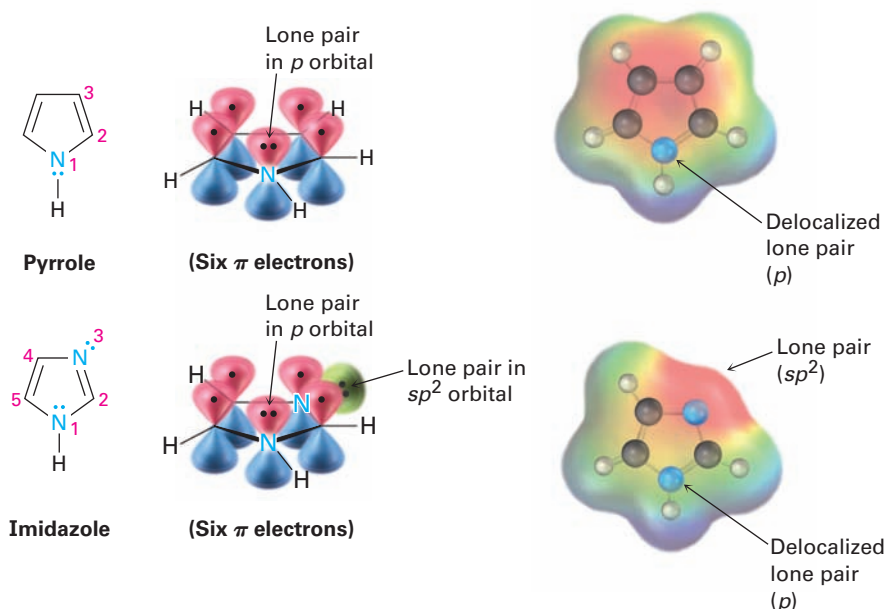
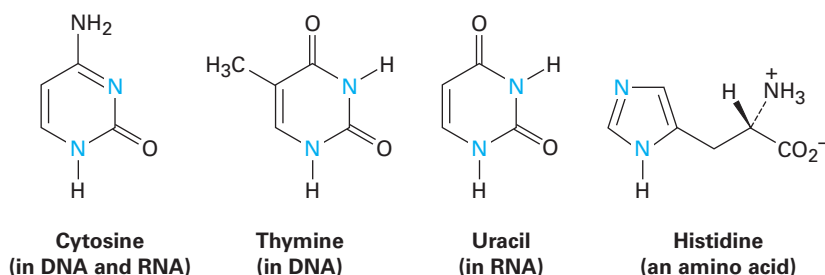


FIGURE 9.7 Structures of pyrrole and imidazole. Both are five-membered, nitrogen-containing heterocycles but have six π electrons and are aromatic. Both also have a lone pair of electrons on nitrogen in a p orbital perpendicular to the ring.

Note that nitrogen atoms have different roles depending on the structure of the molecule. The nitrogen atoms in pyridine and pyrimidine are both in double bonds and contribute only *one* π electron to the aromatic sextet, just as a carbon atom in benzene does. The nitrogen atom in pyrrole, however, is not in a double bond and contributes *two* π electrons (its lone pair) to the aromatic sextet. In imidazole, both kinds of nitrogen are present in the same molecule—a double-bonded “pyridine-like” nitrogen that contributes one π electron and a “pyrrole-like” nitrogen that contributes two.

Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the 20 amino acids found in proteins.



WORKED EXAMPLE 9.1

Accounting for the Aromaticity of a Heterocycle

Thiophene, a sulfur-containing heterocycle, undergoes typical aromatic substitution reactions rather than addition reactions. Why is thiophene aromatic?



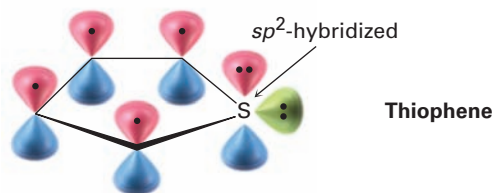
Thiophene

Strategy

Recall the requirements for aromaticity—a planar, cyclic, conjugated molecule with $4n + 2 \pi$ electrons—and see how these requirements apply to thiophene.

Solution

Thiophene is the sulfur analog of pyrrole. The sulfur atom is sp^2 -hybridized and has a lone pair of electrons in a p orbital perpendicular to the plane of the ring. Sulfur also has a second lone pair of electrons in the ring plane.



Thiophene

PROBLEM 9.7

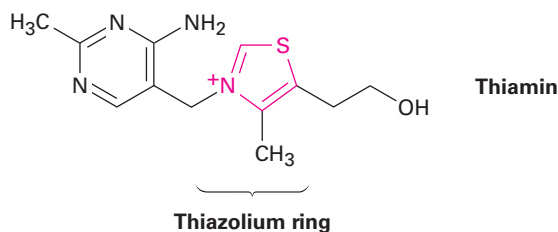
Draw an orbital picture of furan to show how the molecule is aromatic.



Furan

PROBLEM 9.8

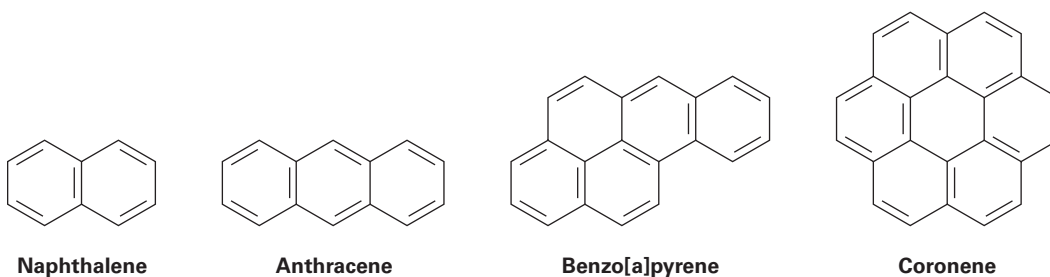
Thiamin, or vitamin B₁, contains a positively charged five-membered nitrogen-sulfur heterocycle called a *thiazolium* ring. Explain why the thiazolium ring is aromatic.



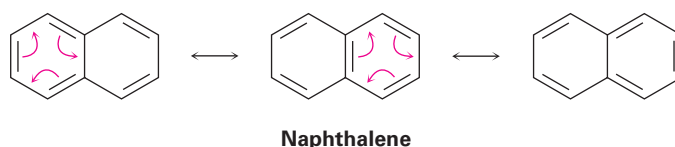
Thiamin

9-5 Polycyclic Aromatic Compounds

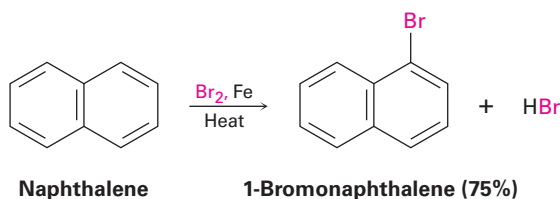
The Hückel rule is strictly applicable only to monocyclic compounds, but the general concept of aromaticity can be extended to include *polycyclic* aromatic compounds. Naphthalene, with two benzene-like rings fused together; anthracene, with three rings; benzo[*a*]pyrene, with five rings; and coronene, with six rings, are all well-known aromatic hydrocarbons. Benzo[*a*]pyrene is particularly interesting because it is one of the cancer-causing substances found in tobacco smoke.



All polycyclic aromatic hydrocarbons can be represented by a number of different resonance forms. Naphthalene, for instance, has three:

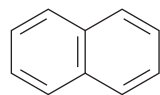


Naphthalene and other polycyclic aromatic hydrocarbons show many of the chemical properties associated with aromaticity. Thus, heat of hydrogenation measurements show an aromatic stabilization energy of approximately 250 kJ/mol (60 kcal/mol). Furthermore, naphthalene reacts slowly with electrophiles such as Br₂ to give substitution products rather than double-bond addition products.

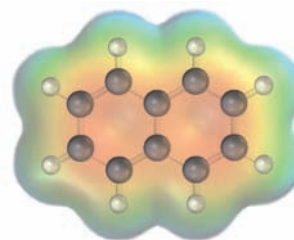
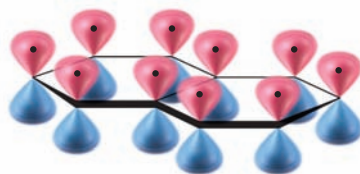


The aromaticity of naphthalene is explained by the orbital picture in **FIGURE 9.8**. Naphthalene has a cyclic, conjugated π electron system, with *p* orbital overlap both around the ten-carbon periphery of the molecule and across the central bond. Since 10 π electrons is a Hückel number, there is π electron delocalization and consequent aromaticity in naphthalene.

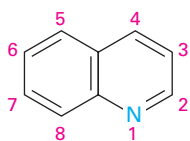
FIGURE 9.8 Orbital picture and electrostatic potential map of naphthalene. The 10 π electrons in naphthalene are fully delocalized throughout both rings.



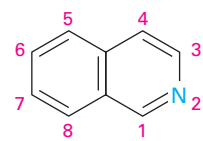
Naphthalene



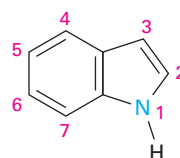
Just as there are heterocyclic analogs of benzene, there are also many heterocyclic analogs of naphthalene. Among the most common are quinoline, isoquinoline, indole, and purine. Quinoline, isoquinoline, and purine all contain pyridine-like nitrogens that are part of a double bond and contribute one electron to the aromatic π system. Indole and purine both contain pyrrole-like nitrogens that contribute two π electrons.



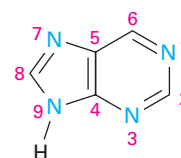
Quinoline



Isoquinoline

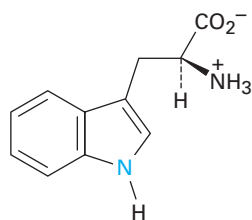


Indole

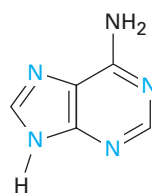


Purine

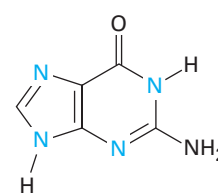
Among the many biological molecules that contain polycyclic aromatic rings, the amino acid tryptophan contains an indole ring and the antimalarial drug quinine contains a quinoline ring. Adenine and guanine, two of the five heterocyclic amine bases found in nucleic acids, have rings based on purine.



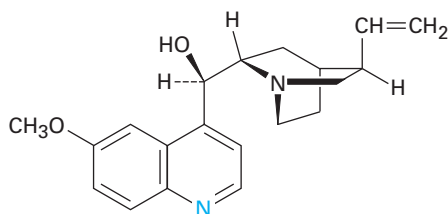
Tryptophan
(an amino acid)



Adenine
(in DNA and RNA)



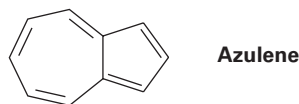
Guanine
(in DNA and RNA)



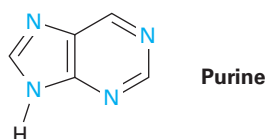
Quinine
(an antimalarial agent)

PROBLEM 9.9

Azulene, a beautiful blue hydrocarbon, is an isomer of naphthalene. Is azulene aromatic? Draw a second resonance form of azulene in addition to the one shown.

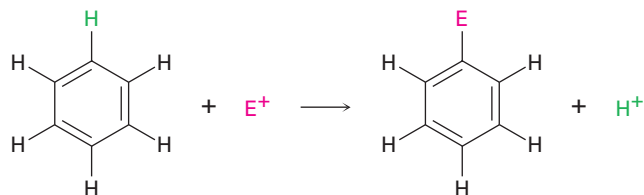
**PROBLEM 9.10**

How many electrons does each of the four nitrogen atoms in purine contribute to the aromatic π system?



9-6 Reactions of Aromatic Compounds: Electrophilic Substitution

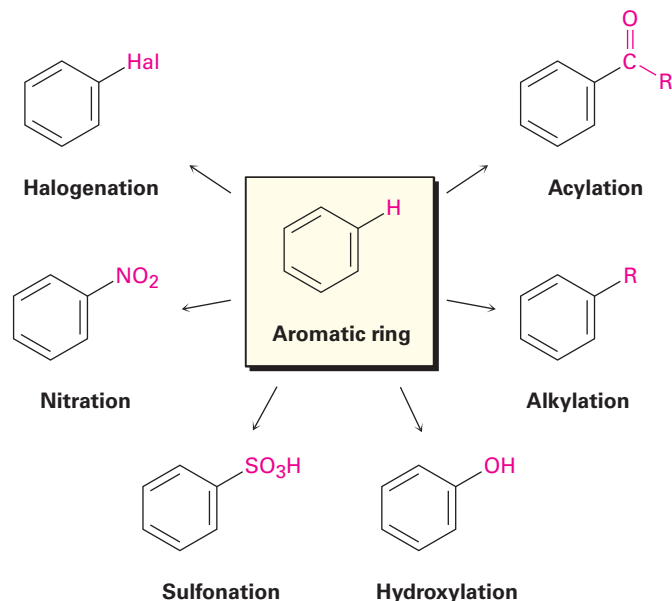
The most common reaction of aromatic compounds is **electrophilic aromatic substitution**, a process in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens:



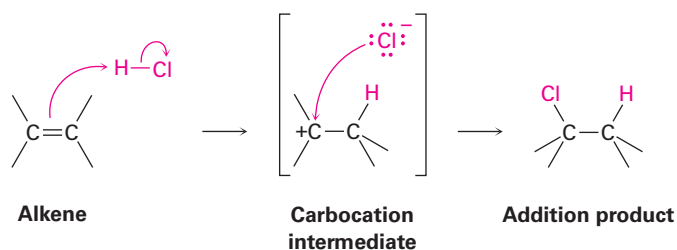
The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.

Many different substituents can be introduced onto an aromatic ring through electrophilic substitution reactions. To list some possibilities, an aromatic ring can be substituted by a halogen ($-Cl$, $-Br$, $-I$), a nitro group ($-NO_2$), a sulfonic acid group ($-SO_3H$), a hydroxyl group ($-OH$), an alkyl group ($-R$),

or an acyl group ($-\text{COR}$). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.

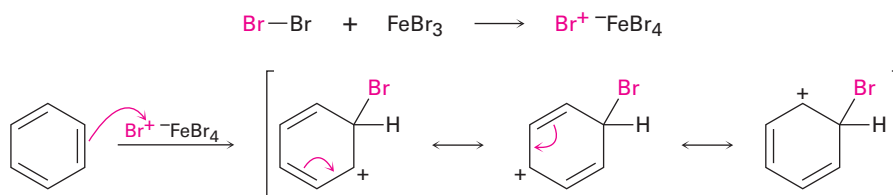


Before seeing how electrophilic aromatic substitutions occur, let's briefly recall what we said in Chapter 6 about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the π electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl^- ion to yield the addition product.



An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes are. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as FeBr_3 is needed. The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give an $\text{FeBr}_4^- \text{Br}^+$ species that reacts as if it were Br^+ . The polarized Br_2 molecule then reacts with the nucleophilic benzene ring to yield

a nonaromatic carbocation intermediate that is doubly allylic (Section 8-12) and has three resonance forms:



Although more stable than a typical alkyl carbocation because of resonance, the intermediate in electrophilic aromatic substitution is nevertheless much less stable than the starting benzene ring itself, with its 150 kJ/mol (36 kcal/mol) of aromatic stability. Thus, the reaction of an electrophile with a benzene ring is endergonic, has a substantial activation energy, and is rather slow.

Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon to give a substitution product. The net effect is the substitution of H^+ by Br^+ by the overall mechanism shown in **FIGURE 9.9**.

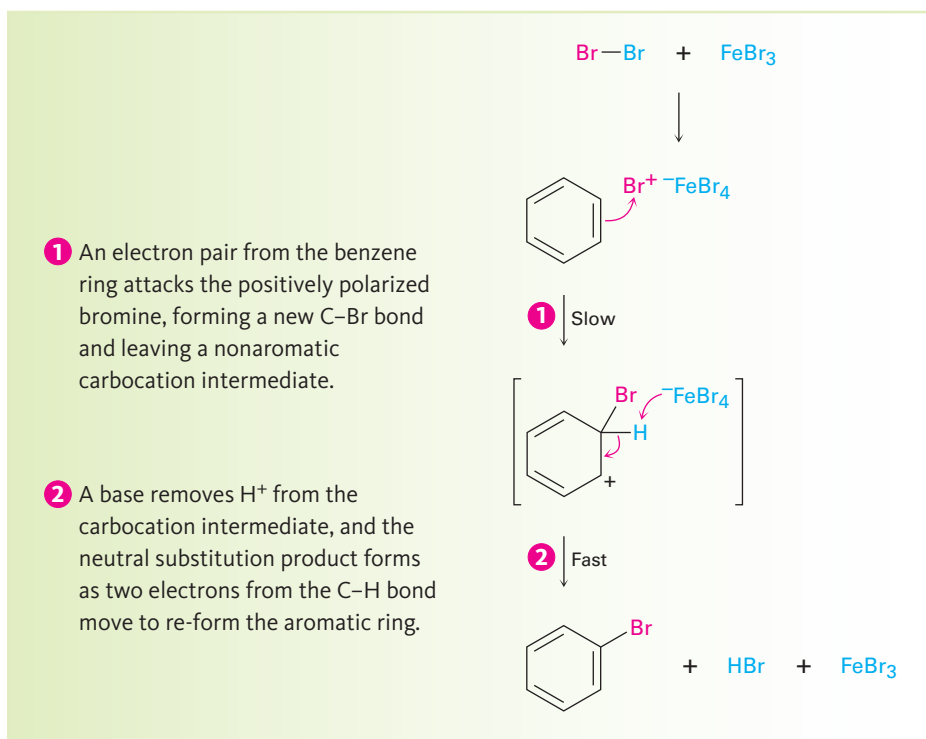
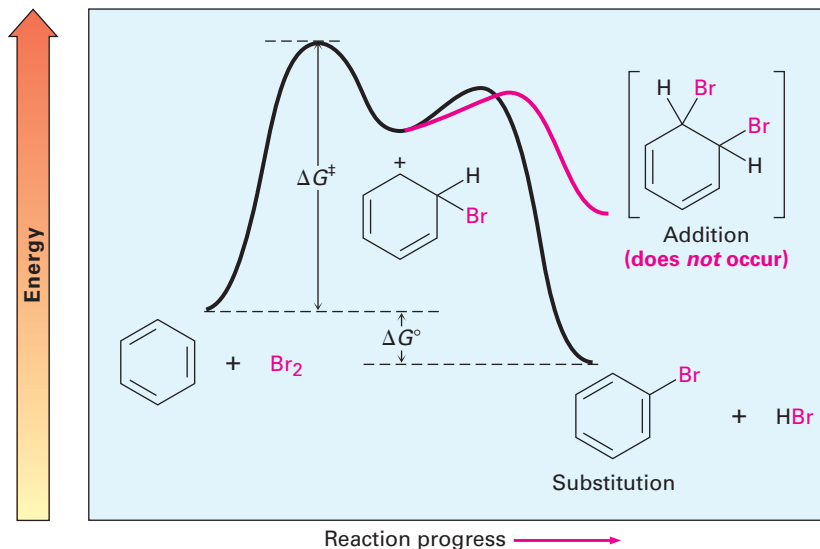


FIGURE 9.9 Mechanism of the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.

Why does the reaction of Br_2 with benzene take a different course than its reaction with an alkene? The answer is straightforward. If *addition* occurred, the 150 kJ/mol stabilization energy of the aromatic ring would be lost and the

overall reaction would be endergonic. When *substitution* occurs, though, the stability of the aromatic ring is retained and the reaction is exergonic. An energy diagram for the overall process is shown in **FIGURE 9.10**.

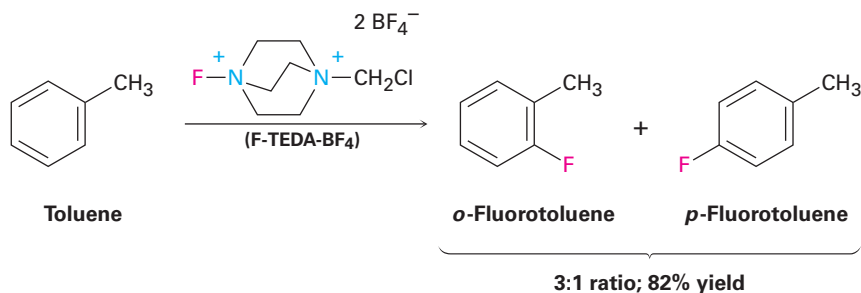
FIGURE 9.10 Energy diagram for the electrophilic bromination of benzene. The overall process is exergonic because the stability of the aromatic ring is retained.



There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

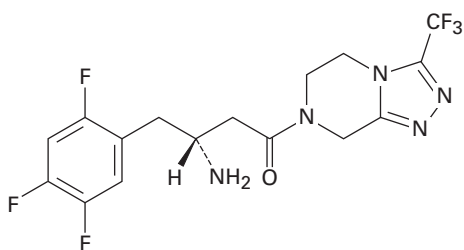
Aromatic Halogenation

Chlorine, bromine, and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of monofluoroaromatic products are obtained by direct fluorination. Instead, other sources of "F⁺" are used in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF₄ and is sold under the name Selectfluor.

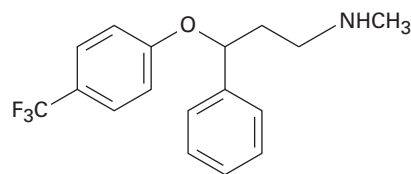


Many fluorine-containing aromatic compounds are particularly valuable as pharmaceutical agents. Approximately 80 pharmaceuticals now on the market, including 18 of the top 100 sellers, contain fluorine. Sitagliptin (Januvia),

used to treat type 2 diabetes, and fluoxetine (Prozac), an antidepressant, are examples.

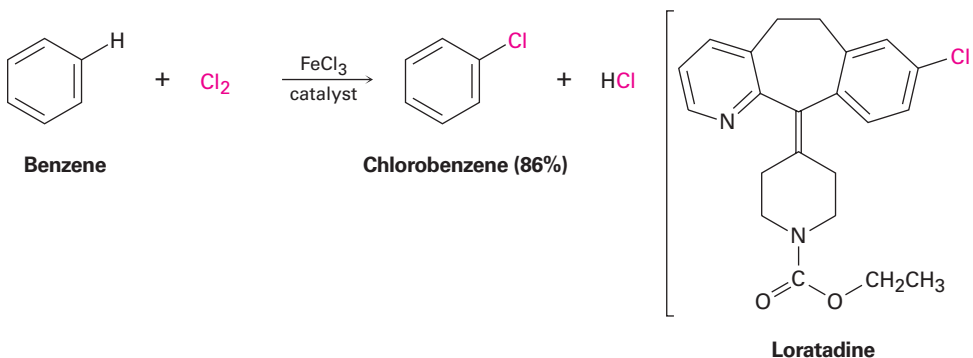


**Sitagliptin
(Januvia)**

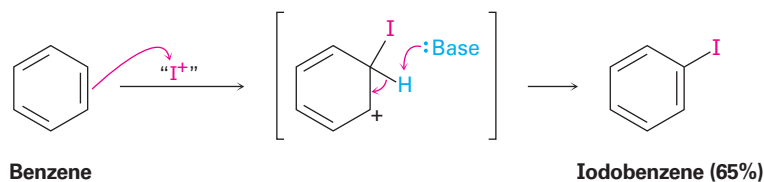


**Fluoxetine
(Prozac)**

Aromatic rings react with Cl_2 in the presence of FeCl_3 catalyst to yield chlorobenzenes, just as they react with Br_2 and FeBr_3 . This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the anti-allergy medication loratadine, marketed as Claritin.

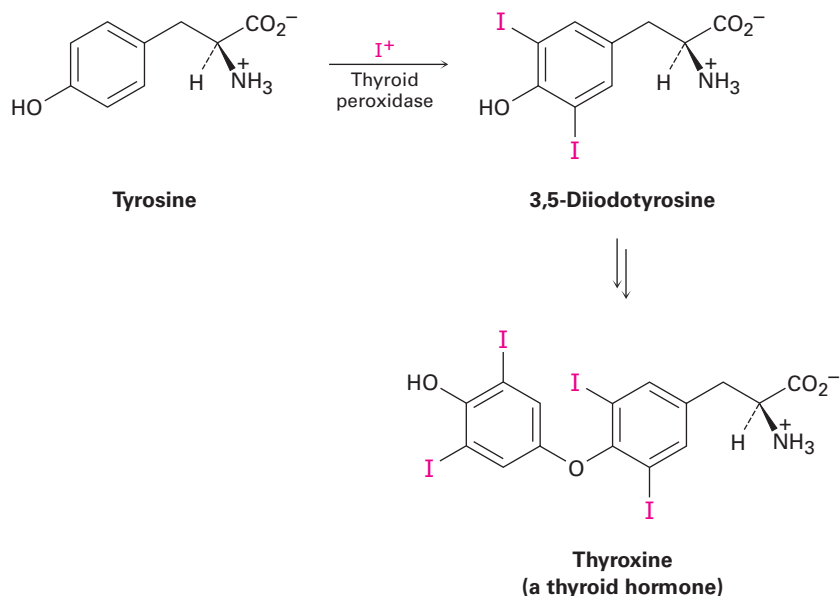


Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as CuCl_2 must be added to the reaction. These substances accelerate the iodination reaction by oxidizing I_2 to a more powerful electrophilic species such as hypoiodous acid HOI or I_2CuCl_2 that reacts as if it were I^+ . The aromatic ring then reacts with I^+ in the typical way, yielding a substitution product.



Electrophilic aromatic halogenations also occur in the biosynthesis of numerous naturally occurring molecules, particularly those produced by

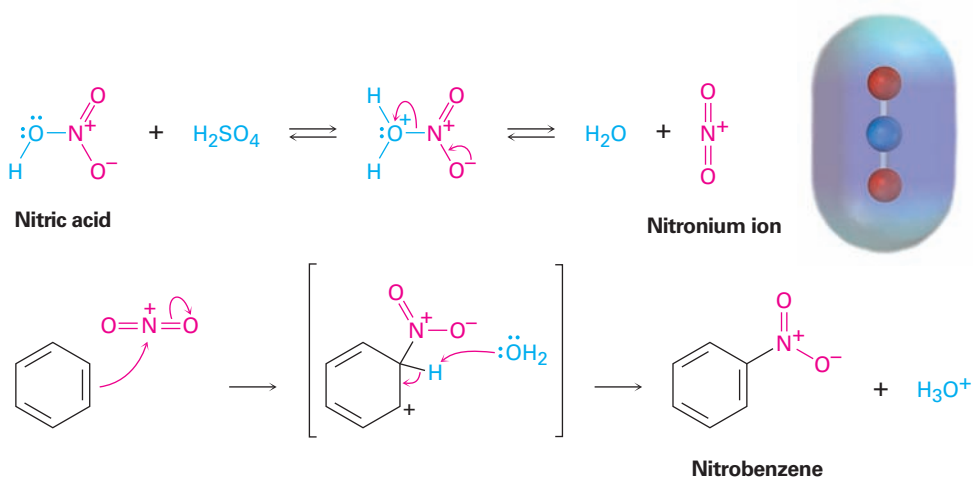
marine organisms. In humans, the best-known example occurs in the thyroid gland during the biosynthesis of thyroxine, a thyroid hormone involved in regulating growth and metabolism. The amino acid tyrosine is first iodinated by thyroid peroxidase, and two of the iodinated tyrosine molecules then couple. The electrophilic iodinating agent is an I^+ species, perhaps HIO .



Aromatic Nitration

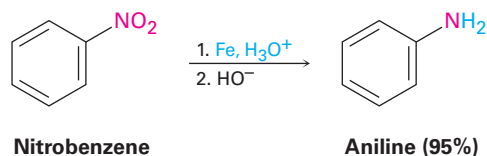
Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2^+ , which is generated from HNO_3 by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+ from this intermediate gives the neutral substitution product, nitrobenzene (FIGURE 9.11).

FIGURE 9.11 Mechanism of electrophilic nitration of an aromatic ring. An electrostatic potential map of the reactive electrophile NO_2^+ shows that the nitrogen atom is most positive.



Nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be

reduced by reagents such as iron, tin, or SnCl_2 to yield an *arylamine*, ArNH_2 , such as aniline. Attachment of an amino group to an aromatic ring by the two-step nitration–reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents.



Aromatic Sulfonation

Aromatic rings can be sulfonated by reaction with fuming sulfuric acid, a mixture of H_2SO_4 and SO_3 . The reactive electrophile is either HSO_3^+ or neutral SO_3 , depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration (FIGURE 9.12).

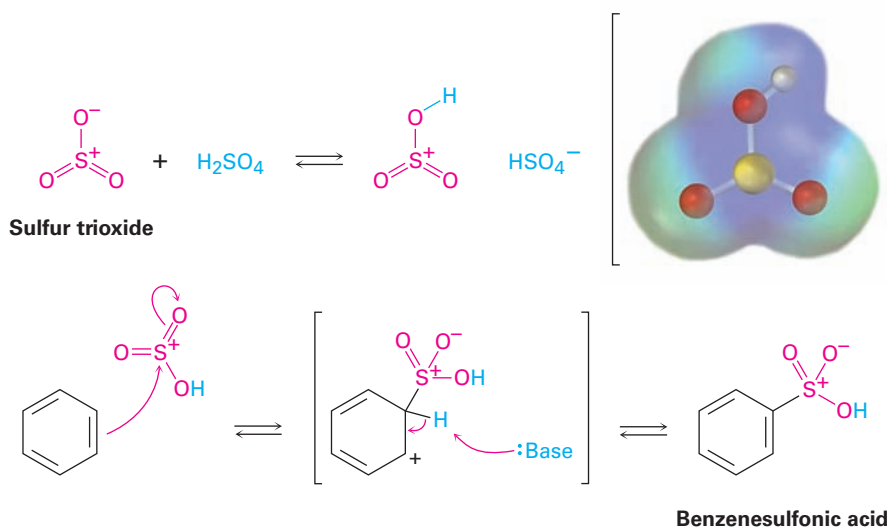
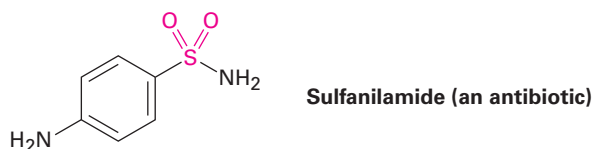


FIGURE 9.12 Mechanism of electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile HSO_2^+ shows that sulfur and hydrogen are the most positive atoms.

Like nitration, aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. Although largely replaced today by more effective agents, sulfa drugs are still used in the treatment of meningitis and urinary tract infections. These drugs are prepared commercially by a process that involves aromatic sulfonation as the key step.



Aromatic Hydroxylation

Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a *phenol*) is difficult and rarely done in the laboratory, but it occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4-dihydroxyphenylacetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular

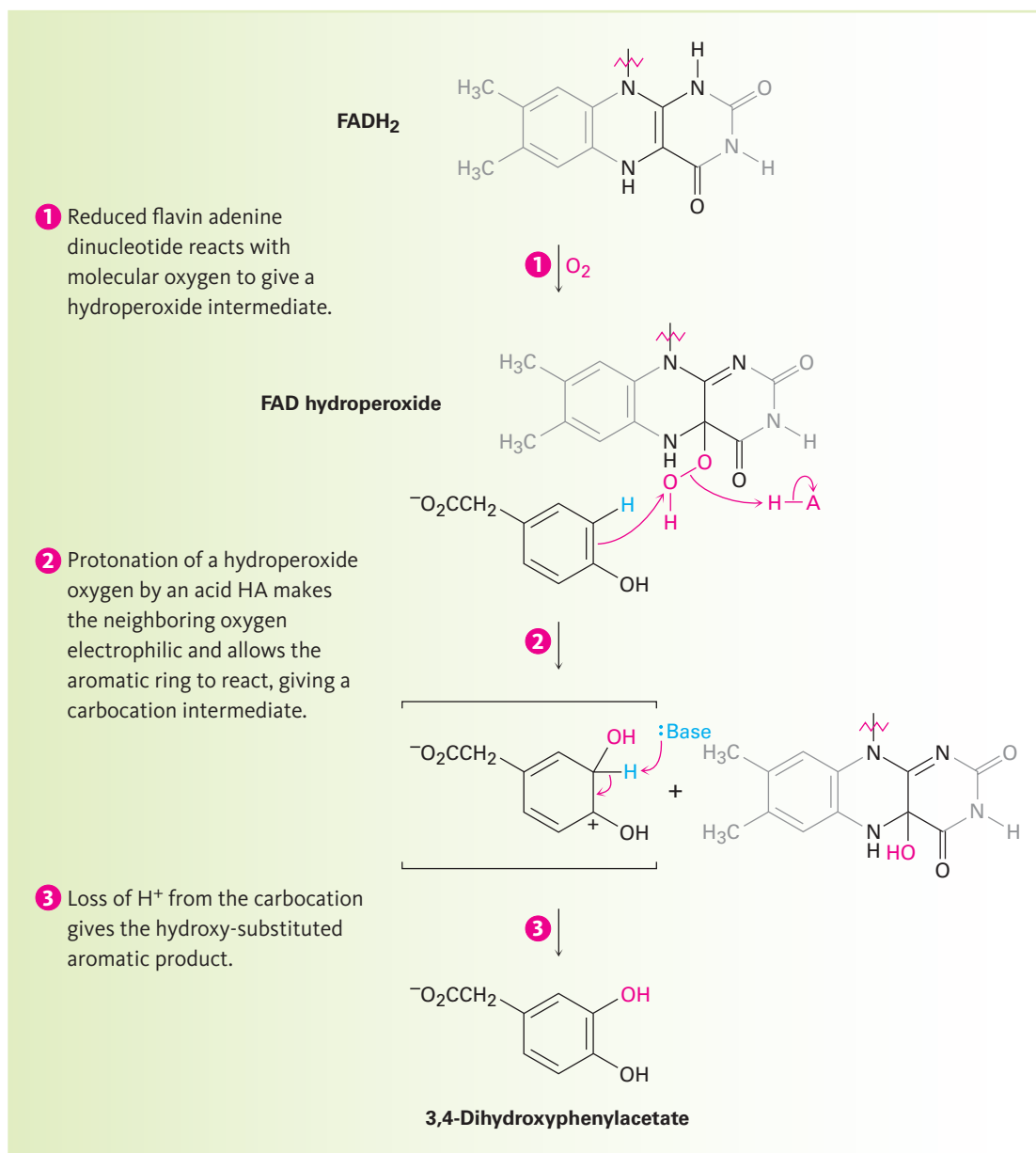
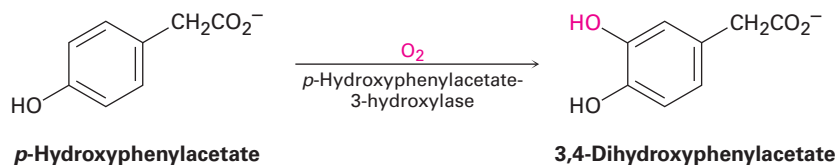


FIGURE 9.13 Mechanism of electrophilic hydroxylation of *p*-hydroxyphenylacetate by reaction with FAD hydroperoxide. The hydroxylating species is an “OH⁺ equivalent” that arises by protonation of FAD hydroperoxide, RO–OH + H⁺ → ROH + OH⁺.

oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated FADH₂.



By analogy with other electrophilic aromatic substitutions, you might expect that an electrophilic oxygen species acting as an “OH⁺ equivalent” is needed for the hydroxylation reaction. That is just what happens, with the electrophilic oxygen arising by protonation of FAD hydroperoxide, RO–OH (FIGURE 9.13); that is, RO–OH + H⁺ → ROH + OH⁺. The FAD hydroperoxide is itself formed by reaction of FADH₂ with O₂.

PROBLEM 9.11

Propose a mechanism for the electrophilic fluorination of benzene with F-TEDA-BF₄.

PROBLEM 9.12

Monobromination of toluene gives a mixture of three bromotoluene products. Draw and name them.

PROBLEM 9.13

How many products might be formed on chlorination of *o*-xylene (*o*-dimethylbenzene), *m*-xylene, and *p*-xylene?

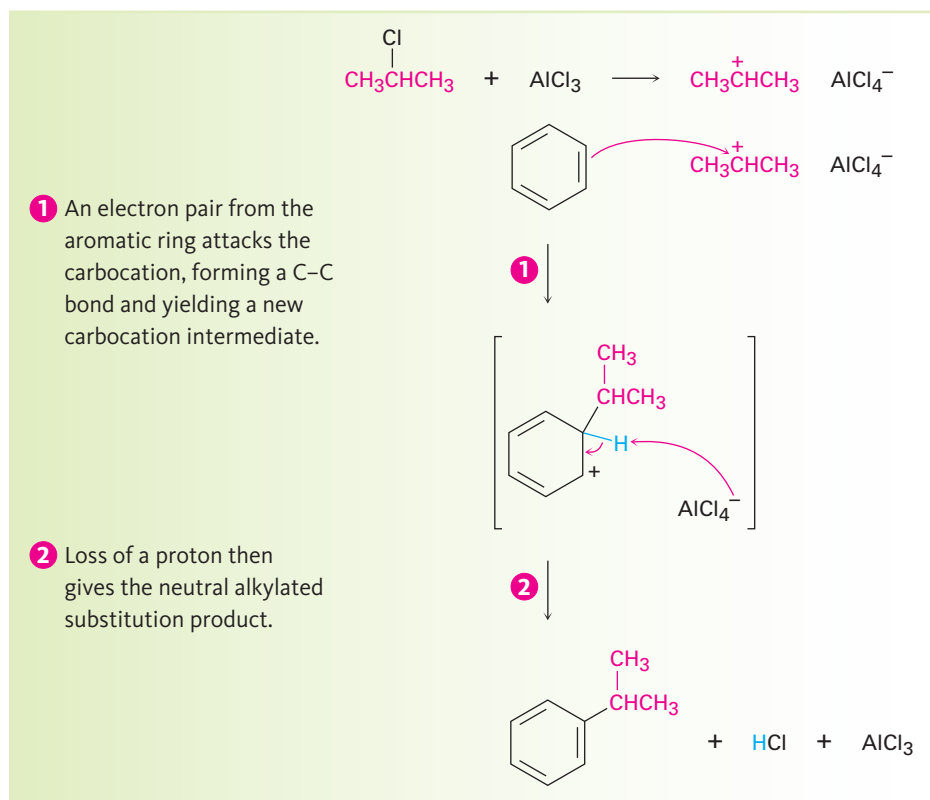
9-7 Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction

Among the most useful electrophilic aromatic substitution reactions in the laboratory is **alkylation**—the introduction of an alkyl group onto the benzene ring. Called the **Friedel–Crafts reaction** after its discoverers, the reaction is carried out by treating the aromatic compound with an alkyl chloride, RCl, in the presence of AlCl₃ to generate a carbocation electrophile, R⁺. Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate in much the same way that FeBr₃ catalyzes aromatic brominations by polarizing Br₂ (Section 9-6). Loss of H⁺ then completes the reaction (FIGURE 9.14).

Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only *alkyl* halides can be used. Aromatic (aryl) halides and vinylic halides don’t react because aryl and vinylic carbocations are too high

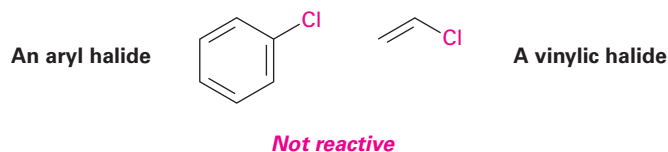
FIGURE 9.14 Mechanism of the Friedel–Crafts alkylation reaction of benzene with 2-chloropropane.

The electrophile is a carbocation, generated by AlCl_3 -assisted dissociation of an alkyl halide.



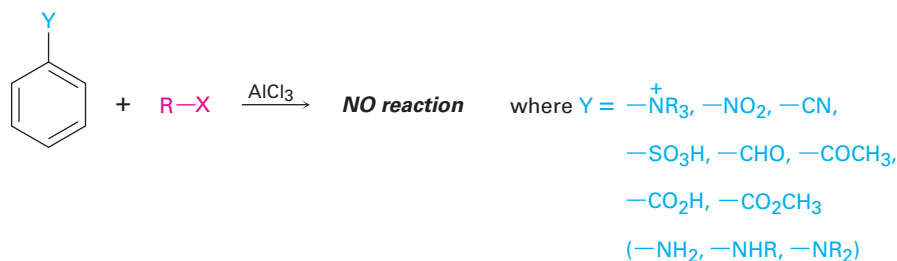
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in energy to form under Friedel–Crafts conditions. (The word *vinyllic* means that a substituent is attached directly to a double bond, $\text{C}=\text{C}-\text{Cl}$.)



Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl ($\text{C}=\text{O}$) or by an amino group ($-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$). We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's subsequent reactivity toward further electrophilic substitution. Rings that contain any of the substituents listed in **FIGURE 9.15** do not undergo Friedel–Crafts alkylation.

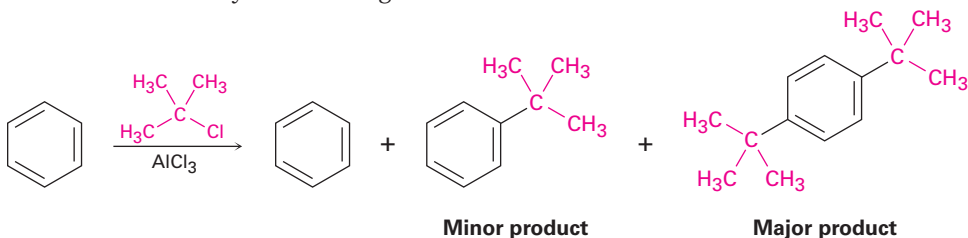
FIGURE 9.15 Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.



A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on

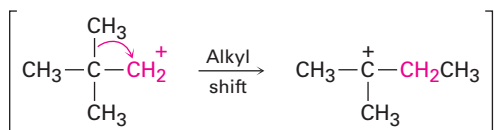
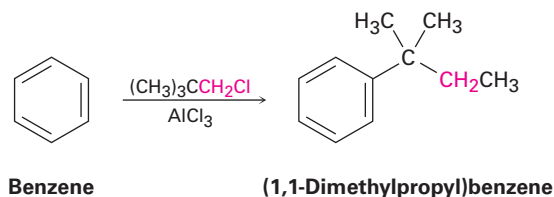
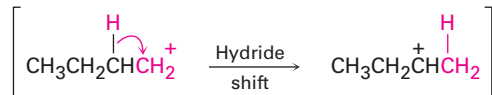
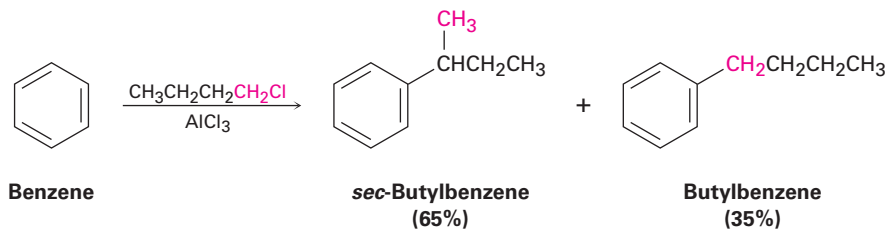
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the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation*. Reaction of benzene with 1 mol equivalent of 2-chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*-butylbenzene and unreacted benzene. A high yield of monoalkylation product is obtained only when a large excess of benzene is used.



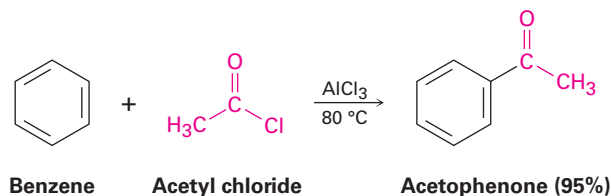
Yet a final limitation to the Friedel-Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2 : 1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

The carbocation rearrangements that accompany Friedel-Crafts reactions are like those that accompany electrophilic additions to alkenes (Section 7-10) and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with AlCl_3 rearranges to the more stable secondary butyl carbocation by shift of a hydrogen atom and its electron pair (a hydride ion, H^-) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2-dimethylpropane yields (1,1-dimethylpropyl)benzene. The initially formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.



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Just as an aromatic ring is alkylated by reaction with an alkyl chloride, it is **acylated** by reaction with a carboxylic acid chloride, RCOCl, in the presence of AlCl₃. That is, an **acyl group** (–COR; pronounced **a-sil**) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.



The mechanism of the Friedel–Crafts acylation reaction is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure 9.15 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acid chloride and AlCl₃ (FIGURE 9.16). As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

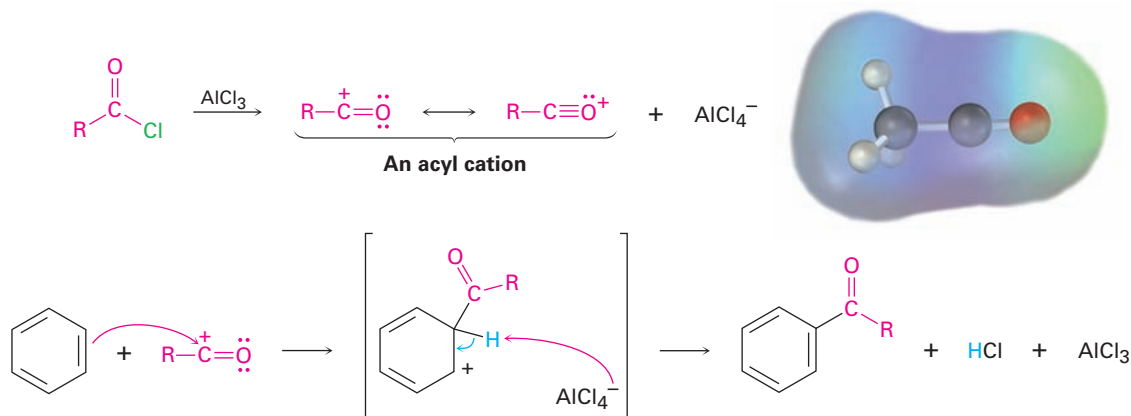
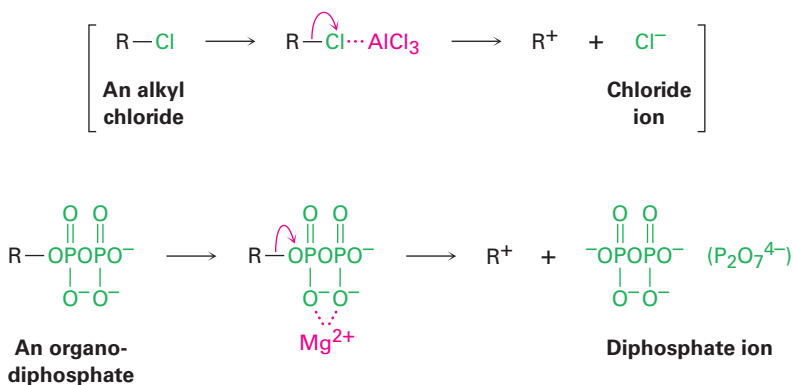


FIGURE 9.16 Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that **carbon is the most positive atom**.

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the nonacylated starting material. We'll account for this reactivity difference in the next section.

Aromatic alkylations occur in numerous biological pathways, although there is of course no AlCl₃ present in living systems to catalyze the reaction. Instead, the carbocation electrophile is typically formed by dissociation of an organodiphosphate. As we'll see on numerous occasions in future chapters, a diphosphate group is a common structural feature of many biological molecules. Among its functions is that it can be expelled as a stable diphosphate ion, much as chloride ion might be expelled from an alkyl chloride. To further strengthen the analogy, just as dissociation of an alkyl chloride is assisted by AlCl₃ in the Friedel–Crafts reaction, the dissociation of an organodiphosphate

in a biological reaction is typically assisted by complexation to a divalent metal cation such as Mg^{2+} to help neutralize charge.



An example of a biological Friedel-Crafts reaction occurs during the biosynthesis of phylloquinone, or vitamin K_1 , the human blood-clotting factor. Phylloquinone is formed by reaction of 1,4-dihydroxynaphthoic acid with phytyl diphosphate. Phytyl diphosphate first dissociates to a resonance-stabilized allylic carbocation, which then substitutes onto the aromatic ring in the typical way. Several further transformations lead to phylloquinone (FIGURE 9.17).

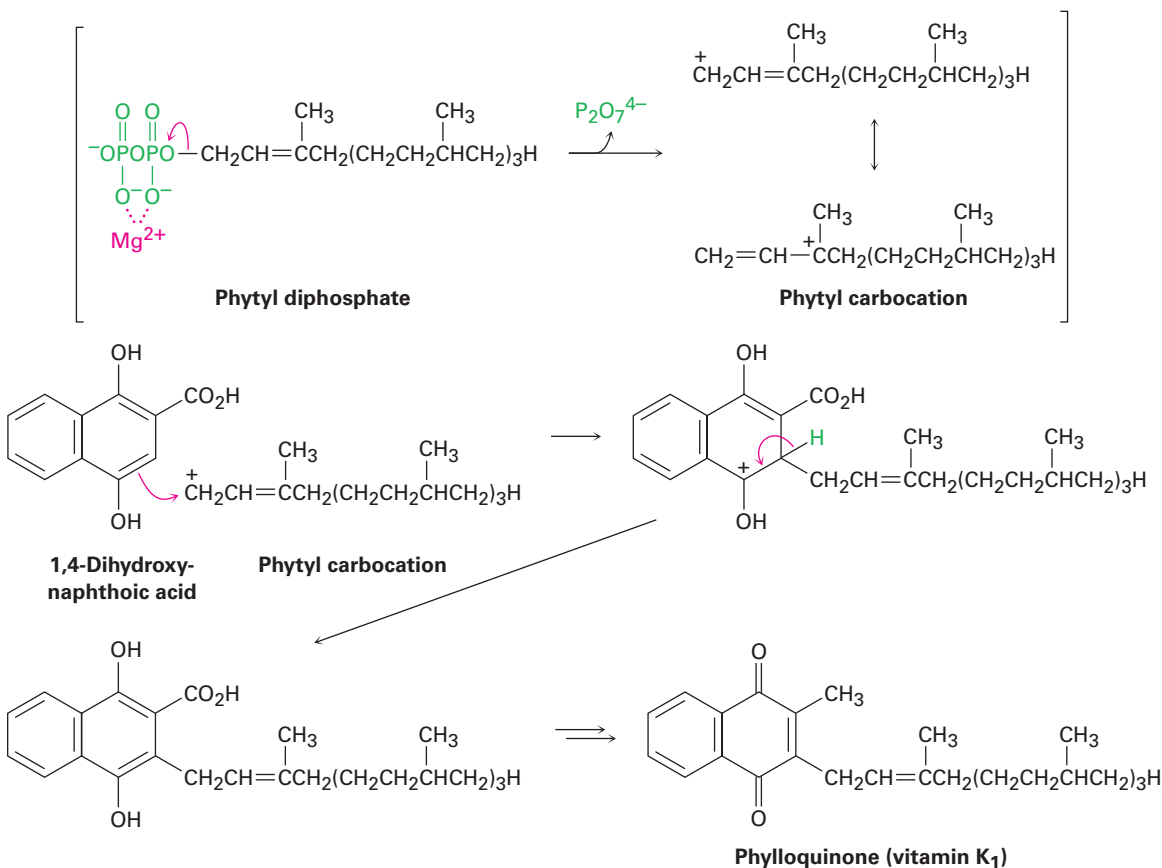


FIGURE 9.17 Biosynthesis of phylloquinone (vitamin K_1) from 1,4-dihydroxynaphthoic acid.

The key step that joins the 20-carbon phytyl side chain to the aromatic ring is a Friedel-Crafts-like electrophilic substitution with a diphosphate ion as the leaving group.

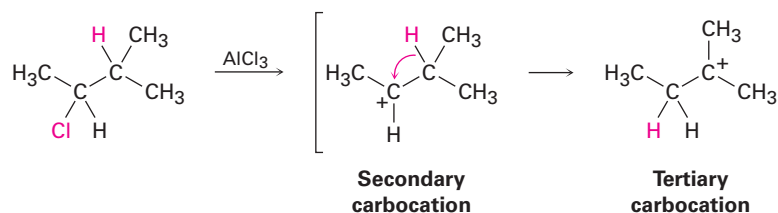
WORKED EXAMPLE 9.2

Predicting the Product of a Carbocation Rearrangement

The Friedel–Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of AlCl_3 occurs with a carbocation rearrangement. What is the structure of the product?

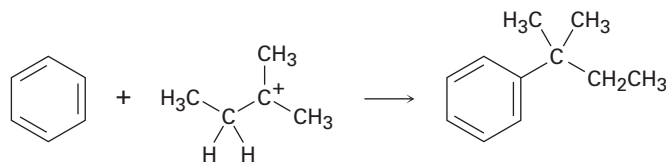
Strategy

A Friedel–Crafts reaction involves initial formation of a carbocation, which can rearrange by either a hydride shift or an alkyl shift to give a more stable carbocation. Draw the initial carbocation, assess its stability, and see if the shift of a hydride ion or an alkyl group from a neighboring carbon will result in increased stability. In the present instance, the initial carbocation is a secondary one that can rearrange to a more stable tertiary one by a hydride shift:



Use this more stable tertiary carbocation to complete the Friedel–Crafts reaction.

Solution



PROBLEM 9.14

Which of the following alkyl halides would you expect to undergo Friedel–Crafts reaction without rearrangement? Explain.

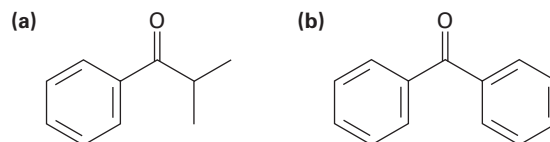
- (a) $\text{CH}_3\text{CH}_2\text{Cl}$ (b) $\text{CH}_3\text{CH}_2\text{CH}(\text{Cl})\text{CH}_3$ (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$
 (d) $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$ (e) Chlorocyclohexane

PROBLEM 9.15

What is the major product from the Friedel–Crafts reaction of benzene with 1-chloro-2-methylpropane in the presence of AlCl_3 ?

PROBLEM 9.16

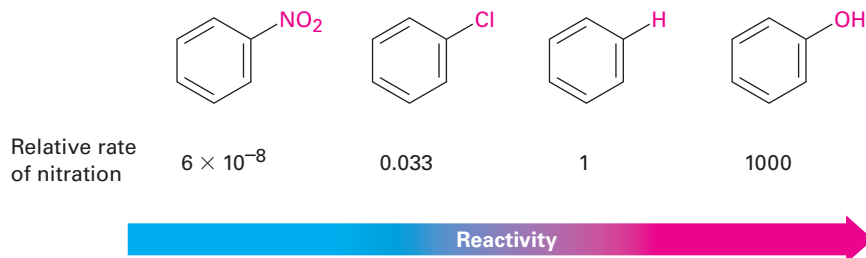
Identify the carboxylic acid chloride that might be used in a Friedel–Crafts acylation reaction to prepare each of the following acylbenzenes:



9-8 Substituent Effects in Electrophilic Substitutions

Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? A substituent already present on the ring has two effects:

- **Substituents affect the reactivity of an aromatic ring.** Some substituents activate a ring, making it more reactive than benzene, and some deactivate a ring, making it less reactive than benzene. In aromatic nitration, for instance, an $-\text{OH}$ substituent makes the ring 1000 times more reactive than benzene, while an $-\text{NO}_2$ substituent makes the ring more than 10 million times less reactive.



- **Substituents affect the orientation of a reaction.** The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent already present on the benzene ring determines the position of the second substitution. An $-\text{OH}$ group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as $-\text{CHO}$ directs substitution primarily toward the meta position. **TABLE 9.2** lists experimental results for the nitration of some substituted benzenes.

TABLE 9.2 Orientation of Nitration in Substituted Benzenes

	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				Ortho- and para-directing deactivators			
$-\text{N}(\text{CH}_3)_3$	2	87	11	$-\text{F}$	13	1	86
$-\text{NO}_2$	7	91	2	$-\text{Cl}$	35	1	64
$-\text{CO}_2\text{H}$	22	76	2	$-\text{Br}$	43	1	56
$-\text{CN}$	17	81	2	$-\text{I}$	45	1	54
$-\text{CO}_2\text{CH}_3$	28	66	6	Ortho- and para-directing activators			
$-\text{COCH}_3$	26	72	2	$-\text{CH}_3$	63	3	34
$-\text{CHO}$	19	72	9	$-\text{OH}$	50	0	50
				$-\text{NHCOCH}_3$	19	2	79

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Substituents can be classified into three groups, as shown in **FIGURE 9.18**: *meta-directing deactivators*, *ortho- and para-directing deactivators*, and *ortho- and para-directing activators*. There are no meta-directing activators. Note how the directing effect of a group correlates with its reactivity. All meta-directing groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

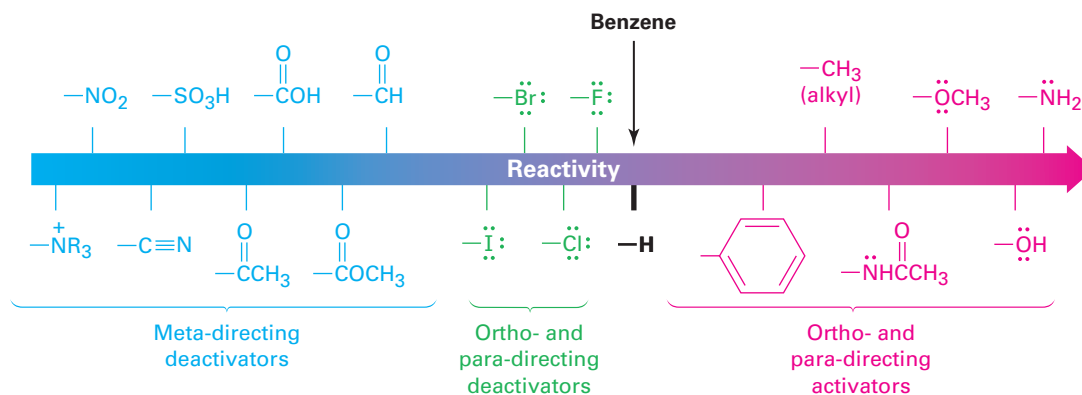
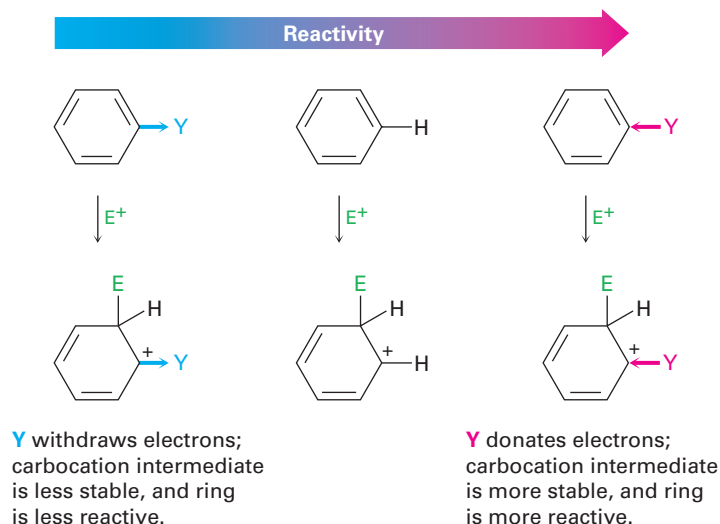


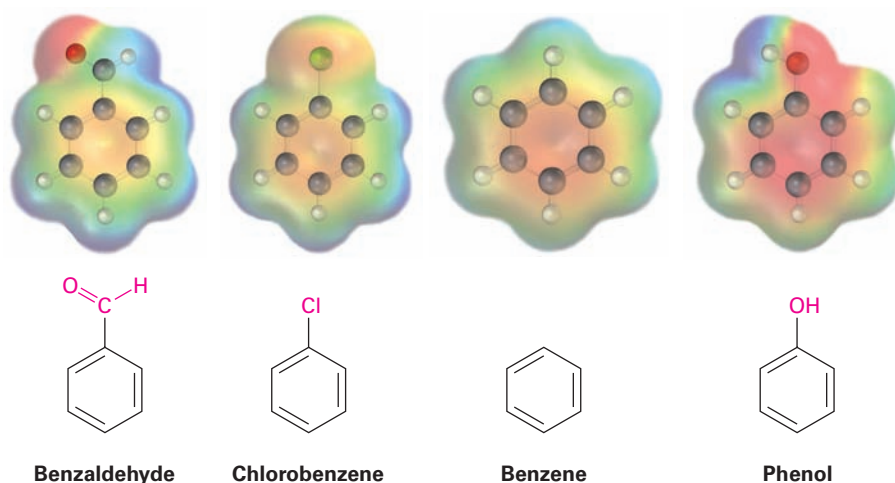
FIGURE 9.18 Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing.

Activating and Deactivating Effects

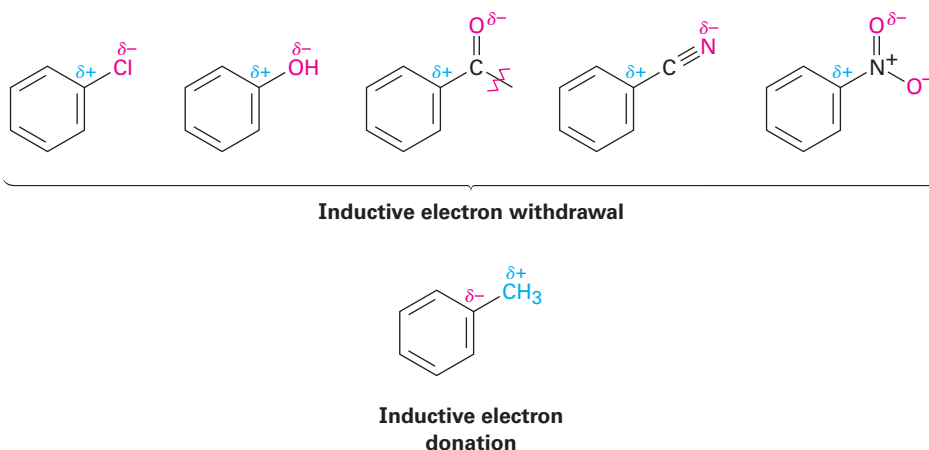
What makes a group either activating or deactivating? The common characteristic of all activating groups is that they *donate* electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they *withdraw* electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. The ring is more positive (yellow) when an electron-withdrawing group such as $-\text{CHO}$ or $-\text{Cl}$ is present and more negative (red) when an electron-donating group such as $-\text{OH}$ is present.

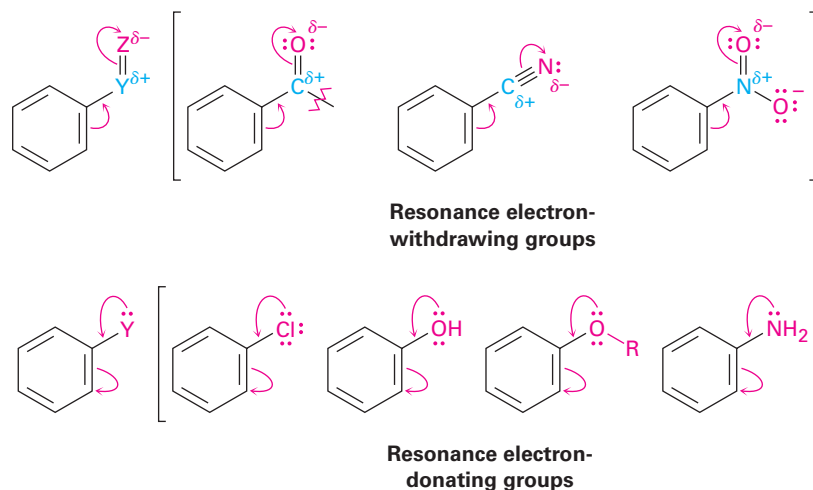


The withdrawal or donation of electrons by a substituent group is controlled by an interplay of inductive effects and resonance effects. Recall from Section 2-1 that an **inductive effect** is the withdrawal or donation of electrons through a σ bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the σ bond linking the substituent to a benzene ring. The effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes (Section 7-5) and carbocations (Section 7-8).



A **resonance effect** is the withdrawal or donation of electrons through a π bond due to the overlap of a p orbital on the substituent with a p orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The π electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electron-withdrawing resonance effect have the general structure $-Y=Z$, where the Z atom is more electronegative than Y.

Conversely, halogen, hydroxyl, alkoxy ($-OR$), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge in the ring. Substituents with an electron-donating resonance effect have the general structure $-\ddot{Y}$, where the Y atom has a lone pair of electrons available for donation to the ring.



One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxy, and amino substituents, for instance, have electron-*withdrawing* inductive effects because of the electronegativity of the $-X$, $-O$, or $-N$ atom bonded to the aromatic ring but have electron-*donating* resonance effects because of the lone-pair electrons on those $-X$, $-O$, or $-N$ atoms. When the two effects act in opposite directions, the stronger effect dominates. Thus, hydroxyl, alkoxy, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Halogens, however, are deactivators because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect.

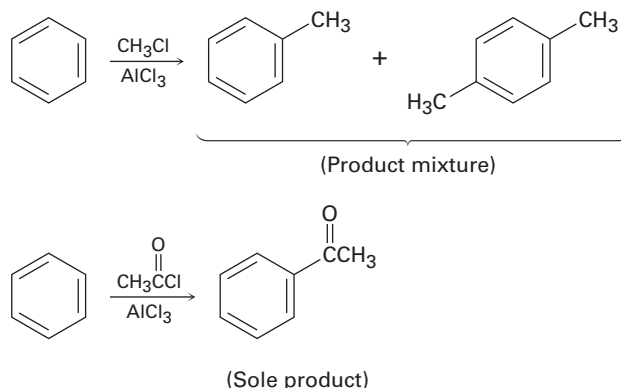
PROBLEM 9.17

Rank the compounds in each group in order of their reactivity to electrophilic substitution:

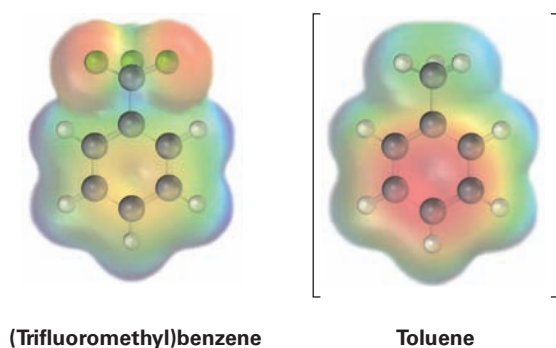
- Nitrobenzene, phenol, toluene, benzene
- Phenol, benzene, chlorobenzene, benzoic acid
- Benzene, bromobenzene, benzaldehyde, aniline

PROBLEM 9.18

Use Figure 9.18 to explain why Friedel–Crafts alkylations often give polysubstitution products but Friedel–Crafts acylations do not.

**PROBLEM 9.19**

An electrostatic potential map of (trifluoromethyl)benzene, $\text{C}_6\text{H}_5\text{CF}_3$, is shown. Would you expect (trifluoromethyl)benzene to be more reactive or less reactive than toluene toward electrophilic substitution? Explain.

**Orienting Effects: Ortho and Para Directors**

Inductive and resonance effects account not only for reactivity but also for the orientation of electrophilic aromatic substitutions. Take alkyl groups, for instance, which have an electron-donating inductive effect and are ortho and para directors. The results of toluene nitration are shown in **FIGURE 9.19**.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in Figure 9.19. Although all three intermediates are resonance-stabilized, the ortho and para intermediates are more stabilized than the meta intermediate. For both the ortho and para reactions, but not for the meta reaction, a resonance form places the positive charge directly on the methyl-substituted carbon, where it is in a tertiary position and can be stabilized by the electron-donating inductive effect of the methyl group. The ortho and para intermediates are thus lower in energy than the meta intermediate and form faster.

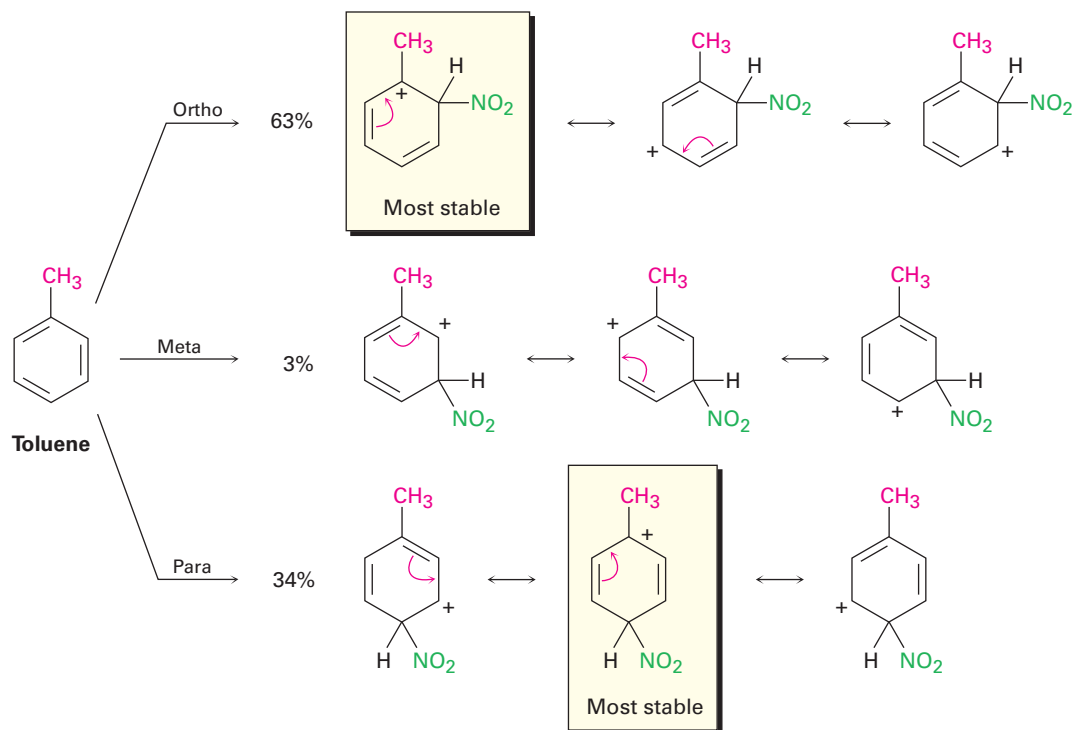


FIGURE 9.19 Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Halogen, hydroxyl, alkoxy, and amino groups are also ortho–para directors, but for a different reason than for alkyl groups. As described earlier in this section, halogen, hydroxyl, alkoxy, and amino groups have an electron-donating resonance effect because the atom attached to the ring—halogen, O, or N—has a lone pair of electrons. When phenol is nitrated, for instance, reaction with the electrophile NO_2^+ can occur either ortho, meta, or para to the $-\text{OH}$ group, giving the carbocation intermediates shown in **FIGURE 9.20**. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. The intermediate from meta reaction has no such stabilization.

Orienting Effects: Meta Directors

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the nitration of benzaldehyde, for instance (**FIGURE 9.21**). Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, but the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the $\text{C}=\text{O}$ group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

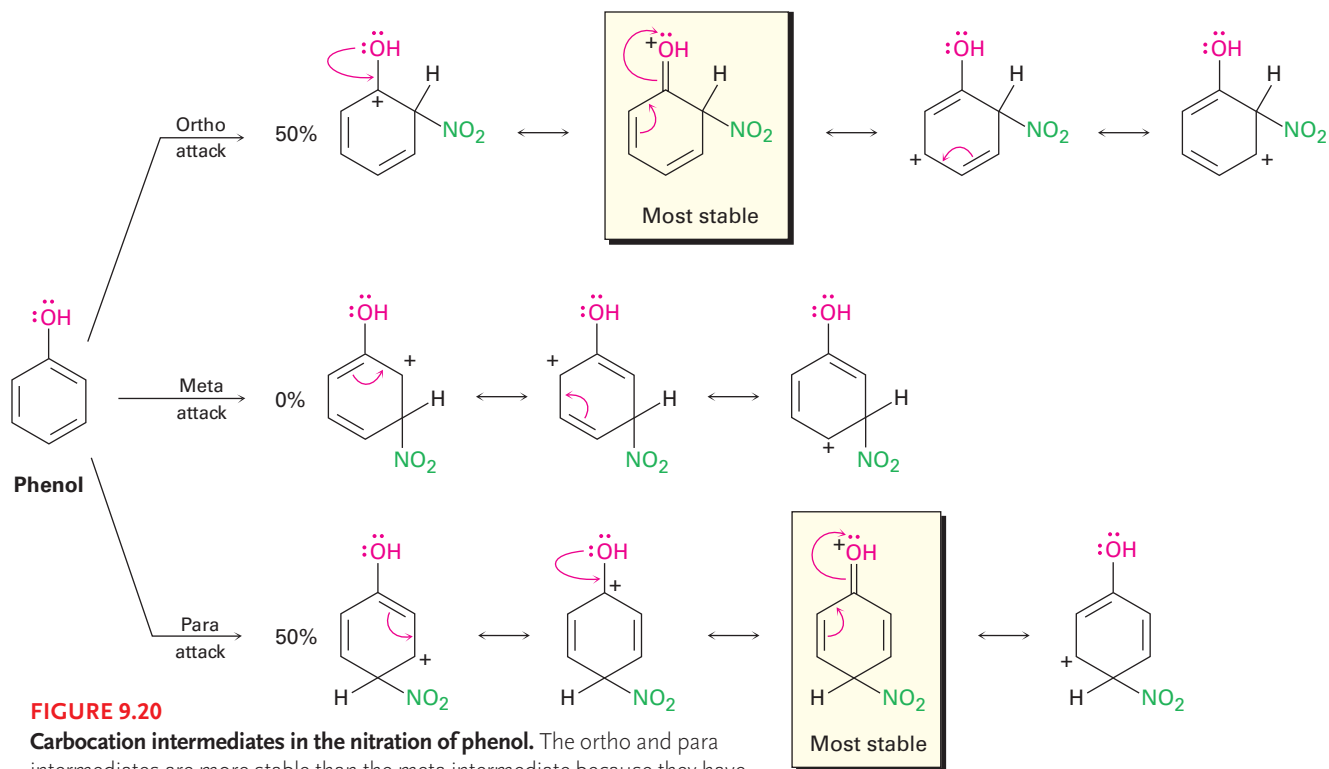


FIGURE 9.20

Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that involves electron donation from the oxygen atom.

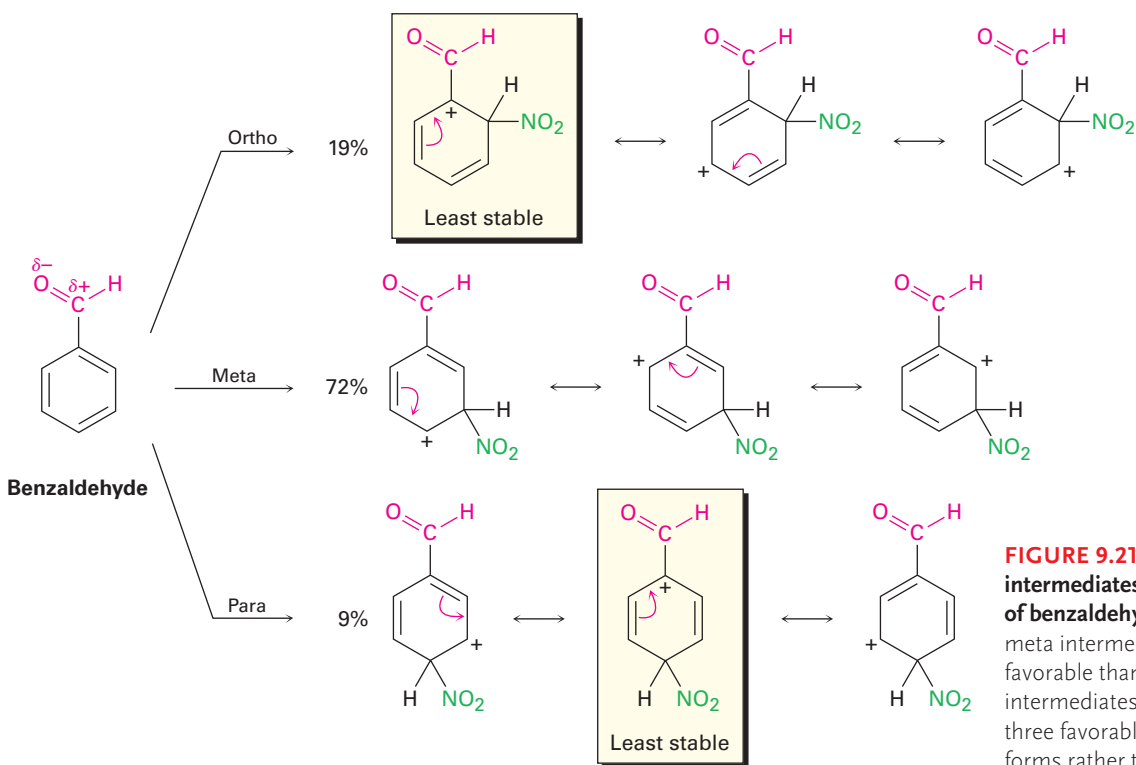


FIGURE 9.21 Carbocation intermediates in the nitration of benzaldehyde. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom ($\delta+$) directly attached to the ring will make one of the resonance forms of the ortho and para intermediates unfavorable and will thus act as a meta director.

A Summary of Substituent Effects in Electrophilic Aromatic Substitutions

A summary of the activating and directing effects of substituents in electrophilic aromatic substitution is shown in TABLE 9.3.

TABLE 9.3 Substituent Effects in Electrophilic Aromatic Substitutions

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
-CH ₃	Activating	Ortho, para	Weak donating	—
-OH, -NH ₂	Activating	Ortho, para	Weak withdrawing	Strong donating
-F, -Cl -Br, -I	Deactivating	Ortho, para	Strong withdrawing	Weak donating
-NO ₂ , -CN, -CHO, -CO ₂ R -COR, -CO ₂ H	Deactivating	Meta	Strong withdrawing	Strong withdrawing

WORKED EXAMPLE 9.3

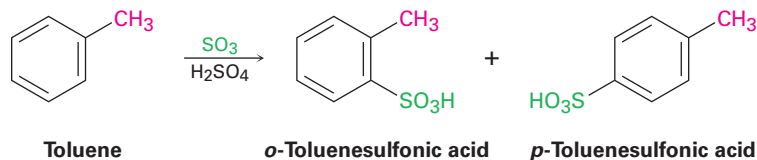
Predicting the Product of an Electrophilic Aromatic Substitution Reaction

Predict the major product of the sulfonation of toluene.

Strategy

Identify the substituent present on the ring, and decide whether it is ortho- and para-directing or meta-directing. According to Figure 9.18, an alkyl substituent is ortho- and para-directing, so sulfonation of toluene will give primarily a mixture of *o*-toluenesulfonic acid and *p*-toluenesulfonic acid.

Solution



PROBLEM 9.20

Predict the major products of the following reactions:

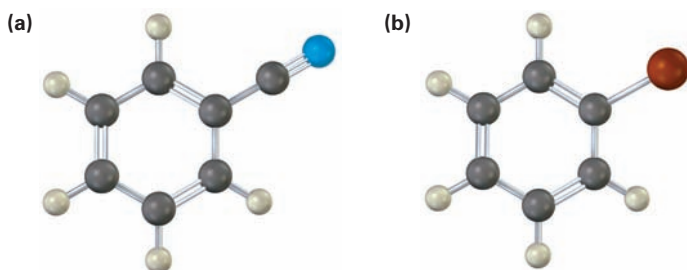
- Nitration of methyl benzoate, C₆H₅CO₂CH₃
- Bromination of nitrobenzene
- Chlorination of phenol
- Bromination of aniline

PROBLEM 9.21

Write resonance structures for *o*-, *m*-, and *p*- intermediates in the nitration of chlorobenzene to show the electron-donating resonance effect of the chloro group.

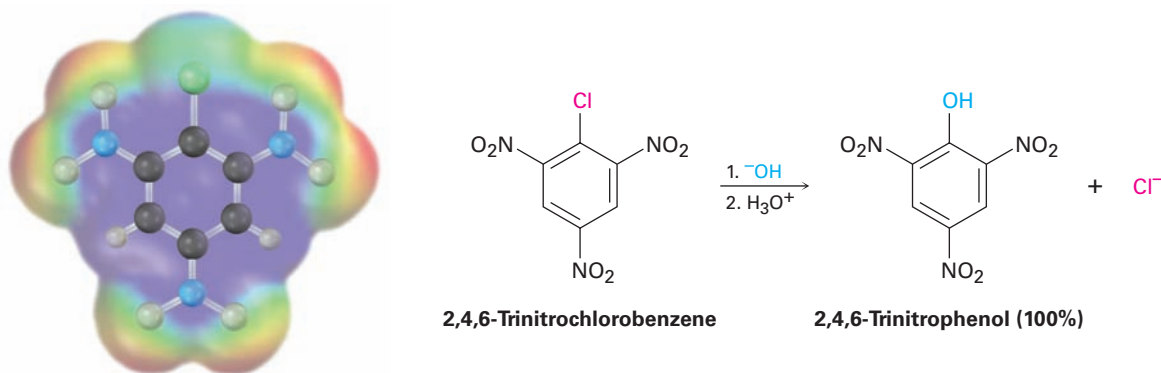
PROBLEM 9.22

Predict the major product you would expect from reaction of each of the following substances with Cl_2 and FeCl_3 (blue = N, reddish brown = Br):

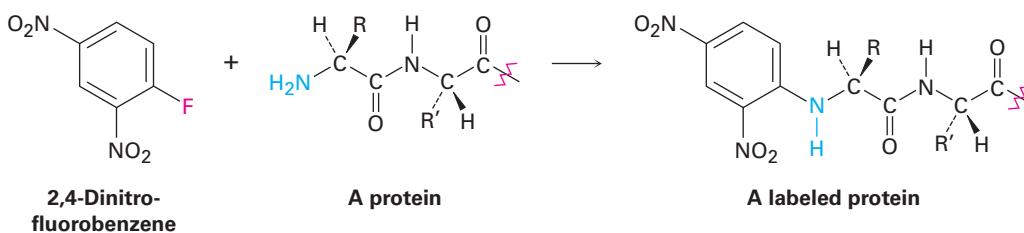


9-9 Nucleophilic Aromatic Substitution

Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. The nucleophile OH^- has substituted for Cl^- .



Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as Sanger's reagent, to attach a "label" to the terminal NH_2 group of the amino acid at one end of the protein chain.



Nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in **FIGURE 9.22**. The nucleophile first adds to the electron-deficient aryl halide, forming a resonance-stabilized negatively charged intermediate called a Meisenheimer complex after its discoverer. Halide ion is then eliminated in the second step.

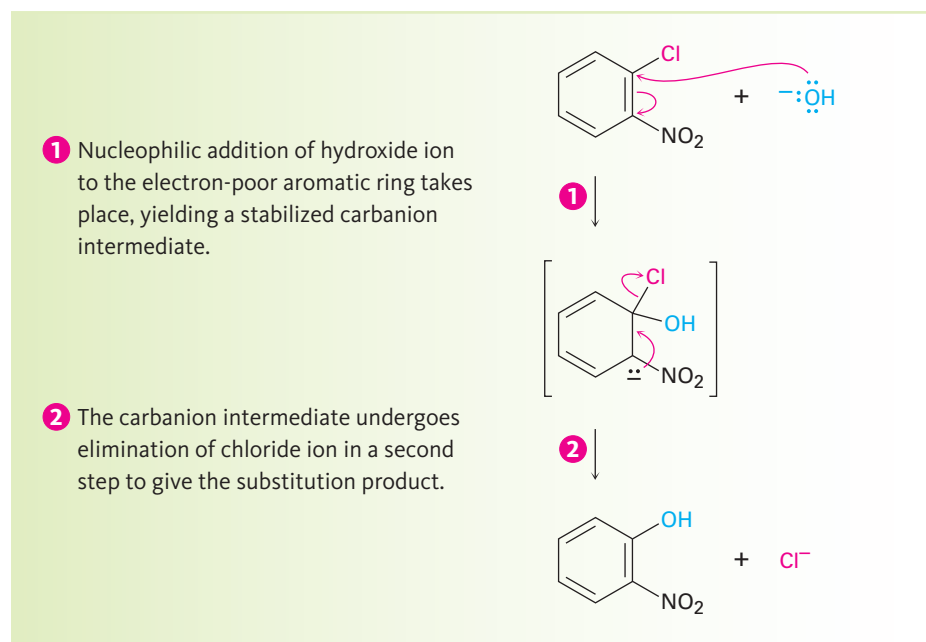


FIGURE 9.22 Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance-stabilized carbanion intermediate.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance (**FIGURE 9.23**). Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion to yield substitution products, but *m*-chloronitrobenzene is inert to OH^- .

Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that *deactivate* rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) *activate* them for nucleophilic substitution. What's more, these groups are meta directors in electrophilic substitution but are ortho-para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a halide ion.

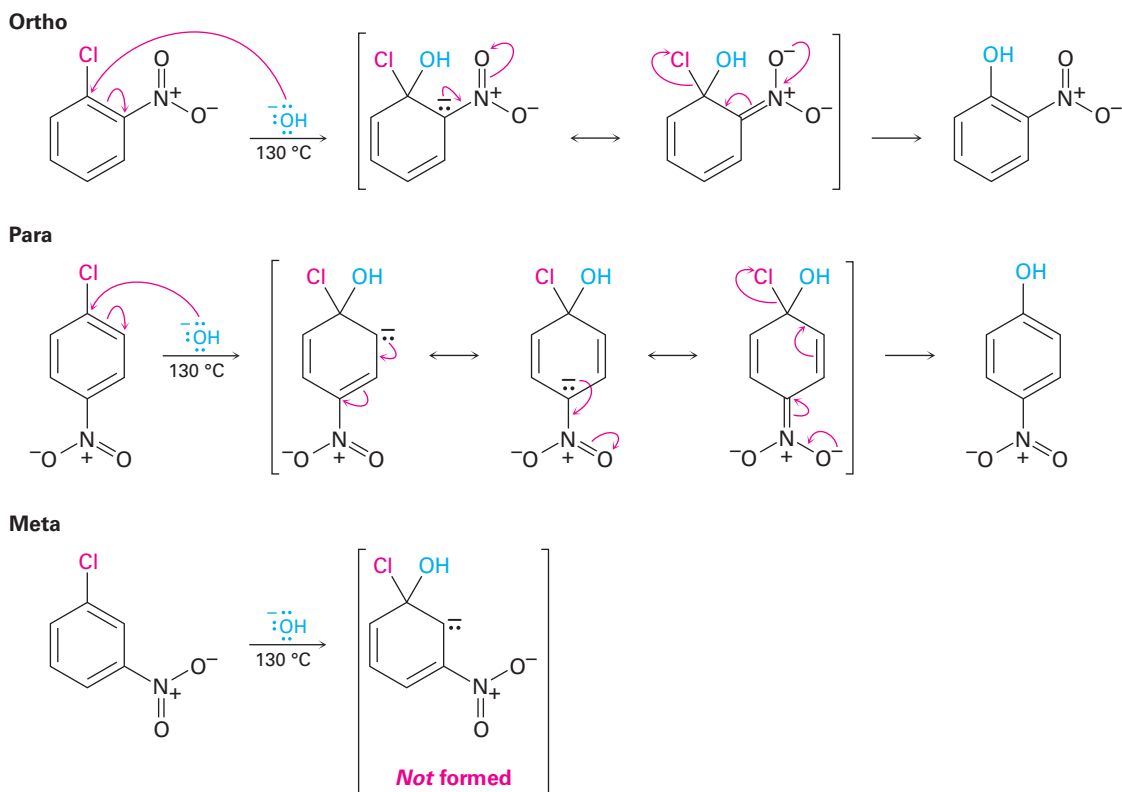
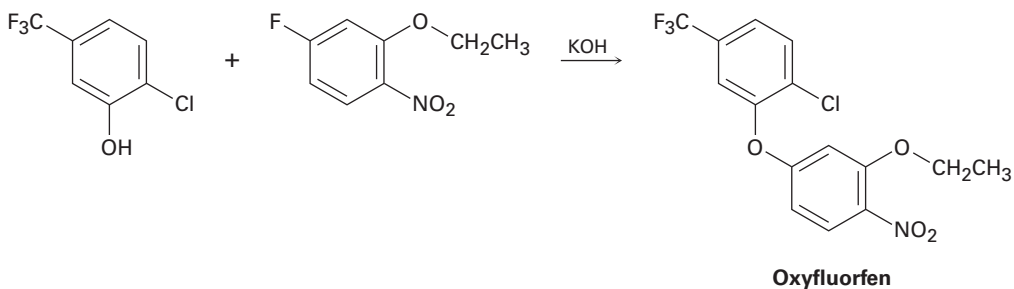


FIGURE 9.23 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

PROBLEM 9.23

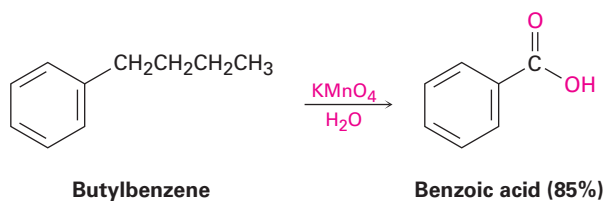
The herbicide oxyfluorfen can be prepared by reaction between a phenol and an aryl fluoride. Propose a mechanism.



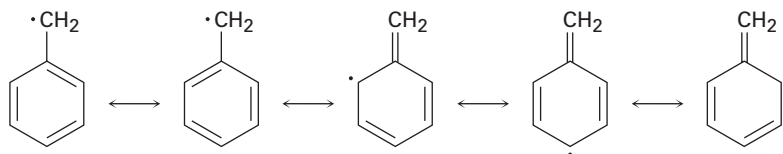
9-10 Oxidation and Reduction of Aromatic Compounds

Oxidation of Alkylbenzenes

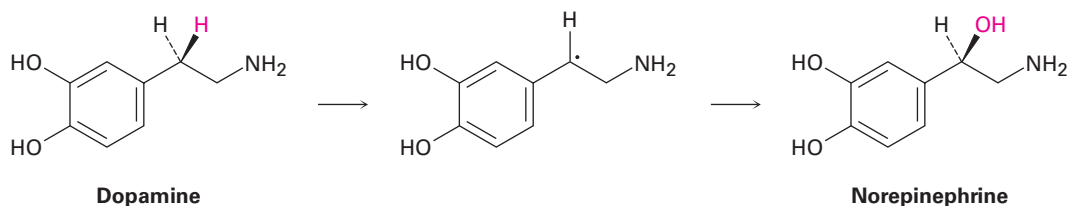
Despite its unsaturation, the benzene ring is inert to oxidizing agents such as KMnO_4 , *m*-chloroperoxybenzoic acid, and OsO_4 , reagents that react readily with alkene double bonds (Sections 8-6–8-8). It turns out, however, that the presence of the aromatic ring has a dramatic effect on alkyl substituents. Alkyl substituents on the aromatic ring react readily with common laboratory oxidizing agents such as aqueous KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ and are converted into carboxyl groups, $-\text{CO}_2\text{H}$. The net effect is conversion of an alkylbenzene into a benzoic acid, $\text{Ar-R} \rightarrow \text{Ar-CO}_2\text{H}$. Butylbenzene is oxidized by aqueous KMnO_4 to give benzoic acid, for instance.



The mechanism of side-chain oxidation is complex and involves reaction of a C–H bond at the position next to the aromatic ring (the **benzylic** position) to form an intermediate radical. Benzylic radicals are stabilized by resonance and thus form more readily than typical alkyl radicals. If the alkylbenzene has no benzylic C–H bonds, however, as in *tert*-butylbenzene, it is inert to oxidation.

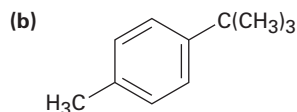
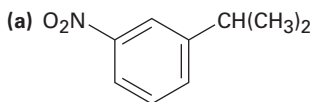


Analogous oxidations occur in various biosynthetic pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine β -monooxygenase and occurs by a radical mechanism. A copper–oxygen species in the enzyme first abstracts the *pro-R* benzylic hydrogen to give a radical, and a hydroxyl is then transferred from copper to carbon.

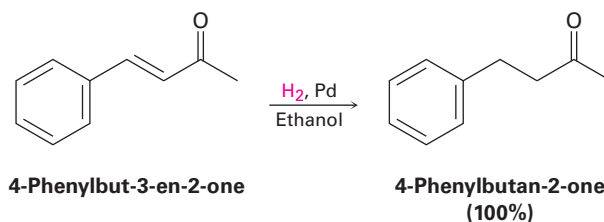


PROBLEM 9.24

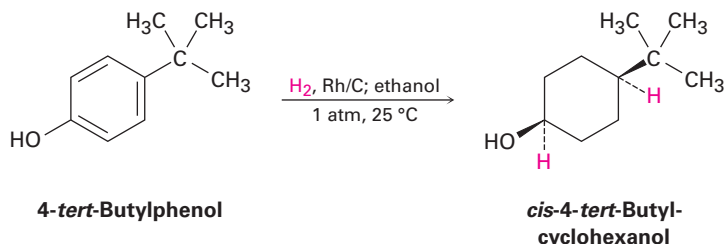
What aromatic products would you obtain from the KMnO_4 oxidation of the following substances?

**Hydrogenation of Aromatic Rings**

Just as aromatic rings are generally inert to oxidation, they're also inert to catalytic hydrogenation under conditions that reduce typical alkene double bonds. As a result, it's possible to reduce an alkene double bond selectively in the presence of an aromatic ring. For example, 4-phenylbut-3-en-2-one is reduced to 4-phenylbutan-2-one using a palladium catalyst at room temperature and atmospheric pressure. Neither the benzene ring nor the ketone carbonyl group is affected.

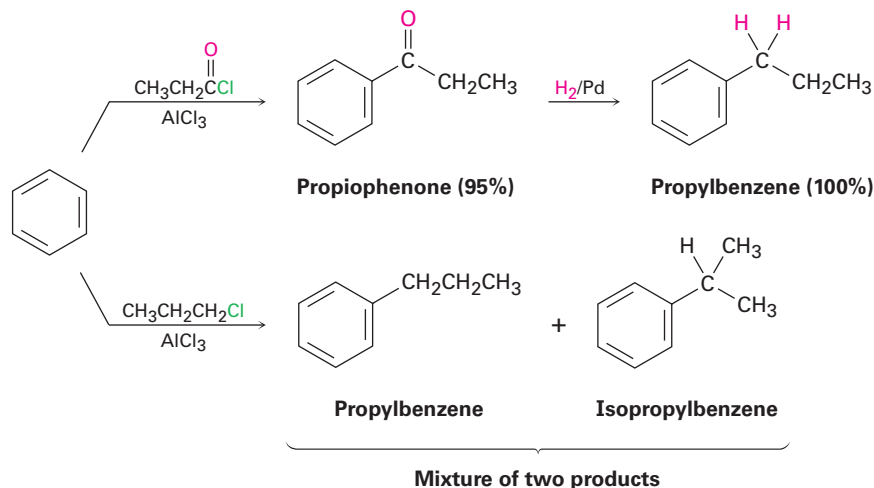


To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at several hundred atmospheres pressure or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For instance, 4-*tert*-butylphenol gives 4-*tert*-butylcyclohexanol.

**Reduction of Aryl Alkyl Ketones**

Just as an aromatic ring activates a neighboring (benzylic) C–H position toward oxidation, it also activates a benzylic carbonyl group toward reduction. Thus, an aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst. Propiophenone, for instance, is reduced to propylbenzene by

catalytic hydrogenation. Since the net effect of Friedel–Crafts acylation followed by reduction is the preparation of a primary alkylbenzene, this two-step sequence of reactions makes it possible to circumvent the carbocation rearrangement problems associated with direct Friedel–Crafts alkylation using a primary alkyl halide (Section 9-7).



PROBLEM 9.25

How might you prepare diphenylmethane, $(\text{Ph})_2\text{CH}_2$, from benzene and an appropriate acid chloride? More than one step is needed.

9-11 An Introduction to Organic Synthesis: Polysubstituted Benzenes

There are many reasons for carrying out the laboratory synthesis of an organic molecule. In the pharmaceutical industry, new molecules are designed and synthesized in the hope that some might be useful new drugs. In the chemical industry, syntheses are done to devise more economical routes to known compounds. In biochemistry laboratories, the synthesis of molecules designed to probe enzyme mechanisms is often undertaken.

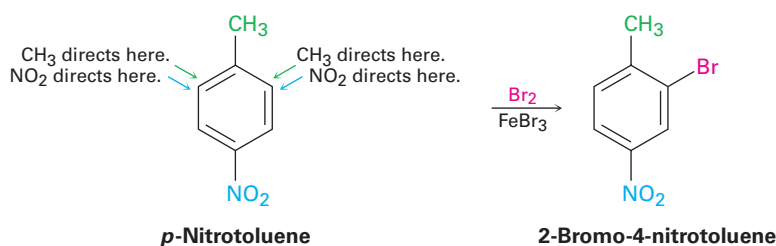
The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of numerous organic reactions. Not only must you know which reactions to use, you must also know when to use them, because the order in which reactions are carried out is often critical to the success of the overall scheme.

There's no secret to planning an organic synthesis: all it takes is a knowledge of the different reactions and some practice. The only real trick is to *work backward*, in what is often called a *retrosynthetic* direction. Don't look at a potential starting material and ask yourself what reactions it might undergo. Instead, look at the final product and ask, "What was the immediate precursor of that product?" For example, if the final product is an alkyl halide, the immediate precursor might be an alkene, to which you could add HX . If the final product is a

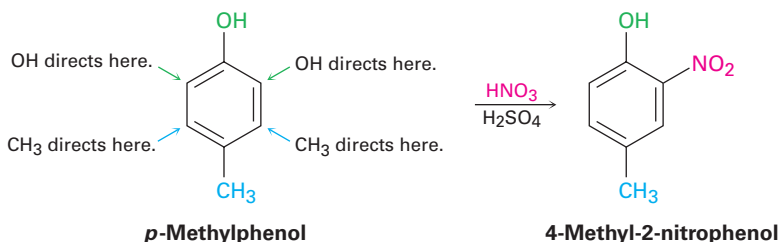
substituted benzoic acid, the immediate precursor might be a substituted alkylbenzene, which could be oxidized. Having found an immediate precursor, work backward again, one step at a time, until you get back to the starting material. You have to keep the starting material in mind, of course, so that you can work back to it, but you don't want that starting material to be your main focus.

Let's look at some examples of synthetic planning using polysubstituted aromatic compounds as the targets. First, however, it's necessary to point out that electrophilic substitution on a disubstituted benzene ring is governed by the same resonance and inductive effects that affect monosubstituted rings. The only difference is that it's necessary to consider the additive effects of two groups. In practice, this isn't as difficult as it sounds; three rules are usually sufficient:

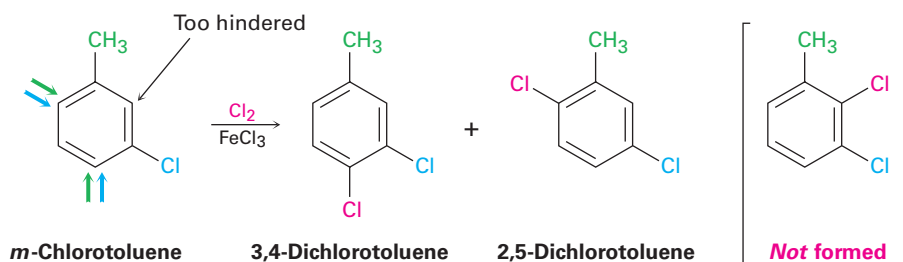
1. If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for instance, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.



2. If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence. For example, nitration of *p*-methylphenol yields primarily 4-methyl-2-nitrophenol because $-\text{OH}$ is a more powerful activator than $-\text{CH}_3$.



3. Further substitution rarely occurs between the two groups in a meta-disubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as the substitution of an ortho-disubstituted compound.



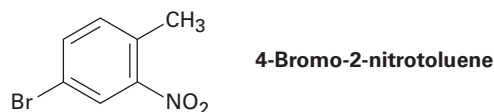
Now let's work several examples:

WORKED EXAMPLE 9.4
Synthesizing a Polysubstituted Benzene

Synthesize 4-bromo-2-nitrotoluene from benzene.

Strategy

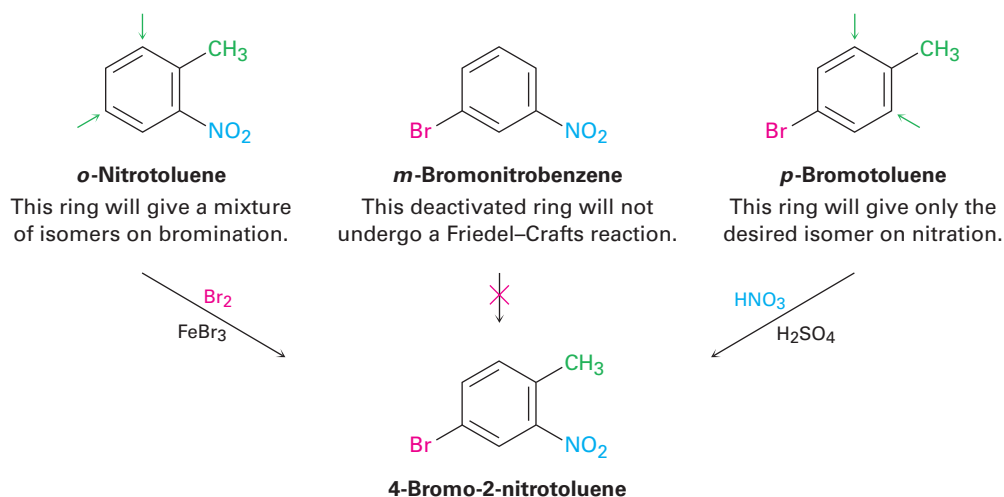
Draw the target molecule, identify the substituents, and recall how each group can be introduced separately. Then plan retrosynthetically.



The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $\text{Br}_2/\text{FeBr}_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $\text{CH}_3\text{Cl}/\text{AlCl}_3$, and a nitro group can be introduced by nitration with $\text{HNO}_3/\text{H}_2\text{SO}_4$.

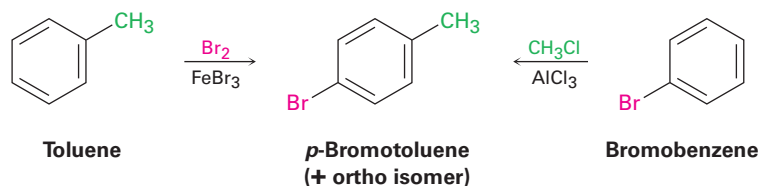
Solution

Ask yourself, “What is an immediate precursor of the target?” The final step will involve introduction of one of three groups—bromine, methyl, or nitro—so we have to consider three possibilities. Of the three, the bromination of *o*-nitrotoluene could be used because the activating methyl group would dominate the deactivating nitro group and direct bromination to the right position. Unfortunately, a mixture of product isomers would be formed. A Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on a nitro-substituted (strongly deactivated) benzene. The best precursor of the desired product is probably *p*-bromotoluene, which can be nitrated ortho to the activating methyl group to give a single product.



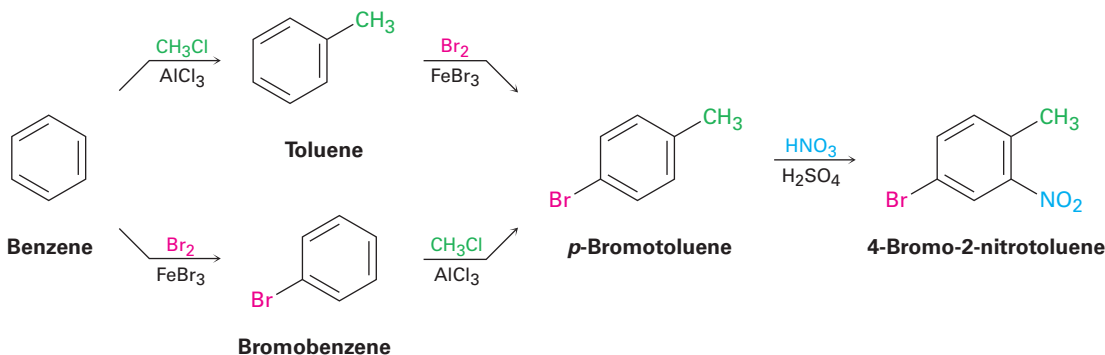
Next ask, “What is an immediate precursor of *p*-bromotoluene?” Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions. Alternatively, bromobenzene

might be an immediate precursor because we could carry out a Friedel–Crafts methylation and obtain a mixture of ortho and para products. Both answers are satisfactory, although both would also lead unavoidably to a product mixture that would have to be separated.



“What is an immediate precursor of toluene?” Benzene, which could be methylated in a Friedel–Crafts reaction. Alternatively, “What is an immediate precursor of bromobenzene?” Benzene, which could be brominated.

The retrosynthetic analysis has provided two valid routes from benzene to 4-bromo-2-nitrotoluene.



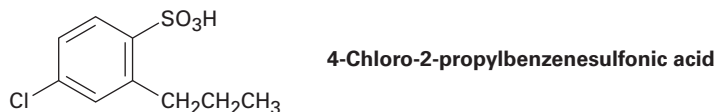
Synthesizing a Polysubstituted Benzene

WORKED EXAMPLE 9.5

Propose a synthesis of 4-chloro-2-propylbenzenesulfonic acid from benzene.

Strategy

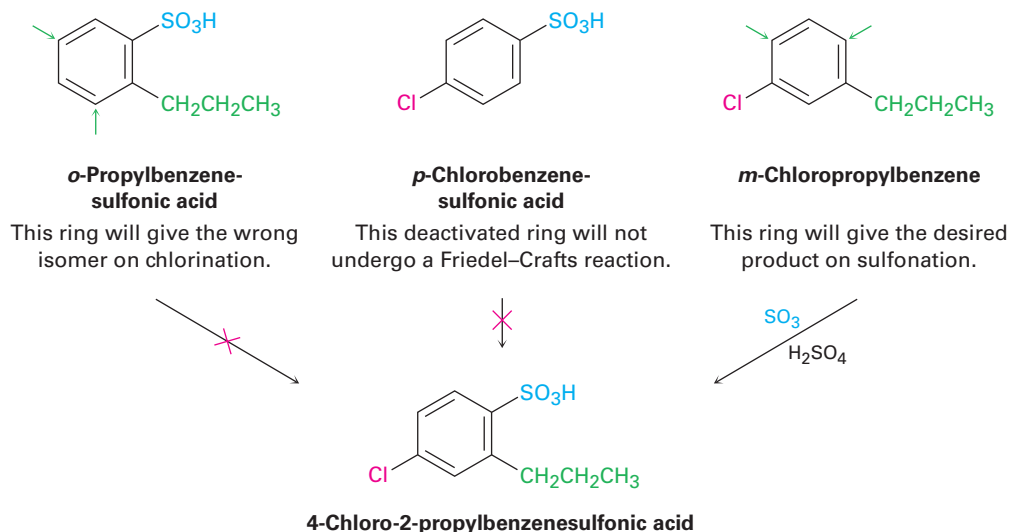
Draw the target molecule, identify its substituents, and recall how each of the three can be introduced. Then plan retrosynthetically.



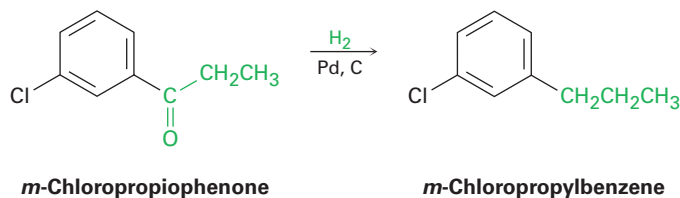
The three substituents on the ring are a chlorine, a propyl group, and a sulfonic acid group. A chlorine can be introduced by chlorination with $\text{Cl}_2/\text{FeCl}_3$, a propyl group can be introduced by Friedel–Crafts acylation with $\text{CH}_3\text{CH}_2\text{COCl}/\text{AlCl}_3$ followed by reduction with H_2/Pd , and a sulfonic acid group can be introduced by sulfonation with $\text{SO}_3/\text{H}_2\text{SO}_4$.

Solution

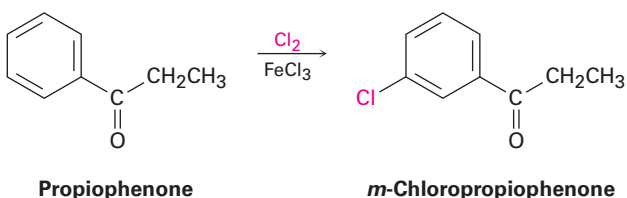
What is an immediate precursor of the target? The final step will involve introduction of one of three groups—chlorine, propyl, or sulfonic acid—so we have to consider three possibilities. Of the three, the chlorination of *o*-propylbenzenesulfonic acid can't be used because the reaction would occur at the wrong position. Similarly, a Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on sulfonic acid–substituted (strongly deactivated) benzenes. Thus, the immediate precursor of the desired product is probably *m*-chloropropylbenzene, which can be sulfonated to give a mixture of product isomers that must then be separated.



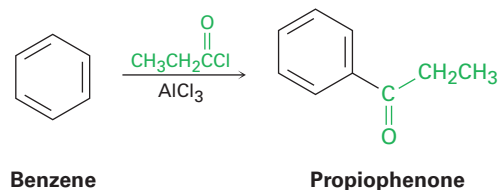
What is an immediate precursor of *m*-chloropropylbenzene? Because the two substituents have a meta relationship, the first substituent placed on the ring must be a meta director so that the second substitution will take place at the proper position. Furthermore, because primary alkyl groups such as propyl can't be introduced directly by Friedel–Crafts alkylation, the precursor of *m*-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced.



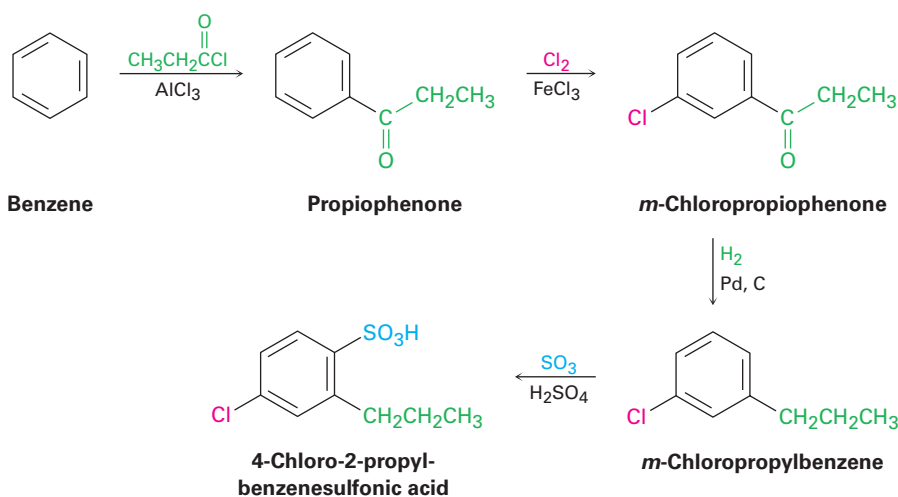
What is an immediate precursor of *m*-chloropropiophenone? Propiophenone, which could be chlorinated in the meta position.



What is an immediate precursor of propiophenone? Benzene, which could undergo Friedel–Crafts acylation with propanoyl chloride and AlCl_3 .



The final synthesis is a four-step route from benzene:



Planning an organic synthesis has been compared with playing chess. There are no tricks; all that's required is a knowledge of the allowable moves (the organic reactions) and the discipline to plan ahead, carefully evaluating the consequences of each move. Practicing may not be easy, but it's a great way to learn organic chemistry.

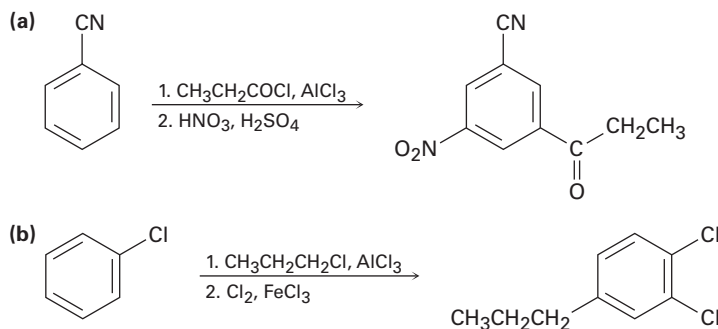
PROBLEM 9.26

How might you synthesize the following substances from benzene?

- m*-Chloronitrobenzene
- m*-Chloroethylbenzene
- p*-Chloropropylbenzene
- 3-Bromo-2-methylbenzenesulfonic acid

PROBLEM 9.27

In planning a synthesis, it's as important to know what not to do as to know what to do. As written, the following reaction schemes have flaws in them. What is wrong with each?



SOMETHING EXTRA

Aspirin, NSAIDs, and COX-2 Inhibitors

Whatever the cause—whether tennis elbow, a sprained ankle, or a wrenched knee—pain and inflammation seem to go together. They are, however, different in their origin, and powerful drugs are available for treating each separately. Codeine, for instance, is a powerful *analgesic*, or pain reliever, used in the management of debilitating pain, while cortisone and related steroids are potent *anti-inflammatory* agents, used for treating arthritis and other crippling inflammations. For minor pains and inflammation, both problems are often treated at the same time by using a common, over-the-counter medication called an *NSAID*, or *non-steroidal anti-inflammatory drug*.

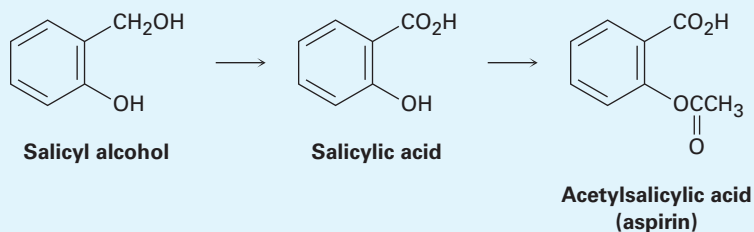
The most common NSAID is aspirin, or acetylsalicylic acid, whose use goes back to the late 1800s. It had been known from before the time of Hippocrates in 400 BC that fevers could be lowered by chewing the bark of willow trees. The active agent in willow bark was found in 1827 to be an aromatic compound called *salicin*, which could be converted by reaction with water into salicyl alcohol and then oxidized to give



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Many athletes rely on NSAIDs to help with pain and soreness.

salicylic acid. Salicylic acid turned out to be even more effective than salicin for reducing fevers and to have analgesic and anti-inflammatory action as well. Unfortunately, it also turned out to be too corrosive to the walls of the stomach for everyday use. Conversion of the phenol $-OH$ group into an acetate ester, however, yielded acetylsalicylic acid, which proved just as potent as salicylic acid but less corrosive to the stomach.



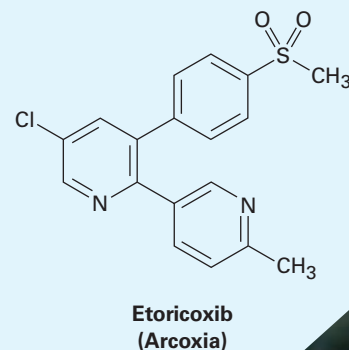
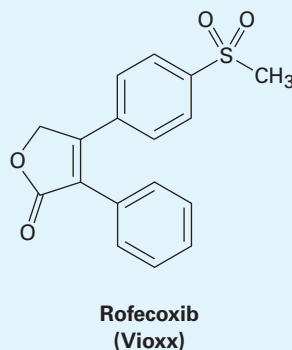
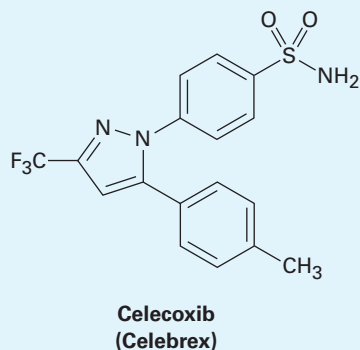
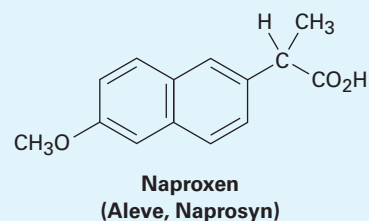
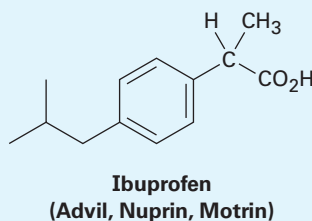
Although extraordinary in its effect, aspirin is also more dangerous than commonly believed. A dose of only about 15 g can be fatal to a small child, and aspirin can cause stomach bleeding and allergic reactions in long-term users. Even more serious is a condition called *Reye's syndrome*, a potentially fatal reaction to aspirin sometimes seen in children recovering from the flu. As a result of these problems, numerous other NSAIDs have been developed in the last several decades, most notably ibuprofen and naproxen.

Like aspirin, both ibuprofen and naproxen are relatively simple aromatic compounds containing a side-chain carboxylic acid group. Ibuprofen, sold under the names Advil, Nuprin, Motrin, and others, has roughly the same potency as aspirin but is less prone to cause stomach upset. Naproxen, sold under the names Aleve and Naprosyn, also has about the same potency as aspirin but remains active in the body six times longer.

Aspirin and other NSAIDs function by blocking the cyclooxygenase (COX) enzymes that carry out the body's synthesis of prostaglandins (Section 6-3). There are two forms of the enzyme: COX-1, which carries out the normal physiological production of prostaglandins and is

responsible for maintaining and protecting the gastrointestinal tract, and COX-2, which mediates the body's response to arthritis and other inflammatory conditions. Unfortunately, both COX-1 and COX-2 enzymes are blocked by aspirin, ibuprofen, and other NSAIDs, thereby shutting down not only the response to inflammation but also various protective functions, including the control mechanism for production of acid in the stomach.

Medicinal chemists have devised a number of drugs that act as selective inhibitors of the COX-2 enzyme, thereby controlling inflammation without blocking protective functions. Originally heralded as a breakthrough in arthritis treatment, some of the first generation of COX-2 inhibitors, including rofecoxib (Vioxx) and valdecoxib (Bextra), turned out to cause potentially serious heart problems, particularly in elderly or compromised patients. Only celecoxib, marketed as Celebrex, appears safe and remains on the market. The second generation of COX-2 inhibitors also appear safer, and etoricoxib (Arcoxia) is approved for use in more than 70 countries worldwide.



KEY WORDS

acyl group, 292
acylation, 292
alkylation, 289
arene, 267
aromatic, 265
benzyl group, 267
benzylic, 306
electrophilic aromatic substitution reaction, 281
Friedel–Crafts reaction, 289
heterocycle, 276
Hückel $4n + 2$ rule, 272
inductive effect, 297
meta (*m*), 267
nucleophilic aromatic substitution reaction, 303
ortho (*o*), 267
para (*p*), 267
phenyl group, 267
resonance effect, 298

SUMMARY

Aromatic rings are a common part of many biological structures and are particularly important in nucleic acid chemistry and in the chemistry of several amino acids. In this chapter, we've seen how and why aromatic compounds are different from such apparently related compounds as cycloalkenes, and we've seen some of their most common reactions.

The word **aromatic** is used for historical reasons to refer to the class of compounds related structurally to benzene. Aromatic compounds are systematically named according to IUPAC rules, but many common names are also used. Disubstituted benzenes are named as *ortho* (1,2 disubstituted), *meta* (1,3 disubstituted), or *para* (1,4 disubstituted) derivatives. The C_6H_5- unit itself is referred to as a **phenyl** group.

Benzene is described by resonance theory as a resonance hybrid of two equivalent structures and is described by molecular orbital theory as a planar, cyclic, conjugated molecule with six π electrons. According to the **Hückel $4n + 2$ rule**, a molecule must have $4n + 2$ π electrons, where $n = 0, 1, 2, 3$, and so on, to be aromatic.

Other kinds of molecules besides benzene-like compounds can also be aromatic. The cyclopentadienyl anion and cycloheptatrienyl cation, for instance, are aromatic ions. Pyridine and pyrimidine are six-membered, nitrogen-containing, aromatic **heterocycles**. Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles. Naphthalene, quinoline, indole, and many others are polycyclic aromatic compounds.

The chemistry of aromatic compounds is dominated by **electrophilic aromatic substitution reactions**, both in the laboratory and in biological pathways. Many variations of the reaction can be carried out, including halogenation, nitration, sulfonation, and hydroxylation. Friedel–Crafts alkylation and acylation, which involve reaction of an aromatic ring with carbocation electrophiles, are particularly useful.

Substituents on the benzene ring affect both the reactivity of the ring toward further substitution and the orientation of that substitution. Groups can be classified as ortho- and para-directing activators, ortho- and para-directing deactivators, or meta-directing deactivators. Substituents influence aromatic rings by a combination of electron-donating and electron-withdrawing effects.

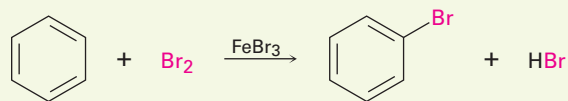
Halobenzenes with a strongly electron-withdrawing substituent in the ortho or para position undergo a *nucleophilic* substitution, which occurs by addition of a nucleophile to the ring, followed by elimination of halide from the intermediate anion.

The entire side chain of an alkylbenzene can be degraded to a carboxyl group by oxidation with aqueous $KMnO_4$. Although aromatic rings are less reactive than isolated alkene double bonds, they can be reduced to cyclohexanes by hydrogenation over a platinum or rhodium catalyst. In addition, aryl alkyl ketones are reduced to alkylbenzenes by hydrogenation over a palladium catalyst.

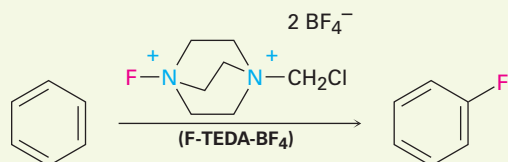
SUMMARY OF REACTIONS

1. Electrophilic aromatic substitution (Section 9-6)

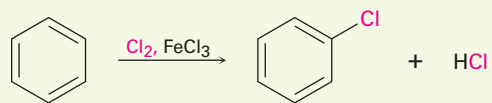
(a) Bromination



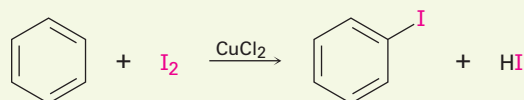
(b) Fluorination



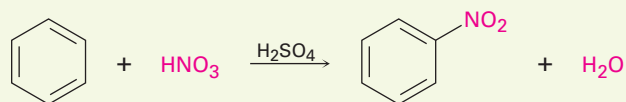
(c) Chlorination



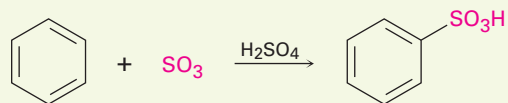
(d) Iodination



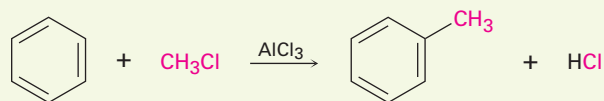
(e) Nitration



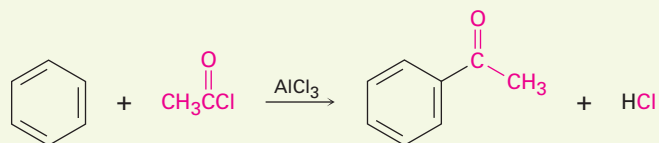
(f) Sulfonation



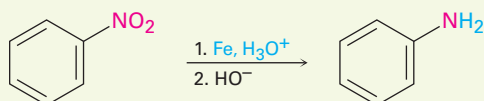
(g) Friedel–Crafts alkylation (Section 9-7)



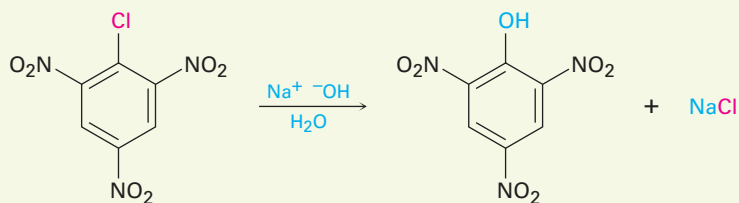
(h) Friedel–Crafts acylation (Section 9-7)



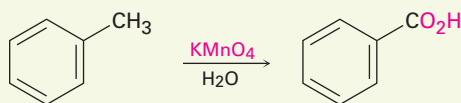
2. Reduction of aromatic nitro groups (Section 9-6)



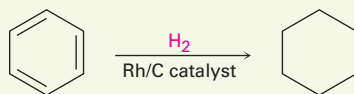
3. Nucleophilic aromatic substitution (Section 9-9)



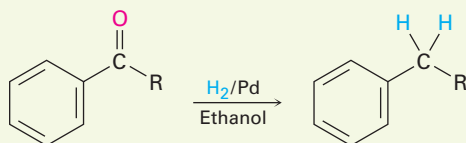
4. Oxidation of alkylbenzene side chain (Section 9-10)



5. Catalytic hydrogenation of aromatic rings (Section 9-10)



6. Reduction of aryl alkyl ketones (Section 9-10)



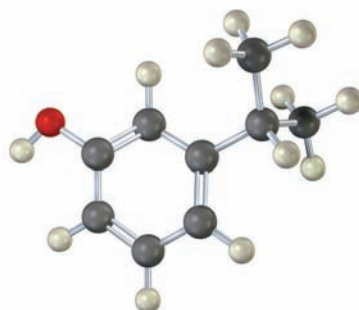
EXERCISES

VISUALIZING CHEMISTRY

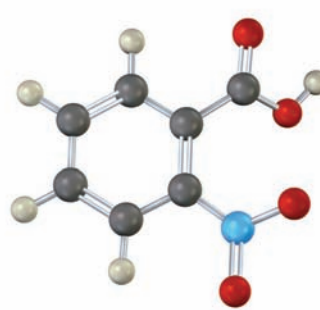
(Problems 9.1–9.27 appear within the chapter.)

9.28 Give IUPAC names for the following substances (red = O, blue = N):

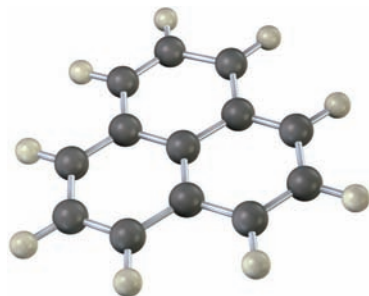
(a)



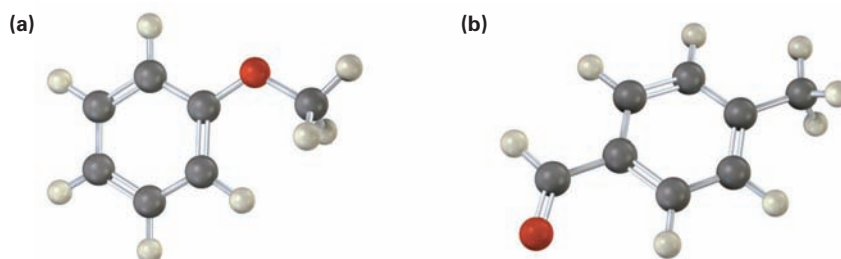
(b)



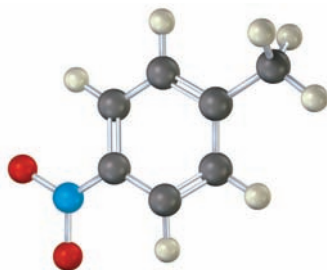
- 9.29 The following molecular model is that of a carbocation. Draw two resonance structures for the carbocation, indicating the positions of the double bonds.



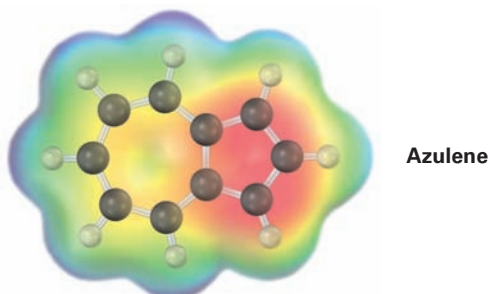
- 9.30 Draw the product from reaction of each of the following substances with (a) Br_2 , FeBr_3 and (b) CH_3COCl , AlCl_3 (red = O).



- 9.31 How would you synthesize the following compound starting from benzene? More than one step is needed (red = O, blue = N).



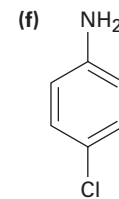
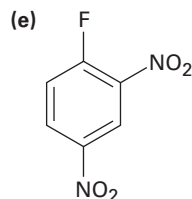
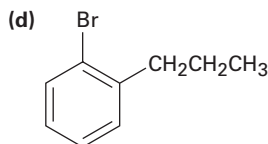
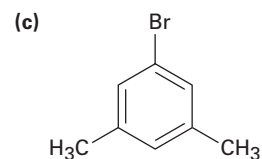
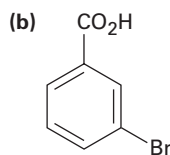
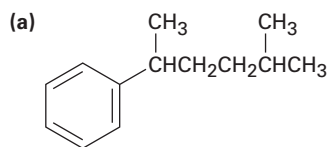
- 9.32 Azulene, an isomer of naphthalene, has a remarkably large dipole moment for a hydrocarbon ($\mu = 1.0$ D). Explain using resonance structures.



ADDITIONAL PROBLEMS

Naming Aromatic Compounds

9.33 Give IUPAC names for the following compounds:



9.34 Draw structures corresponding to the following names:

(a) 3-Methyl-2-nitrobenzoic acid (b) Benzene-1,3,5-triol

(c) 3-Methyl-2-phenylhexane (d) *o*-Aminobenzoic acid

(e) *m*-Bromophenol (f) 2,4,6-Trinitrophenol (picric acid)

9.35 Draw and name all possible isomers of the following:

(a) Dinitrobenzene (b) Bromodimethylbenzene (c) Trinitrophenol

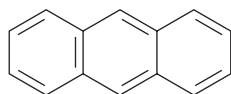
9.36 Draw and name all possible aromatic compounds with the formula C_7H_7Cl .

9.37 Draw and name all possible aromatic compounds with the formula C_8H_9Br . (There are 14.)

Resonance in Aromatic Compounds

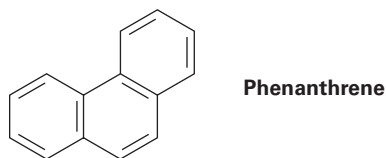
9.38 Look at the three resonance structures of naphthalene shown in Section 9-5, and account for the fact that not all carbon-carbon bonds have the same length. The C1-C2 bond is 136 pm long, whereas the C2-C3 bond is 139 pm long.

9.39 Anthracene has four resonance structures, one of which is shown. Draw the other three.

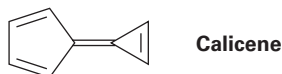


Anthracene

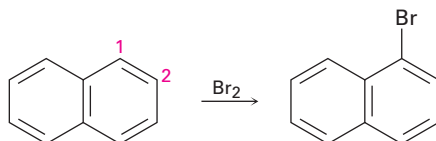
- 9.40 Phenanthrene has five resonance structures, one of which is shown. Draw the other four.



- 9.41 Look at the five resonance structures for phenanthrene (Problem 9.40) and predict which of its carbon–carbon bonds is shortest.
- 9.42 Calicene, like azulene (Problem 9.32), has an unusually large dipole moment for a hydrocarbon. Explain using resonance structures.

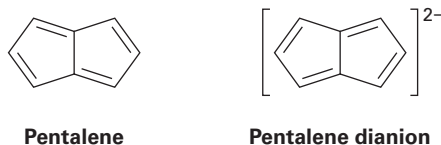


- 9.43 Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic substitution at C1 rather than C2.

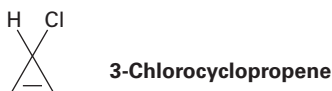


Aromaticity and Hückel's Rule

- 9.44 Which would you expect to be most stable, cyclononatetraenyl radical, cation, or anion?
- 9.45 How might you convert cyclonona-1,3,5,7-tetraene to an aromatic substance?
- 9.46 Pentalene is a most elusive molecule that has been isolated only at liquid-nitrogen temperature. The pentalene dianion, however, is well known and quite stable. Explain.



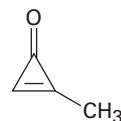
- 9.47 3-Chlorocyclopropene, on treatment with AgBF_4 , gives a precipitate of AgCl and a stable solution of a carbocation product. What is a likely structure for the product, and what is its relation to Hückel's rule?



- 9.48 Cyclopropanone is highly reactive because of its large amount of angle strain. But methylcyclopropanone, although even more strained than cyclopropanone, is nevertheless quite stable and can even be distilled. Explain, taking the polarity of the carbonyl group into account.

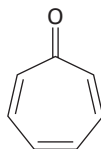


Cyclopropanone

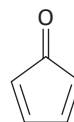


Methylcyclopropanone

- 9.49 Cycloheptatrienone is stable, but cyclopentadienone is so reactive that it can't be isolated. Explain, taking the polarity of the carbonyl group into account.

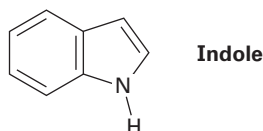


Cycloheptatrienone



Cyclopentadienone

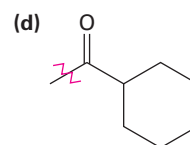
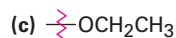
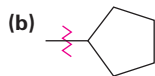
- 9.50 Indole is an aromatic heterocycle that has a benzene ring fused to a pyrrole ring. Draw an orbital picture of indole.
- (a) How many π electrons does indole have?
- (b) What is the electronic relationship of indole to naphthalene?



Indole

Reactivity and Orientation of Electrophilic Aromatic Substitutions

- 9.51 Identify each of the following groups as an activator or deactivator and as an *o*,*p*-director or *m*-director:



- 9.52 Predict the major product(s) of mononitration of the following substances. Which react faster than benzene, and which slower?
- (a) Bromobenzene (b) Benzonitrile (c) Benzoic acid
 (d) Nitrobenzene (e) Benzenesulfonic acid (f) Methoxybenzene

9.53 Rank the following aromatic compounds in their expected order of reactivity toward Friedel–Crafts alkylation. Which compounds are unreactive?

- (a) Bromobenzene (b) Toluene (c) Phenol
(d) Benzoic acid (e) Nitrobenzene (f) *p*-Bromotoluene

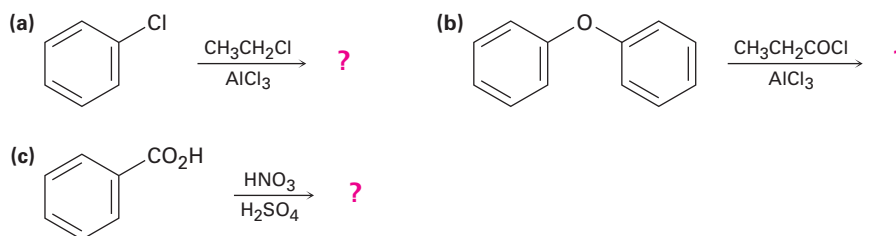
9.54 Rank the compounds in each group according to their reactivity toward electrophilic substitution.

- (a) Chlorobenzene, *o*-dichlorobenzene, benzene
(b) *p*-Bromonitrobenzene, nitrobenzene, phenol
(c) Fluorobenzene, benzaldehyde, *o*-xylene
(d) Benzonitrile, *p*-methylbenzonitrile, *p*-methoxybenzonitrile

9.55 Propose structures for aromatic hydrocarbons that meet the following descriptions:

- (a) C₉H₁₂; gives only one C₉H₁₁Br product on substitution with bromine
(b) C₁₀H₁₄; gives only one C₁₀H₁₃Cl product on substitution with chlorine
(c) C₈H₁₀; gives three C₈H₉Br products on substitution with bromine
(d) C₁₀H₁₄; gives two C₁₀H₁₃Cl products on substitution with chlorine

9.56 Predict the major product(s) of the following reactions:



9.57 Predict the major monoalkylation products you would expect to obtain from reaction of the following substances with chloromethane and AlCl₃:

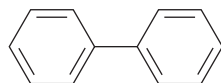
- (a) *p*-Chloroaniline (b) *m*-Bromophenol
(c) 2,4-Dichlorophenol (d) 2,4-Dichloronitrobenzene
(e) *p*-Methylbenzenesulfonic acid (f) 2,5-Dibromotoluene

9.58 Name and draw the major product(s) of electrophilic chlorination of the following compounds:

- (a) *m*-Nitrophenol (b) *o*-Xylene (dimethylbenzene)
(c) *p*-Nitrobenzoic acid (d) *p*-Bromobenzenesulfonic acid

Mechanisms of Electrophilic Aromatic Substitutions

- 9.59** Aromatic iodination can be carried out with a number of reagents, including iodine monochloride, ICl. What is the direction of polarization of ICl? Propose a mechanism for the iodination of an aromatic ring with ICl.
- 9.60** When benzene is treated with D₂SO₄, deuterium slowly replaces all six hydrogens in the aromatic ring. Explain.
- 9.61** The carbocation electrophile in a Friedel–Crafts reaction can be generated in ways other than by reaction of an alkyl chloride with AlCl₃. For example, reaction of benzene with 2-methylpropene in the presence of H₃PO₄ yields *tert*-butylbenzene. Propose a mechanism for this reaction.
- 9.62** The nitroso group, –N=O, is one of the few nonhalogens that is an ortho- and para-directing deactivator. Explain by drawing resonance structures of the carbocation intermediates in ortho, meta, and para electrophilic reaction on nitrosobenzene, C₆H₅N=O.
- 9.63** The *N,N,N*-trimethylammonium group, –N⁺(CH₃)₃, is one of the few groups that is a meta-directing deactivator yet has no electron-withdrawing resonance effect. Explain.
- 9.64** Using resonance structures of the intermediates, explain why bromination of biphenyl occurs at ortho and para positions rather than at meta.

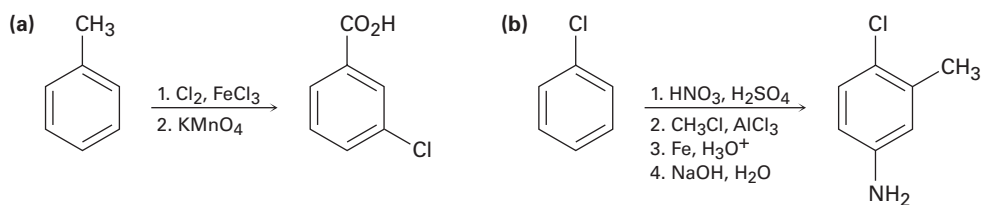


Biphenyl

Organic Synthesis

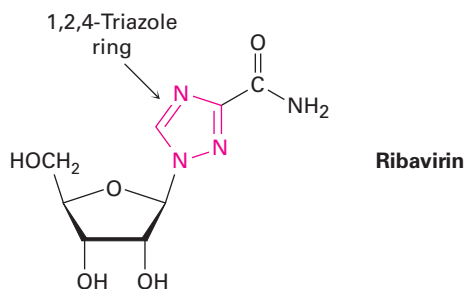
- 9.65** How would you synthesize the following substances starting from benzene? Assume that ortho- and para-substitution products can be separated.
- (a) *p*-Bromoaniline (b) *m*-Bromoaniline
- (c) 2,4,6-Trinitrobenzoic acid (d) 3,5-Dinitrobenzoic acid
- 9.66** Starting with either benzene or toluene, how would you synthesize the following substances? Assume that ortho and para isomers can be separated.
- (a) 2-Bromo-4-nitrotoluene (b) 2,4,6-Tribromoaniline
- (c) 3-Bromo-4-*tert*-butylbenzoic acid (d) 1,3-Dichloro-5-ethylbenzene

- 9.67 As written, the following syntheses have flaws. What is wrong with each?

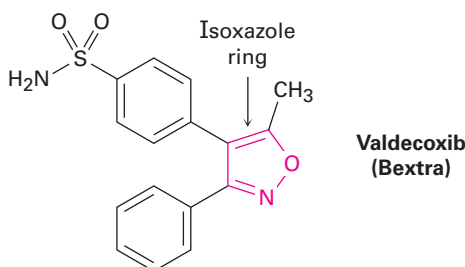


General Problems

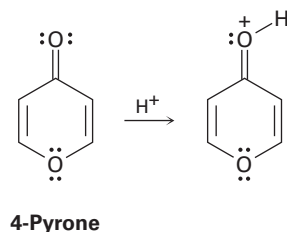
- 9.68 Ribavirin, an antiviral agent used against hepatitis C and viral pneumonia, contains a 1,2,4-triazole ring. Why is the ring aromatic?



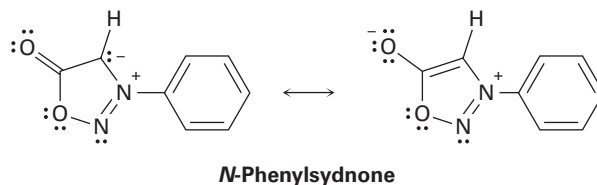
- 9.69 Valdecoxib (Bextra), a COX-2 inhibitor once used in the treatment of osteoarthritis, contains an isoxazole ring. Why is the ring aromatic?



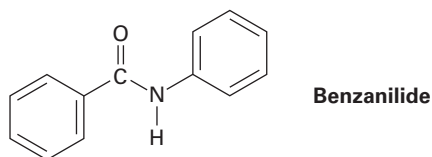
- 9.70 On reaction with acid, 4-pyrone is protonated on the carbonyl-group oxygen to give a stable cationic product. Using resonance structures and the Hückel $4n + 2$ rule, explain why the protonated product is so stable.



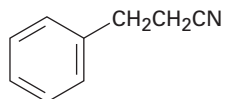
- 9.71 *N*-Phenylsydnone, so named because it was first studied at the University of Sydney, Australia, behaves like a typical aromatic molecule. Explain using the Hückel $4n + 2$ rule.



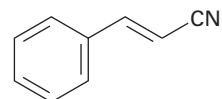
- 9.72 Draw resonance structures of the potential ortho, meta, and para intermediates, and explain at what position and on what ring you would expect bromination of benzanilide to occur.



- 9.73 Electrophilic substitution on 3-phenylpropanenitrile occurs at the ortho and para positions, but reaction with 3-phenylpropenenitrile occurs at the meta position. Explain, using resonance structures of the intermediates.

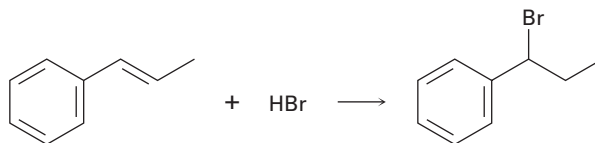


3-Phenylpropanenitrile



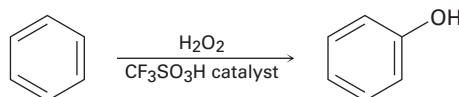
3-Phenylpropenenitrile

- 9.74 Addition of HBr to 1-phenylpropene yields only (1-bromopropyl)benzene. Propose a mechanism for the reaction, and explain using resonance structures why none of the other regioisomer is produced.

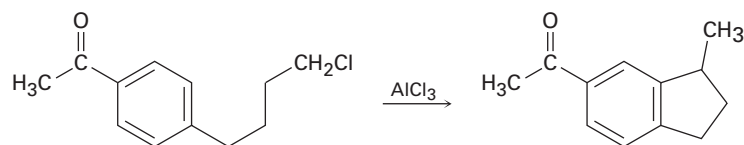


- 9.75 Phenylboronic acid, $C_6H_5B(OH)_2$, is nitrated to give 15% ortho-substitution product and 85% meta. Explain the meta-directing effect of the $-B(OH)_2$ group.

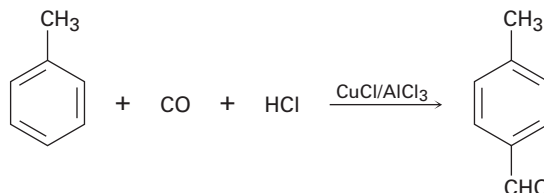
- 9.76 Benzene and alkyl-substituted benzenes can be hydroxylated by reaction with H_2O_2 in the presence of a strong acid catalyst. What is the likely structure of the reactive electrophile? Review Figure 9.13 on page 288, and then propose a mechanism for the reaction.



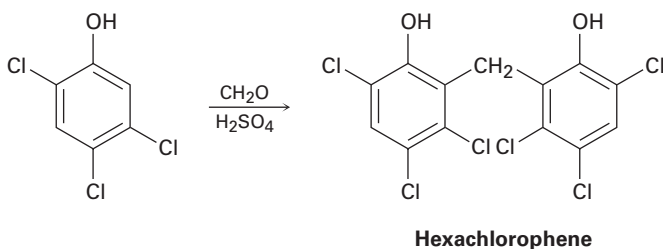
9.77 Propose a mechanism to account for the following reaction:



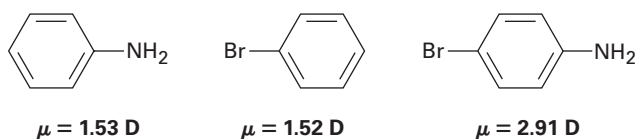
9.78 In the *Gatterman–Koch reaction*, a formyl group ($-\text{CHO}$) is introduced directly onto a benzene ring. For example, reaction of toluene with CO and HCl in the presence of AlCl_3 gives *p*-methylbenzaldehyde. Propose a mechanism.



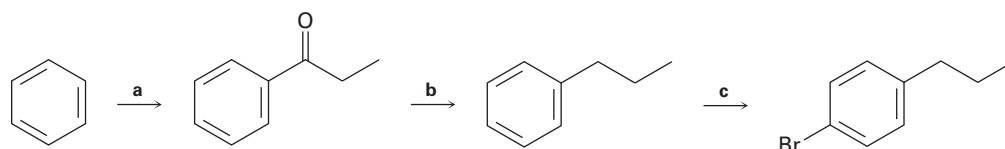
9.79 Hexachlorophene, a substance used in the manufacture of germicidal soaps, is prepared by reaction of 2,4,5-trichlorophenol with formaldehyde in the presence of concentrated sulfuric acid. Propose a mechanism for the reaction.



9.80 Use your knowledge of directing effects, along with the following data, to deduce the directions of the dipole moments in aniline and bromobenzene.



9.81 Identify the reagents represented by the letters **a–c** in the following scheme:



- 9.82** Phenols (ArOH) are relatively acidic, and the presence of a substituent group on the aromatic ring has a large effect. The pK_a of unsubstituted phenol, for example, is 9.89, while that of *p*-nitrophenol is 7.15. Draw resonance structures of the corresponding phenoxide anions, and explain the data.
- 9.83** In light of your answer to Problem 9.82, would you expect *p*-methylphenol to be more acidic or less acidic than unsubstituted phenol? What about *p*-bromophenol? Explain.

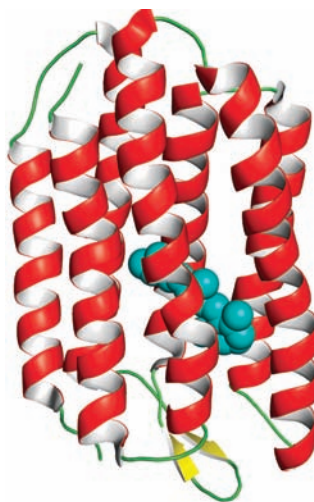
Structure Determination: Mass Spectrometry, Infrared Spectroscopy, and Ultraviolet Spectroscopy

10

CONTENTS

- 10-1** Mass Spectrometry of Small Molecules: Magnetic-Sector Instruments
- 10-2** Interpreting Mass Spectra
- 10-3** Mass Spectrometry of Some Common Functional Groups
- 10-4** Mass Spectrometry in Biological Chemistry: Time-of-Flight (TOF) Instruments
- 10-5** Spectroscopy and the Electromagnetic Spectrum
- 10-6** Infrared Spectroscopy
- 10-7** Interpreting Infrared Spectra
- 10-8** Infrared Spectra of Some Common Functional Groups
- 10-9** Ultraviolet Spectroscopy
- 10-10** Interpreting Ultraviolet Spectra: The Effect of Conjugation
- 10-11** Conjugation, Color, and the Chemistry of Vision

SOMETHING EXTRA
X-Ray Crystallography



Bacteriorhodopsin is a membrane protein involved in the chemistry of vision.

WHY THIS CHAPTER?

Finding the structures of new molecules, whether small ones synthesized in the laboratory or large proteins and nucleic acids found in living organisms, is central to progress in chemistry and biochemistry. We can only scratch the surface of structure determination in this book, but after reading this and the following chapter, you should have a good idea of the range of structural techniques available and of how and when each is used.

Every time a reaction is run, the products must be identified, and every time a new compound is found in nature, its structure must be determined. Determining the structure of an organic compound was a difficult and time-consuming process until the mid-20th century, but powerful techniques and specialized instruments are now available that greatly simplify the problem. In this and the next chapter, we'll look at four such techniques—mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet spectroscopy (UV), and nuclear magnetic resonance spectroscopy (NMR)—and we'll see the kind of information that can be obtained from each.

Mass spectrometry

What is the size and formula?

Infrared spectroscopy

What functional groups are present?

Ultraviolet spectroscopy

Is a conjugated π electron system present?

Nuclear magnetic resonance spectroscopy

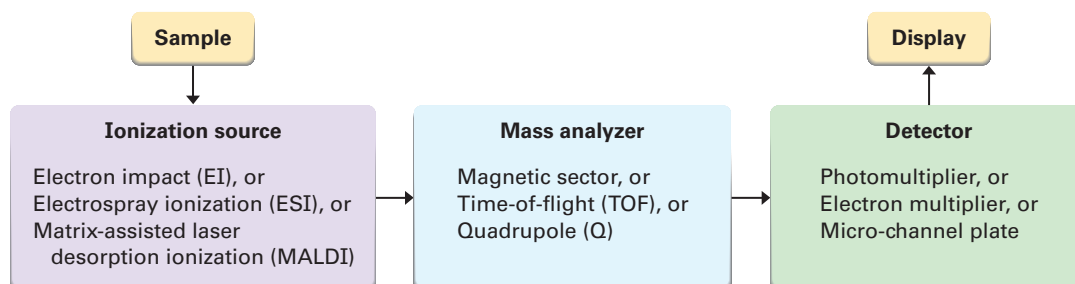
What is the carbon–hydrogen framework?



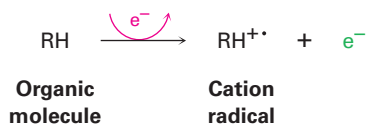
10-1 Mass Spectrometry of Small Molecules: Magnetic-Sector Instruments

At its simplest, **mass spectrometry (MS)** is a technique for measuring the mass, and therefore the molecular weight (MW), of a molecule. In addition, it's often possible to gain structural information about a molecule by measuring the masses of fragments produced when molecules are broken apart.

More than 20 different kinds of commercial mass spectrometers are available, depending on the intended application, but all have three basic parts: an *ionization source* in which sample molecules are given an electrical charge, a *mass analyzer* in which ions are separated by their mass-to-charge ratio, and a *detector* in which the separated ions are observed and counted.



Among the simplest type of mass spectrometers used for routine purposes in the laboratory is the electron-impact, magnetic-sector instrument shown schematically in **FIGURE 10.1**. A small amount of sample is vaporized into the ionization source, where it is bombarded by a stream of high-energy electrons. The energy of the electron beam can be varied but is commonly around 70 electron volts (eV), or 6700 kJ/mol. When a high-energy electron strikes an organic molecule, it dislodges a valence electron from the molecule, producing a *cation radical*—*cation* because the molecule has lost an electron and now has a positive charge; *radical* because the molecule now has an odd number of electrons.



Electron bombardment transfers so much energy that most of the cation radicals fragment after formation. They fly apart into smaller pieces, some of which retain the positive charge, and some of which are neutral. The fragments then flow through a curved pipe in a strong magnetic field, which deflects them into different paths according to their mass-to-charge ratio (m/z). Neutral fragments are not deflected by the magnetic field and are lost on the walls of the pipe, but positively charged fragments are sorted by the mass spectrometer onto a detector, which records them as peaks at the various m/z ratios. Since the number of charges z on each ion is usually 1, the value of m/z for each ion is simply its mass, m . Masses up to approximately 2500 atomic mass units (amu) can be analyzed.

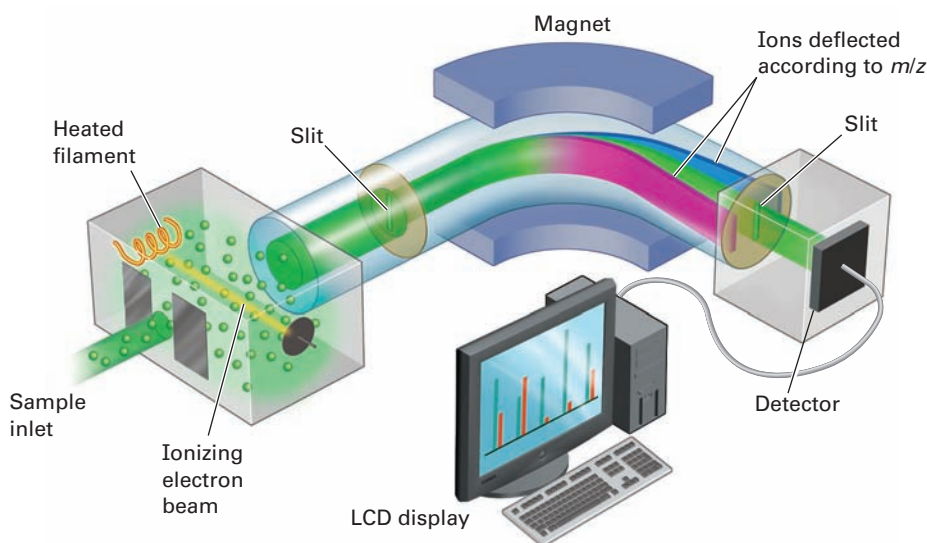


FIGURE 10.1 Representation of an electron-ionization, magnetic-sector mass spectrometer.

Molecules are ionized by collision with high-energy electrons, causing some of the molecules to fragment. Passage of the charged fragments through a magnetic field then sorts them according to their mass.

The **mass spectrum** of a compound is typically presented as a bar graph with masses (m/z values) on the x -axis and intensity, or relative abundance of ions of a given m/z striking the detector, on the y -axis. The tallest peak, assigned an intensity of 100%, is called the **base peak**, and the peak that corresponds to the unfragmented cation radical is called the **parent peak**, or the **molecular ion** (M^+). **FIGURE 10.2** shows the mass spectrum of propane.

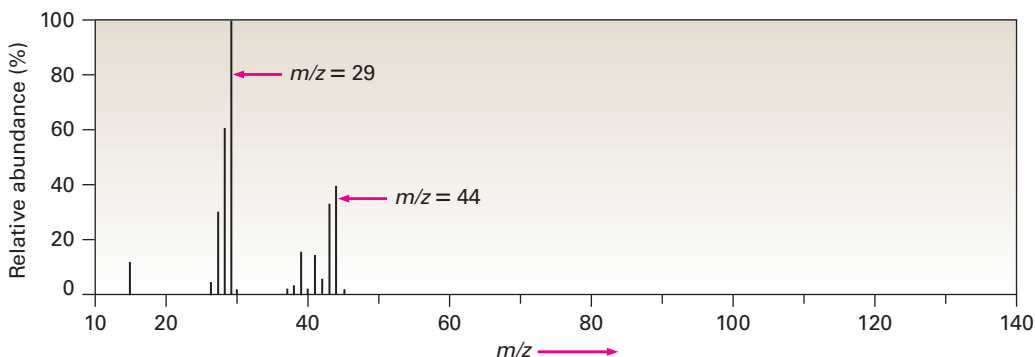


FIGURE 10.2 Mass spectrum of propane (C_3H_8 ; MW = 44).

Mass spectral fragmentation patterns are usually complex, and the molecular ion is often not the base peak. The mass spectrum of propane in Figure 10.2, for instance, shows a molecular ion at $m/z = 44$ that is only about 30% as high as the base peak at $m/z = 29$. In addition, many other fragment ions are present.

10-2 Interpreting Mass Spectra

What kinds of information can we get from a mass spectrum? The most obvious information is the molecular weight of the sample, which in itself can be invaluable. If we were given samples of hexane (MW = 86), hex-1-ene (MW = 84), and hex-1-yne (MW = 82), for example, mass spectrometry would easily distinguish them.

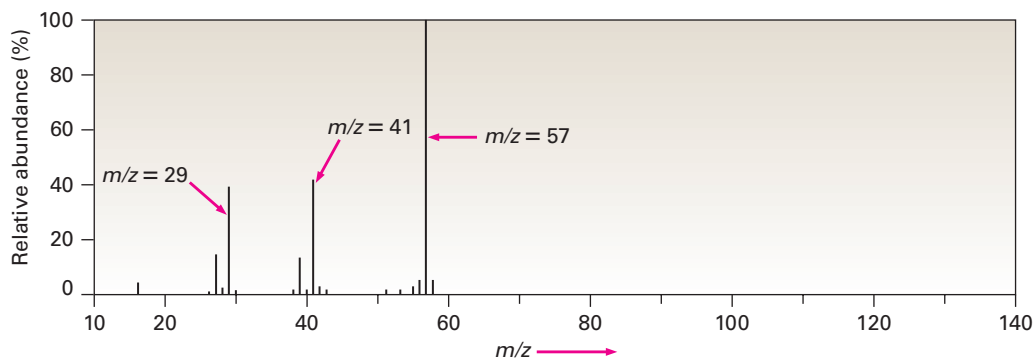
Some instruments, called *double-focusing mass spectrometers*, have such high resolution that they provide exact mass measurements accurate to 5 ppm, or about 0.0005 amu, making it possible to distinguish between two formulas with the same nominal mass. Both C_5H_{12} and C_4H_8O have $MW = 72$, for example, but they differ slightly beyond the decimal point: C_5H_{12} has an exact mass of 72.0939 amu, whereas C_4H_8O has an exact mass of 72.0575 amu. A high-resolution instrument can easily distinguish between them. Note, however, that exact mass measurements refer to molecules with specific isotopic compositions. Thus, the sum of the exact atomic masses of the specific isotopes in a molecule is measured—1.00783 amu for 1H , 12.00000 amu for ^{12}C , 14.00307 amu for ^{14}N , 15.99491 amu for ^{16}O , and so on—rather than the sum of the average atomic weights of elements as found on a periodic table.

Unfortunately, not every compound shows a molecular ion in its electron-impact mass spectrum. Although M^+ is usually easy to identify if it's abundant, some compounds, such as 2,2-dimethylpropane, fragment so easily that no molecular ion is observed (FIGURE 10.3). In such cases, alternative “soft” ionization methods that do not use electron bombardment can prevent or minimize fragmentation.

FIGURE 10.3

Mass spectrum of 2,2-dimethylpropane (C_5H_{12} ; $MW = 72$).

No molecular ion is observed when electron-impact ionization is used. (What do you think is the formula and structure of the peak at $m/z = 57$?)



Knowing the molecular weight makes it possible to narrow greatly the choices of molecular formula. For example, if the mass spectrum of an unknown compound shows a molecular ion at $m/z = 110$, the molecular formula is likely to be C_8H_{14} , $C_7H_{10}O$, $C_6H_6O_2$, or $C_6H_{10}N_2$. There are always a number of molecular formulas possible for all but the lowest molecular weights, and a computer can easily generate a list of choices.

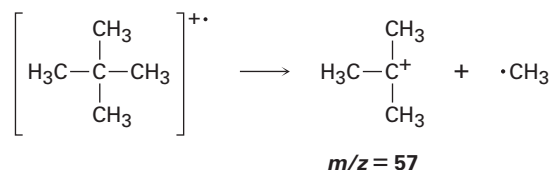
A further point about mass spectrometry, noticeable in the spectra of both propane (Figure 10.2) and 2,2-dimethylpropane (Figure 10.3), is that the peak for the molecular ion is not at the highest m/z value. There is also a small peak at $M+1$ because of the presence of different isotopes in the molecules. Although ^{12}C is the most abundant carbon isotope, a small amount (1.10% natural abundance) of ^{13}C is also present. Thus, a certain percentage of the molecules analyzed in the mass spectrometer are likely to contain a ^{13}C atom, giving rise to the observed $M+1$ peak. In addition, a small amount of 2H (deuterium; 0.015% natural abundance) is present, making a further contribution to the $M+1$ peak.

Mass spectrometry would be useful even if molecular weight and formula were the only information that could be obtained, but in fact we can get much more. For one thing, the mass spectrum of a compound serves as a kind of “molecular fingerprint.” Each organic compound fragments in a unique way

depending on its structure, and the likelihood of two compounds having identical mass spectra is small. Thus, it's sometimes possible to identify an unknown by computer-based matching of its mass spectrum to one of the more than 592,000 spectra recorded in a database called the *Registry of Mass Spectral Data*.

It's also possible to derive structural information about a molecule by interpreting its fragmentation pattern. Fragmentation occurs when the high-energy cation radical flies apart by spontaneous cleavage of a chemical bond. One of the two fragments retains the positive charge and is a carbocation, while the other fragment is a neutral radical.

Not surprisingly, the positive charge often remains with the fragment that is best able to stabilize it. In other words, a relatively stable carbocation is often formed during fragmentation. For example, 2,2-dimethylpropane tends to fragment in such a way that the positive charge remains with the *tert*-butyl group. 2,2-Dimethylpropane therefore has a base peak at $m/z = 57$, corresponding to $C_4H_9^+$ (Figure 10.3).



Because mass-spectral fragmentation patterns are usually complex, it's often difficult to assign structures to fragment ions. Most hydrocarbons fragment in many ways, as the mass spectrum of hexane shown in **FIGURE 10.4** demonstrates. The hexane spectrum shows a moderately abundant molecular ion at $m/z = 86$ and fragment ions at $m/z = 71$, 57, 43, and 29. Since all the carbon-carbon bonds of hexane are electronically similar, all break to a similar extent, giving rise to the observed mixture of ions.

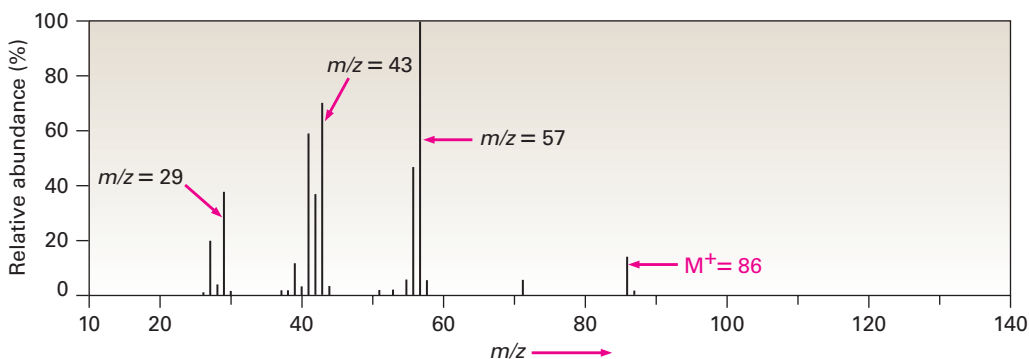


FIGURE 10.4 Mass spectrum of hexane (C_6H_{14} ; MW = 86). The base peak is at $m/z = 57$, and numerous other ions are present.

FIGURE 10.5 shows how the hexane fragments might arise. The loss of a methyl radical from the hexane cation radical ($M^+ = 86$) gives rise to a fragment of mass 71, the loss of an ethyl radical accounts for a fragment of mass 57, the loss of a propyl radical accounts for a fragment of mass 43, and the loss of a butyl radical accounts for a fragment of mass 29. With skill and practice, chemists can learn to analyze the fragmentation patterns of unknown compounds and work backward to a structure that is compatible with the data.

Strategy

Look at the possible structures and determine how they differ. Then think about how any of these differences in structure might give rise to differences in mass spectra. Methylcyclohexane, for instance, has a $-\text{CH}_3$ group, and ethylcyclopentane has a $-\text{CH}_2\text{CH}_3$ group, which should affect the fragmentation patterns.

Solution

The mass spectra of both samples show molecular ions at $M^+ = 98$, corresponding to C_7H_{14} , but the two spectra differ in their fragmentation patterns. Sample **A** has its base peak at $m/z = 69$, corresponding to the loss of a CH_2CH_3 group (29 mass units), but **B** has a rather small peak at $m/z = 69$. Sample **B** shows a base peak at $m/z = 83$, corresponding to the loss of a CH_3 group (15 mass units), but sample **A** has only a small peak at $m/z = 83$. We can therefore be reasonably certain that **A** is ethylcyclopentane and **B** is methylcyclohexane.

PROBLEM 10.1

The male sex hormone testosterone contains only C, H, and O and has a mass of 288.2089 amu, as determined by high-resolution mass spectrometry. What is the likely molecular formula of testosterone?

PROBLEM 10.2

Two mass spectra are shown in **FIGURE 10.7**. One spectrum corresponds to 2-methylpent-2-ene; the other, to hex-2-ene. Which is which? Explain.

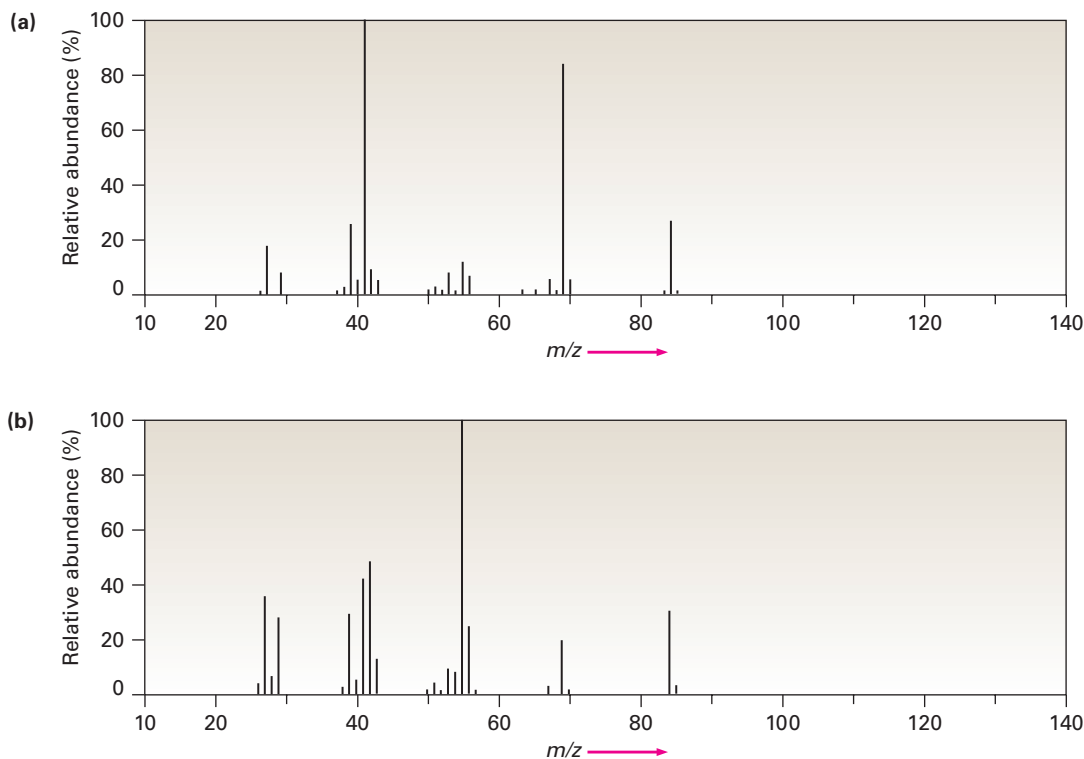


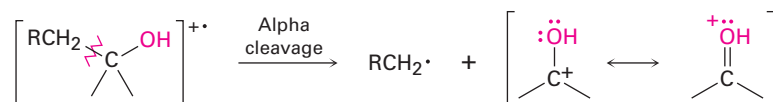
FIGURE 10.7
Mass spectra for
Problem 10.2.

10-3 Mass Spectrometry of Some Common Functional Groups

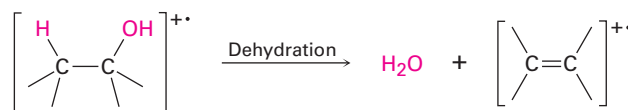
As each functional group is discussed in future chapters, mass-spectral fragmentations characteristic of that group will be described. As a preview, though, we'll point out some distinguishing features of several common functional groups.

Alcohols

Alcohols undergo fragmentation in the mass spectrometer by two pathways: *alpha cleavage* and *dehydration*. In the α -cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation.

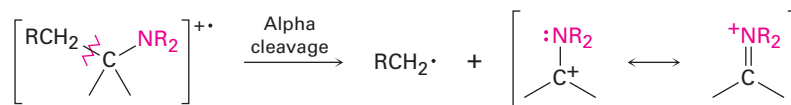


In the dehydration pathway, water is eliminated, yielding an alkene radical cation with a mass 18 units less than M^+ :



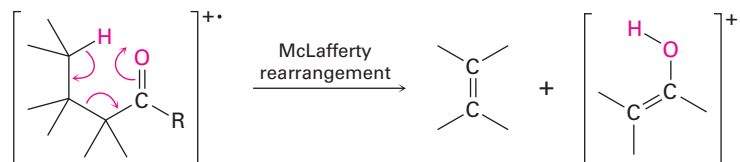
Amines

Aliphatic amines undergo a characteristic α cleavage in the mass spectrometer, similar to that observed for alcohols. A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.

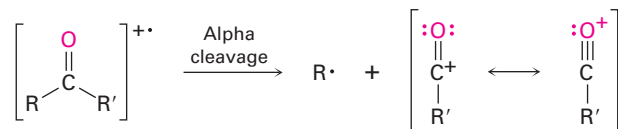


Carbonyl Compounds

Ketones and aldehydes that have a hydrogen on a carbon three atoms away from the carbonyl group undergo a characteristic mass-spectral cleavage called the *McLafferty rearrangement*. The hydrogen atom is transferred to the carbonyl oxygen, a C–C bond is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition, ketones and aldehydes frequently undergo α cleavage of the bond between the carbonyl group and the neighboring carbon. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.



Identifying Fragmentation Patterns in a Mass Spectrum

WORKED EXAMPLE 10.2

The mass spectrum of 2-methylpentan-3-ol is shown in **FIGURE 10.8**. What fragments can you identify?

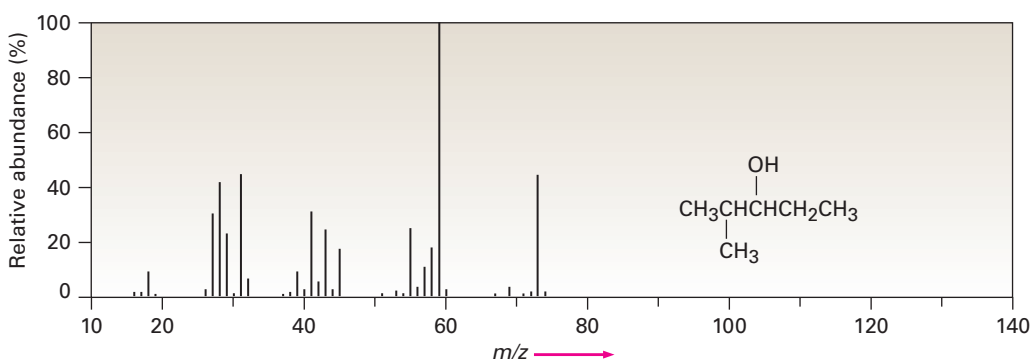


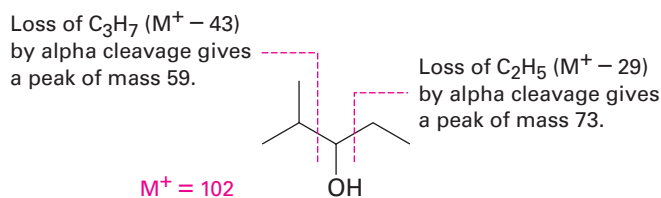
FIGURE 10.8
Mass spectrum of
2-methylpentan-3-ol for
Worked Example 10.2.

Strategy

Calculate the mass of the molecular ion, and identify the functional groups in the molecule. Then write the fragmentation processes you might expect, and compare the masses of the resultant fragments with the peaks present in the spectrum.

Solution

2-Methylpentan-3-ol, an open-chain alcohol, has $M^+ = 102$ and might be expected to fragment by α cleavage and by dehydration. These processes would lead to fragment ions of $m/z = 84$, 73 , and 59 . Of the three expected fragments, dehydration is not observed (no $m/z = 84$ peak), but both α cleavages take place ($m/z = 73$, 59).



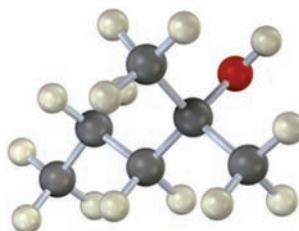
PROBLEM 10.3

What are the masses of the charged fragments produced in the following cleavage pathways?

- (a) Alpha cleavage of pentan-2-one ($\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_3$)
- (b) Dehydration of cyclohexanol
- (c) McLafferty rearrangement of 4-methylpentan-2-one [$\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$]
- (d) Alpha cleavage of triethylamine [$(\text{CH}_3\text{CH}_2)_3\text{N}$]

PROBLEM 10.4

List the masses of the parent ion and of several fragments that you might expect to find in the mass spectrum of the following molecule:



10-4 Mass Spectrometry in Biological Chemistry: Time-of-Flight (TOF) Instruments

Most biochemical analyses by MS use either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), typically linked to a time-of-flight (TOF) mass analyzer. Both ESI and MALDI are soft ionization methods that produce charged molecules with little fragmentation, even with biological samples of very high molecular weight.

In an ESI source, the sample is dissolved in a polar solvent and sprayed through a steel capillary tube. As it exits the tube, it is subjected to a high voltage that causes it to become protonated by removing one or more H^+ ions from the solvent. The volatile solvent is then evaporated, giving variably protonated sample molecules ($\text{M} + \text{H}_n^{n+}$). In a MALDI source, the sample is adsorbed onto a suitable matrix compound, such as 2,5-dihydroxybenzoic acid, which is ionized by a short burst of laser light. The matrix compound then transfers the energy to the sample and protonates it, forming $\text{M} + \text{H}_n^{n+}$ ions.

Following ion formation, the variably protonated sample molecules are electrically focused into a small packet with a narrow spatial distribution, and the packet is given a sudden kick of energy by an accelerator electrode. Since each molecule in the packet is given the same energy, $E = mv^2/2$, it begins moving with a velocity that depends on the square root of its mass, $v = \sqrt{2E/m}$. Lighter molecules move faster, and heavier molecules move slower. The analyzer itself—the *drift tube*—is simply an electrically grounded metal tube inside of which the different charged molecules become separated as they move along at different velocities and take different amounts of time to complete their flight.

The TOF technique is considerably more sensitive than the magnetic-sector alternative, and protein samples of up to 100 kilodaltons (100,000 amu) can be separated with a mass accuracy of 3 ppm. **FIGURE 10.9** shows a MALDI-TOF spectrum of chicken egg-white lysozyme, MW = 14,306.7578 daltons. (Biochemists generally use the unit *dalton*, abbreviated Da, instead of amu.)

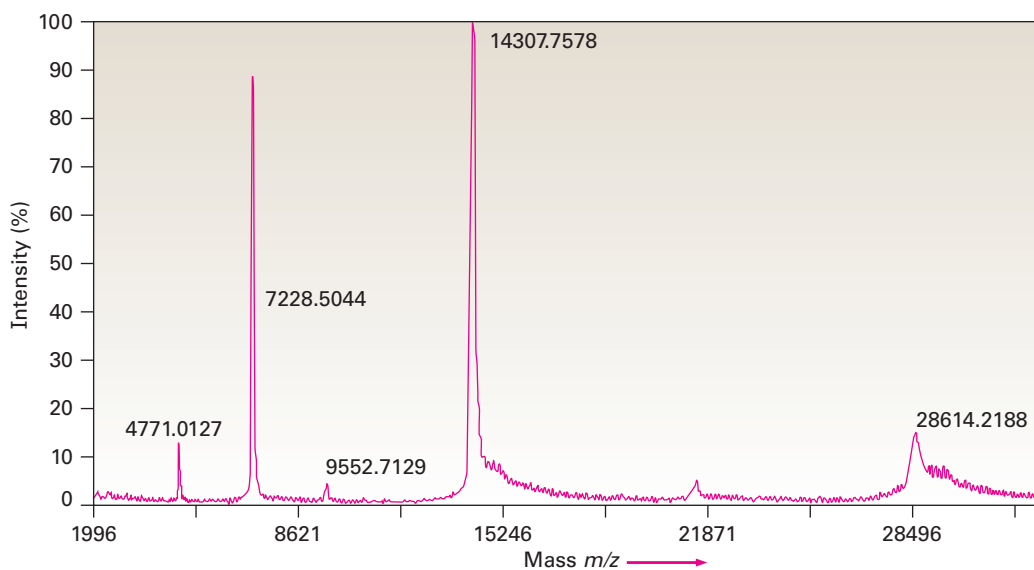


FIGURE 10.9 MALDI-TOF mass spectrum of chicken egg-white lysozyme. The peak at 14,307.7578 daltons (amu) is due to the monoprotonated protein, $M+H^+$, and the peak at 28,614.2188 daltons is due to an impurity formed by dimerization of the protein. Other peaks are various protonated species, $M+H_n^{n+}$.

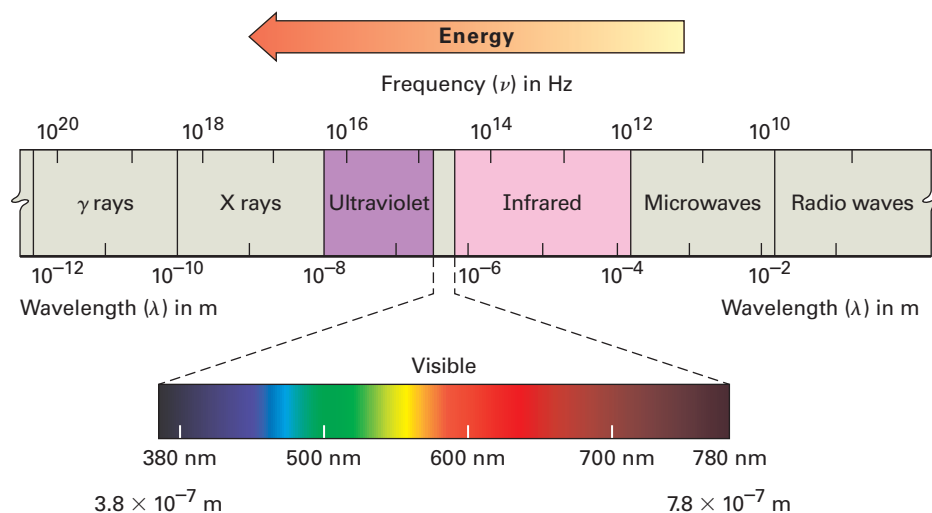
10-5 Spectroscopy and the Electromagnetic Spectrum

Infrared, ultraviolet, and nuclear magnetic resonance spectroscopies differ from mass spectrometry in that they are nondestructive and involve the interaction of molecules with electromagnetic energy rather than with an ionizing source. Before beginning a study of these techniques, however, let's briefly review the nature of radiant energy and the electromagnetic spectrum.

Visible light, X rays, microwaves, radio waves, and so forth are all different kinds of *electromagnetic radiation*. Collectively, they make up the **electromagnetic spectrum**, shown in **FIGURE 10.10**. The spectrum is arbitrarily divided into regions, with the familiar visible region accounting for only a small portion, from 3.8×10^{-7} m to 7.8×10^{-7} m in wavelength. The visible region is flanked by the infrared and ultraviolet regions.

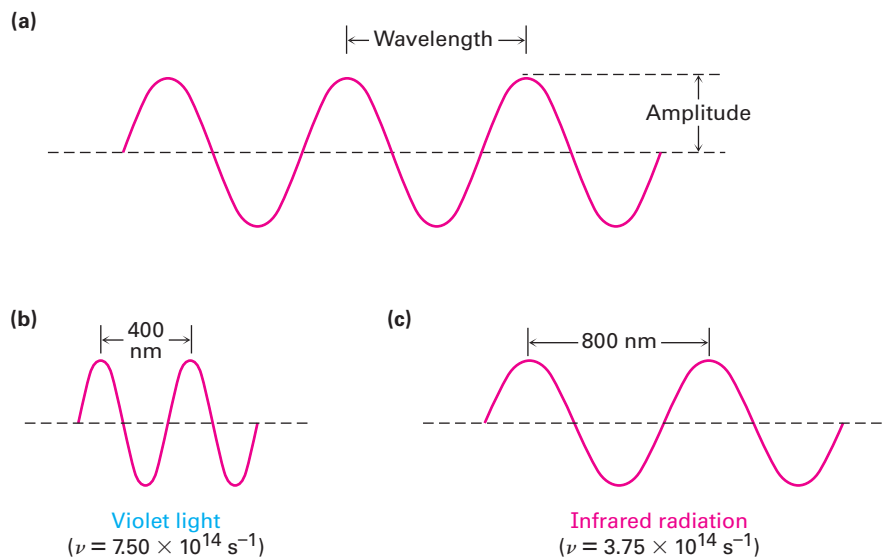
Electromagnetic radiation is often said to have dual behavior. In some respects, it has the properties of a particle called a *photon*, yet in other respects it behaves as an energy wave. Like all waves, electromagnetic radiation is characterized by a *wavelength*, a *frequency*, and an *amplitude* (**FIGURE 10.11**). The **wavelength**, λ (Greek lambda), is the distance from one

FIGURE 10.10 The electromagnetic spectrum. The spectrum covers a continuous range of wavelengths and frequencies, from radio waves at the low-frequency end to gamma (γ) rays at the high-frequency end. The familiar visible region accounts for only a small portion near the middle of the spectrum.



wave maximum to the next. The **frequency**, ν (Greek nu), is the number of waves that pass by a fixed point per unit time, usually given in reciprocal seconds (s^{-1}), or **hertz**, **Hz** ($1 \text{ Hz} = 1 \text{ s}^{-1}$). The **amplitude** is the height of a wave, measured from midpoint to peak. The intensity of radiant energy, whether a feeble glow or a blinding glare, is proportional to the square of the wave's amplitude.

FIGURE 10.11 Electromagnetic waves. All waves are characterized by a wavelength, a frequency, and an amplitude. **(a)** Wavelength (λ) is the distance between two successive wave maxima. Amplitude is the height of the wave measured from the center. **(b), (c)** What we perceive as different kinds of electromagnetic radiation are simply waves with different wavelengths and frequencies.



Multiplying the wavelength of a wave in meters (m) by its frequency in reciprocal seconds (s^{-1}) gives the speed of the wave in meters per second (m/s). The rate of travel of all electromagnetic radiation in a vacuum is a constant value, commonly called the "speed of light" and abbreviated c . Its numerical value is defined as exactly $2.997\,924\,58 \times 10^8 \text{ m/s}$, often rounded off to $3.00 \times 10^8 \text{ m/s}$.

Wavelength \times Frequency = Speed

$$\lambda \text{ (m)} \times \nu \text{ (s}^{-1}\text{)} = c \text{ (m/s)}$$

$$\lambda = \frac{c}{\nu} \quad \text{or} \quad \nu = \frac{c}{\lambda}$$

Just as matter comes only in discrete units called atoms, electromagnetic energy is transmitted only in discrete amounts called *quanta*. The amount of energy, ϵ , corresponding to 1 quantum of energy (1 photon) of a given frequency ν is expressed by the Planck equation

$$\epsilon = h\nu = \frac{hc}{\lambda}$$

where h = Planck's constant ($6.62 \times 10^{-34} \text{ J} \cdot \text{s} = 1.58 \times 10^{-34} \text{ cal} \cdot \text{s}$).

The Planck equation says that the energy of a given photon varies directly with its frequency ν but inversely with its wavelength λ . High frequencies and short wavelengths correspond to high-energy radiation such as gamma rays; low frequencies and long wavelengths correspond to low-energy radiation such as radio waves. Multiplying ϵ by Avogadro's number, N_A , gives the same equation in more familiar units, where E represents the energy of Avogadro's number (one "mole") of photons of wavelength λ :

$$E = \frac{N_A hc}{\lambda} = \frac{1.20 \times 10^{-4} \text{ kJ/mol}}{\lambda \text{ (m)}} \quad \text{or} \quad \frac{2.86 \times 10^{-5} \text{ kcal/mol}}{\lambda \text{ (m)}}$$

When an organic compound is exposed to a beam of electromagnetic radiation, it absorbs energy of some wavelengths but passes, or transmits, energy of other wavelengths. If we irradiate the sample with energy of many different wavelengths and determine which are absorbed and which are transmitted, we can measure the **absorption spectrum** of the compound.

An example of an absorption spectrum—that of ethanol exposed to infrared radiation—is shown in **FIGURE 10.12**. The horizontal axis records the wavelength, and the vertical axis records the intensity of the various energy absorptions in percent transmittance. The baseline corresponding to 0% absorption (or 100% transmittance) runs along the top of the chart, so a downward spike means that energy absorption has occurred at that wavelength.

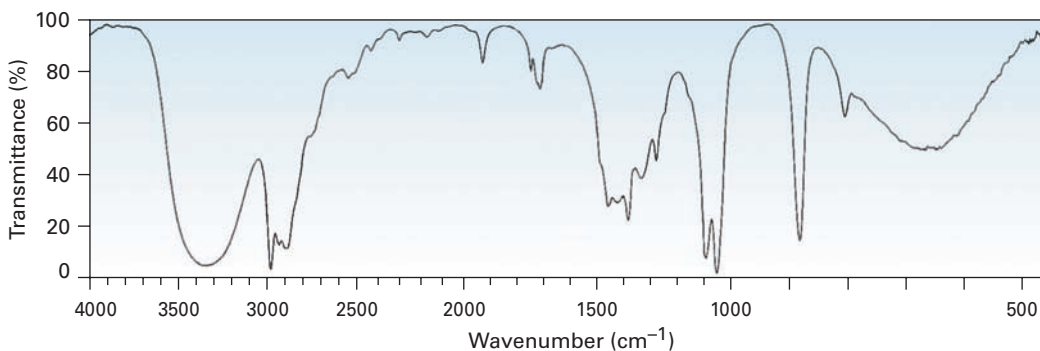


FIGURE 10.12 Infrared absorption spectrum of ethanol, $\text{CH}_3\text{CH}_2\text{OH}$. A transmittance of 100% means that all the energy is passing through the sample, whereas a lower transmittance means that some energy is being absorbed. Thus, each downward spike corresponds to an energy absorption.

The energy a molecule gains when it absorbs radiation must be distributed over the molecule in some way. With infrared radiation, the absorbed energy causes bonds to stretch and bend more vigorously. With ultraviolet radiation, the energy causes an electron to jump from a lower-energy orbital to a higher-energy one. Different radiation frequencies affect molecules in different ways, but each provides structural information when the results are interpreted.

There are many kinds of spectroscopies, which differ according to the region of the electromagnetic spectrum used. We'll look at three: infrared spectroscopy, ultraviolet spectroscopy, and nuclear magnetic resonance spectroscopy. Let's begin by seeing what happens when an organic sample absorbs infrared energy.

WORKED EXAMPLE 10.3**Correlating Energy and Frequency of Radiation**

Which is higher in energy, FM radio waves with a frequency of 1.015×10^8 Hz (101.5 MHz) or visible green light with a frequency of 5×10^{14} Hz?

Strategy

Remember the equations $\epsilon = h\nu$ and $\epsilon = hc/\lambda$, which say that energy increases as frequency increases and as wavelength decreases.

Solution

Since visible light has a higher frequency than radio waves, it is higher in energy.

PROBLEM 10.5

Which has higher energy, infrared radiation with $\lambda = 1.0 \times 10^{-6}$ m or an X ray with $\lambda = 3.0 \times 10^{-9}$ m? Radiation with $\nu = 4.0 \times 10^9$ Hz or with $\lambda = 9.0 \times 10^{-6}$ m?

PROBLEM 10.6

It's useful to develop a feeling for the amounts of energy that correspond to different parts of the electromagnetic spectrum. Calculate the energies in kJ/mol of each of the following kinds of radiation:

- A gamma ray with $\lambda = 5.0 \times 10^{-11}$ m
- An X ray with $\lambda = 3.0 \times 10^{-9}$ m
- Ultraviolet light with $\nu = 6.0 \times 10^{15}$ Hz
- Visible light with $\nu = 7.0 \times 10^{14}$ Hz
- Infrared radiation with $\lambda = 2.0 \times 10^{-5}$ m
- Microwave radiation with $\nu = 1.0 \times 10^{11}$ Hz

10-6 Infrared Spectroscopy

The **infrared (IR)** region of the electromagnetic spectrum covers the range from just above the visible (7.8×10^{-7} m) to approximately 10^{-4} m, but only the midportion from 2.5×10^{-6} m to 2.5×10^{-5} m is used by organic chemists (**FIGURE 10.13**). Wavelengths within the IR region are usually given

in micrometers ($1 \mu\text{m} = 10^{-6} \text{ m}$), and frequencies are given in *wavenumbers* rather than in hertz. The **wavenumber** ($\tilde{\nu}$) is the reciprocal of the wavelength in centimeters and is therefore expressed in units of cm^{-1} :

$$\text{Wavenumber: } \tilde{\nu}(\text{cm}^{-1}) = \frac{1}{\lambda (\text{cm})}$$

Thus, the useful IR region is from 4000 to 400 cm^{-1} , corresponding to energies of 48.0 kJ/mol to 4.80 kJ/mol (11.5 – 1.15 kcal/mol).

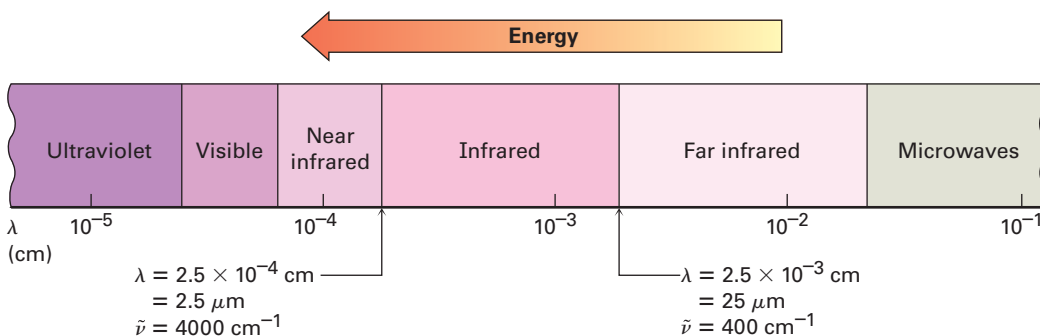
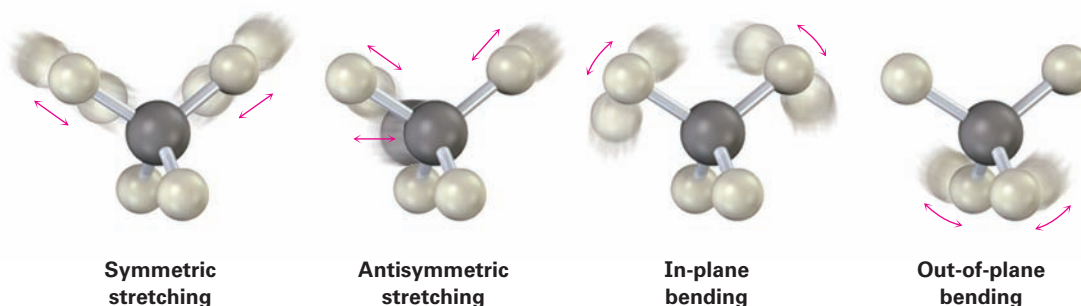


FIGURE 10.13
Infrared and adjacent regions of the electromagnetic spectrum.

Why does an organic molecule absorb some wavelengths of IR radiation but not others? All molecules have a certain amount of energy and are in constant motion. Their bonds stretch and contract, atoms wag back and forth, and other molecular vibrations occur. Some of the kinds of allowed vibrations are shown below:



The amount of energy a molecule contains is not continuously variable but is *quantized*. That is, a molecule can stretch or bend only at specific frequencies corresponding to specific energy levels. Take bond stretching, for example. Although we usually speak of bond lengths as if they were fixed, the numbers given are really averages. In fact, a typical C–H bond with an average bond length of 110 pm is actually vibrating at a specific frequency, alternately stretching and contracting as if there were a spring connecting the two atoms.

When a molecule is irradiated with electromagnetic radiation, energy is absorbed if the frequency of the radiation matches the frequency of the vibration. The result of this energy absorption is an increased amplitude for the vibration; in other words, the “spring” connecting the two atoms stretches and compresses a bit further. Since each frequency absorbed by a molecule corresponds to a specific molecular motion, we can find what kinds of motions a molecule has by measuring its IR spectrum. By then interpreting those

motions, we can find out what kinds of bonds (functional groups) are present in the molecule.

IR spectrum → **What molecular motions?** → **What functional groups?**

10-7 Interpreting Infrared Spectra

The complete interpretation of an IR spectrum is difficult because most organic molecules have dozens of different bond stretching and bending motions and thus have dozens of absorptions. On the one hand, this complexity is a problem because it generally limits the laboratory use of IR spectroscopy to pure samples of fairly small molecules—little can be learned about large, complex biomolecules using IR spectroscopy. On the other hand, the complexity is useful because an IR spectrum acts as a unique fingerprint of a compound. In fact, the complex region of the IR spectrum from 1500 cm^{-1} to around 400 cm^{-1} is called the *fingerprint region*. If two samples have identical IR spectra, they are almost certainly identical compounds.

Fortunately, we don't need to interpret an IR spectrum fully to get useful structural information. Most functional groups have characteristic IR absorption bands that don't change from one compound to another. The C=O absorption of a ketone is almost always in the range 1670 to 1750 cm^{-1} , the O–H absorption of an alcohol is almost always in the range 3400 to 3650 cm^{-1} , the C=C absorption of an alkene is almost always in the range 1640 to 1680 cm^{-1} , and so forth. By learning where characteristic functional-group absorptions occur, it's possible to get structural information from IR spectra. **TABLE 10.1** lists the characteristic IR bands of some common functional groups.

TABLE 10.1 Characteristic IR Absorptions of Some Functional Groups

Functional Group	Absorption (cm^{-1})	Intensity	Functional Group	Absorption (cm^{-1})	Intensity
Alkane			Amine		
C–H	2850–2960	Medium	N–H	3300–3500	Medium
Alkene			C–N	1030–1230	Medium
=C–H	3020–3100	Medium	Carbonyl compound		
C=C	1640–1680	Medium	C=O	1670–1780	Strong
Alkyne			Aldehyde	1730	Strong
C–H	3300	Strong	Ketone	1715	Strong
C≡C	2100–2260	Medium	Ester	1735	Strong
Alkyl halide			Amide	1690	Strong
C–Cl	600–800	Strong	Carboxylic acid	1710	Strong
C–Br	500–600	Strong	Carboxylic acid		
Alcohol			O–H	2500–3100	Strong, broad
O–H	3400–3650	Strong, broad	Nitrile		
C–O	1050–1150	Strong	C≡N	2210–2260	Medium
Arene			Nitro		
C–H	3030	Weak	NO ₂	1540	Strong
Aromatic ring	1660–2000	Weak			
	1450–1600	Medium			

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Look at the IR spectra of hexane, hex-1-ene, and hex-1-yne in **FIGURE 10.14** to see an example of how IR spectroscopy can be used. Although all three IR spectra contain many peaks, there are characteristic absorptions of the C=C and C≡C functional groups that allow the three compounds to be distinguished. Thus, hex-1-ene shows a characteristic C=C absorption at 1660 cm^{-1} and a vinylic =C–H absorption at 3100 cm^{-1} , whereas hex-1-yne has a C≡C absorption at 2100 cm^{-1} and a terminal alkyne ≡C–H absorption at 3300 cm^{-1} .

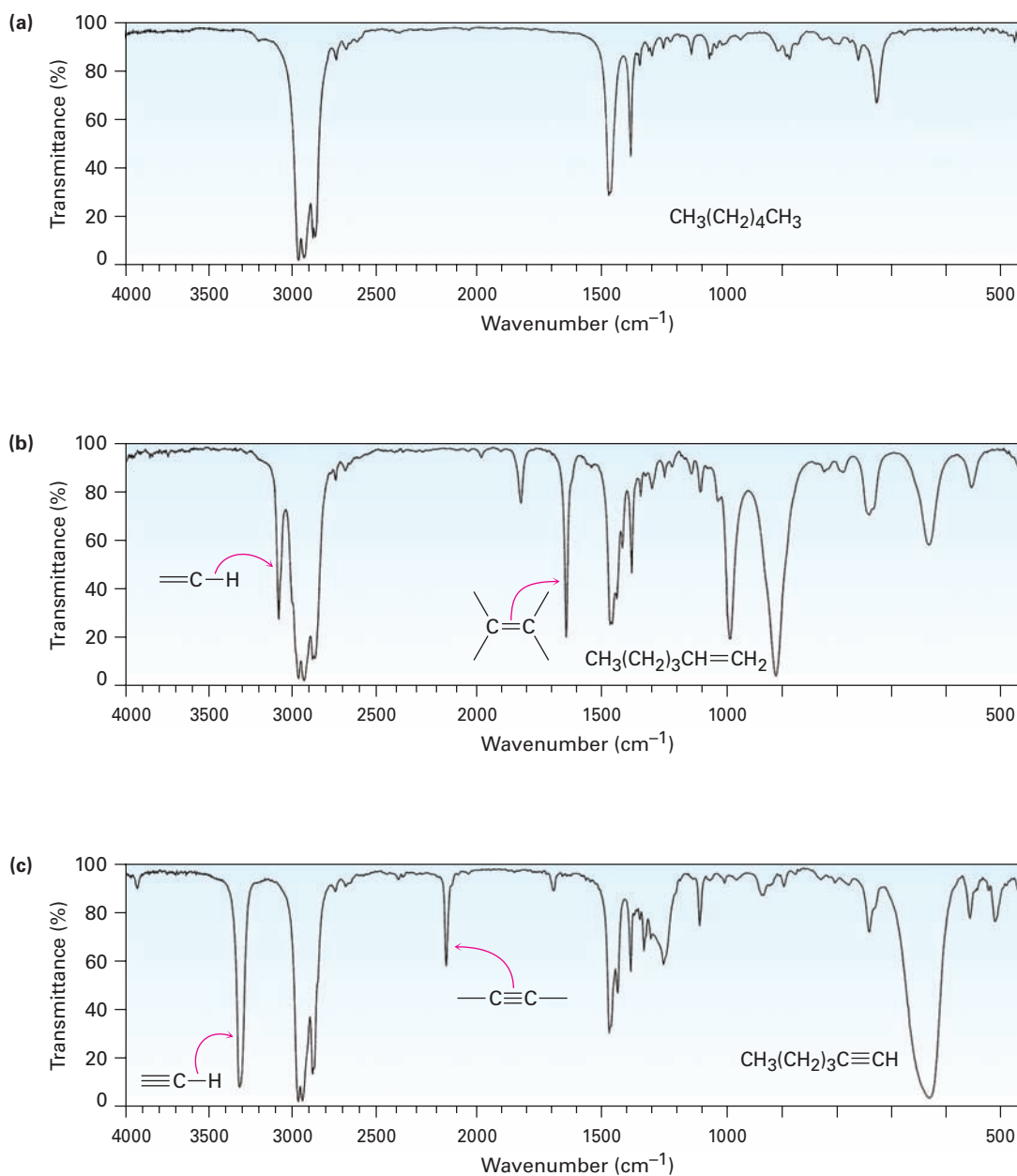
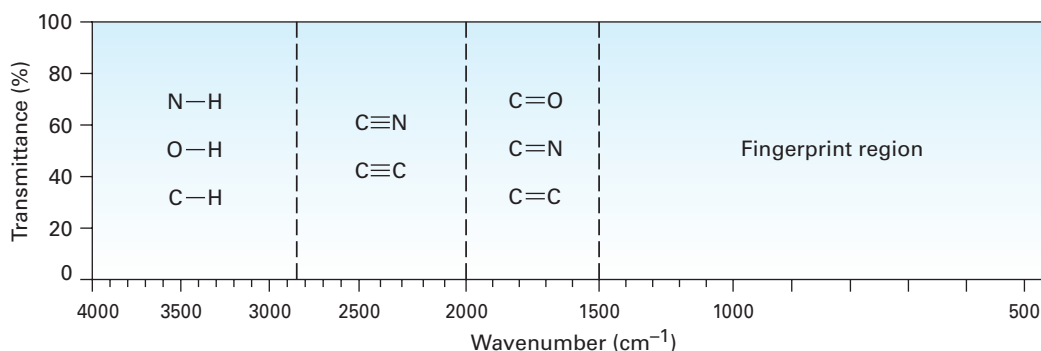


FIGURE 10.14 IR spectra of (a) hexane, (b) hex-1-ene, and (c) hex-1-yne. Spectra like these are easily obtained on submilligram amounts of material in a few minutes using commercially available instruments.

It helps in remembering the position of specific IR absorptions to divide the IR region from 4000 cm^{-1} to 400 cm^{-1} into four parts, as shown in **FIGURE 10.15**.

- The region from 4000 to 2500 cm^{-1} corresponds to absorptions caused by N–H, C–H, and O–H single-bond stretching motions. N–H and O–H bonds absorb in the 3300 to 3600 cm^{-1} range; C–H bond stretching occurs near 3000 cm^{-1} .
- The region from 2500 to 2000 cm^{-1} is where triple-bond stretching occurs. Both $\text{C}\equiv\text{N}$ and $\text{C}\equiv\text{C}$ bonds absorb here.
- The region from 2000 to 1500 cm^{-1} is where double bonds ($\text{C}=\text{O}$, $\text{C}=\text{N}$, and $\text{C}=\text{C}$) absorb. Carbonyl groups generally absorb in the range 1670 to 1780 cm^{-1} , and alkene stretching normally occurs in the narrow range 1640 to 1680 cm^{-1} .
- The region below 1500 cm^{-1} is the fingerprint portion of the IR spectrum. A large number of absorptions due to a variety of C–C, C–O, C–N, and C–X single-bond vibrations occur here.

FIGURE 10.15 The four regions of the infrared spectrum: single bonds to hydrogen, triple bonds, double bonds, and fingerprint.



Why do different functional groups absorb where they do? As noted previously, a good analogy is that of two weights (atoms) connected by a spring (a bond). Short, strong bonds vibrate at a higher energy and higher frequency than do long, weak bonds, just as a short, strong spring vibrates faster than a long, weak spring. Thus, triple bonds absorb at a higher frequency than double bonds, which in turn absorb at a higher frequency than single bonds. In addition, springs connecting small weights vibrate faster than springs connecting large weights. Thus, C–H, O–H, and N–H bonds vibrate at a higher frequency than bonds between heavier C, O, and N atoms.

WORKED EXAMPLE 10.4

Distinguishing Isomeric Compounds by IR Spectroscopy

Acetone (CH_3COCH_3) and prop-2-en-1-ol ($\text{H}_2\text{C}=\text{CHCH}_2\text{OH}$) are isomers. How could you distinguish them by IR spectroscopy?

Strategy

Identify the functional groups in each molecule, and refer to Table 10.1.

Solution

Acetone has a strong $\text{C}=\text{O}$ absorption at 1715 cm^{-1} , while prop-2-en-1-ol has an $-\text{OH}$ absorption at 3500 cm^{-1} and a $\text{C}=\text{C}$ absorption at 1660 cm^{-1} .

PROBLEM 10.7

What functional groups might the following molecules contain?

- (a) A compound with a strong absorption at 1710 cm^{-1}
- (b) A compound with a strong absorption at 1540 cm^{-1}
- (c) A compound with strong absorptions at 1720 cm^{-1} and at 2500 to 3100 cm^{-1}

PROBLEM 10.8

How might you use IR spectroscopy to distinguish between the following pairs of isomers?

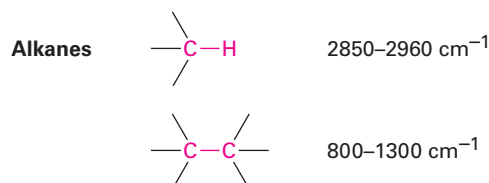
- (a) $\text{CH}_3\text{CH}_2\text{OH}$ and CH_3OCH_3
- (b) Cyclohexane and hex-1-ene
- (c) $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$ and $\text{HOCH}_2\text{CH}_2\text{CHO}$

10-8 Infrared Spectra of Some Common Functional Groups

As each functional group is discussed in future chapters, the spectroscopic properties of that group will be described. For the present, we'll point out some distinguishing features of the hydrocarbon functional groups already studied and briefly preview some other common functional groups. We should also point out, however, that in addition to interpreting absorptions that *are* present in an IR spectrum, it's also possible to get structural information by noticing which absorptions are *not* present. If the spectrum of a compound has no absorptions at 3300 and 2150 cm^{-1} , the compound is not a terminal alkyne; if the spectrum has no absorption near 3400 cm^{-1} , the compound is not an alcohol; and so on.

Alkanes


The IR spectrum of an alkane is fairly uninformative because no functional groups are present and all absorptions are due to C–H and C–C bonds. Alkane C–H bonds show a strong absorption from 2850 to 2960 cm^{-1} , and saturated C–C bonds show a number of bands in the 800 to 1300 cm^{-1} range. Since most organic compounds contain saturated alkane-like portions, most organic compounds have these characteristic IR absorptions. The C–H and C–C bands are clearly visible in the three spectra shown in Figure 10.14.



Alkenes

Alkenes show several characteristic stretching absorptions. Vinylic $=\text{C}-\text{H}$ bonds absorb from 3020 to 3100 cm^{-1} , and alkene $\text{C}=\text{C}$ bonds usually absorb near 1650 cm^{-1} , although in some cases the peaks can be rather small and difficult to see clearly. Both absorptions are visible in the hex-1-ene spectrum in Figure 10.14b.

Monosubstituted and disubstituted alkenes have characteristic $=\text{C}-\text{H}$ out-of-plane bending absorptions in the 700 to 1000 cm^{-1} range, thereby allowing the substitution pattern on a double bond to be determined. Monosubstituted alkenes such as hex-1-ene show strong characteristic bands at 910 and 990 cm^{-1} , and 2,2-disubstituted alkenes ($\text{R}_2\text{C}=\text{CH}_2$) have an intense band at 890 cm^{-1} .

Alkenes	$=\text{C}-\text{H}$	$3020\text{--}3100\text{ cm}^{-1}$
		$1640\text{--}1680\text{ cm}^{-1}$
	$\text{RCH}=\text{CH}_2$	910 and 990 cm^{-1}
	$\text{R}_2\text{C}=\text{CH}_2$	890 cm^{-1}



Alkynes

Alkynes show a $\text{C}\equiv\text{C}$ stretching absorption at 2100 to 2260 cm^{-1} , an absorption that is much more intense for terminal alkynes than for internal alkynes. In fact, symmetrically substituted triple bonds like that in hex-3-yne show no absorption at all, for reasons we won't go into. Terminal alkynes such as hex-1-yne also have a characteristic $\equiv\text{C}-\text{H}$ stretch at 3300 cm^{-1} (Figure 10.14c). This band is diagnostic for terminal alkynes because it is fairly intense and quite sharp.

Alkynes	$-\text{C}\equiv\text{C}-$	$2100\text{--}2260\text{ cm}^{-1}$
	$\equiv\text{C}-\text{H}$	3300 cm^{-1}

Aromatic Compounds

Aromatic compounds, such as benzene, have a weak $\text{C}-\text{H}$ stretching absorption at 3030 cm^{-1} , just to the left of a typical saturated $\text{C}-\text{H}$ band. In addition, up to four absorptions are observed in the 1450 to 1600 cm^{-1} region because of complex molecular motions of the ring itself. Two bands, one at 1500 cm^{-1} and one at 1600 cm^{-1} , are usually the most intense. In addition, aromatic compounds show weak absorptions in the 1660 to 2000 cm^{-1} region and strong absorptions in the 690 to 900 cm^{-1} range due to $\text{C}-\text{H}$ out-of-plane bending. The exact position of both sets of absorptions is diagnostic of the substitution pattern of the aromatic ring.

Aromatic compounds		3030 cm ⁻¹ (weak)	
		Ring	
Monosubstituted	690–710 cm ⁻¹ 730–770 cm ⁻¹	<i>m</i>-Disubstituted	690–710 cm ⁻¹ 810–850 cm ⁻¹
<i>o</i>-Disubstituted	735–770 cm ⁻¹	<i>p</i>-Disubstituted	810–840 cm ⁻¹

The IR spectrum of toluene in **FIGURE 10.16** shows these characteristic absorptions.

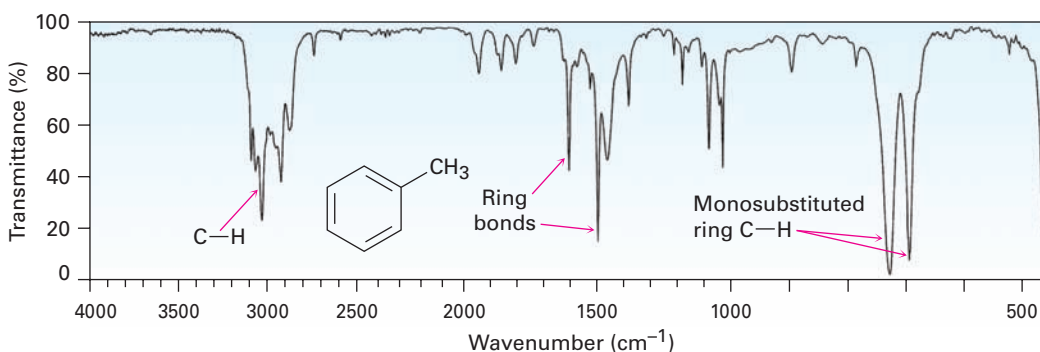


FIGURE 10.16
Infrared spectrum
of toluene.

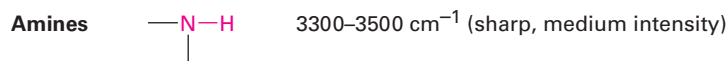
Alcohols

The O–H functional group of alcohols is easy to spot. Alcohols have a characteristic band in the range 3400 to 3650 cm⁻¹ that is usually broad and intense. If present, it's hard to miss this band or to confuse it with anything else.



Amines

The N–H functional group of amines is also easy to spot in the IR, with a characteristic absorption in the 3300 to 3500 cm⁻¹ range. Although alcohols absorb in the same range, an N–H absorption is sharper and less intense than an O–H band.

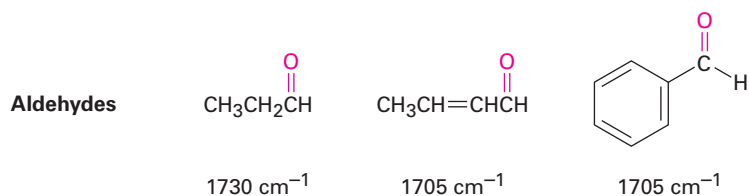


Carbonyl Compounds

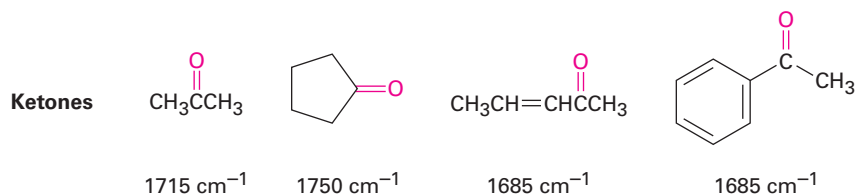
Carbonyl functional groups are the easiest to identify of all IR absorptions because of their sharp, intense peak in the range 1670 to 1780 cm⁻¹. Most

important, the exact position of absorption within the range can often be used to identify the exact kind of carbonyl functional group—aldehyde, ketone, ester, and so forth.

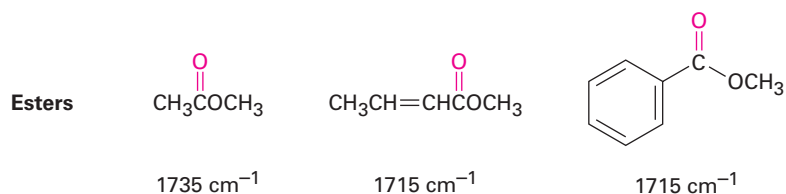
ALDEHYDES Saturated aldehydes absorb at 1730 cm^{-1} ; aldehydes next to either a double bond or an aromatic ring absorb at 1705 cm^{-1} .



KETONES Saturated open-chain ketones and six-membered cyclic ketones absorb at 1715 cm^{-1} , five-membered cyclic ketones absorb at 1750 cm^{-1} , and ketones next to a double bond or an aromatic ring absorb at 1685 cm^{-1} .

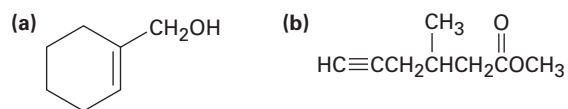


ESTERS Saturated esters absorb at 1735 cm^{-1} ; esters next to either a double bond or an aromatic ring absorb at 1715 cm^{-1} .



WORKED EXAMPLE 10.5 Predicting IR Absorptions of Compounds

Where might the following compounds have IR absorptions?



Strategy

Identify the functional groups in each molecule, and check Table 10.1 to see where those groups absorb.

Solution

- (a) *Absorptions:* $3400\text{--}3650\text{ cm}^{-1}$ (O–H), $3020\text{--}3100\text{ cm}^{-1}$ (=C–H), $1640\text{--}1680\text{ cm}^{-1}$ (C=C). This molecule has an alcohol O–H group and an alkene double bond.
- (b) *Absorptions:* 3300 cm^{-1} ($\equiv\text{C}\text{--}\text{H}$), $2100\text{--}2260\text{ cm}^{-1}$ (C \equiv C), 1735 cm^{-1} (C=O). This molecule has a terminal alkyne triple bond and a saturated ester carbonyl group.

Identifying Functional Groups from an IR Spectrum**WORKED EXAMPLE 10.6**

The IR spectrum of an unknown compound is shown in **FIGURE 10.17**. What functional groups does the compound contain?

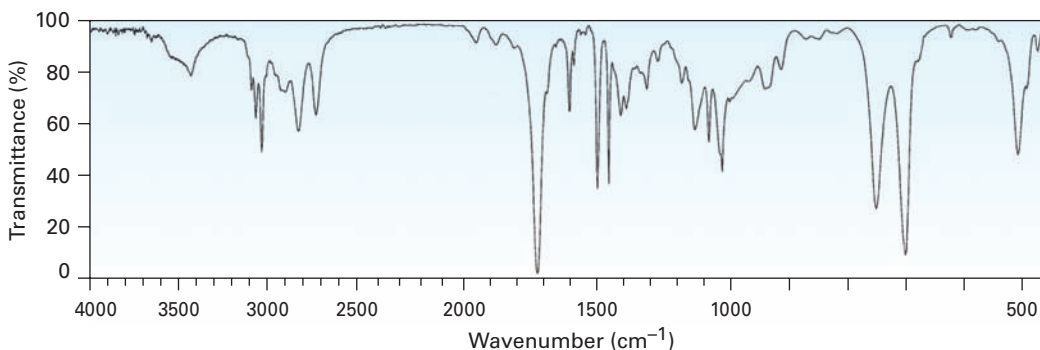


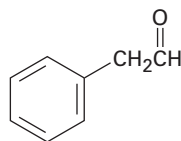
FIGURE 10.17 IR spectrum for Worked Example 10.6.

Strategy

All IR spectra have many absorptions, but those useful for identifying specific functional groups are usually found in the region from 1500 cm^{-1} to 3300 cm^{-1} . Pay particular attention to the carbonyl region (1670 to 1780 cm^{-1}), the aromatic region (1660 to 2000 cm^{-1}), the triple-bond region (2000 to 2500 cm^{-1}), and the C–H region (2500 to 3500 cm^{-1}).

Solution

The spectrum shows an intense absorption at 1725 cm^{-1} due to a carbonyl group (perhaps an aldehyde, --CHO), a series of weak absorptions from 1800 to 2000 cm^{-1} characteristic of aromatic compounds, and a C–H absorption near 3030 cm^{-1} , also characteristic of aromatic compounds. In fact, the compound is phenylacetaldehyde.

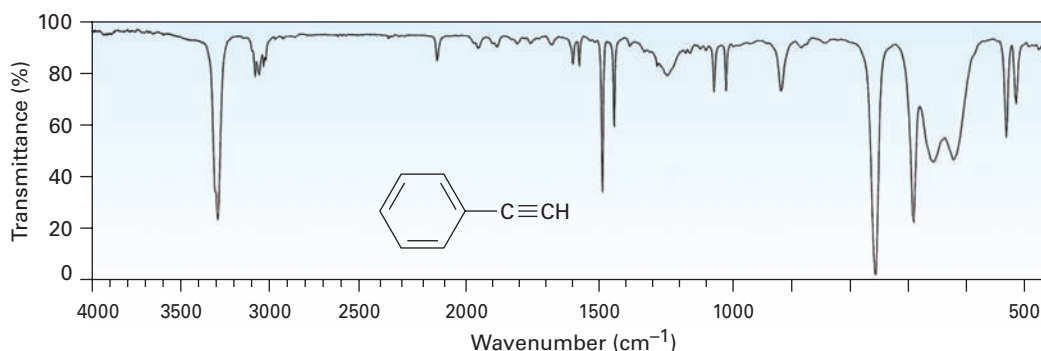


Phenylacetaldehyde

PROBLEM 10.9

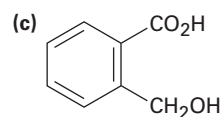
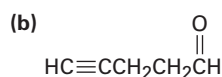
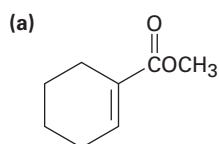
The IR spectrum of phenylacetylene is shown in **FIGURE 10.18**. What absorption bands can you identify?

FIGURE 10.18
IR spectrum of
phenylacetylene for
Problem 10.9.



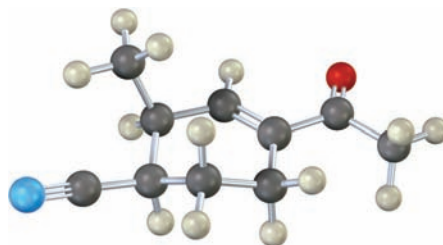
PROBLEM 10.10

Where might the following compounds have IR absorptions?



PROBLEM 10.11

Where might the following compound have IR absorptions?



10-9 Ultraviolet Spectroscopy

The **ultraviolet (UV)** region of the electromagnetic spectrum extends from the short-wavelength end of the visible region (4×10^{-7} m) to the long-wavelength end of the X-ray region (10^{-8} m), but the narrow range from 2×10^{-7} m to 4×10^{-7} m is the part of greatest interest to organic chemists. Absorptions in this region are usually measured in nanometers (nm), where $1 \text{ nm} = 10^{-9}$ m. Thus, the ultraviolet range of interest is from 200 to 400 nm (**FIGURE 10.19**).

We've just seen that when a molecule is subjected to IR irradiation, the energy absorbed corresponds to the amount necessary to increase molecular vibrations. With UV radiation, the energy absorbed corresponds to the amount necessary to promote an electron from one orbital to another in a conjugated molecule. The conjugated diene buta-1,3-diene, for example, has four π molecular orbitals, as shown previously in Figure 8.12 on page 244. The two lower-energy, bonding MOs are occupied in the ground state, and the two higher-energy, antibonding MOs are unoccupied.

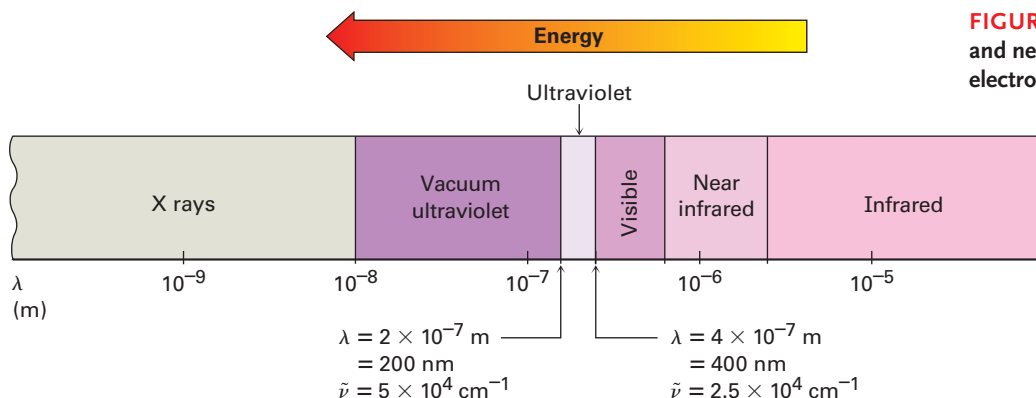


FIGURE 10.19 Ultraviolet (UV) and neighboring regions of the electromagnetic spectrum.

On irradiation with ultraviolet light ($h\nu$), buta-1,3-diene absorbs energy and a π electron is promoted from the **highest occupied molecular orbital**, or **HOMO**, to the **lowest unoccupied molecular orbital**, or **LUMO**. Since the electron is promoted from a bonding π molecular orbital to an antibonding π molecular orbital, we call this a $\pi \rightarrow \pi^*$ excitation (read as “pi to pi star”). The energy gap between the HOMO and the LUMO of buta-1,3-diene is such that UV light of 217 nm wavelength is required to accomplish the $\pi \rightarrow \pi^*$ electronic transition (**FIGURE 10.20**).

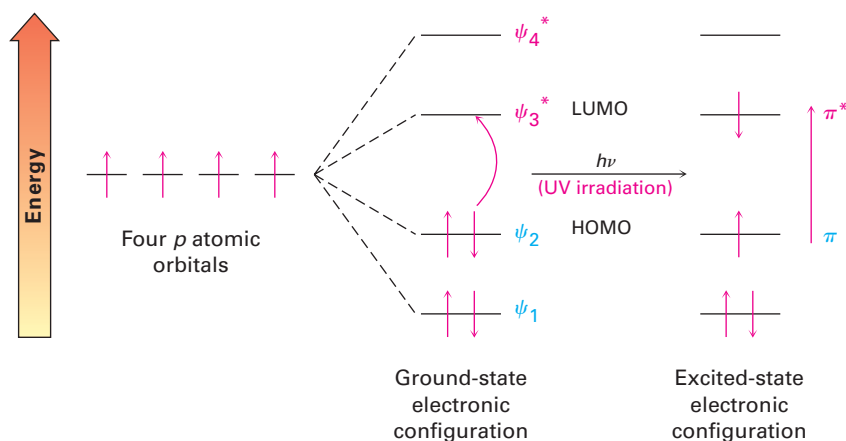


FIGURE 10.20 Ultraviolet irradiation of buta-1,3-diene. Irradiation results in promotion of an electron from ψ_2 , the highest occupied molecular orbital (HOMO), to ψ_3^* , the lowest unoccupied molecular orbital (LUMO).

An ultraviolet spectrum is recorded by irradiating the sample with UV light of continuously changing wavelength. When the wavelength corresponds to the energy level required to excite an electron to a higher level, energy is absorbed. This absorption is detected and displayed on a chart that plots wavelength versus *absorbance* (A), defined as

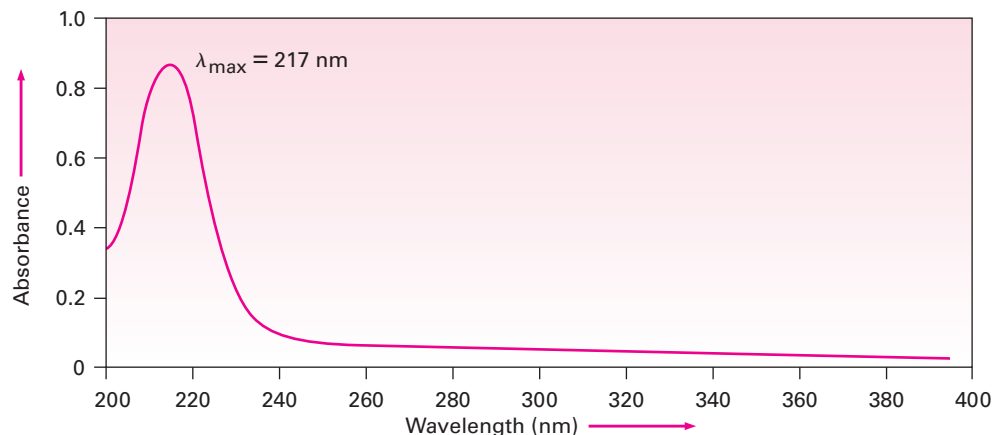
$$A = \log \frac{I_0}{I}$$

where I_0 is the intensity of the incident light and I is the intensity of the light transmitted through the sample.

Note that UV spectra differ from IR spectra in the way they are presented. For historical reasons, IR spectra are usually displayed so that the baseline corresponding to zero absorption runs across the top of the chart and a valley

indicates an absorption, whereas UV spectra are displayed with the baseline at the bottom of the chart so that a peak indicates an absorption (FIGURE 10.21).

FIGURE 10.21 Ultraviolet spectrum of buta-1,3-diene, $\lambda_{\max} = 217 \text{ nm}$.



The amount of UV light absorbed is expressed as the sample's *molar absorptivity* (ϵ), defined by the equation

$$\epsilon = \frac{A}{c \times l}$$

where A = Absorbance
 c = Concentration in mol/L
 l = Sample pathlength in cm

Molar absorptivity is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular π electron system in the molecule. Typical values for conjugated dienes are in the range $\epsilon = 10,000$ to $25,000$. The units for molar absorptivity, $\text{L}/(\text{mol} \cdot \text{cm})$, are usually dropped.

A particularly important use of this equation comes from rearranging it to the form $c = A / (\epsilon \cdot l)$, which lets us measure the concentration of a sample in solution when A , ϵ , and l are known. As an example, β -carotene, the pigment responsible for the orange color of carrots, has $\epsilon = 138,000 \text{ L}/(\text{mol} \cdot \text{cm})$. If a sample of β -carotene is placed in a cell with a pathlength of 1.0 cm and the UV absorbance reads 0.37 , then the concentration of β -carotene in the sample is

$$\begin{aligned} c &= \frac{A}{\epsilon l} = \frac{0.37}{\left(1.38 \times 10^5 \frac{\text{L}}{\text{mol} \cdot \text{cm}}\right)(1.00 \text{ cm})} \\ &= 2.7 \times 10^{-6} \text{ mol/L} \end{aligned}$$

Unlike IR spectra, which show many absorptions for a given molecule, UV spectra are usually quite simple—often only a single peak. The peak is usually broad, and we identify its position by noting the wavelength at the very top of the peak— λ_{\max} , read as “lambda max.”

PROBLEM 10.12

Calculate the energy range of radiation in the UV region of the spectrum from 200 to 400 nm. How does this value compare with the value calculated previously for IR radiation in Section 10-6?

PROBLEM 10.13

If pure vitamin A has $\lambda_{\max} = 325$ ($\epsilon = 50,100$), what is the vitamin A concentration in a sample whose absorbance at 325 nm is $A = 0.735$ in a cell with a pathlength of 1.00 cm?



10-10 Interpreting Ultraviolet Spectra: The Effect of Conjugation

The wavelength necessary to effect the $\pi \rightarrow \pi^*$ transition in a conjugated molecule depends on the energy gap between HOMO and LUMO, which in turn depends on the nature of the conjugated system. Thus, by measuring the UV spectrum of an unknown, we can derive structural information about the nature of any conjugated π electron system present in a molecule.

One of the most important factors affecting the wavelength of UV absorption by a molecule is the extent of conjugation. Molecular orbital calculations show that the energy difference between HOMO and LUMO decreases as the extent of conjugation increases. Thus, buta-1,3-diene absorbs at $\lambda_{\max} = 217$ nm, hexa-1,3,5-triene absorbs at $\lambda_{\max} = 258$ nm, and octa-1,3,5,7-tetraene absorbs at $\lambda_{\max} = 290$ nm. (Remember: longer wavelength means lower energy.)

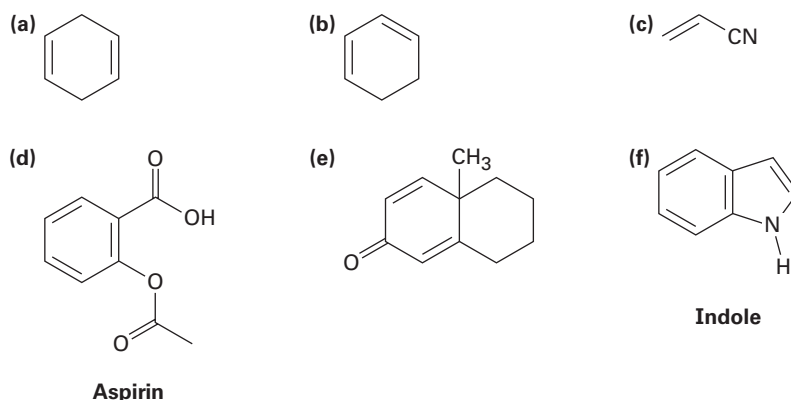
Other kinds of conjugated systems, such as conjugated enones and aromatic rings, also have characteristic UV absorptions that are useful in structure determination. The UV absorption maxima of some representative conjugated molecules are given in **TABLE 10.2**.

TABLE 10.2 Ultraviolet Absorptions of Some Conjugated Molecules

Name	Structure	λ_{\max} (nm)
2-Methylbuta-1,3-diene	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{C}=\text{C}-\text{CH}=\text{CH}_2 \end{array}$	220
Cyclohexa-1,3-diene		256
Hexa-1,3,5-triene	$\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$	258
Octa-1,3,5,7-tetraene	$\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$	290
But-3-en-2-one	$\begin{array}{c} \text{O} \\ \\ \text{H}_2\text{C}=\text{CH}-\text{C}-\text{CH}_3 \end{array}$	219
Benzene		203

PROBLEM 10.14

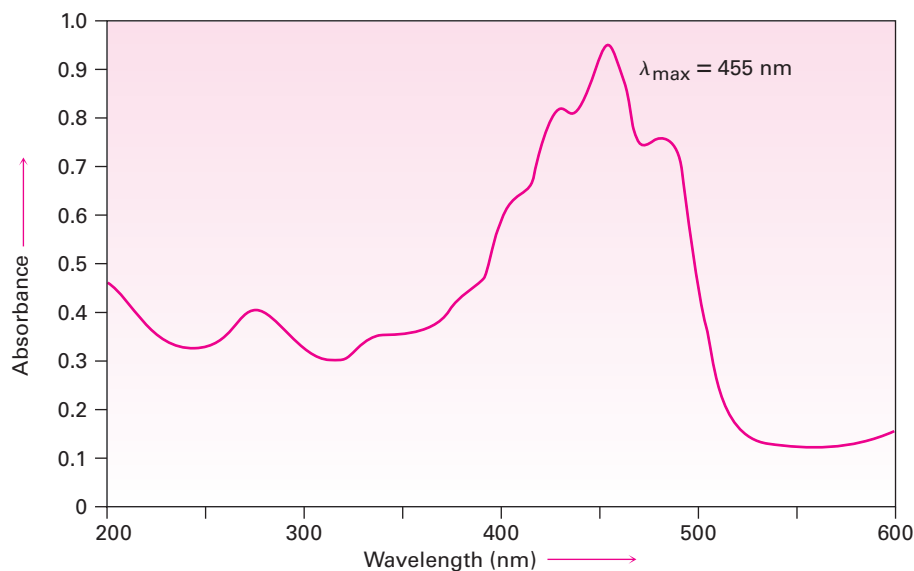
Which of the following compounds would you expect to show ultraviolet absorptions in the 200 to 400 nm range?

**10-11 Conjugation, Color, and the Chemistry of Vision**

Why are some organic compounds colored while others are not? β -Carotene, the pigment in carrots, is purple-orange, for instance, while cholesterol is colorless. The answer involves both the chemical structure of colored molecules and the way we perceive light.

The visible region of the electromagnetic spectrum is adjacent to the ultraviolet region, extending from approximately 400 to 800 nm. Colored compounds have such extended systems of conjugation that their “UV” absorptions extend into the visible region. β -Carotene, for example, has 11 double bonds in conjugation, and its absorption occurs at $\lambda_{\text{max}} = 455 \text{ nm}$ (FIGURE 10.22).

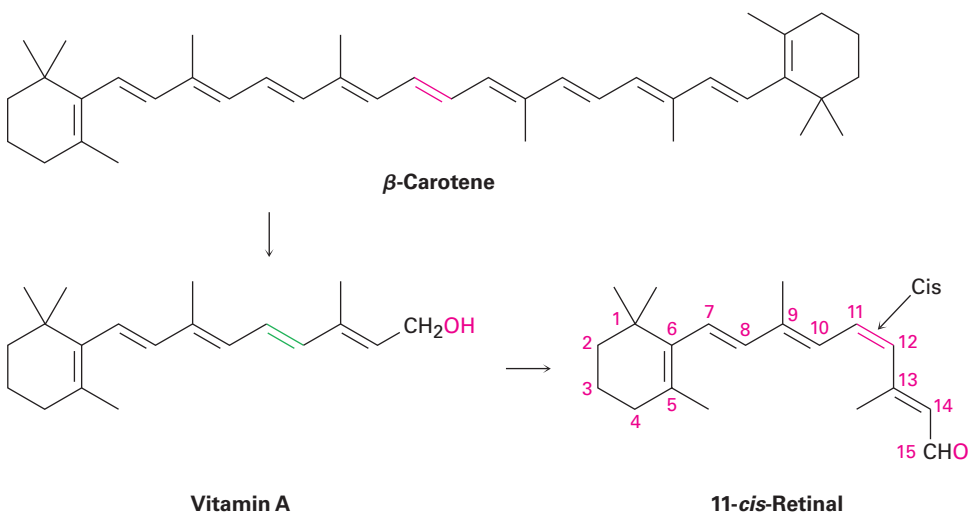
FIGURE 10.22 Ultraviolet spectrum of β -carotene, a conjugated molecule with 11 double bonds. The absorption occurs in the visible region, giving β -carotene a deep orange color.



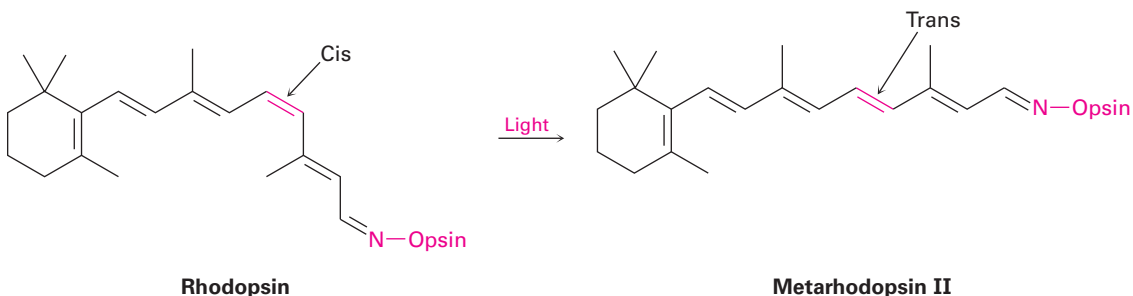
“White” light from the sun or from a lamp consists of all wavelengths in the visible region. When white light strikes β -carotene, the wavelengths from 400 to 500 nm (blue) are absorbed while all other wavelengths are transmitted

and reach our eyes. We therefore see the white light with the blue removed, and we perceive a yellow-orange color for β -carotene.

Conjugation is crucial not only for the colors we see in organic molecules but also for the light-sensitive molecules on which our visual system is based. The key substance for vision is dietary β -carotene, which is converted to vitamin A by enzymes in the liver, oxidized to an aldehyde called 11-*trans*-retinal, and then isomerized by a change in geometry of the C11–C12 double bond to produce 11-*cis*-retinal.



There are two main types of light-sensitive receptor cells in the retina of the human eye, *rod* cells and *cone* cells. The 3 million or so rod cells are primarily responsible for seeing in dim light, whereas the 100 million cone cells are responsible for seeing in bright light and for the perception of bright colors. In the rod cells of the eye, 11-*cis*-retinal is converted into rhodopsin, a light-sensitive substance formed from the protein opsin and 11-*cis*-retinal. When light strikes the rod cells, isomerization of the C11–C12 double bond occurs and *trans*-rhodopsin, called metarhodopsin II, is produced. In the absence of light, this *cis*–*trans* isomerization takes approximately 1100 years, but in the presence of light, it occurs within 200 femtoseconds, or 2×10^{-13} seconds! Isomerization of rhodopsin is accompanied by a change in molecular geometry, which in turn causes a nerve impulse to be sent through the optic nerve to the brain, where it is perceived as vision.



Metarhodopsin II is then recycled back into rhodopsin by a multistep sequence involving cleavage to all-*trans*-retinal and *cis*–*trans* isomerization back to 11-*cis*-retinal.

SOMETHING EXTRA

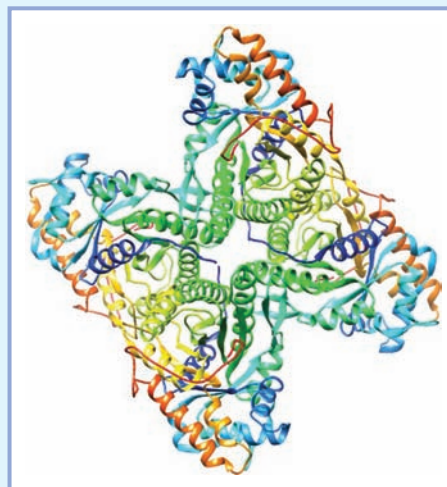
X-Ray Crystallography

The various spectroscopic techniques described in this and the next chapters are enormously important in chemistry and have been fine-tuned to such a degree that the structure of almost any molecule can be found. Nevertheless, wouldn't it be nice if you could simply look at a molecule and "see" its structure with your eyes?

Determining the three-dimensional shape of an object around you is easy—you just look at it, let your eyes focus the light rays reflected from the object, and let your brain assemble the data into a recognizable image. If the object is small, you use a microscope and let the microscope lens focus the visible light. Unfortunately, there is a limit to what you can see, even with the best optical microscope. Called the diffraction limit, you can't see anything smaller than the wavelength of light you are using for the observation. Visible light has wavelengths of several hundred nanometers, but atoms in molecules have dimension on the order of 0.1 nm. Thus, to "see" a molecule—whether a small one in the laboratory or a large, complex enzyme with a molecular weight in the tens of thousands—you need wavelengths in the 0.1 nm range, which corresponds to X rays.

Let's say that we want to determine the structure and shape of an enzyme or other biological molecule. The technique used is called *X-ray crystallography*. First, the molecule is crystallized (which often turns out to be the most difficult and time-consuming part of the entire process) and a small crystal with a dimension of 0.4–0.5 mm on its longest axis is glued to the end of a glass fiber. The fiber and attached crystal are then mounted in an instrument called an X-ray diffractometer, which consists of a radiation source, a sample positioning and orienting device that can rotate the crystal in any direction, a detector, and a controlling computer.

Once mounted in the diffractometer, the crystal is irradiated with X rays,



PDB ID: 1ALD, Gamblin, S.J., Davies, G.J., Grimes, J.M., Jackson, R.M., Littlechild, J.A., Watson, H.C., (1981) *J.Mol.Biol.* 219: 573-576

The structure of human muscle fructose-1,6-bisphosphate aldolase, as determined by X-ray crystallography and downloaded from the Protein Data Bank, 1ALD.

usually so-called $\text{CuK}\alpha$ radiation with a wavelength of 0.154 nm. When the X rays strike the enzyme crystal, they interact with electrons in the molecule and are scattered into a diffraction pattern which, when detected and visualized, appears as a series of intense spots against a null background.

Manipulation of the diffraction pattern to extract three-dimensional molecular data is a complex process, but the final result is that an electron-density map of the molecule is produced. Because electrons are largely localized around atoms, any two centers of electron density located within bonding distance of each other are assumed to represent bonded atoms, leading to a recognizable chemical structure. This structural information is so important for biochemistry that an online database of more than 94,000 biological substances has been created. Operated by Rutgers University and funded by the U.S. National Science Foundation, the Protein Data Bank (PDB) is a worldwide repository for processing and distributing three-dimensional structural data for biological macromolecules. We'll see how to access the PDB in the Chapter 19 *Something Extra*.

SUMMARY

Finding the structure of a new molecule, whether a small one synthesized in the laboratory or a large protein found in living organisms, is central to progress in chemistry and biochemistry. The structure of an organic molecule is usually determined using spectroscopic methods, including mass spectrometry, infrared spectroscopy, and ultraviolet spectroscopy. **Mass spectrometry (MS)** tells the molecular weight and formula of a molecule, **infrared (IR) spectroscopy** identifies the functional groups present in the molecule, and **ultraviolet (UV) spectroscopy** tells whether the molecule has a conjugated π -electron system.

In small-molecule mass spectrometry, molecules are first ionized by collision with a high-energy electron beam. The ions then fragment into smaller pieces, which are magnetically sorted according to their mass-to-charge ratio (m/z). The ionized sample molecule is called the *molecular ion*, M^+ , and measurement of its mass gives the molecular weight of the sample. Structural clues about unknown samples can be obtained by interpreting the fragmentation pattern of the molecular ion. Mass-spectral fragmentations are usually complex, however, and interpretation is often difficult. In biological mass spectrometry, molecules are protonated using either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), and the protonated molecules are separated by time-of-flight (TOF).

Infrared spectroscopy involves the interaction of a molecule with **electromagnetic radiation**. When an organic molecule is irradiated with infrared energy, certain **frequencies** are absorbed by the molecule. The frequencies absorbed correspond to the amounts of energy needed to increase the amplitude of specific molecular vibrations, such as bond stretchings and bendings. Since every functional group has a characteristic combination of bonds, every functional group has a characteristic set of infrared absorptions. By observing which frequencies of infrared radiation are absorbed by a molecule and which are not, it's possible to determine the functional groups a molecule contains.

Ultraviolet spectroscopy is applicable only to conjugated π -electron systems. When a conjugated molecule is irradiated with ultraviolet light, energy absorption occurs and a π electron is promoted from the **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**. The greater the extent of conjugation, the less the energy needed and the longer the wavelength of radiation required.

KEY WORDS

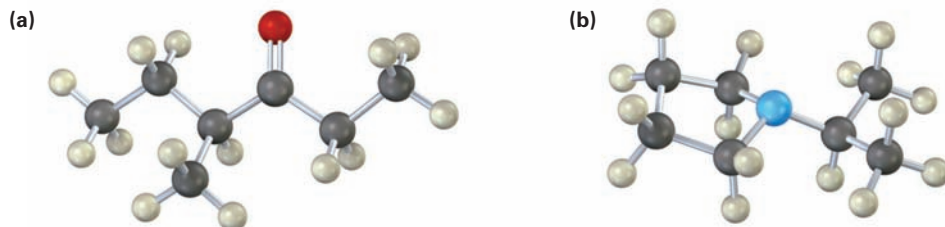
- absorption spectrum, 331
- amplitude, 330
- base peak, 321
- electromagnetic spectrum, 329
- frequency, (ν), 330
- hertz (Hz), 330
- highest occupied molecular orbital (HOMO), 343
- infrared (IR) spectroscopy, 332
- lowest unoccupied molecular orbital (LUMO), 343
- mass spectrometry (MS), 320
- mass spectrum, 321
- parent peak, 321
- ultraviolet (UV) spectroscopy, 342
- wavelength, (λ), 329
- wavenumber ($\bar{\nu}$), 333

EXERCISES

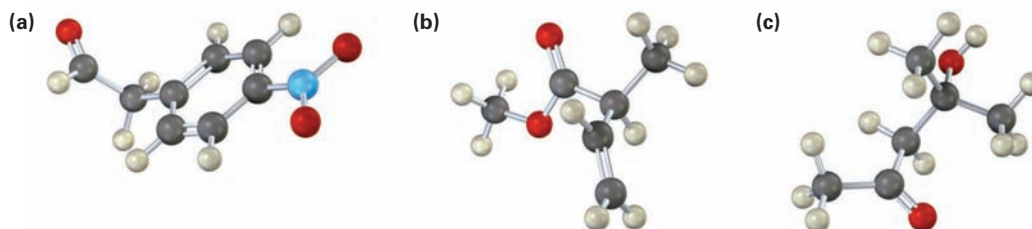
VISUALIZING CHEMISTRY

(Problems 10.1–10.14 appear within the chapter.)

10.15 Show the structures of the likely fragments you would expect in the mass spectra of the following molecules:



10.16 Where in the IR spectrum would you expect each of the following molecules to absorb?



10.17 Which, if any, of the compounds shown in Problems 10.15 and 10.16 have UV absorptions?

ADDITIONAL PROBLEMS

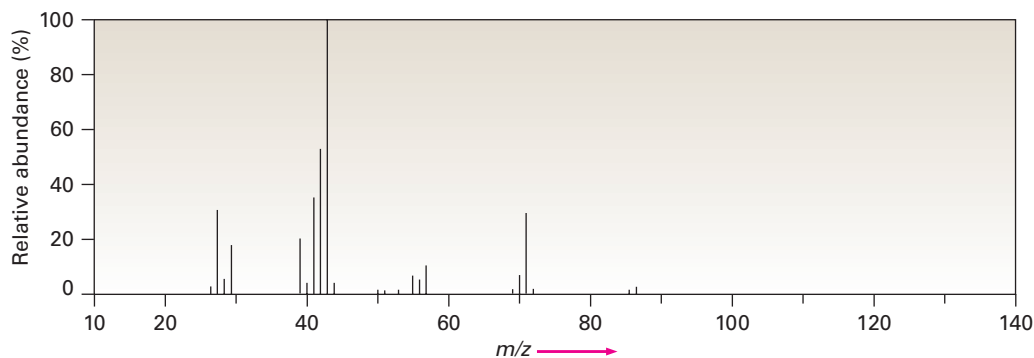
Mass Spectrometry

10.18 Propose structures for compounds consistent with the following mass-spectral data:

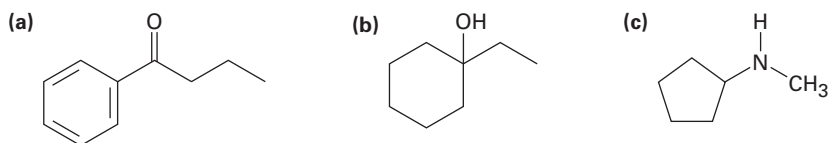
- (a) A hydrocarbon with $M^+ = 132$
- (b) A hydrocarbon with $M^+ = 166$
- (c) A hydrocarbon with $M^+ = 84$

- 10.19** Write molecular formulas for compounds that show the following molecular ions in their high-resolution mass spectra, assuming that C, H, N, and O might be present. The exact atomic masses are: 1.007 83 (^1H), 12.000 00 (^{12}C), 14.003 07 (^{14}N), 15.994 91 (^{16}O).
- (a) $M^+ = 98.0844$ (b) $M^+ = 123.0320$
- 10.20** Camphor, a saturated monoketone from the Asian camphor tree, is used as a moth repellent and as a constituent of embalming fluid, among other things. If camphor has $M^+ = 152.1201$ by high-resolution mass spectrometry, what is its molecular formula?
- 10.21** The *nitrogen rule* of mass spectrometry says that a compound containing an odd number of nitrogens has an odd-numbered molecular ion. Conversely, a compound containing an even number of nitrogens has an even-numbered M^+ peak. Explain.
- 10.22** In light of the nitrogen rule mentioned in Problem 10.21, what is the molecular formula of pyridine, $M^+ = 79$?
- 10.23** Nicotine is a diamino compound isolated from dried tobacco leaves. Nicotine has two rings and $M^+ = 162.1157$ by high-resolution mass spectrometry. Give a molecular formula for nicotine, and calculate the number of double bonds it contains.
- 10.24** The hormone cortisone contains C, H, and O, and shows a molecular ion at $M^+ = 360.1937$ by high-resolution mass spectrometry. What is the molecular formula of cortisone? (The degree of unsaturation of cortisone is 8.)
- 10.25** Halogenated compounds are particularly easy to identify by their mass spectra because both chlorine and bromine occur naturally as mixtures of two abundant isotopes. Chlorine occurs as ^{35}Cl (75.8%) and ^{37}Cl (24.2%); bromine occurs as ^{79}Br (50.7%) and ^{81}Br (49.3%). At what masses do the molecular ions occur for the following formulas? What are the relative percentages of each molecular ion?
- (a) Bromomethane, CH_3Br (b) 1-Chlorohexane, $\text{C}_6\text{H}_{13}\text{Cl}$
- 10.26** Propose structures for compounds that fit the following data:
- (a) A ketone with $M^+ = 86$ and fragments at $m/z = 71$ and $m/z = 43$
- (b) An alcohol with $M^+ = 88$ and fragments at $m/z = 73$, $m/z = 70$, and $m/z = 59$

- 10.27** 2-Methylpentane (C_6H_{14}) has the mass spectrum shown. Which peak represents M^+ ? Which is the base peak? Propose structures for fragment ions of $m/z = 71$, 57, 43, and 29. Why does the base peak have the mass it does?



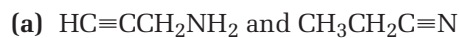
- 10.28** Assume that you are in a laboratory carrying out the catalytic hydrogenation of cyclohexene to cyclohexane. How could you use mass spectrometry to determine when the reaction is finished?
- 10.29** What fragments might you expect in the mass spectra of the following compounds?



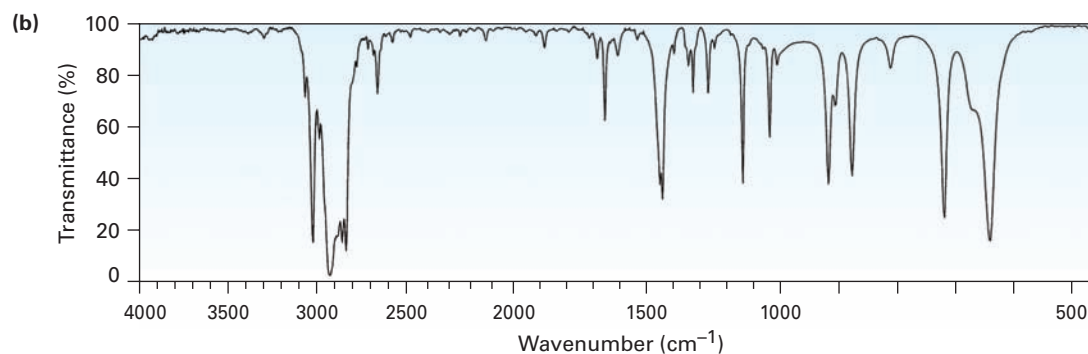
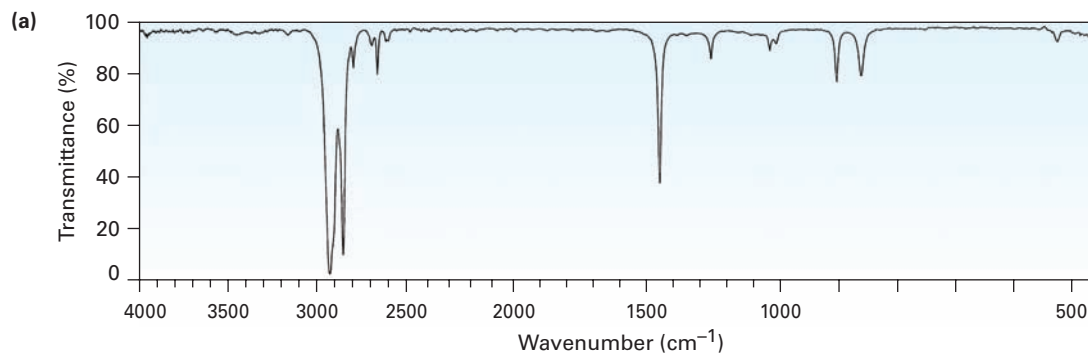
Infrared Spectroscopy

- 10.30** How might you use IR spectroscopy to distinguish among the three isomers but-1-yne, buta-1,3-diene, and but-2-yne?
- 10.31** Would you expect two enantiomers such as (*R*)-2-bromobutane and (*S*)-2-bromobutane to have identical or different IR spectra? Explain.
- 10.32** Would you expect two diastereomers such as *meso*-2,3-dibromobutane and (*2R,3R*)-dibromobutane to have identical or different IR spectra? Explain.
- 10.33** Propose structures for compounds that meet the following descriptions:
- C_5H_8 , with IR absorptions at 3300 and 2150 cm^{-1}
 - C_4H_8O , with a strong IR absorption at 3400 cm^{-1}
 - C_4H_8O , with a strong IR absorption at 1715 cm^{-1}
 - C_8H_{10} , with IR absorptions at 1600 and 1500 cm^{-1}

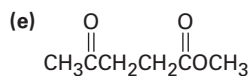
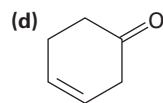
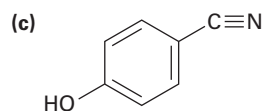
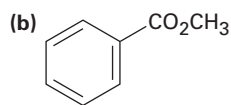
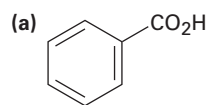
10.34 How could you use infrared spectroscopy to distinguish between the following pairs of isomers?



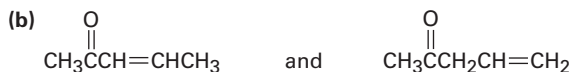
10.35 Two infrared spectra are shown. One is the spectrum of cyclohexane, and the other is the spectrum of cyclohexene. Identify them, and explain your answer.



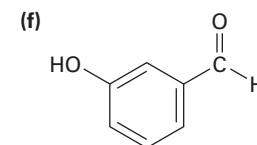
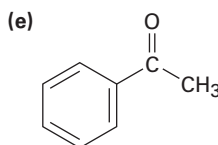
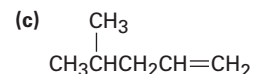
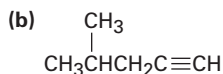
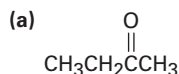
10.36 At what approximate positions might the following compounds show IR absorptions?



10.37 How would you use infrared spectroscopy to distinguish between the following pairs of constitutional isomers?



10.38 At what approximate positions might the following compounds show IR absorptions?



10.39 Assume that you are carrying out the dehydration of 1-methylcyclohexanol to yield 1-methylcyclohexene. How could you use infrared spectroscopy to determine when the reaction is complete?

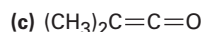
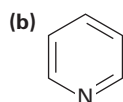
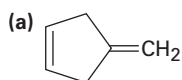
10.40 Assume that you are carrying out an elimination reaction on 3-bromo-3-methylpentane to yield an alkene. How could you use IR spectroscopy to tell which of two possible elimination products is formed, 3-methylpent-2-ene or 2-ethylbut-1-ene?

10.41 Which is stronger, the C=O bond in an ester (1735 cm^{-1}) or the C=O bond in a saturated ketone (1715 cm^{-1})? Explain.

Ultraviolet Spectroscopy

10.42 Would you expect allene, $\text{H}_2\text{C}=\text{C}=\text{CH}_2$, to show a UV absorption in the 200 to 400 nm range? Explain.

10.43 Which of the following compounds would you expect to have a $\pi \rightarrow \pi^*$ UV absorption in the 200 to 400 nm range?



A ketene

Pyridine

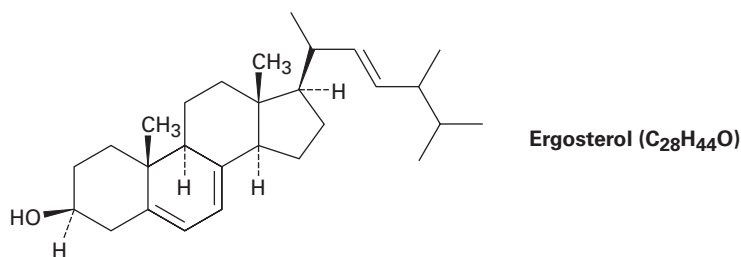
10.44 The following ultraviolet absorption maxima have been measured:

Buta-1,3-diene	217 nm
2-Methylbuta-1,3-diene	220 nm
Penta-1,3-diene	223 nm
2,3-Dimethylbuta-1,3-diene	226 nm
Hexa-2,4-diene	227 nm
2,4-Dimethylpenta-1,3-diene	232 nm
2,5-Dimethylhexa-2,4-diene	240 nm

What conclusion can you draw about the effect of alkyl substitution on UV absorption maxima? Approximately what effect does each added alkyl group have?

10.45 Hexa-1,3,5-triene has $\lambda_{\text{max}} = 258 \text{ nm}$. In light of your answer to Problem 10.44, approximately where would you expect 2,3-dimethylhexa-1,3,5-triene to absorb? Explain.

10.46 Ergosterol, a precursor of vitamin D, has $\lambda_{\text{max}} = 282 \text{ nm}$ and molar absorptivity $\epsilon = 11,900$. What is the concentration of ergosterol in a solution whose absorbance $A = 0.065$ with a sample pathlength $l = 1.00 \text{ cm}$?

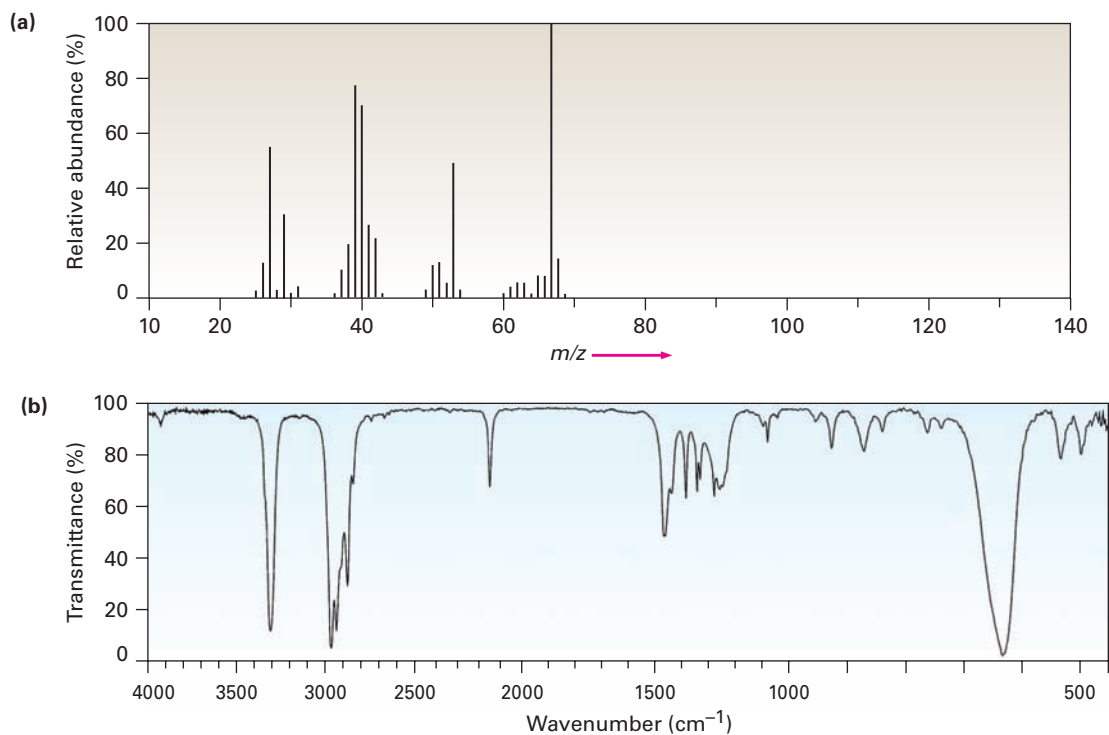


General Problems

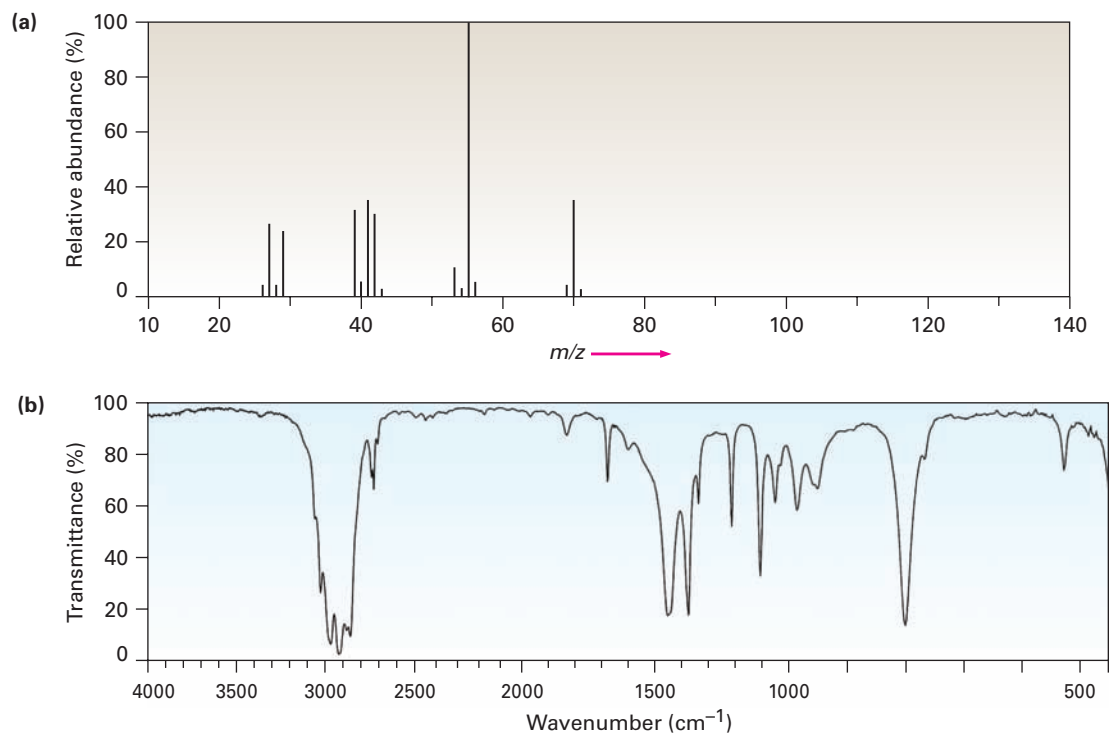
10.47 Carvone is an unsaturated ketone responsible for the odor of spearmint. If carvone has $M^+ = 150$ in its mass spectrum and contains three double bonds and one ring, what is its molecular formula?

10.48 Carvone (Problem 10.47) has an intense infrared absorption at 1690 cm^{-1} . What kind of ketone does carvone contain?

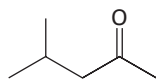
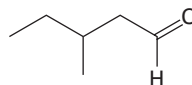
10.49 The mass spectrum (a) and the infrared spectrum (b) of an unknown hydrocarbon are shown. Propose as many structures as you can.



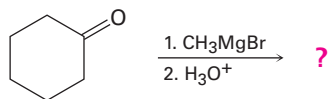
10.50 The mass spectrum (a) and the infrared spectrum (b) of another unknown hydrocarbon are shown. Propose as many structures as you can.



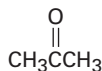
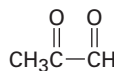
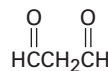
- 10.51** Propose structures for compounds that meet the following descriptions:
- (a) An optically active compound $C_5H_{10}O$ with an IR absorption at 1730 cm^{-1}
- (b) An optically inactive compound C_5H_9N with an IR absorption at 2215 cm^{-1}
- 10.52** 4-Methylpentan-2-one and 3-methylpentanal are isomers. Explain how you could tell them apart, both by mass spectrometry and by infrared spectroscopy.

**4-Methylpentan-2-one****3-Methylpentanal**

- 10.53** Organomagnesium halides ($R-Mg-X$), called *Grignard reagents*, undergo a general and very useful reaction with ketones. Methylmagnesium bromide, for example, reacts with cyclohexanone to yield a product with the formula $C_7H_{14}O$. What is the structure of this product if it has an IR absorption at 3400 cm^{-1} ?

**Cyclohexanone**

- 10.54** What is the concentration of cytosine, a constituent of nucleic acids, if its molar absorptivity is $6.1 \times 10^3\text{ L}/(\text{mol} \cdot \text{cm})$ and its absorbance is 0.20 in a cell with a 1.0 cm pathlength?
- 10.55** β -Ocimene is a pleasant-smelling hydrocarbon found in the leaves of certain herbs. It has the molecular formula $C_{10}H_{16}$ and a UV absorption maximum at 232 nm. On hydrogenation with a palladium catalyst, 2,6-dimethyloctane is obtained. Ozonolysis of β -ocimene, followed by treatment with zinc and acetic acid, produces the following four fragments:

**Acetone****Formaldehyde****Pyruvaldehyde****Malonaldehyde**

- (a) How many double bonds does β -ocimene have?
- (b) Is β -ocimene conjugated or nonconjugated?
- (c) Propose a structure for β -ocimene.
- (d) Write the reactions, showing starting material and products.

- 10.56** Myrcene, $C_{10}H_{16}$, is found in oil of bay leaves and is isomeric with β -ocimene (Problem 10.55). It has an ultraviolet absorption at 226 nm and can be catalytically hydrogenated to yield 2,6-dimethyloctane. On ozonolysis followed by zinc/acetic acid treatment, myrcene yields formaldehyde, acetone, and 2-oxopentanedial:

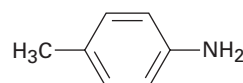


Propose a structure for myrcene, and write the reactions, showing starting material and products.

- 10.57** Benzene has an ultraviolet absorption at $\lambda_{\text{max}} = 204$ nm, and *p*-toluidine has $\lambda_{\text{max}} = 235$ nm. How do you account for this difference?

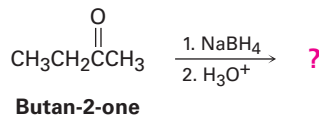


Benzene
($\lambda_{\text{max}} = 204$ nm)



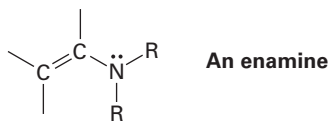
***p*-Toluidine**
($\lambda_{\text{max}} = 235$ nm)

- 10.58** Ketones undergo a reduction when treated with sodium borohydride, NaBH_4 . What is the structure of the compound produced by reaction of butan-2-one with NaBH_4 if it has an IR absorption at 3400 cm^{-1} and $M^+ = 74$ in the mass spectrum?



- 10.59** Nitriles, $\text{R}-\text{C}\equiv\text{N}$, undergo a *hydrolysis* reaction when heated with aqueous acid. What is the structure of the compound produced by hydrolysis of propanenitrile, $\text{CH}_3\text{CH}_2\text{C}\equiv\text{N}$, if it has IR absorptions at $2500\text{--}3100\text{ cm}^{-1}$ and 1710 cm^{-1} and has $M^+ = 74$?

- 10.60** *Enamines* (C=C–N; *alkene* + *amine*) typically have a UV absorption near $\lambda_{\text{max}} = 230 \text{ nm}$ and are much more nucleophilic than alkenes. Assuming that the nitrogen atom is sp^2 -hybridized, explain both the UV absorption and the nucleophilicity of enamines.

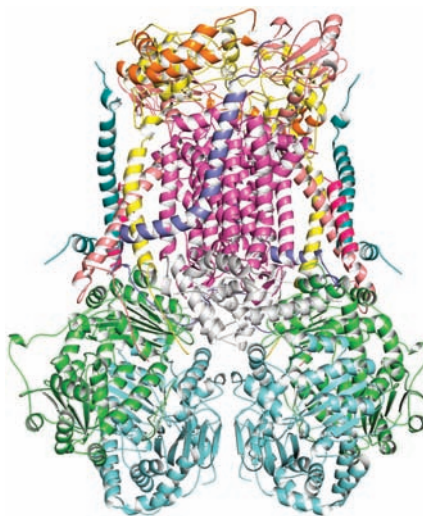


CONTENTS

- 11-1 Nuclear Magnetic Resonance Spectroscopy
- 11-2 The Nature of NMR Absorptions
- 11-3 Chemical Shifts
- 11-4 ^{13}C NMR Spectroscopy: Signal Averaging and FT-NMR
- 11-5 Characteristics of ^{13}C NMR Spectroscopy
- 11-6 DEPT ^{13}C NMR Spectroscopy
- 11-7 Uses of ^{13}C NMR Spectroscopy
- 11-8 ^1H NMR Spectroscopy and Proton Equivalence
- 11-9 Chemical Shifts in ^1H NMR Spectroscopy
- 11-10 Integration of ^1H NMR Absorptions: Proton Counting
- 11-11 Spin–Spin Splitting in ^1H NMR Spectra
- 11-12 More Complex Spin–Spin Splitting Patterns
- 11-13 Uses of ^1H NMR Spectroscopy

SOMETHING EXTRA

Magnetic Resonance Imaging (MRI)



Ubiquinone-cytochrome *c* reductase catalyzes a redox pathway called the Q cycle, a crucial step in biological energy production.

WHY THIS CHAPTER?

The opening sentence in this chapter says it all: NMR is by far the most valuable spectroscopic technique for structure determination. Although we'll just give an overview of the subject in this chapter, focusing on NMR applications to small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

Nuclear magnetic resonance (NMR) spectroscopy is the most valuable spectroscopic technique available to laboratory organic chemists. It's the method of structure determination that organic chemists turn to first.

We saw in Chapter 10 that mass spectrometry gives a molecule's formula, infrared spectroscopy identifies a molecule's functional groups, and ultraviolet spectroscopy identifies a molecule's conjugated π -electron system. Nuclear magnetic resonance spectroscopy complements these other techniques by mapping a molecule's carbon–hydrogen framework. Taken together, mass spectrometry, IR, UV, and NMR make it possible to determine the structures of even very complex molecules.

Mass spectrometry	Molecular formula
Infrared spectroscopy	Functional groups
Ultraviolet spectroscopy	Extent of conjugation
NMR spectroscopy	Map of carbon–hydrogen framework

11-1 Nuclear Magnetic Resonance Spectroscopy

Many kinds of nuclei behave as if they were spinning about an axis, much as the earth spins daily. Because they're positively charged, these spinning nuclei act like tiny magnets and interact with an external magnetic field, denoted B_0 . Not all nuclei act this way, but fortunately for organic chemists, both the proton (^1H) and the ^{13}C nucleus do have spins. (In speaking about



NMR, the words *proton* and *hydrogen* are often used interchangeably, since a hydrogen nucleus is just a proton.) Let's see what the consequences of nuclear spin are and how we can use the results.

In the absence of an external magnetic field, the spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^1H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy, however, and aren't equally likely. The parallel orientation is slightly lower in energy by an amount that depends on the strength of the external field, making this spin state slightly favored over the antiparallel orientation (**FIGURE 11.1**).

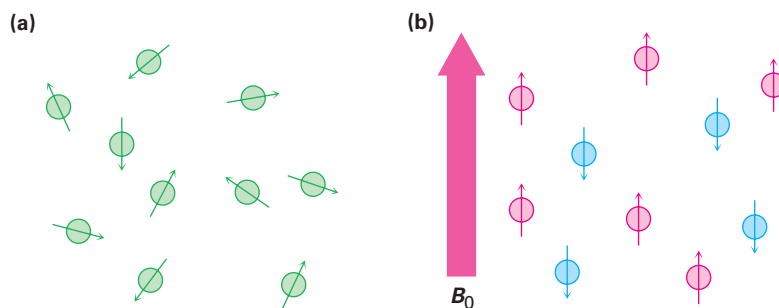


FIGURE 11.1 Nuclear spin states. (a) The spins are oriented randomly in the absence of an external magnetic field but (b) have a specific orientation in the presence of an external field, B_0 . Some of the spins are aligned **parallel to the external field**, while others are **antiparallel**. The parallel spin state is lower in energy and therefore favored.

If the oriented nuclei are irradiated with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower-energy state “spin-flips” to the higher-energy state. When this spin-flip occurs, the nuclei are said to be in resonance with the applied radiation—hence the name *nuclear magnetic resonance*.

The exact frequency necessary for resonance depends both on the strength of the external magnetic field and on the identity of the nuclei. If a very strong magnetic field is applied, the energy difference between the two spin states is larger and higher-frequency (higher-energy) radiation is required for a spin-flip. If a weaker magnetic field is applied, less energy is required to effect the transition between nuclear spin states (**FIGURE 11.2**).

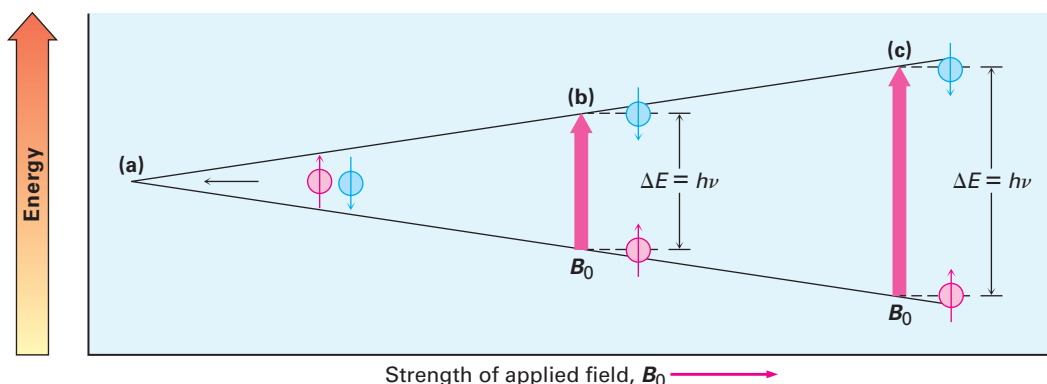


FIGURE 11.2 Energies of nuclear spin states. The energy difference ΔE between nuclear spin states depends on the strength of the applied magnetic field. Absorption of energy with frequency ν converts a nucleus from a lower spin state to a higher spin state. (a) Spin states have equal energies in the absence of an applied magnetic field but (b) have unequal energies in the presence of a magnetic field. At $\nu = 300$ MHz, $\Delta E = 1.2 \times 10^{-4}$ kJ/mol (2.9×10^{-5} kcal/mol). (c) The energy difference between spin states is greater at larger applied fields. At $\nu = 500$ MHz, $\Delta E = 2.0 \times 10^{-4}$ kJ/mol.

TABLE 11.1
The NMR Behavior of
Some Common Nuclei

Magnetic nuclei	Nonmagnetic nuclei
^1H	^{12}C
^{13}C	^{16}O
^2H	^{32}S
^{14}N	
^{19}F	
^{31}P	

In practice, superconducting magnets that produce enormously powerful fields up to 23.5 tesla (T) are sometimes used, but field strengths in the range of 7.0 to 11.7 T are more common. At a magnetic field strength of 7.0 T, so-called radiofrequency (rf) energy in the 300 MHz range ($1 \text{ MHz} = 10^6 \text{ Hz}$) brings a ^1H nucleus into resonance, and rf energy of 75 MHz brings a ^{13}C nucleus into resonance. At the highest field strength currently available in commercial instruments (23.5 T), 1000 MHz (1.0 GHz) energy is required for ^1H spectroscopy. These energies needed for NMR are much smaller than those required for IR spectroscopy; 300 MHz rf energy corresponds to only $1.2 \times 10^{-4} \text{ kJ/mol}$ versus the 4.8 to 48 kJ/mol needed for IR spectroscopy.

^1H and ^{13}C nuclei are not unique in their ability to exhibit the NMR phenomenon. All nuclei with an odd number of protons (^1H , ^2H , ^{14}N , ^{19}F , ^{31}P , for example) and all nuclei with an odd number of neutrons (^{13}C , for example) show magnetic properties. Only nuclei with even numbers of both protons and neutrons (^{12}C , ^{16}O , ^{32}S) do not give rise to magnetic phenomena (TABLE 11.1).

PROBLEM 11.1

The amount of energy required to spin-flip a nucleus depends both on the strength of the external magnetic field and on the nucleus. At a field strength of 4.7 T, rf energy of 200 MHz is required to bring a ^1H nucleus into resonance but energy of only 187 MHz will bring a ^{19}F nucleus into resonance. Calculate the amount of energy required to spin-flip a ^{19}F nucleus. Is this amount greater or less than that required to spin-flip a ^1H nucleus?

PROBLEM 11.2

Calculate the amount of energy required to spin-flip a proton in a spectrometer operating at 300 MHz. Does increasing the spectrometer frequency from 200 to 300 MHz increase or decrease the amount of energy necessary for resonance?

11-2 The Nature of NMR Absorptions

From the description thus far, you might expect all ^1H nuclei in a molecule to absorb energy at the same frequency and all ^{13}C nuclei to absorb at the same frequency. If so, we would observe only a single NMR absorption band in the ^1H or ^{13}C spectrum of a molecule, a situation that would be of little use. In fact, the absorption frequency is not the same for all ^1H or all ^{13}C nuclei.

All nuclei in molecules are surrounded by electrons. When an external magnetic field is applied to a molecule, the electrons moving around nuclei set up tiny local magnetic fields of their own. These local magnetic fields act in opposition to the applied field so that the effective field actually felt by the nucleus is a bit weaker than the applied field.

$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

In describing the effect of local fields, we say that nuclei are **shielded** from the full effect of the applied field by the surrounding electrons. Because each chemically distinct nucleus in a molecule is in a slightly different electronic environment, each nucleus is shielded to a slightly different extent and the

effective magnetic field felt by each is slightly different. These tiny differences in the effective magnetic fields experienced by different nuclei can be detected, and we thus see a distinct NMR signal for each chemically distinct ^{13}C or ^1H nucleus in a molecule. As a result, an NMR spectrum effectively maps the carbon–hydrogen framework of an organic molecule. With practice, it's possible to read the map and derive structural information.

FIGURE 11.3 shows both the ^1H and the ^{13}C NMR spectra of methyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_3$. The horizontal axis shows the effective field strength felt by the nuclei, and the vertical axis indicates the intensity of absorption of rf energy. Each peak in the NMR spectrum corresponds to a chemically distinct ^1H or ^{13}C nucleus in the molecule. Note that NMR spectra are formatted with the zero absorption line at the bottom, whereas IR spectra are formatted with the zero absorption line at the top (Section 10-5). Note also that ^1H and ^{13}C spectra can't be observed simultaneously on the same spectrometer because different amounts of energy are required to spin-flip the different kinds of nuclei. The two spectra must be recorded separately.

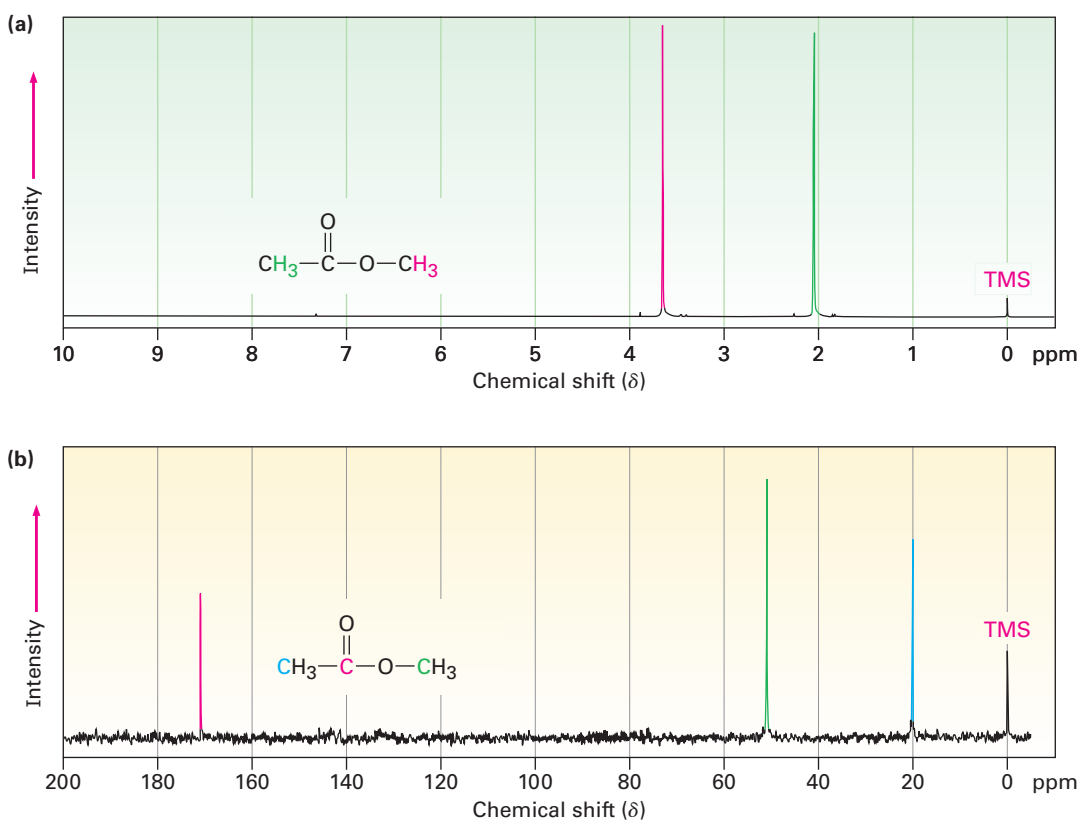


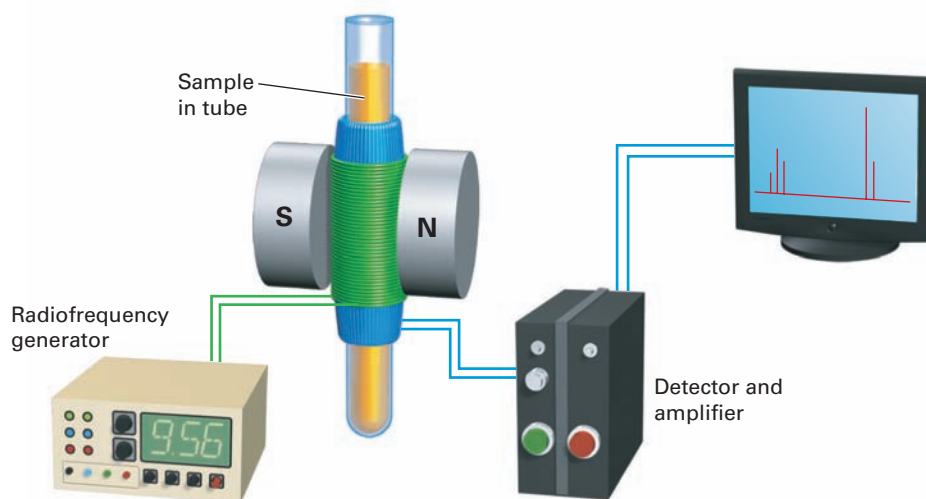
FIGURE 11.3 (a) The ^1H NMR spectrum and (b) the ^{13}C NMR spectrum of methyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_3$. The small peak labeled “TMS” at the far right of each spectrum is a calibration peak, as explained in the next section.

The ^{13}C spectrum of methyl acetate in Figure 11.3b shows three peaks, one for each of the three chemically distinct carbon atoms in the molecule. The ^1H NMR spectrum in Figure 11.3a shows only two peaks, however, even though methyl acetate has six hydrogens. One peak is due to the

$\text{CH}_3\text{C}=\text{O}$ hydrogens, and the other to the $-\text{OCH}_3$ hydrogens. Because the three hydrogens in each methyl group have the same chemical and electronic environment, they are shielded to the same extent and are said to be *equivalent*. Chemically equivalent nuclei always show a single absorption. The two methyl groups themselves, however, are nonequivalent, so the two sets of hydrogens absorb at different positions.

The operation of a basic NMR spectrometer is illustrated in **FIGURE 11.4**. An organic sample is dissolved in a suitable solvent (usually deuteriochloroform, CDCl_3 , which has no hydrogens) and placed in a thin glass tube between the poles of a magnet. The strong magnetic field causes the ^1H and ^{13}C nuclei in the molecule to align in one of the two possible orientations, and the sample is irradiated with rf energy. If the frequency of the rf irradiation is held constant and the strength of the applied magnetic field is varied, each nucleus comes into resonance at a slightly different field strength. A sensitive detector monitors the absorption of rf energy, and the electronic signal is then amplified and displayed as a peak.

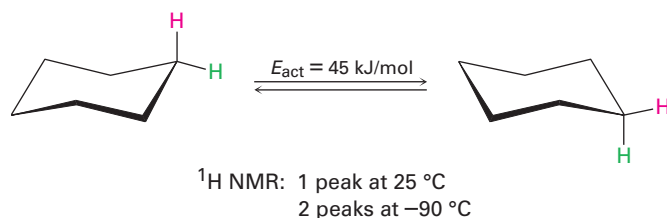
FIGURE 11.4 Schematic operation of a basic NMR spectrometer. A thin glass tube containing the sample solution is placed between the poles of a strong magnet and irradiated with rf energy.



NMR spectroscopy differs from IR spectroscopy (Sections 10-6–10-8) in that the timescales of the two techniques are different. The absorption of infrared energy by a molecule giving rise to a change in vibrational amplitude is an essentially instantaneous process (about 10^{-13} s), but the NMR process is much slower (about 10^{-3} s). This difference in timescales between IR and NMR spectroscopy is analogous to the difference between cameras operating at very fast and very slow shutter speeds. The fast camera (IR) takes an instantaneous picture and freezes the action. If two rapidly interconverting species are present, IR spectroscopy records the spectra of both. The slow camera (NMR), however, takes a blurred, time-averaged picture. If two species interconverting faster than 10^3 times per second are present in a sample, NMR records only a single, averaged spectrum, rather than separate spectra of the two discrete species.

Because of this blurring effect, NMR spectroscopy can be used to measure the rates and activation energies of very fast processes. In cyclohexane, for example, a ring-flip (Section 4-6) occurs so rapidly at room temperature that axial and equatorial hydrogens can't be distinguished by NMR; only a single, averaged ^1H NMR absorption is seen for cyclohexane at 25 °C. At -90 °C,

however, the ring-flip is slowed down enough that two absorption peaks are seen, one for the six axial hydrogens and one for the six equatorial hydrogens. Knowing the temperature and the rate at which signal blurring begins to occur, it's possible to calculate that the activation energy for the cyclohexane ring-flip is 45 kJ/mol (10.8 kcal/mol).



PROBLEM 11.3

2-Chloropropene shows signals for three kinds of protons in its ${}^1\text{H NMR}$ spectrum. Explain.

11-3 Chemical Shifts

NMR spectra are displayed on charts that show the applied field strength increasing from left to right (FIGURE 11.5). Thus, the left part of the chart is the low-field, or **downfield**, side, and the right part is the high-field, or **upfield**, side. Nuclei that absorb on the downfield side of the chart require a lower field strength for resonance, implying that they have less shielding. Nuclei that absorb on the upfield side require a higher field strength for resonance, implying that they have more shielding.

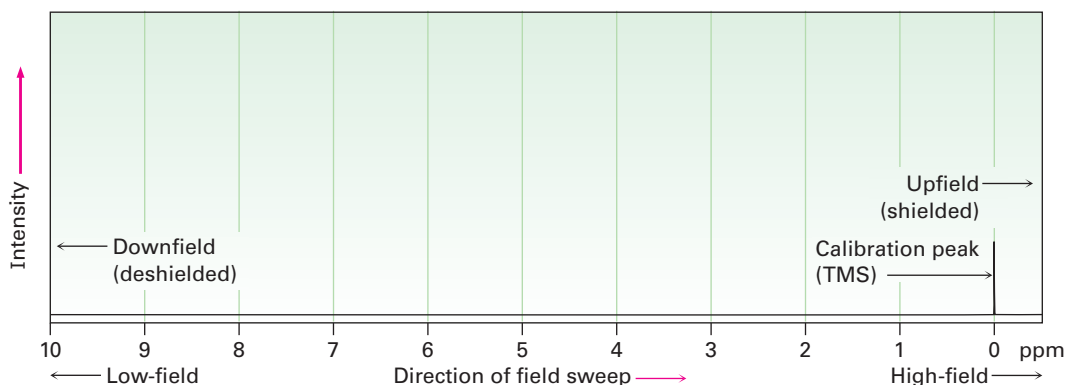


FIGURE 11.5 The NMR chart. The downfield, deshielded side is on the left, and the upfield, shielded side is on the right. The tetramethylsilane (TMS) absorption is used as reference point.

To define the position of an absorption, the NMR chart is calibrated and a reference point is used. In practice, a small amount of tetramethylsilane [TMS; $(\text{CH}_3)_4\text{Si}$] is added to the sample so that a reference absorption peak is produced when the spectrum is run. TMS is used as reference for both ${}^1\text{H}$ and ${}^{13}\text{C}$ measurements because it produces in both a single peak that

occurs upfield of other absorptions normally found in organic compounds. The ^1H and ^{13}C spectra of methyl acetate in Figure 11.3 have the TMS reference peak indicated.

The position on the chart at which a nucleus absorbs is called its **chemical shift**. The chemical shift of TMS is set as the zero point, and other absorptions normally occur downfield, to the left on the chart. NMR charts are calibrated using an arbitrary scale called the **delta (δ) scale**, where 1 δ equals 1 part per million (1 ppm) of the spectrometer operating frequency. For example, if we were measuring the ^1H NMR spectrum of a sample using an instrument operating at 200 MHz, 1 δ would be 1 millionth of 200,000,000 Hz, or 200 Hz. If we were measuring the spectrum using a 500 MHz instrument, 1 $\delta = 500$ Hz. The following equation can be used for any absorption:

$$\delta = \frac{\text{Chemical shift (number of Hz downfield from TMS)}}{\text{Spectrometer frequency in MHz}}$$

Although this method of calibrating NMR charts may seem complex, there's a good reason for it. As we saw earlier, the rf frequency required to bring a given nucleus into resonance depends on the spectrometer's magnetic field strength. But because there are many different kinds of spectrometers with many different magnetic field strengths available, chemical shifts given in frequency units (Hz) vary from one instrument to another. Thus, a resonance that occurs at 120 Hz downfield from TMS on one spectrometer might occur at 600 Hz downfield from TMS on another spectrometer with a more powerful magnet.

By using a system of measurement in which NMR absorptions are expressed in relative terms (parts per million relative to spectrometer frequency) rather than absolute terms (Hz), it's possible to compare spectra obtained on different instruments. *The chemical shift of an NMR absorption in δ units is constant, regardless of the operating frequency of the spectrometer.* A ^1H nucleus that absorbs at 2.0 δ on a 200 MHz instrument also absorbs at 2.0 δ on a 500 MHz instrument.

The range in which most NMR absorptions occur is quite narrow. Almost all ^1H NMR absorptions occur from 0 to 10 δ downfield from the proton absorption of TMS, and almost all ^{13}C absorptions occur from 1 to 220 δ downfield from the carbon absorption of TMS. Thus, there is a likelihood that accidental overlap of nonequivalent signals will occur. The advantage of using an instrument with higher field strength (say, 500 MHz) rather than lower field strength (200 MHz) is that different NMR absorptions are more widely separated at the higher field strength. The chances that two signals will accidentally overlap are therefore lessened, and interpretation of spectra becomes easier. For example, two signals that are only 20 Hz apart at 200 MHz (0.1 ppm) are 50 Hz apart at 500 MHz (still 0.1 ppm).

PROBLEM 11.4

The following ^1H NMR peaks were recorded on a spectrometer operating at 200 MHz. Convert each into δ units.

- (a) CHCl_3 ; 1454 Hz (b) CH_3Cl ; 610 Hz
(c) CH_3OH ; 693 Hz (d) CH_2Cl_2 ; 1060 Hz

PROBLEM 11.5

When the ^1H NMR spectrum of acetone, CH_3COCH_3 , is recorded on an instrument operating at 200 MHz, a single sharp resonance at 2.1 δ is seen.

- How many hertz downfield from TMS does the acetone resonance correspond to?
- If the ^1H NMR spectrum of acetone were recorded at 500 MHz, what would the position of the absorption be in δ units?
- How many hertz downfield from TMS does this 500 MHz resonance correspond to?

11-4 ^{13}C NMR Spectroscopy: Signal Averaging and FT-NMR

Everything we've said thus far about NMR spectroscopy applies to both ^1H and ^{13}C spectra. Now, though, let's focus only on ^{13}C spectroscopy because it's much easier to interpret. What we learn now about interpreting ^{13}C spectra will simplify the subsequent discussion of ^1H spectra.

In some ways, it's surprising that carbon NMR is even possible. After all, ^{12}C , the most abundant carbon isotope, has no nuclear spin and can't be seen by NMR. Carbon-13 is the only naturally occurring carbon isotope with a nuclear spin, but its natural abundance is only 1.1%. Thus, only about 1 of every 100 carbons in an organic sample is observable by NMR. The problem of low abundance has been overcome, however, by the use of *signal averaging* and *Fourier-transform NMR (FT-NMR)*. Signal averaging increases instrument sensitivity, and FT-NMR increases instrument speed.

The low natural abundance of ^{13}C means that any individual NMR spectrum is extremely "noisy." That is, the signals are so weak that they are cluttered with random background electronic noise, as shown in **FIGURE 11.6a**. If, however, hundreds or thousands of individual runs are added together by a computer and then averaged, a greatly improved spectrum results (**FIGURE 11.6b**). Background noise, because of its random nature, averages to zero, while the nonzero NMR signals stand out clearly. Unfortunately, the value of signal averaging is limited when using the method of NMR spectrometer operation described in Section 11-2, because it takes about 5 to 10 minutes to obtain a single spectrum. Thus, a faster way to obtain spectra is needed if signal averaging is to be used.

In the method of NMR spectrometer operation described in Section 11-2, the rf frequency is held constant while the strength of the magnetic field is varied so that all signals in the spectrum are recorded sequentially. In the FT-NMR technique used by modern spectrometers, however, all the signals are recorded simultaneously. A sample is placed in a magnetic field of constant strength and is irradiated with a short pulse of rf energy that covers the entire range of useful frequencies. All ^1H or ^{13}C nuclei in the sample resonate at once, giving a complex, composite signal that is mathematically manipulated using so-called Fourier transforms and then displayed in the usual way. Because all resonance signals are collected at once, it takes only a few seconds rather than a few minutes to record an entire spectrum.

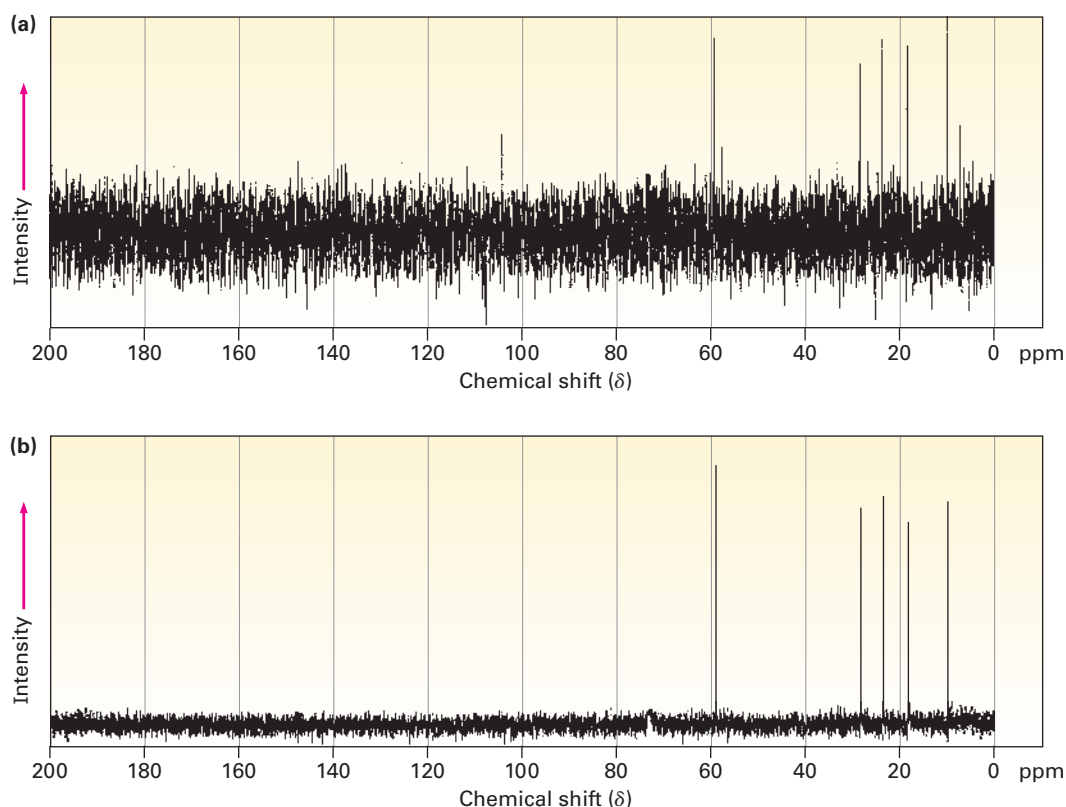


FIGURE 11.6 ^{13}C NMR spectra of pentan-1-ol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$. Spectrum (a) is a single run, showing the large amount of background noise. Spectrum (b) is an average of 200 runs.

Combining the speed of FT-NMR with the sensitivity enhancement of signal averaging is what gives modern NMR spectrometers their power. Literally thousands of spectra can be taken and averaged in a few hours, resulting in sensitivity so high that a ^{13}C NMR spectrum can be obtained on less than 0.1 mg of sample, and a ^1H spectrum can be recorded on only a few *micrograms*.

11-5 Characteristics of ^{13}C NMR Spectroscopy

At its simplest, ^{13}C NMR makes it possible to count the number of different carbon atoms in a molecule. Look at the ^{13}C NMR spectra of methyl acetate and pentan-1-ol shown previously in Figures 11.3b and 11.6b. In each case, a single sharp resonance line is observed for each different carbon atom.

Most ^{13}C resonances are between 0 and 220 δ downfield from the TMS reference line, with the exact chemical shift of each ^{13}C resonance dependent on that carbon's electronic environment within the molecule. **FIGURE 11.7** shows the correlation of chemical shift with environment.

The factors that determine chemical shifts are complex, but it's possible to make some generalizations from the data in Figure 11.7. One trend is that a carbon's chemical shift is affected by the electronegativity of nearby atoms. Carbons bonded to oxygen, nitrogen, or halogen absorb downfield (to the left) of typical alkane carbons. Because electronegative atoms attract electrons, they pull electrons away from neighboring carbon atoms, causing those carbons to be deshielded and to come into resonance at a lower field.

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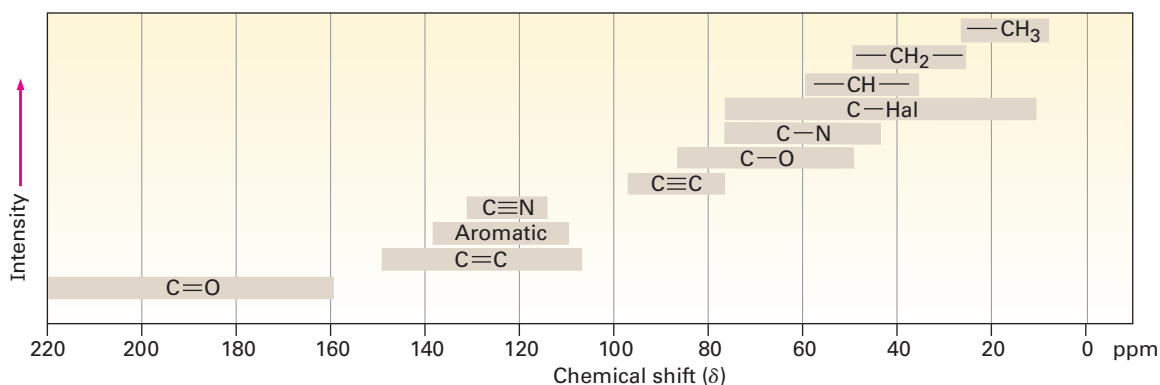


FIGURE 11.7 Chemical shift correlations for ^{13}C NMR.

Another trend is that sp^3 -hybridized carbons generally absorb from 0 to 90 δ , while sp^2 carbons absorb from 110 to 220 δ . Carbonyl carbons ($\text{C}=\text{O}$) are particularly distinct in ^{13}C NMR and are always found at the low-field end of the spectrum, from 160 to 220 δ . **FIGURE 11.8** shows the ^{13}C NMR spectra of butan-2-one and *p*-bromoacetophenone and indicates the peak assignments. Note that the $\text{C}=\text{O}$ carbons are at the left edge of the spectrum in each case.

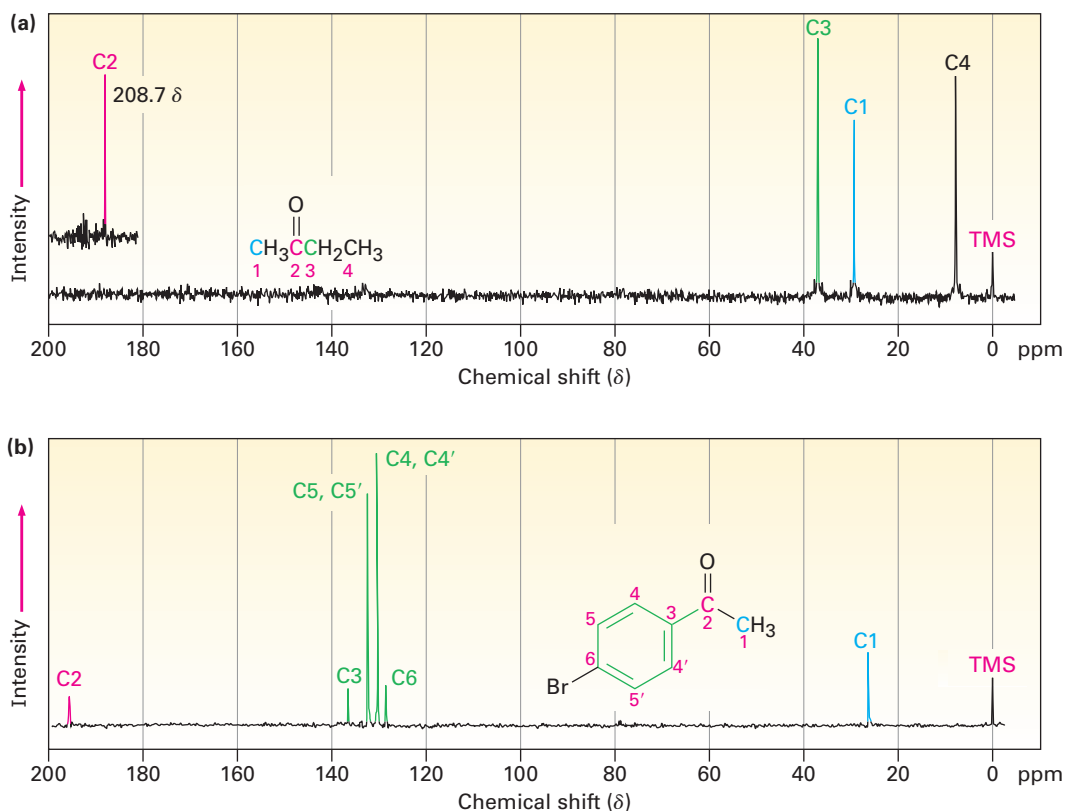
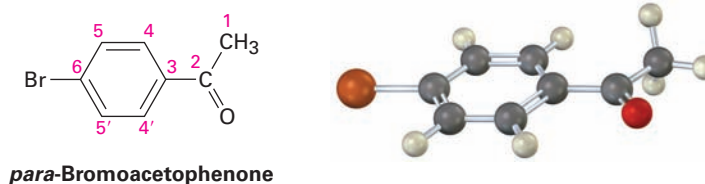


FIGURE 11.8 ^{13}C NMR spectra of (a) butan-2-one and (b) *p*-bromoacetophenone.

The ^{13}C NMR spectrum of *p*-bromoacetophenone is interesting in several ways. Note particularly that only six carbon absorptions are observed, even though the molecule has eight carbons. *p*-Bromoacetophenone has a symmetry

plane that makes ring carbons 4 and 4', and ring carbons 5 and 5' equivalent. Thus, the six ring carbons show only four absorptions in the range 128 to 137 δ .



A second interesting point about both spectra in Figure 11.8 is that the peaks aren't uniform in size. Some peaks are larger than others even though they are one-carbon resonances (except for the two 2-carbon peaks of *p*-bromoacetophenone). This difference in peak size is a general feature of ^{13}C NMR spectra.

WORKED EXAMPLE 11.1

Predicting Chemical Shifts in ^{13}C NMR Spectra

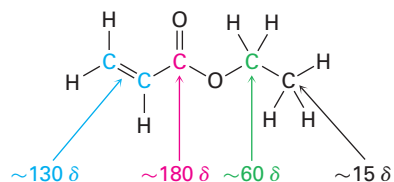
At what approximate positions would you expect ethyl acrylate, $\text{H}_2\text{C}=\text{CHCO}_2\text{CH}_2\text{CH}_3$, to show ^{13}C NMR absorptions?

Strategy

Identify the distinct carbons in the molecule, and note whether each is alkyl, vinylic, aromatic, or in a carbonyl group. Then predict where each absorbs, using Figure 11.7 as necessary.

Solution

Ethyl acrylate has five chemically distinct carbons: two different $\text{C}=\text{C}$, one $\text{C}=\text{O}$, one $\text{O}-\text{C}$, and one alkyl C . From Figure 11.7, the likely absorptions are



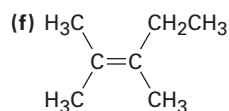
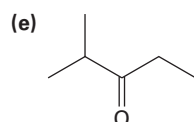
The actual absorptions are at 14.1, 60.5, 128.5, 130.3, and 166.0 δ .

PROBLEM 11.6

How many carbon resonance lines would you expect in the ^{13}C NMR spectra of the following compounds?

(a) Methylcyclopentane (b) 1-Methylcyclohexene

(c) 1,2-Dimethylbenzene (d) 2-Methylbut-2-ene



PROBLEM 11.7

Propose structures for compounds that fit the following descriptions:

- (a) A hydrocarbon with seven lines in its ^{13}C NMR spectrum
- (b) A six-carbon compound with only five lines in its ^{13}C NMR spectrum
- (c) A four-carbon compound with three lines in its ^{13}C NMR spectrum

PROBLEM 11.8

Assign the resonances in the ^{13}C NMR spectrum of methyl propanoate, $\text{CH}_3\text{CH}_2\text{CO}_2\text{CH}_3$ (FIGURE 11.9).

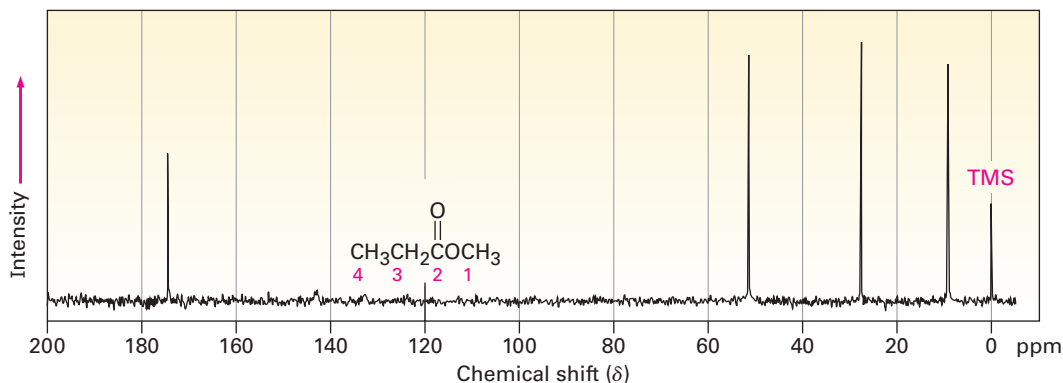


FIGURE 11.9 ^{13}C NMR spectrum of methyl propanoate for Problem 11.8.

11-6 DEPT ^{13}C NMR Spectroscopy

Numerous techniques developed in recent years have made it possible to obtain enormous amounts of information from ^{13}C NMR spectra. Among these techniques is one called DEPT-NMR, for *distortionless enhancement by polarization transfer*, which makes it possible to distinguish among signals due to CH_3 , CH_2 , CH , and quaternary carbons. That is, the number of hydrogens attached to each carbon in a molecule can be determined.

A DEPT experiment is usually done in three stages, as shown in FIGURE 11.10 for 6-methylhept-5-en-2-ol. The first stage is to run an ordinary spectrum (called a broadband-decoupled spectrum) to locate the chemical shifts of all carbons. Next, a second spectrum called a DEPT-90 is run, using special conditions under which only signals due to CH carbons appear. Signals due to CH_3 , CH_2 , and quaternary carbons are absent. Finally, a third spectrum called a DEPT-135 is run, using conditions under which CH_3 and CH resonances appear as positive signals, CH_2 resonances appear as *negative* signals—that is, as peaks below the baseline—and quaternary carbons are again absent.

Putting together the information from all three spectra makes it possible to tell the number of hydrogens attached to each carbon. The CH carbons are identified in the DEPT-90 spectrum, the CH_2 carbons are identified as the negative

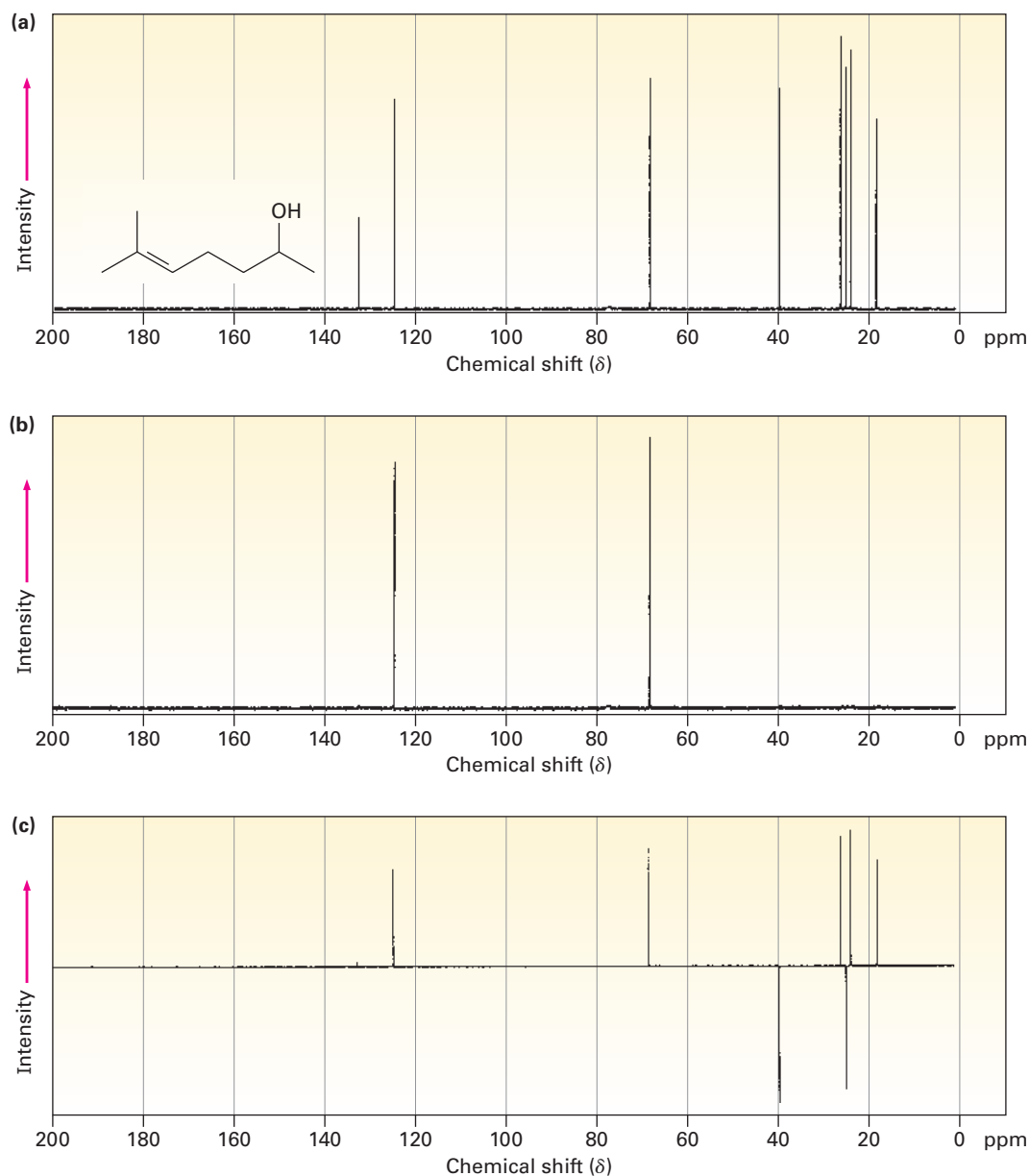


FIGURE 11.10 DEPT-NMR spectra for 6-methylhept-5-en-2-ol. Part (a) is an ordinary broadband-decoupled spectrum, which shows signals for all eight carbons. Part (b) is a DEPT-90 spectrum, which shows signals only for the two CH carbons. Part (c) is a DEPT-135 spectrum, which shows positive signals for the two CH and three CH₃ carbons and negative signals for the two CH₂ carbons.

peaks in the DEPT-135 spectrum, the CH₃ carbons are identified by subtracting the CH peaks from the positive peaks in the DEPT-135 spectrum, and quaternary carbons are identified by subtracting all peaks in the DEPT-135 spectrum from the peaks in the broadband-decoupled spectrum.

Broadband-decoupled	DEPT-90	DEPT-135
C, CH, CH ₂ , CH ₃	CH	CH ₃ , CH are positive CH ₂ is negative
C		
CH		
CH ₂		
CH ₃		
	Subtract DEPT-135 from broadband-decoupled spectrum	
	DEPT-90	
	Negative DEPT-135	
	Subtract DEPT-90 from positive DEPT-135	

Assigning a Chemical Structure from a ^{13}C NMR Spectrum

WORKED EXAMPLE 11.2

Propose a structure for an alcohol, $\text{C}_4\text{H}_{10}\text{O}$, that has the following ^{13}C NMR spectral data:

Broadband-decoupled ^{13}C NMR: 19.0, 31.7, 69.5 δ

DEPT-90: 31.7 δ

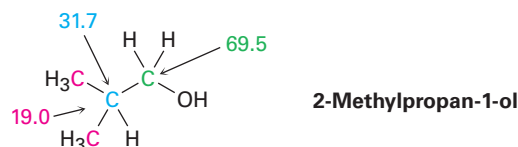
DEPT-135: positive peak at 19.0 δ , negative peak at 69.5 δ

Strategy

As noted in Section 7-1, it usually helps with compounds of known formula but unknown structure to calculate the compound's degree of unsaturation. In the present instance, a formula of $\text{C}_4\text{H}_{10}\text{O}$ corresponds to a saturated, open-chain molecule.

To gain information from the ^{13}C data, let's begin by noting that the unknown alcohol has four carbon atoms, yet has only three NMR absorptions, which implies that two carbons must be equivalent. Looking at chemical shifts, two of the absorptions are in the typical alkane region (19.0 and 31.7 δ) while one is in the region of a carbon bonded to an electronegative atom (69.5 δ)—oxygen in this instance. The DEPT-90 spectrum tells us that the alkyl carbon at 31.7 δ is tertiary (CH); the DEPT-135 spectrum tells us that the alkyl carbon at 19.0 δ is a methyl (CH₃) and that the carbon bonded to oxygen (69.5 δ) is secondary (CH₂). The two equivalent carbons are probably both methyls bonded to the same tertiary carbon, (CH₃)₂CH-. We can now put the pieces together to propose a structure: 2-methylpropan-1-ol.

Solution

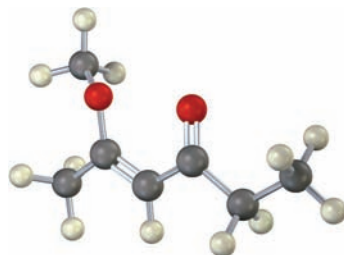


PROBLEM 11.9

Assign a chemical shift to each carbon in 6-methylhept-5-en-2-ol (Figure 11.10).

PROBLEM 11.10

Estimate the chemical shift of each carbon in the following molecule. Predict which carbons will appear in the DEPT-90 spectrum, which will give positive peaks in the DEPT-135 spectrum, and which will give negative peaks in the DEPT-135 spectrum.

**PROBLEM 11.11**

Propose a structure for an aromatic hydrocarbon, $C_{11}H_{16}$, that has the following ^{13}C NMR spectrum:

Broadband-decoupled: 29.5, 31.8, 50.2, 125.5, 127.5, 130.3, 139.8 δ

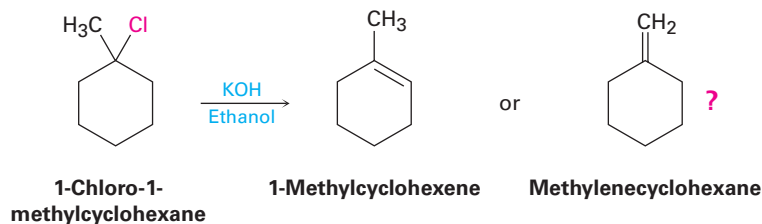
DEPT-90: 125.5, 127.5, 130.3 δ

DEPT-135: positive peaks at 29.5, 125.5, 127.5, 130.3 δ ; negative peak at 50.2 δ

11-7 Uses of ^{13}C NMR Spectroscopy

The information derived from ^{13}C NMR spectroscopy is extraordinarily useful for structure determination. Not only can we count the number of nonequivalent carbon atoms in a molecule, we can also get information about the electronic environment of each carbon and find how many protons each is attached to. As a result, we can answer many structural questions that go unanswered by IR spectroscopy or mass spectrometry.

Here's an example: Does the elimination reaction of 1-chloro-1-methylcyclohexane on treatment with a strong base give predominantly the trisubstituted alkene 1-methylcyclohexene or the disubstituted alkene methylenecyclohexane?



1-Methylcyclohexene will have five sp^3 -carbon resonances in the 20 to 50 δ range and two sp^2 -carbon resonances in the 100 to 150 δ range. Methylenecyclohexane, however, because of its symmetry, will have only three sp^3 -carbon resonance peaks and two sp^2 -carbon peaks. The spectrum of the actual reaction

product, shown in **FIGURE 11.11**, clearly identifies 1-methylcyclohexene as the product of this elimination reaction. In fact, we'll see in the next chapter (Section 12-12) that this result is general. Elimination reactions usually give the more highly substituted alkene product rather than the less highly substituted alkene.

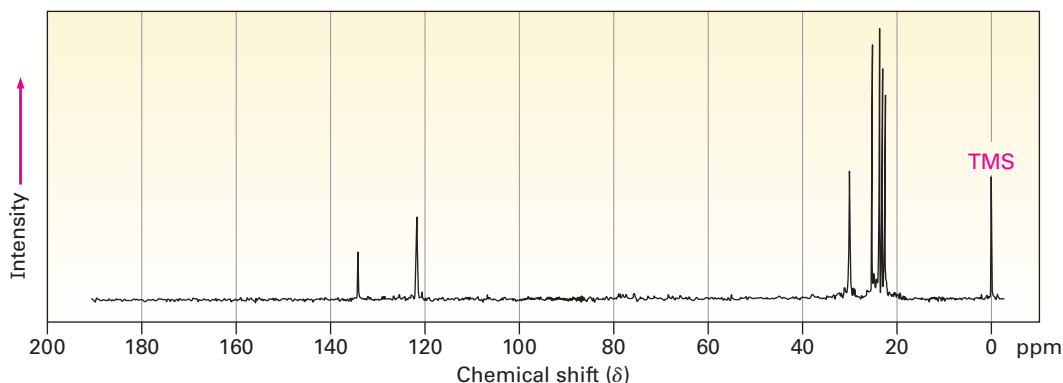


FIGURE 11.11 ^{13}C NMR spectrum of 1-methylcyclohexene, formed by treatment of 1-chloro-1-methylcyclohexane with a strong base.

PROBLEM 11.12

We saw in Section 8-15 that addition of HBr to a terminal alkyne leads to the Markovnikov addition product, with the Br bonding to the more highly substituted carbon. How could you use ^{13}C NMR to identify the product of the addition of 1 equivalent of HBr to hex-1-yne?

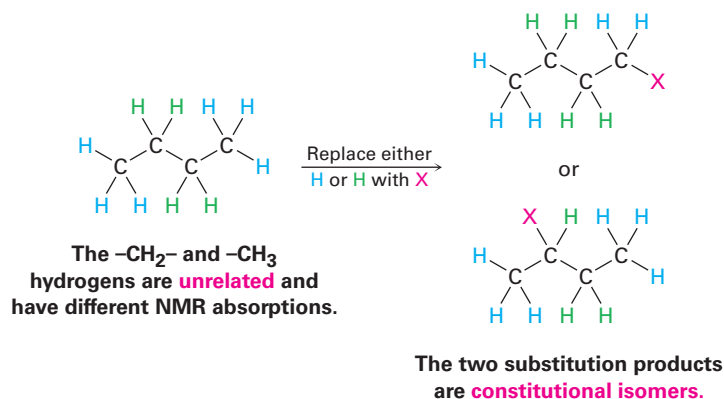
11-8 ^1H NMR Spectroscopy and Proton Equivalence

Having looked at ^{13}C spectra, let's now focus on ^1H NMR spectroscopy. Because each electronically distinct hydrogen in a molecule has its own unique absorption, one use of ^1H NMR is to find out how many kinds of electronically nonequivalent hydrogens are present. In the ^1H NMR spectrum of methyl acetate shown previously in Figure 11.3a, for instance, there are two signals, corresponding to the two kinds of nonequivalent protons present, $\text{CH}_3\text{C}=\text{O}$ protons and $-\text{OCH}_3$ protons.

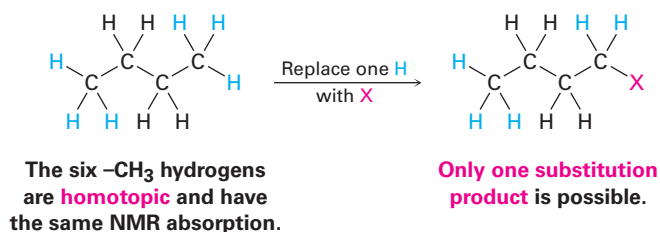
For relatively small molecules, a quick look at a structure is often enough to decide how many kinds of protons are present and thus how many NMR absorptions might appear. If in doubt, though, the equivalence or nonequivalence of two protons can be determined by comparing the structures that would be formed if each hydrogen were replaced by an X group. There are four possibilities:

- One possibility is that the protons are chemically unrelated and thus nonequivalent. If so, the products formed on replacement of H by X would be different constitutional isomers. In butane, for instance, the $-\text{CH}_3$ protons are different from the $-\text{CH}_2-$ protons. They therefore give different products

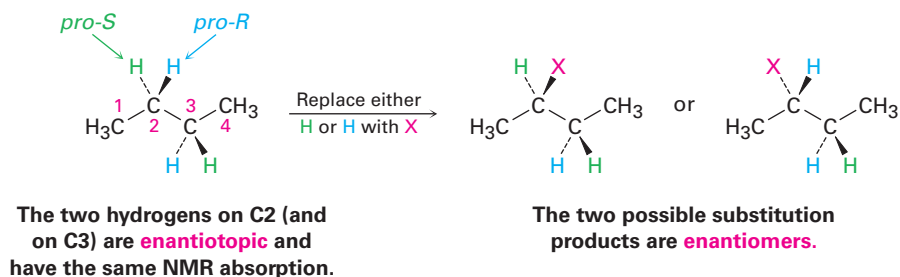
on substitution by X than the $-\text{CH}_2-$ protons and would likely show different NMR absorptions.



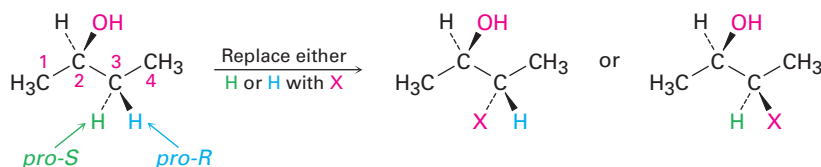
- A second possibility is that the protons are chemically identical and thus electronically equivalent. If so, the same product would be formed regardless of which H is replaced by X. In butane, for instance, the six $-\text{CH}_3$ hydrogens on C1 and C4 are identical, would give the identical structure on replacement by X, and would show the identical NMR absorption. Such protons are said to be **homotopic**.



- The third possibility is a bit more subtle. Although they might at first seem homotopic, the two $-\text{CH}_2-$ hydrogens on C2 in butane (and the two $-\text{CH}_2-$ hydrogens on C3) are in fact not identical. Replacement of a hydrogen at C2 (or C3) would form a new chirality center, so different enantiomers (Section 5-1) would result depending on whether the *pro-R* or *pro-S* hydrogen were replaced (Section 5-11). Such hydrogens, whose replacement by X would lead to different enantiomers, are said to be **enantiotopic**. Enantiotopic hydrogens, even though not identical, are nevertheless electronically equivalent and thus have the same NMR absorption.



- The fourth possibility arises in chiral molecules, such as *R*-butan-2-ol. The two –CH₂– hydrogens at C3 are neither homotopic nor enantiotopic. Since substitution of a hydrogen at C3 would form a *second* chirality center, different diastereomers (Section 5-6) would result depending on whether the *pro-R* or *pro-S* hydrogen were replaced. Such hydrogens, whose replacement by X leads to different diastereomers, are said to be **diastereotopic**. Diastereotopic hydrogens are neither chemically nor electronically equivalent. They are different and would likely show different NMR absorptions.

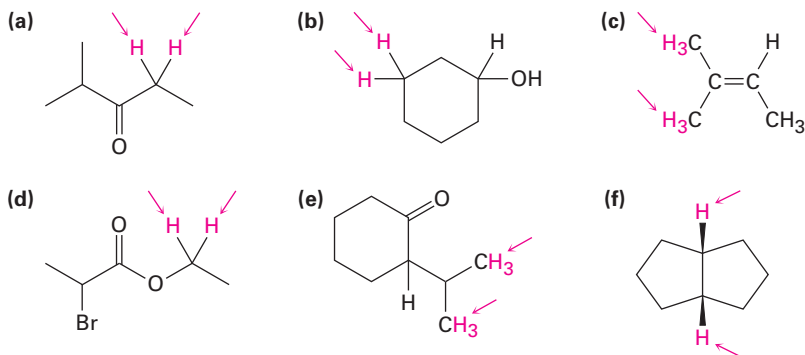


The two hydrogens on C3 are **diastereotopic** and have different NMR absorptions.

The two possible substitution products are **diastereomers**.

PROBLEM 11.13

Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



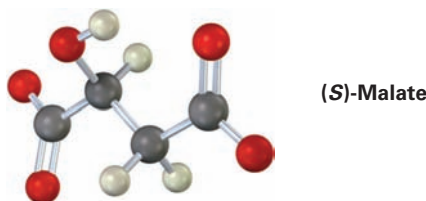
PROBLEM 11.14

How many kinds of electronically nonequivalent protons are present in each of the following compounds, and thus how many NMR absorptions might you expect in each?

- (a) CH₃CH₂Br (b) CH₃OCH₂CH(CH₃)₂ (c) CH₃CH₂CH₂NO₂
 (d) Toluene (e) 2-Methylbut-1-ene (f) *cis*-Hex-3-ene

PROBLEM 11.15

How many absorptions would you expect (*S*)-malate, an intermediate in carbohydrate metabolism, to have in its ^1H NMR spectrum? Explain.



11-9 Chemical Shifts in ^1H NMR Spectroscopy

As we said previously, differences in chemical shifts are caused by the small local magnetic fields of electrons surrounding the different nuclei. Nuclei that are more strongly shielded by electrons require a higher applied field to bring them into resonance and therefore absorb on the right side of the NMR chart. Nuclei that are less strongly shielded need a lower applied field for resonance and therefore absorb on the left of the NMR chart.

Most ^1H chemical shifts fall within the 0 to 10 δ range, which can be divided into the five regions shown in TABLE 11.2. By remembering the positions of these regions, it's often possible to tell at a glance what kinds of protons a molecule contains.

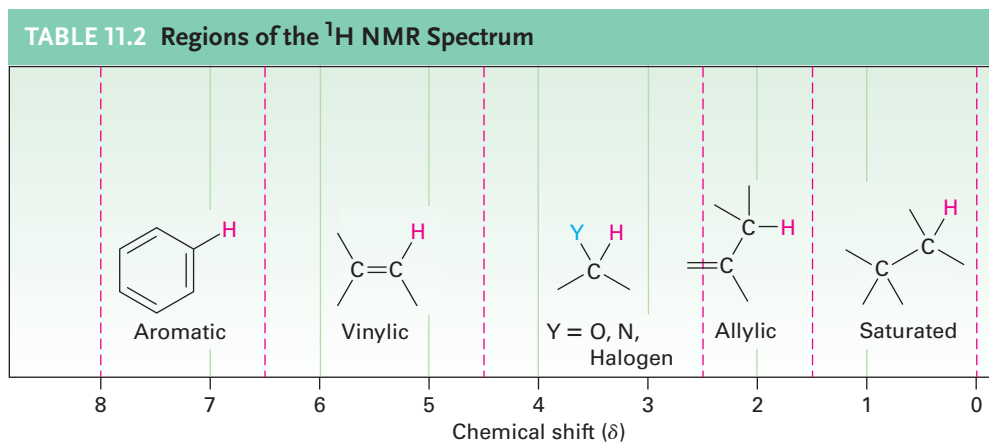


TABLE 11.3 shows the correlation of ^1H chemical shift with electronic environment in more detail. In general, protons bonded to saturated, sp^3 -hybridized carbons absorb at higher fields, whereas protons bonded to sp^2 -hybridized carbons absorb at lower fields. Protons on carbons that are bonded to electronegative atoms, such as N, O, or halogen, also absorb at lower fields.

TABLE 11.3 Correlation of ^1H Chemical Shift with Environment

Type of hydrogen	Chemical shift (δ)	Type of hydrogen	Chemical shift (δ)
Reference	$\text{Si}(\text{CH}_3)_4$ 0	Alcohol	$\begin{array}{c} \\ -\text{C}-\text{O}-\text{H} \\ \end{array}$ 2.5–5.0
Alkyl (primary)	$-\text{CH}_3$ 0.7–1.3	Alcohol, ether	$\begin{array}{c} \text{H} \\ \\ -\text{C}-\text{O}- \\ \end{array}$ 3.3–4.5
Alkyl (secondary)	$-\text{CH}_2-$ 1.2–1.6	Vinylic	$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{C} \\ \end{array}$ 4.5–6.5
Alkyl (tertiary)	$\begin{array}{c} \\ -\text{CH}- \\ \end{array}$ 1.4–1.8	Aryl	$\text{Ar}-\text{H}$ 6.5–8.0
Allylic	$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{C}-\text{C}- \\ \end{array}$ 1.6–2.2	Aldehyde	$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{H} \end{array}$ 9.7–10.0
Methyl ketone	$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{CH}_3 \end{array}$ 2.0–2.4	Carboxylic acid	$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{O}-\text{H} \end{array}$ 11.0–12.0
Aromatic methyl	$\text{Ar}-\text{CH}_3$ 2.4–2.7		
Alkynyl	$-\text{C}\equiv\text{C}-\text{H}$ 2.5–3.0		
Alkyl halide	$\begin{array}{c} \text{H} \\ \\ -\text{C}-\text{Hal} \\ \end{array}$ 2.5–4.0		

Predicting Chemical Shifts in ^1H NMR Spectra

WORKED EXAMPLE 11.3

Methyl 2,2-dimethylpropanoate $(\text{CH}_3)_3\text{CCO}_2\text{CH}_3$ has two peaks in its ^1H NMR spectrum. What are their approximate chemical shifts?

Strategy

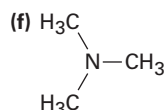
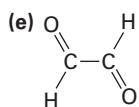
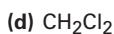
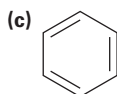
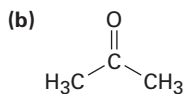
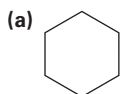
Identify the types of hydrogens in the molecule, and note whether each is alkyl, vinylic, or next to an electronegative atom. Then predict where each absorbs, using Table 11.3 if necessary.

Solution

The $-\text{OCH}_3$ protons absorb around 3.5 to 4.0 δ because they are on carbon bonded to oxygen. The $(\text{CH}_3)_3\text{C}-$ protons absorb near 1.0 δ because they are typical alkane-like protons.

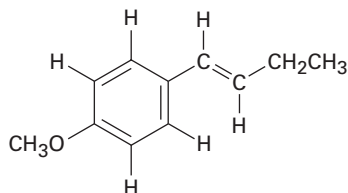
PROBLEM 11.16

Each of the following compounds has a single ^1H NMR peak. Approximately where would you expect each compound to absorb?



PROBLEM 11.17

Identify the different kinds of nonequivalent protons in the following molecule, and tell where you would expect each to absorb:



11-10 Integration of ^1H NMR Absorptions: Proton Counting

Look at the ^1H NMR spectrum of methyl 2,2-dimethylpropanoate in **FIGURE 11.12**. There are two peaks, corresponding to the two kinds of protons, but the peaks aren't the same size. The peak at 1.20 δ , due to the $(\text{CH}_3)_3\text{C}-$ protons, is larger than the peak at 3.65 δ , due to the $-\text{OCH}_3$ protons.

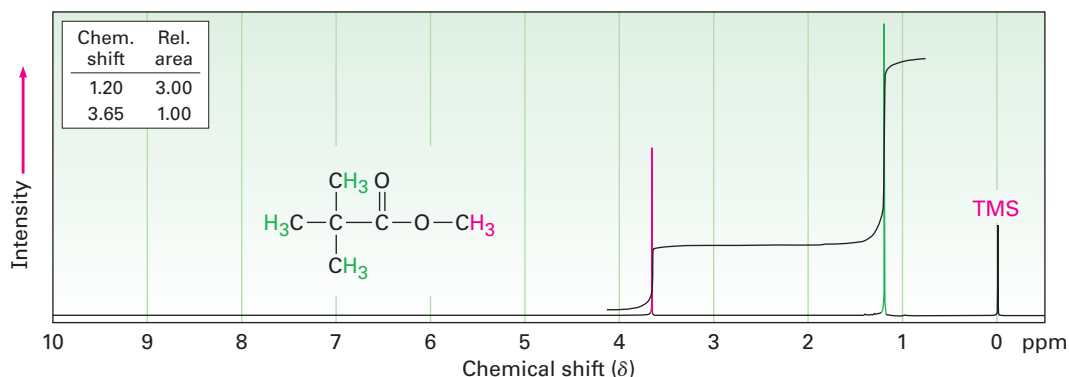


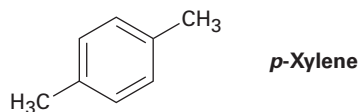
FIGURE 11.12 ^1H NMR spectrum of methyl 2,2-dimethylpropanoate. Integrating the two peaks in a stair-step manner shows that they have a 1:3 ratio, corresponding to the 3:9 ratio of protons responsible. Modern instruments give a direct digital readout of relative peak areas.

The area under each peak is proportional to the number of protons causing that peak. By electronically measuring, or **integrating**, the area under each peak, it's possible to measure the relative numbers of the different kinds of protons in a molecule.

Modern NMR instruments provide a digital readout of relative peak areas, but an older, more visual method displays the integrated peak areas as a stair-step line, with the height of each step proportional to the area under the peak, and therefore proportional to the relative number of protons causing the peak. For example, the two steps for the peaks in methyl 2,2-dimethylpropanoate are found to have a 1:3 (or 3:9) height ratio when integrated—exactly what we expect since the three $-\text{OCH}_3$ protons are equivalent and the nine $(\text{CH}_3)_3\text{C}-$ protons are equivalent.

PROBLEM 11.18

How many peaks would you expect in the ^1H NMR spectrum of 1,4-dimethylbenzene (*p*-xylene)? What ratio of peak areas would you expect on integration of the spectrum? Refer to Table 11.3 for approximate chemical shifts, and sketch what the spectrum would look like.

**11-11 Spin-Spin Splitting in ^1H NMR Spectra**

In the ^1H NMR spectra we've seen thus far, each different kind of proton in a molecule has given rise to a single peak. It often happens, though, that the absorption of a proton splits into *multiple* peaks, called a **multiplet**. For example, in the ^1H NMR spectrum of bromoethane shown in **FIGURE 11.13**, the $-\text{CH}_2\text{Br}$ protons appear as four peaks (a *quartet*) centered at 3.42 δ and the $-\text{CH}_3$ protons appear as three peaks (a *triplet*) centered at 1.68 δ .

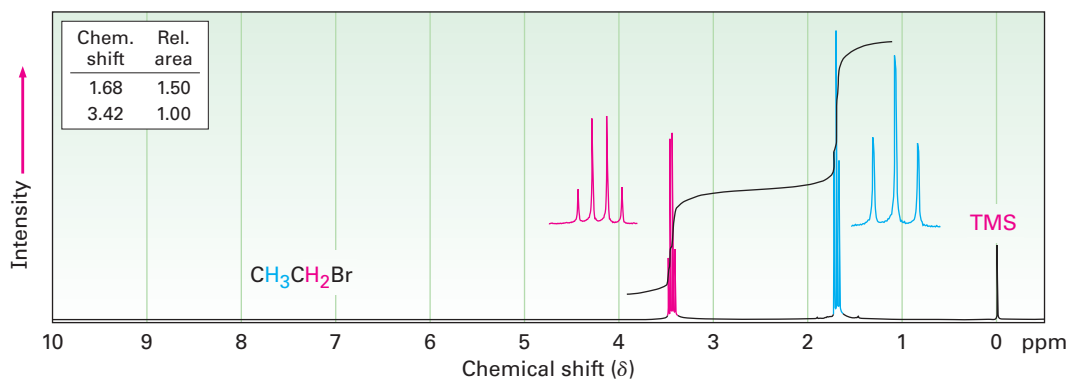


FIGURE 11.13 ^1H NMR spectrum of bromoethane, $\text{CH}_3\text{CH}_2\text{Br}$. The $-\text{CH}_2\text{Br}$ protons appear as a **quartet** at 3.42 δ , and the $-\text{CH}_3$ protons appear as a **triplet** at 1.68 δ .

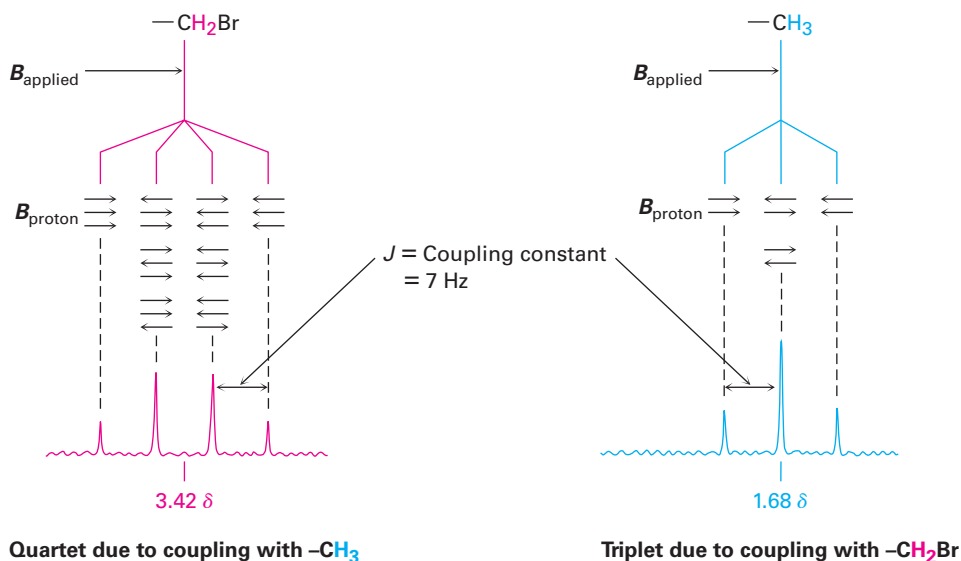
Called **spin-spin splitting**, multiple absorptions of a nucleus are caused by the interaction, or **coupling**, of the spins of nearby nuclei. In other words, the tiny magnetic field produced by one nucleus affects the magnetic field felt by a neighboring nucleus. Look at the $-\text{CH}_3$ protons in bromoethane, for example. The three equivalent $-\text{CH}_3$ protons are neighbored by two other magnetic nuclei—the two protons on the adjacent $-\text{CH}_2\text{Br}$ group. Each of the neighboring $-\text{CH}_2\text{Br}$ protons has its own nuclear spin, which can align either with or against the applied field, producing a tiny effect that is felt by the $-\text{CH}_3$ protons.

There are three ways in which the spins of the two $-\text{CH}_2\text{Br}$ protons can align, as shown in **FIGURE 11.14**. If both proton spins align with the applied field, the total effective field felt by the neighboring $-\text{CH}_3$ protons is slightly larger

than it would otherwise be. Consequently, the applied field necessary to cause resonance is slightly reduced. Alternatively, if one of the $-\text{CH}_2\text{Br}$ proton spins aligns with the field and one aligns against the field, there is no effect on the neighboring $-\text{CH}_3$ protons. (This arrangement can occur in two ways, depending on which of the two proton spins aligns which way.) Finally, if both $-\text{CH}_2\text{Br}$ proton spins align against the applied field, the effective field felt by the $-\text{CH}_3$ protons is slightly smaller than it would otherwise be and the applied field needed for resonance is slightly increased.

FIGURE 11.14 Origin of spin-spin splitting in bromoethane.

The nuclear spins of neighboring protons, indicated by horizontal arrows, align either with or against the applied field, causing the splitting of absorptions into multiplets.



Any given molecule has only one of the three possible alignments of $-\text{CH}_2\text{Br}$ spins, but in a large collection of molecules, all three spin states are represented in a 1 : 2 : 1 statistical ratio. We therefore find that the neighboring $-\text{CH}_3$ protons come into resonance at three slightly different values of the applied field, and we see a 1 : 2 : 1 triplet in the NMR spectrum. One resonance is a little above where it would be without coupling, one is at the same place it would be without coupling, and the third resonance is a little below where it would be without coupling.

In the same way that the $-\text{CH}_3$ absorption of bromoethane is split into a triplet, the $-\text{CH}_2\text{Br}$ absorption is split into a quartet. The three spins of the neighboring $-\text{CH}_3$ protons can align in four possible combinations: all three with the applied field, two with and one against (three ways), one with and two against (three ways), or all three against. Thus, four peaks are produced for the $-\text{CH}_2\text{Br}$ protons in a 1 : 3 : 3 : 1 ratio.

As a general rule, called the **$n + 1$ rule**, protons that have n equivalent neighboring protons show $n + 1$ peaks in their NMR spectrum. For example, the spectrum of 2-bromopropane in **FIGURE 11.15** shows a doublet at 1.71δ and a seven-line multiplet, or *septet*, at 4.28δ . The septet is caused by splitting of the $-\text{CHBr}-$ proton signal by six equivalent neighboring protons on the two methyl groups ($n = 6$ leads to $6 + 1 = 7$ peaks). The doublet is due to signal splitting of the six equivalent methyl protons by the single $-\text{CHBr}-$ proton ($n = 1$ leads to 2 peaks). Integration confirms the expected 6 : 1 ratio.

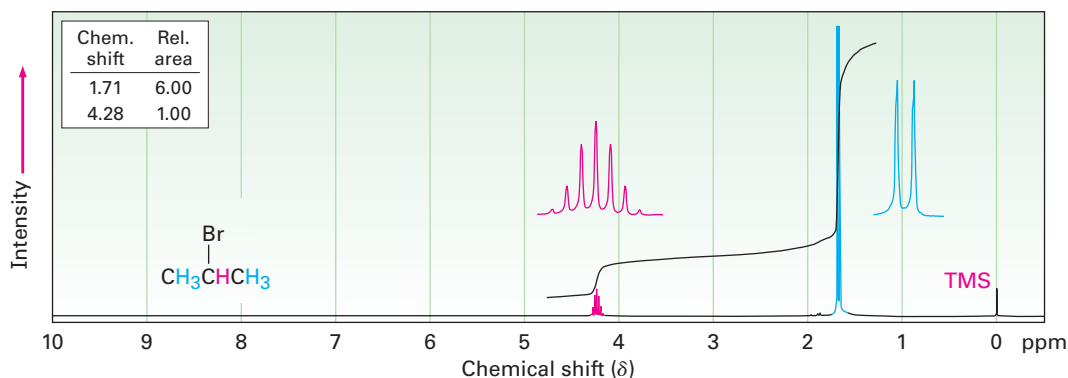


FIGURE 11.15 ^1H NMR spectrum of 2-bromopropane. The $-\text{CH}_3$ proton signal at 1.71 δ is split into a **doublet**, and the $-\text{CHBr}-$ proton signal at 4.28 δ is split into a **septet**. Note that the distance between peaks—the *coupling constant*—is the same in both multiplets. Note also that the outer two peaks of the septet are so small as to be nearly lost.

The distance between peaks in a multiplet is called the **coupling constant** and is denoted J . Coupling constants are measured in hertz and generally fall in the range 0 to 18 Hz. The exact value of the coupling constant between two neighboring protons depends on the geometry of the molecule, but a typical value for an open-chain alkane is $J = 6$ to 8 Hz. The same coupling constant is shared by both groups of hydrogens whose spins are coupled and is independent of spectrometer field strength. In bromoethane, for instance, the $-\text{CH}_2\text{Br}$ protons are coupled to the $-\text{CH}_3$ protons and appear as a quartet with $J = 7$ Hz. The $-\text{CH}_3$ protons appear as a triplet with the same $J = 7$ Hz coupling constant.

Because coupling is a reciprocal interaction between two adjacent groups of protons, it's sometimes possible to tell which multiplets in a complex NMR spectrum are related to each other. If two multiplets have the same coupling constant, they are probably related and the protons causing those multiplets are therefore adjacent in the molecule.

The most commonly observed coupling patterns and the relative intensities of lines in their multiplets are listed in **TABLE 11.4**. Note that it's not possible for a given proton to have five equivalent neighboring protons. (Why not?) A six-line multiplet, or sextet, is therefore found only when a proton has five *nonequivalent* neighboring protons that coincidentally happen to be coupled with an identical coupling constant J .

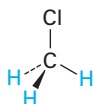
TABLE 11.4 Common Spin Multiplicities

Number of equivalent adjacent protons	Multiplet	Ratio of intensities
0	Singlet	1
1	Doublet	1:1
2	Triplet	1:2:1
3	Quartet	1:3:3:1
4	Quintet	1:4:6:4:1
6	Septet	1:6:15:20:15:6:1

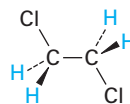
Spin–spin splitting in ^1H NMR can be summarized in three rules:

Rule 1

Chemically equivalent protons don't show spin–spin splitting. The equivalent protons may be on the same carbon or on different carbons, but their signals don't split.



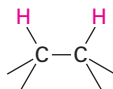
Three C–H protons are chemically equivalent; no splitting occurs.



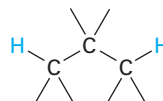
Four C–H protons are chemically equivalent; no splitting occurs.

Rule 2

The signal of a proton with n equivalent neighboring protons is split into a multiplet of $n + 1$ peaks with coupling constant J . Protons that are farther than two carbon atoms apart don't usually couple, although they sometimes show small coupling when they are separated by a π bond.



Splitting observed



Splitting not usually observed

Rule 3

Two groups of protons coupled to each other have the same coupling constant, J .

The spectrum of *p*-methoxypropiophenone in **FIGURE 11.16** further illustrates the three rules. The downfield absorptions at 6.91 and 7.93 δ are due to the four aromatic ring protons. There are two kinds of aromatic protons, each of which gives a signal that is split into a doublet by its neighbor. The $-\text{OCH}_3$ signal is unsplit and appears as a sharp singlet at 3.84 δ . The $-\text{CH}_2-$ protons next to the carbonyl group appear at 2.93 δ in the region expected for protons on carbon next to an unsaturated center, and their signal is split into a quartet by coupling with the protons of the neighboring methyl group. The methyl protons appear as a triplet at 1.20 δ in the usual upfield region.

One further question needs to be answered before leaving the topic of spin–spin splitting: Why is spin–spin splitting seen only for ^1H NMR? Why is there no splitting of *carbon* signals into multiplets in ^{13}C NMR? After all, you might expect that the spin of a given ^{13}C nucleus would couple with the spin of an adjacent magnetic nucleus, either ^{13}C or ^1H .

No coupling of a ^{13}C nucleus with nearby carbons is seen because their low natural abundance makes it unlikely that two ^{13}C nuclei will be adjacent. No coupling of a ^{13}C nucleus with nearby hydrogens is seen because ^{13}C spectra, as previously noted (Section 11-6), are normally recorded using broadband decoupling. At the same time that the sample is irradiated with a pulse of rf

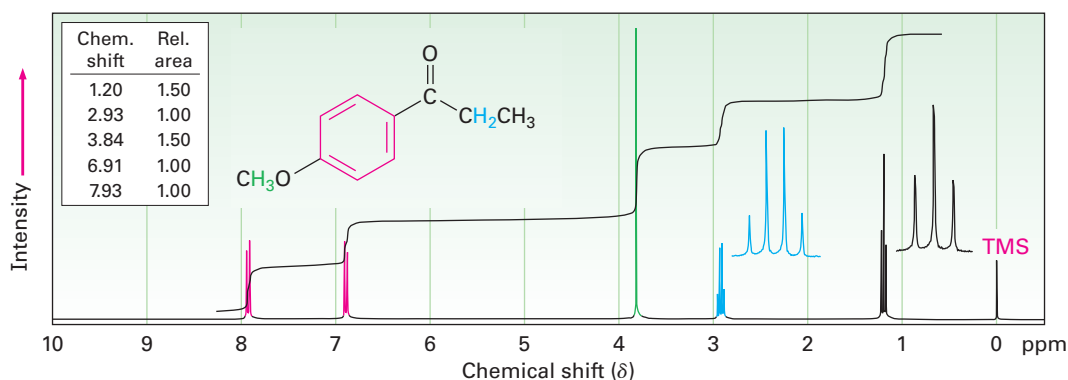


FIGURE 11.16
 ^1H NMR spectrum of *p*-methoxypropio-phenone.

energy to cover the carbon resonance frequencies, it is also irradiated by a second band of rf energy covering all the hydrogen resonance frequencies. This second irradiation makes the hydrogens spin-flip so rapidly that their local magnetic fields average to zero and no coupling with carbon spins occurs.

Assigning a Chemical Structure from a ^1H NMR Spectrum

WORKED EXAMPLE 11.4

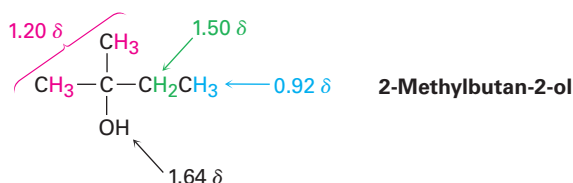
Propose a structure for a compound, $\text{C}_5\text{H}_{12}\text{O}$, that fits the following ^1H NMR data: 0.92 δ (3 H, triplet, $J = 7$ Hz), 1.20 δ (6 H, singlet), 1.50 δ (2 H, quartet, $J = 7$ Hz), 1.64 δ (1 H, broad singlet).

Strategy

As noted in Worked Example 11.2, it's best to begin solving structural problems by calculating a molecule's degree of unsaturation. In the present instance, a formula of $\text{C}_5\text{H}_{12}\text{O}$ corresponds to a saturated, open-chain molecule, either an alcohol or an ether.

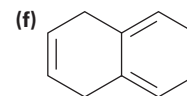
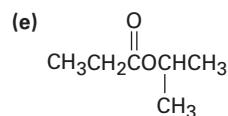
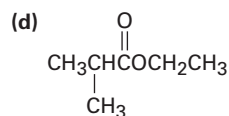
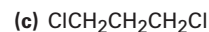
To interpret the NMR information, let's look at each absorption individually. The three-proton absorption at 0.92 δ is due to a methyl group in an alkane-like environment, and the triplet splitting pattern implies that the CH_3 is next to a CH_2 . Thus, our molecule contains an ethyl group, CH_3CH_2- . The six-proton singlet at 1.20 δ is due to two equivalent alkane-like methyl groups attached to a carbon with no hydrogens, $(\text{CH}_3)_2\text{C}$, and the two-proton quartet at 1.50 δ is due to the CH_2 of the ethyl group. All 5 carbons and 11 of the 12 hydrogens in the molecule are now accounted for. The remaining hydrogen, which appears as a broad one-proton singlet at 1.64 δ , is probably due to an OH group, since there is no other way to account for it. Putting the pieces together gives the structure: 2-methylbutan-2-ol.

Solution

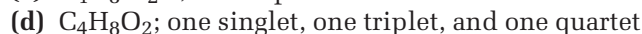
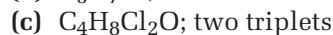
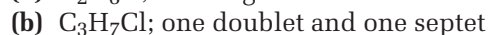
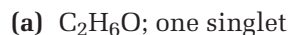


PROBLEM 11.19

Predict the splitting patterns you would expect for each proton in the following molecules:

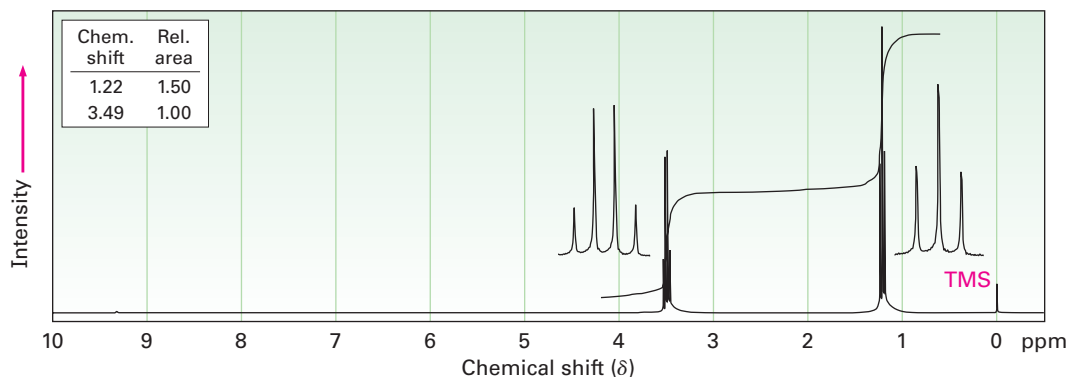
**PROBLEM 11.20**

Draw structures for compounds that meet the following descriptions:

**PROBLEM 11.21**

The integrated ^1H NMR spectrum of a compound of formula $\text{C}_4\text{H}_{10}\text{O}$ is shown in **FIGURE 11.17**. Propose a structure.

FIGURE 11.17
Integrated ^1H
NMR spectrum for
Problem 11.21.



11-12 More Complex Spin-Spin Splitting Patterns

In the ^1H NMR spectra we've seen thus far, the chemical shifts of different protons have been distinct and the spin-spin splitting patterns have been straightforward. It often happens, however, that different kinds of hydrogens in a molecule have accidentally overlapping signals. The spectrum of toluene in **FIGURE 11.18**, for example, shows that the five aromatic ring protons give a complex, overlapping pattern centered at 7.19 δ , even though they aren't all equivalent.

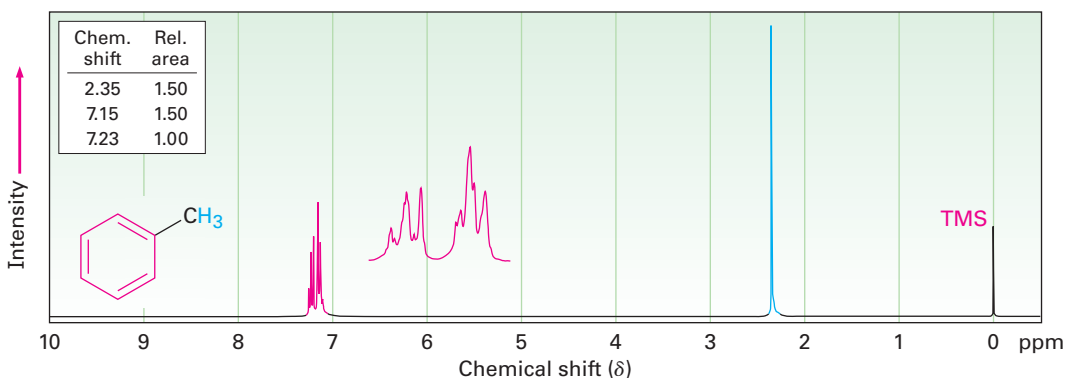


FIGURE 11.18
 ^1H NMR spectrum of toluene. Accidental overlap of the five nonequivalent aromatic ring protons occurs.

Yet another complication in ^1H NMR spectroscopy arises when a signal is split by two or more *nonequivalent* kinds of protons, as is the case with *trans*-cinnamaldehyde, isolated from oil of cinnamon (**FIGURE 11.19**). Although the $n + 1$ rule predicts splitting caused by *equivalent* protons, splittings caused by nonequivalent protons are more complex.

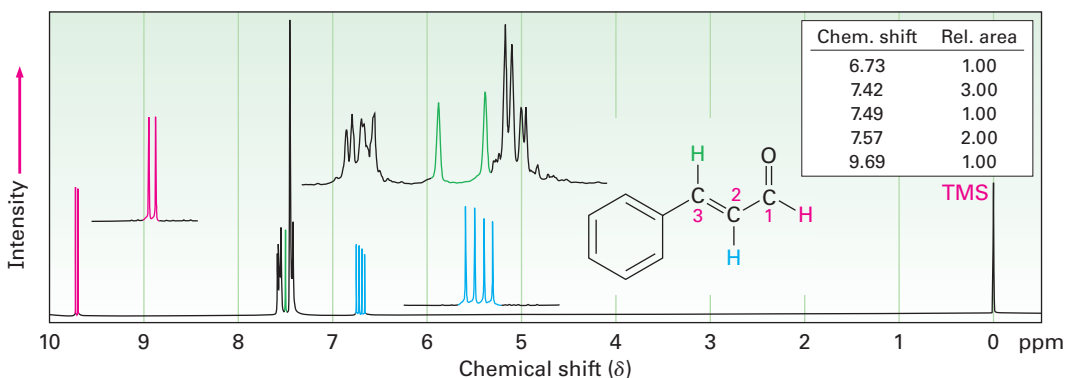


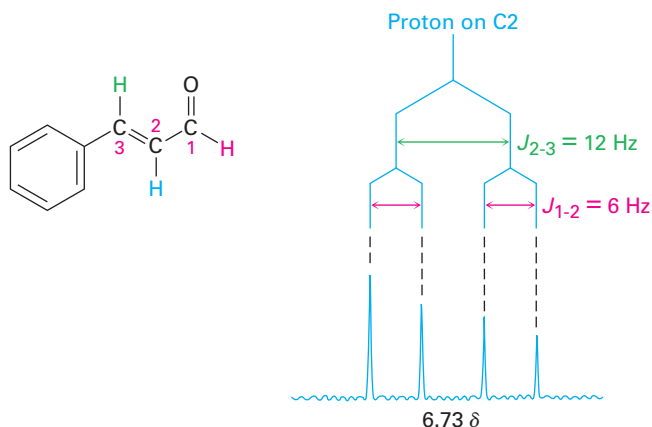
FIGURE 11.19
 ^1H NMR spectrum of *trans*-cinnamaldehyde. The signal of the proton at C_2 is split into four peaks—a doublet of doublets—by the two nonequivalent neighboring protons.

To understand the ^1H NMR spectrum of *trans*-cinnamaldehyde, we have to isolate the different parts and look at the signal of each proton individually:

- The five aromatic proton signals (black in Figure 11.19) overlap into a complex pattern with a large peak at 7.42δ and a broad absorption at 7.57δ .
- The aldehyde proton signal at C_1 (red) appears in the normal downfield position at 9.69δ and is split into a doublet with $J = 6 \text{ Hz}$ by the adjacent proton at C_2 .
- The vinylic proton at C_3 (green) is next to the aromatic ring and is therefore shifted downfield from the normal vinylic region. This C_3 proton signal appears as a doublet centered at 7.49δ . Because it has one neighbor proton at C_2 , its signal is split into a doublet, with $J = 12 \text{ Hz}$.
- The C_2 vinylic proton signal (blue) appears at 6.73δ and shows an interesting four-line absorption pattern. It is coupled to the two nonequivalent protons at C_1 and C_3 with two different coupling constants: $J_{1-2} = 6 \text{ Hz}$ and $J_{2-3} = 12 \text{ Hz}$.

A good way to understand the effect of multiple coupling such as occurs for the C2 proton of *trans*-cinnamaldehyde is to draw a *tree diagram*, like that in **FIGURE 11.20**. The diagram shows the individual effect of each coupling constant on the overall pattern. Coupling with the C3 proton splits the signal of the C2 proton in *trans*-cinnamaldehyde into a doublet with $J = 12$ Hz. Further coupling with the aldehyde proton then splits each peak of the doublet into new doublets with $J = 6$ Hz, and we therefore observe a four-line spectrum for the C2 proton.

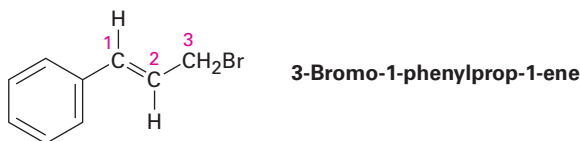
FIGURE 11.20 Tree diagram for the C2 proton of *trans*-cinnamaldehyde. The C2 proton is coupled to the C1 and C3 protons with different coupling constants.



One further point evident in the cinnamaldehyde spectrum is that the four peaks of the C2 proton signal are not all the same size. The two left-hand peaks are somewhat larger than the two right-hand peaks. Such a size difference occurs whenever coupled nuclei have similar chemical shifts—in this case, 7.49δ for the C3 proton and 6.73δ for the C2 proton. The peaks nearer the signal of the coupled partner are always larger, and the peaks farther from the signal of the coupled partner are always smaller. Thus, the left-hand peaks of the C2 proton multiplet at 6.73δ are closer to the C3 proton absorption at 7.49δ and are larger than the right-hand peaks. At the same time, the right-hand peak of the C3 proton doublet at 7.49δ is larger than the left-hand peak because it is closer to the C2 proton multiplet at 6.73δ . This skewing effect on multiplets can often be useful because it tells where to look in the spectrum to find the coupled partner: look in the direction of the larger peaks.

PROBLEM 11.22

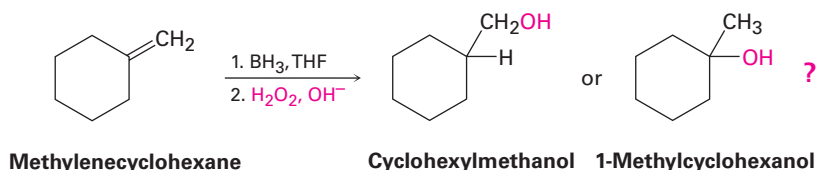
3-Bromo-1-phenylprop-1-ene shows a complex NMR spectrum in which the vinylic proton at C2 is coupled with both the C1 vinylic proton ($J = 16$ Hz) and the C3 methylene protons ($J = 8$ Hz). Draw a tree diagram for the C2 proton signal, and account for the fact that a five-line multiplet is observed.



11-13 Uses of ^1H NMR Spectroscopy

NMR is used to help identify the product of nearly every reaction run in the laboratory. For example, we said in Section 8-4 that hydroboration–oxidation of alkenes occurs with non-Markovnikov regiochemistry to yield the less highly substituted alcohol. With the help of NMR, we can prove this statement.

Does hydroboration–oxidation of methylenecyclohexane yield cyclohexylmethanol or 1-methylcyclohexanol?



The ^1H NMR spectrum of the reaction product is shown in **FIGURE 11.21a**. The spectrum shows a two-proton peak at 3.40 δ , indicating that the product has a $-\text{CH}_2-$ group bonded to an electronegative oxygen atom ($-\text{CH}_2\text{OH}$). Furthermore, the spectrum shows *no* large three-proton singlet absorption near 1 δ , where we would expect the signal of a quaternary $-\text{CH}_3$ group to appear. (**FIGURE 11.21b** gives the spectrum of 1-methylcyclohexanol, the alternative product.) Thus, it's clear that cyclohexylmethanol is the reaction product.

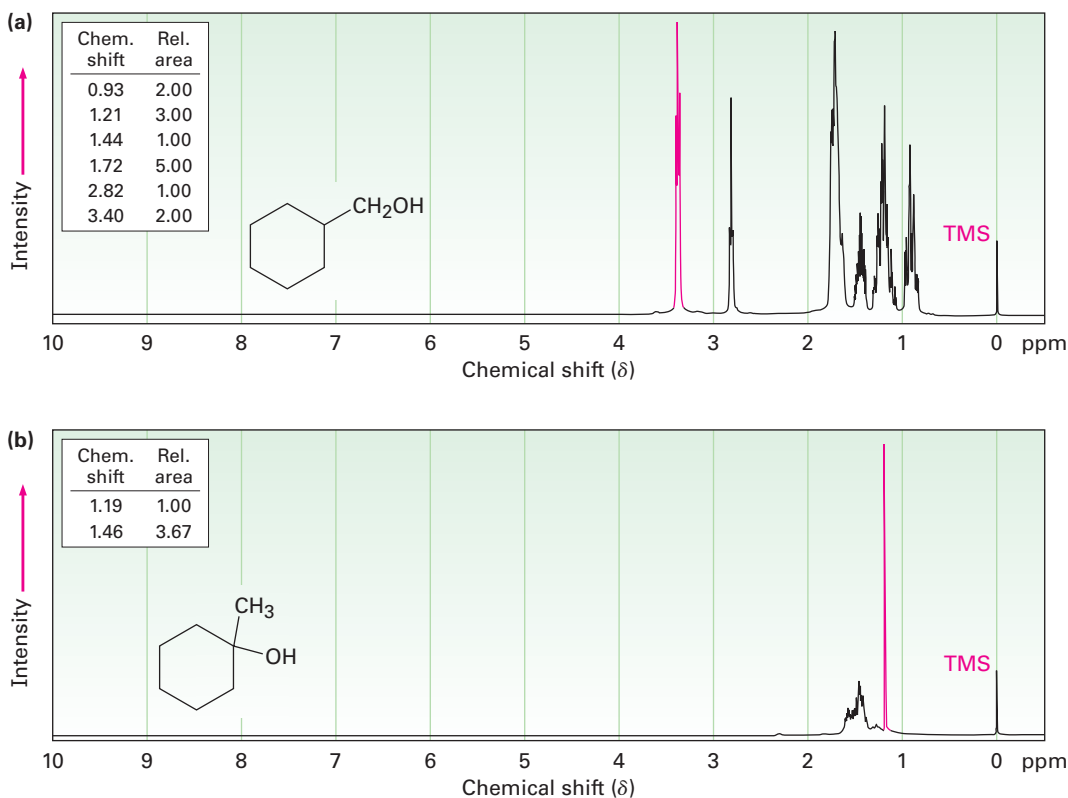


FIGURE 11.21 ^1H NMR spectra of (a) cyclohexylmethanol, the product from hydroboration/oxidation of methylenecyclohexane, and (b) 1-methylcyclohexanol, the possible alternative reaction product.

PROBLEM 11.23

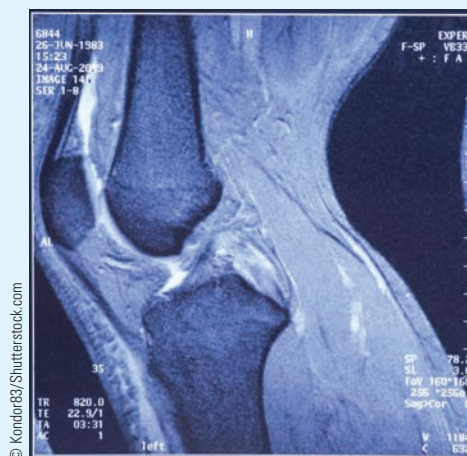
How could you use ^1H NMR to determine the regiochemistry of electrophilic addition to alkenes? For example, does addition of HCl to 1-methylcyclohexene yield 1-chloro-1-methylcyclohexane or 1-chloro-2-methylcyclohexane?

SOMETHING EXTRA

Magnetic Resonance Imaging (MRI)

As practiced by organic chemists, NMR spectroscopy is a powerful method of structure determination. A small amount of sample, typically a few milligrams or less, is dissolved in a small amount of solvent, the solution is placed in a thin glass tube, and the tube is placed into the narrow (1–2 cm) gap between the poles of a strong magnet. Imagine, though, that a much larger NMR instrument were available. Instead of a few milligrams, the sample size could be tens of kilograms; instead of a narrow gap between magnet poles, the gap could be large enough for a whole person to climb into so that an NMR spectrum of body parts could be obtained. That large instrument is exactly what's used for *magnetic resonance imaging (MRI)*, a diagnostic technique of enormous value to the medical community.

Like NMR spectroscopy, MRI takes advantage of the magnetic properties of certain nuclei, typically hydrogen, and of the signals emitted when those nuclei are stimulated by radiofrequency energy. Unlike what happens in NMR spectroscopy, though, MRI instruments use data manipulation techniques to look at the three-dimensional *location* of magnetic nuclei in the body rather than at the chemical nature of the nuclei. As noted, most MRI instruments currently look at hydrogen, present in abundance wherever there is water or fat in the body.



If you're a runner, you really don't want this to happen to you. The MRI of this left knee shows the presence of a torn anterior cruciate ligament.

The signals detected by MRI vary with the density of hydrogen atoms and with the nature of their surroundings, allowing identification of different types of tissue and even allowing the visualization of motion. For example, the volume of blood leaving the heart in a single stroke can be measured, and heart motion can be observed. Soft tissues that don't show up well on X rays can be seen clearly, allowing diagnosis of brain tumors, strokes, and other conditions. The technique is also valuable in diagnosing damage to knees or other joints and is a noninvasive alternative to surgical explorations.

Several types of atoms in addition to hydrogen can be detected by MRI, and the applications of images based on ^{31}P atoms are being explored. The technique holds great promise for studies of metabolism.

SUMMARY

Nuclear magnetic resonance spectroscopy, or **NMR**, is the most valuable of the numerous spectroscopic techniques used for structure determination. Although we focused in this chapter on NMR applications to small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

When magnetic nuclei, such as ^1H and ^{13}C , are placed in a strong magnetic field, their spins orient either with or against the field. On irradiation with radiofrequency (rf) waves, energy is absorbed and the nuclei “spin-flip” from the lower energy state to the higher energy state. This absorption of rf energy is detected, amplified, and displayed as an NMR spectrum.

Each electronically distinct ^1H or ^{13}C nucleus in a molecule comes into resonance at a slightly different value of the applied field, thereby producing a unique absorption signal. The exact position of each peak is called the **chemical shift**. Chemical shifts are caused by electrons setting up tiny local magnetic fields that **shield** a nearby nucleus from the applied field.

The NMR chart is calibrated in **delta units (δ)**, where $1 \delta = 1 \text{ ppm}$ of spectrometer frequency. Tetramethylsilane (TMS) is used as a reference point because it shows both ^1H and ^{13}C absorptions at unusually high values of the applied magnetic field. The TMS absorption occurs at the right-hand (**upfield**) side of the chart and is arbitrarily assigned a value of 0δ .

^{13}C spectra are run on Fourier-transform NMR (**FT-NMR**) spectrometers using broadband decoupling of proton spins so that each chemically distinct carbon shows a single unsplit resonance line. As with ^1H NMR, the chemical shift of each ^{13}C signal provides information about a carbon’s chemical environment in the sample. In addition, the number of protons attached to each carbon can be determined using the DEPT-NMR technique.

In ^1H NMR spectra, the area under each absorption peak can be electronically **integrated** to determine the relative number of hydrogens responsible for each peak. In addition, neighboring nuclear spins can **couple**, causing the **spin-spin splitting** of NMR peaks into **multiplets**. The NMR signal of a hydrogen neighbored by n equivalent adjacent hydrogens splits into $n + 1$ peaks (the **$n + 1$ rule**) with **coupling constant J** .

KEY WORDS

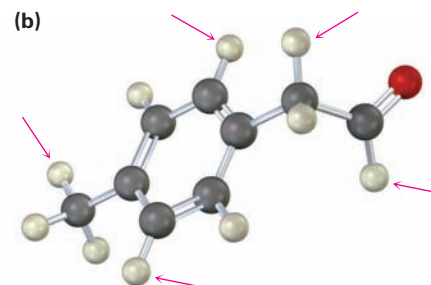
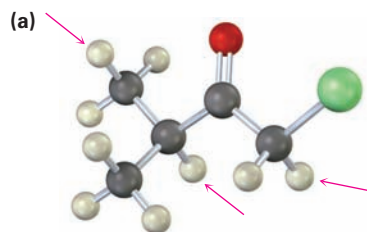
chemical shift,	356
coupling,	371
coupling constant (J),	373
delta (δ) scale,	356
diastereotopic,	367
downfield,	355
enantiotopic,	366
FT-NMR,	357
homotopic,	366
integration,	370
multiplet,	371
$n + 1$ rule,	372
nuclear magnetic resonance (NMR) spectroscopy,	350
shielding,	352
spin-spin splitting,	371
upfield,	355

EXERCISES

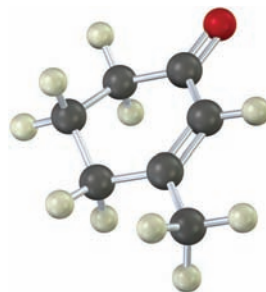
VISUALIZING CHEMISTRY

(Problems 11.1–11.23 appear within the chapter.)

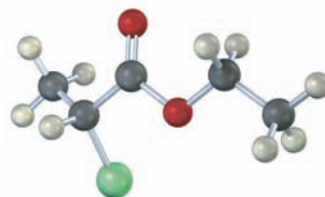
- 11.24 Into how many peaks would you expect the ^1H NMR signals of the indicated protons to be split? (Green = Cl.)



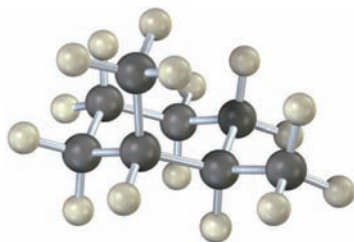
- 11.25 How many absorptions would you expect the following compound to have in its ^1H and ^{13}C NMR spectra?



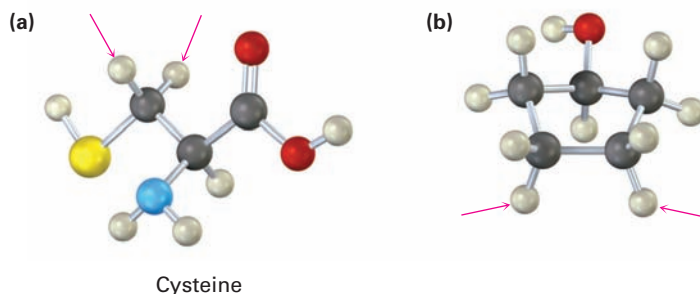
- 11.26 Sketch what you might expect the ^1H and ^{13}C NMR spectra of the following compound to look like (green = Cl):



- 11.27 How many electronically nonequivalent kinds of protons and how many kinds of carbons are present in the following compound? Don't forget that cyclohexane rings can ring-flip.



- 11.28 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or diastereotopic:



ADDITIONAL PROBLEMS

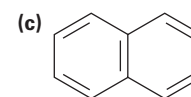
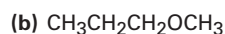
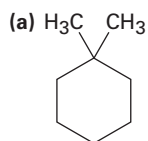
Chemical Shifts and NMR Spectroscopy

- 11.29 The following ^1H NMR absorptions were obtained on a spectrometer operating at 200 MHz and are given in hertz downfield from the TMS standard. Convert the absorptions to δ units.
- (a) 436 Hz (b) 956 Hz (c) 1504 Hz
- 11.30 The following ^1H NMR absorptions were obtained on a spectrometer operating at 300 MHz. Convert the chemical shifts from δ units to hertz downfield from TMS.
- (a) 2.1 δ (b) 3.45 δ (c) 6.30 δ (d) 7.70 δ
- 11.31 When measured on a spectrometer operating at 200 MHz, chloroform (CHCl_3) shows a single sharp absorption at 7.3 δ .
- (a) How many parts per million downfield from TMS does chloroform absorb?
- (b) How many hertz downfield from TMS would chloroform absorb if the measurement were carried out on a spectrometer operating at 360 MHz?
- (c) What would be the position of the chloroform absorption in δ units when measured on a 360 MHz spectrometer?

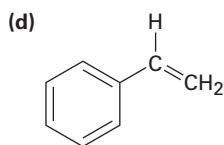
- 11.32** Why do you suppose accidental overlap of signals is much more common in ^1H NMR than in ^{13}C NMR?
- 11.33** Is a nucleus that absorbs at $6.50\ \delta$ more shielded or less shielded than a nucleus that absorbs at $3.20\ \delta$? Does the nucleus that absorbs at $6.50\ \delta$ require a stronger applied field or a weaker applied field to come into resonance than the nucleus that absorbs at $3.20\ \delta$?

^1H NMR Spectroscopy

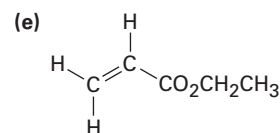
- 11.34** How many types of nonequivalent protons are present in each of the following molecules?



Naphthalene



Styrene

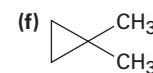
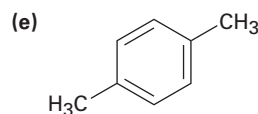
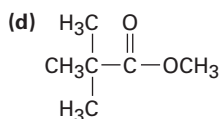
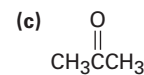
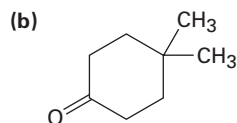
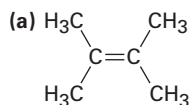


Ethyl acrylate

- 11.35** The following compounds all show a single line in their ^1H NMR spectra. List them in expected order of increasing chemical shift.

CH4, CH2Cl2, cyclohexane, CH3COCH3, H2C=CH2, benzene

- 11.36** How many signals would you expect each of the following molecules to have in its ^1H and ^{13}C spectra?



- 11.37** Propose structures for compounds with the following formulas that show only one peak in their ^1H NMR spectra:

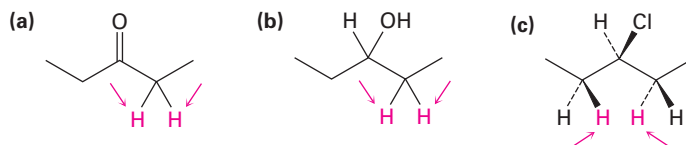


11.38 Predict the splitting pattern for each kind of hydrogen in the following molecules:

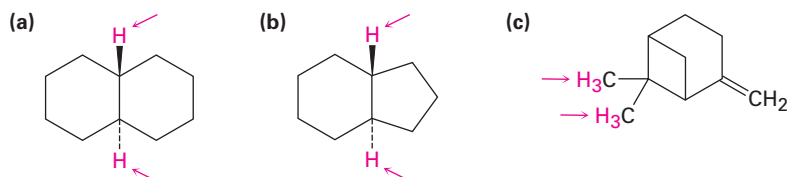


11.39 Predict the splitting pattern for each kind of hydrogen in isopropyl propanoate, $\text{CH}_3\text{CH}_2\text{CO}_2\text{CH}(\text{CH}_3)_2$.

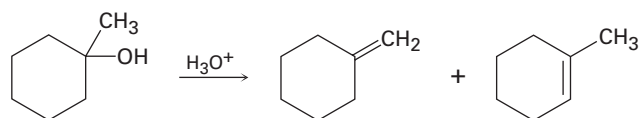
11.40 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



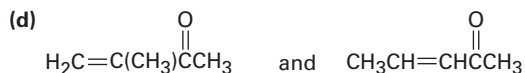
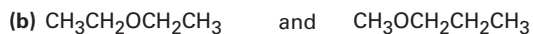
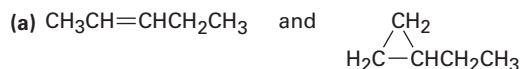
11.41 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



11.42 Treatment of 1-methylcyclohexanol with strong acid causes an elimination of water and yields a mixture of two alkenes. How could you use ^1H NMR to help you decide which was which?



11.43 How could you use ^1H NMR to distinguish between the following pairs of isomers?

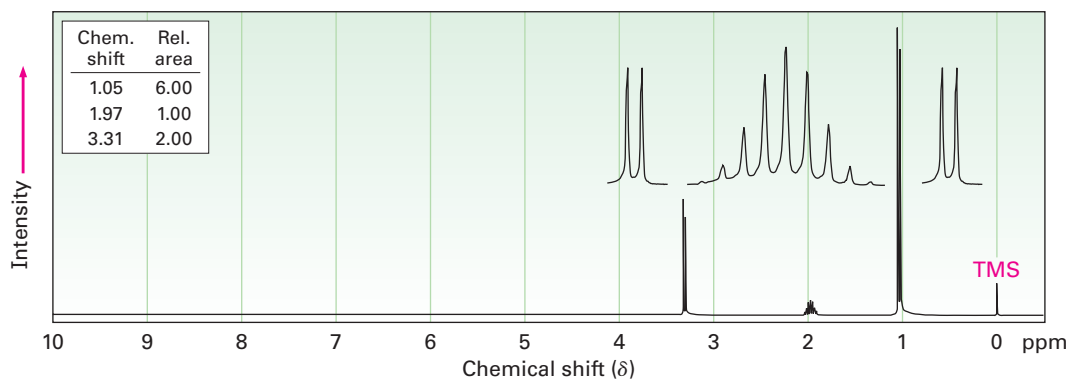


11.44 Propose structures for compounds that fit the following ^1H NMR data:

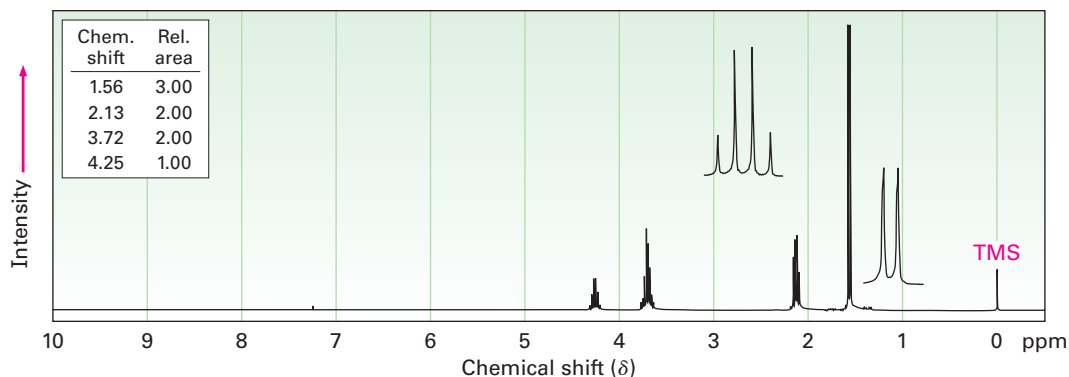
- | | |
|--|---|
| <p>(a) $\text{C}_5\text{H}_{10}\text{O}$
 0.95 δ (6 H, doublet, $J = 7$ Hz)
 2.10 δ (3 H, singlet)
 2.43 δ (1 H, multiplet)</p> | <p>(b) $\text{C}_3\text{H}_5\text{Br}$
 2.32 δ (3 H, singlet)
 5.35 δ (1 H, broad singlet)
 5.54 δ (1 H, broad singlet)</p> |
|--|---|

11.45 Propose structures for the two compounds whose ^1H NMR spectra are shown.

(a) $\text{C}_4\text{H}_9\text{Br}$



(b) $\text{C}_4\text{H}_8\text{Cl}_2$



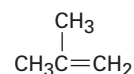
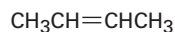
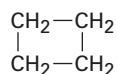
^{13}C NMR Spectroscopy

11.46 How many ^{13}C NMR absorptions would you expect for *cis*-1,3-dimethylcyclohexane? For *trans*-1,3-dimethylcyclohexane? Explain.

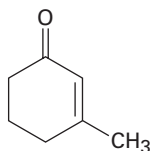
11.47 How many absorptions would you expect to observe in the ^{13}C NMR spectra of the following compounds?

- | | |
|--|---|
| (a) 1,1-Dimethylcyclohexane | (b) $\text{CH}_3\text{CH}_2\text{OCH}_3$ |
| (c) <i>tert</i> -Butylcyclohexane | (d) 3-Methylpent-1-yne |
| (e) <i>cis</i> -1,2-Dimethylcyclohexane | (f) Cyclohexanone |

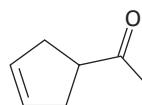
- 11.48 Suppose you ran a DEPT-135 spectrum for each substance in Problem 11.47. Which carbon atoms in each molecule would show positive peaks, and which would show negative peaks?
- 11.49 How could you use ^1H and ^{13}C NMR to help you distinguish among the following isomeric compounds of formula C_4H_8 ?



- 11.50 How could you use ^1H NMR, ^{13}C NMR, IR, and UV spectroscopy to help you distinguish between the following structures?

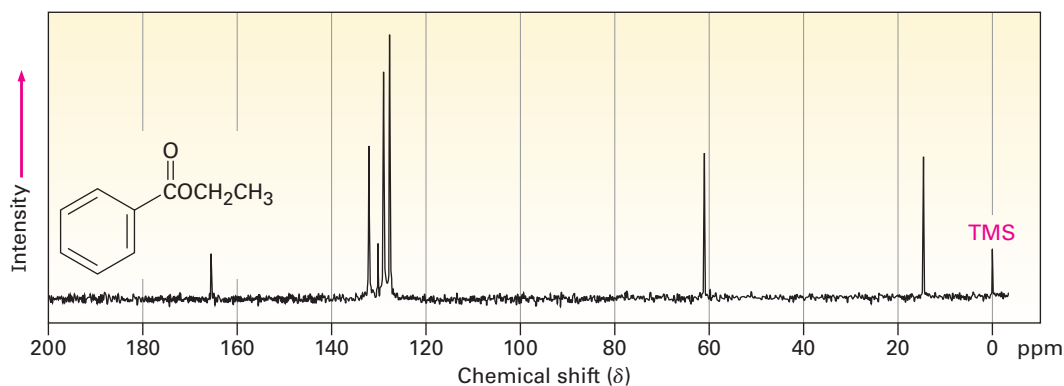


3-Methylcyclohex-2-enone



Cyclopent-3-enyl methyl ketone

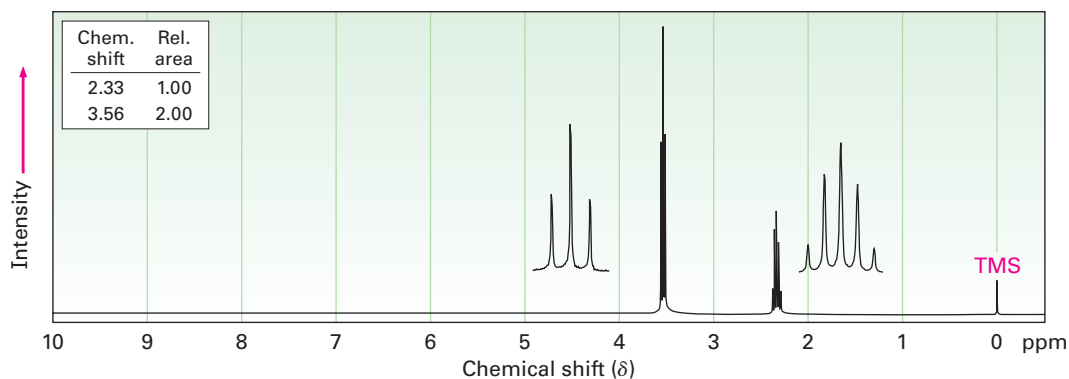
- 11.51 Assign as many of the resonances as you can to specific carbon atoms in the ^{13}C NMR spectrum of ethyl benzoate.



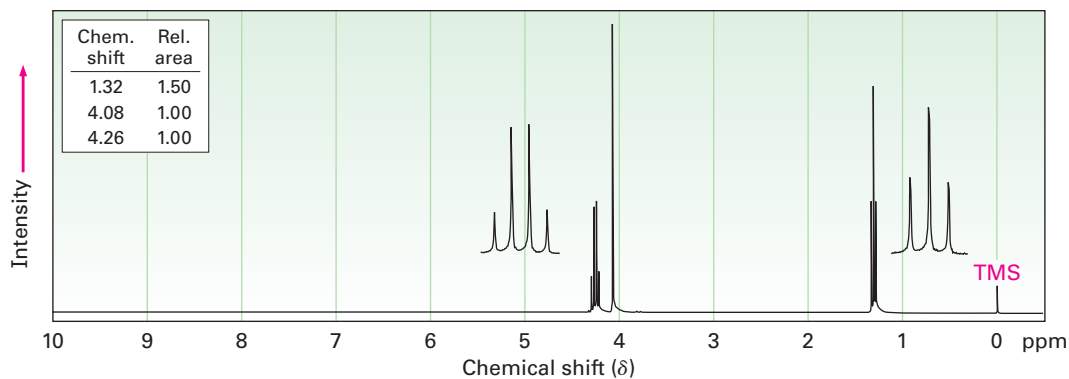
General Problems

- 11.52 Assume that you have a compound with formula $\text{C}_3\text{H}_6\text{O}$.
- How many double bonds and/or rings does your compound contain?
 - Propose as many structures as you can that fit the molecular formula.
 - If your compound shows an infrared absorption peak at 1715 cm^{-1} , what functional group does it have?
 - If your compound shows a single ^1H NMR absorption peak at $2.1\ \delta$, what is its structure?

11.53 The compound whose ^1H NMR spectrum is shown has the molecular formula $\text{C}_3\text{H}_6\text{Br}_2$. Propose a structure.



11.54 The compound whose ^1H NMR spectrum is shown has the molecular formula $\text{C}_4\text{H}_7\text{O}_2\text{Cl}$ and has an infrared absorption peak at 1740 cm^{-1} . Propose a structure.



11.55 Propose structures for compounds that fit the following ^1H NMR data:

(a) $\text{C}_4\text{H}_6\text{Cl}_2$

- 2.18 δ (3 H, singlet)
- 4.16 δ (2 H, doublet, $J = 7$ Hz)
- 5.71 δ (1 H, triplet, $J = 7$ Hz)

(b) $\text{C}_{10}\text{H}_{14}$

- 1.30 δ (9 H, singlet)
- 7.30 δ (5 H, singlet)

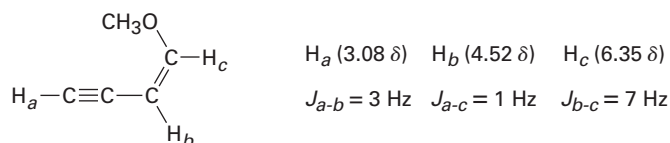
(c) $\text{C}_4\text{H}_7\text{BrO}$

- 2.11 δ (3 H, singlet)
- 3.52 δ (2 H, triplet, $J = 6$ Hz)
- 4.40 δ (2 H, triplet, $J = 6$ Hz)

(d) $\text{C}_9\text{H}_{11}\text{Br}$

- 2.15 δ (2 H, quintet, $J = 7$ Hz)
- 2.75 δ (2 H, triplet, $J = 7$ Hz)
- 3.38 δ (2 H, triplet, $J = 7$ Hz)
- 7.22 δ (5 H, singlet)

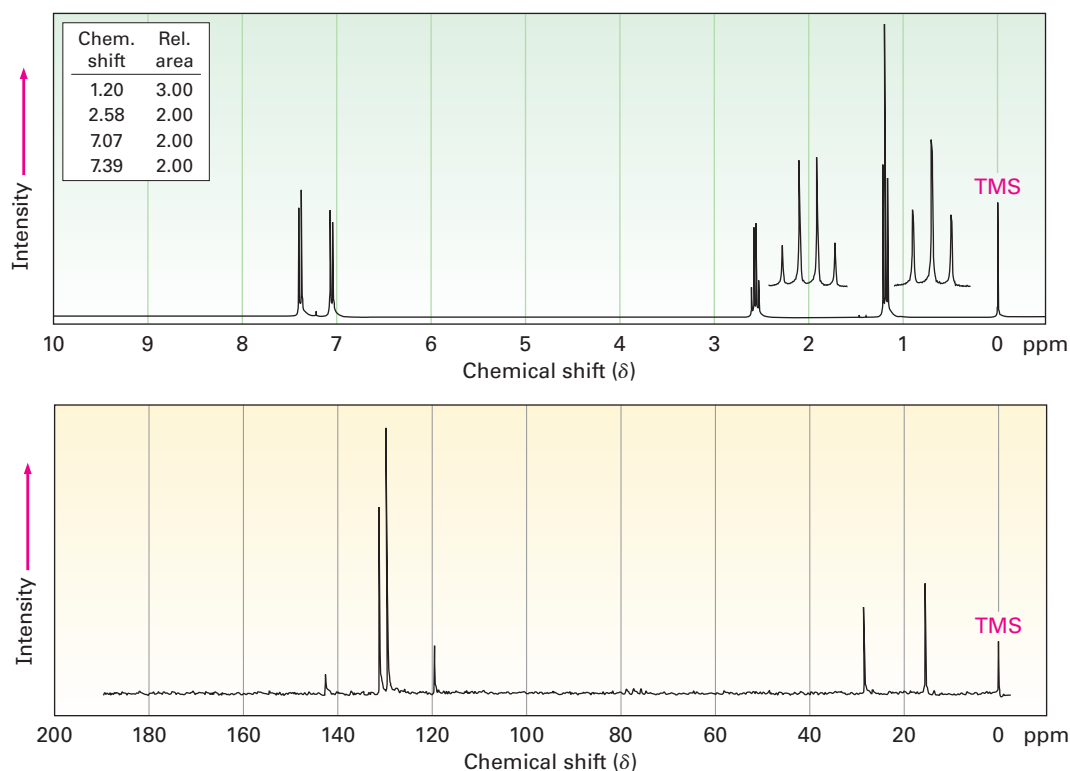
- 11.56** Long-range coupling between protons more than two carbon atoms apart is sometimes observed when π bonds intervene. An example is found in 1-methoxybut-1-en-3-yne. Not only does the acetylenic proton, H_a , couple with the vinylic proton H_b , it also couples with the vinylic proton H_c , four carbon atoms away. The data are:



1-Methoxybut-1-en-3-yne

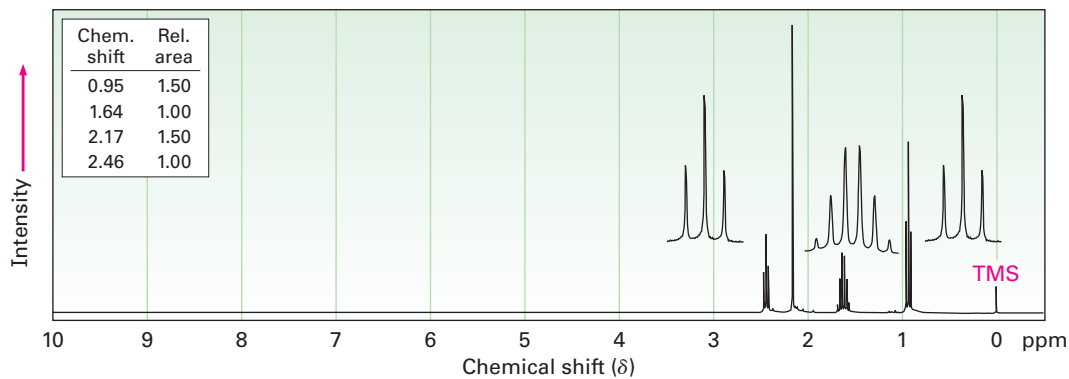
Construct tree diagrams that account for the observed splitting patterns of H_a , H_b , and H_c .

- 11.57** The ^1H and ^{13}C NMR spectra of compound **A**, $\text{C}_8\text{H}_9\text{Br}$, are shown. Propose a structure for **A**, and assign peaks in the spectra to your structure.

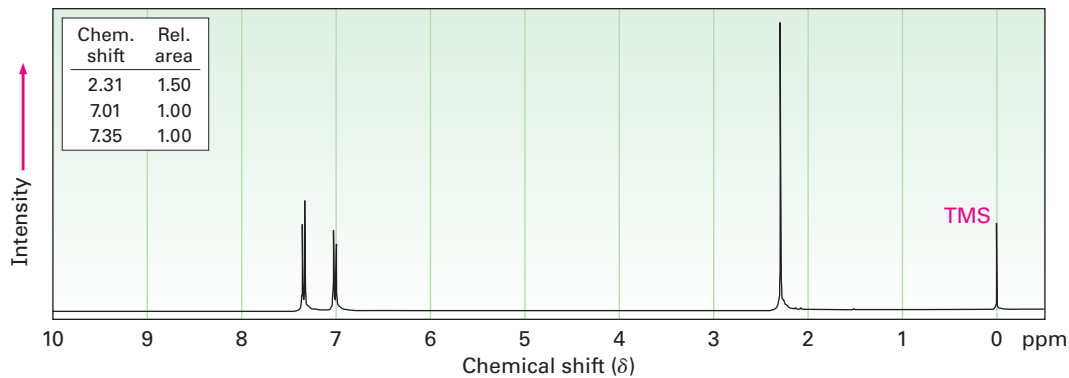


11.58 Propose structures for the three compounds whose ^1H NMR spectra are shown.

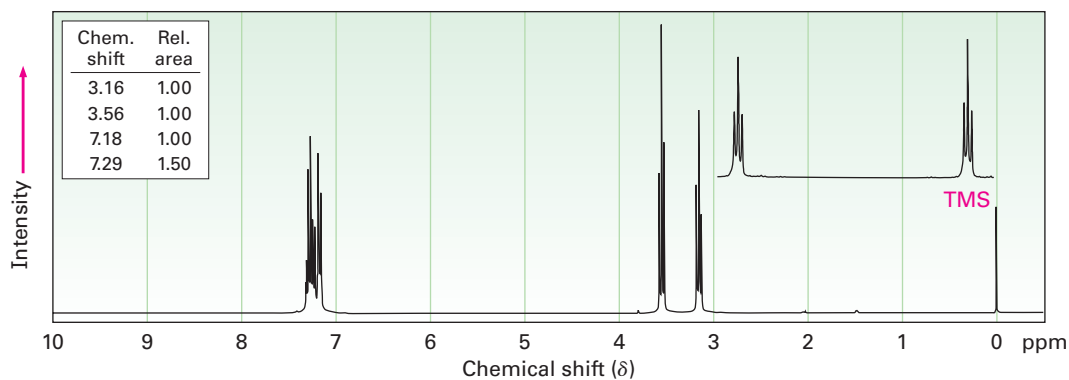
(a) $\text{C}_5\text{H}_{10}\text{O}$



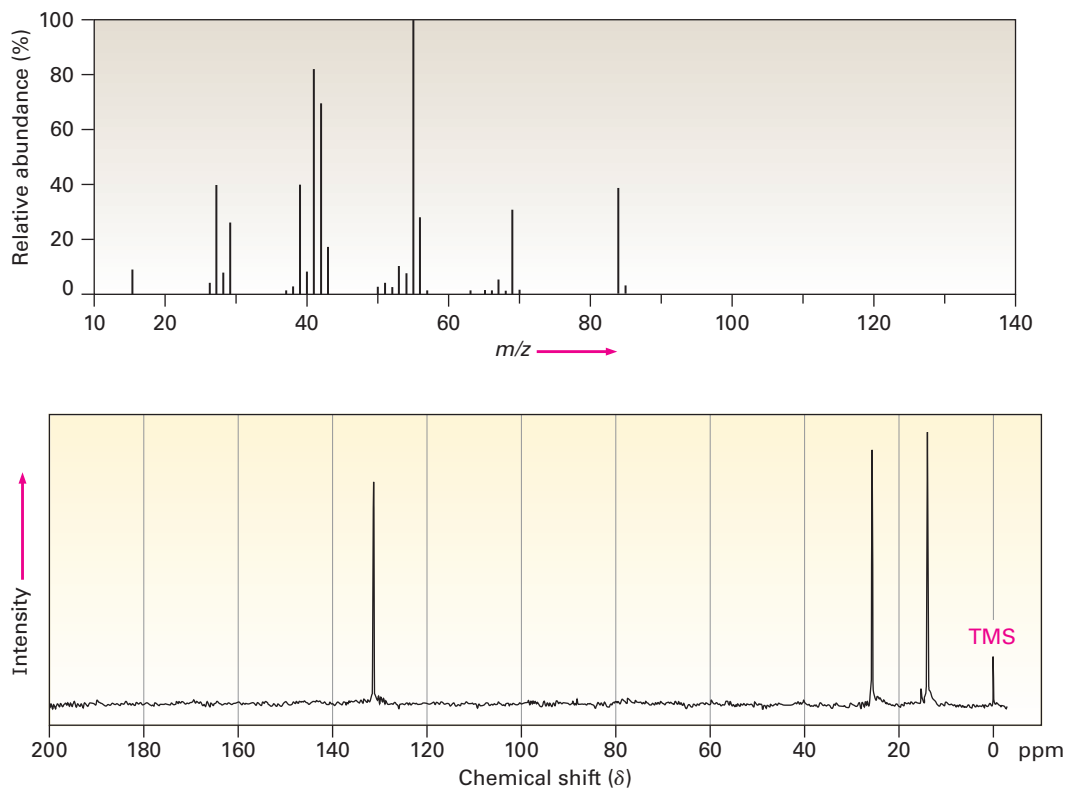
(b) $\text{C}_7\text{H}_7\text{Br}$



(c) $\text{C}_8\text{H}_9\text{Br}$



- 11.59 The mass spectrum and ^{13}C NMR spectrum of a hydrocarbon are shown. Propose a structure for this hydrocarbon, and explain the spectral data.



- 11.60 Compound **A**, a hydrocarbon with $M^+ = 96$ in its mass spectrum, has the ^{13}C spectral data given below. On reaction with BH_3 followed by treatment with basic H_2O_2 , **A** is converted into **B**, whose ^{13}C spectral data are also given below. Propose structures for **A** and **B**.

Compound A

Broadband-decoupled ^{13}C NMR: 26.8, 28.7, 35.7, 106.9, 149.7 δ

DEPT-90: no peaks

DEPT-135: no positive peaks; negative peaks at 26.8, 28.7, 35.7, 106.9 δ

Compound B

Broadband-decoupled ^{13}C NMR: 26.1, 26.9, 29.9, 40.5, 68.2 δ

DEPT-90: 40.5 δ

DEPT-135: positive peak at 40.5 δ ; negative peaks at 26.1, 26.9, 29.9, 68.2 δ

- 11.61** Propose a structure for compound **C**, which has $M^+ = 86$ in its mass spectrum, an IR absorption at 3400 cm^{-1} , and the following ^{13}C NMR spectral data:

Compound C

Broadband-decoupled ^{13}C NMR: 30.2, 31.9, 61.8, 114.7, 138.4 δ

DEPT-90: 138.4 δ

DEPT-135: positive peak at 138.4 δ ; negative peaks at 30.2, 31.9, 61.8, 114.7 δ

- 11.62** Compound **D** is isomeric with compound **C** (Problem 11.61) and has the following ^{13}C NMR spectral data. Propose a structure.

Compound D

Broadband-decoupled ^{13}C NMR: 9.7, 29.9, 74.4, 114.4, 141.4 δ

DEPT-90: 74.4, 141.4 δ

DEPT-135: positive peaks at 9.7, 74.4, 141.4 δ ; negative peaks at 29.9, 114.4 δ

- 11.63** Propose a structure for compound **E**, $\text{C}_7\text{H}_{12}\text{O}_2$, which has the following ^{13}C NMR spectral data:

Compound E

Broadband-decoupled ^{13}C NMR: 19.1, 28.0, 70.5, 129.0, 129.8, 165.8 δ

DEPT-90: 28.0, 129.8 δ

DEPT-135: positive peaks at 19.1, 28.0, 129.8 δ ; negative peaks at 70.5, 129.0 δ

- 11.64** Compound **F**, a hydrocarbon with $M^+ = 96$ in its mass spectrum, undergoes reaction with HBr to yield compound **G**. Propose structures for **F** and **G**, whose ^{13}C NMR spectral data are given below.

Compound F

Broadband-decoupled ^{13}C NMR: 27.6, 29.3, 32.2, 132.4 δ

DEPT-90: 132.4 δ

DEPT-135: positive peak at 132.4 δ ; negative peaks at 27.6, 29.3, 32.2 δ

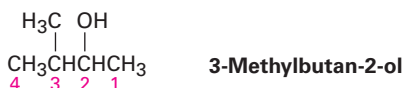
Compound G

Broadband-decoupled ^{13}C NMR: 25.1, 27.7, 39.9, 56.0 δ

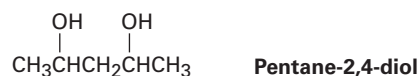
DEPT-90: 56.0 δ

DEPT-135: positive peak at 56.0 δ ; negative peaks at 25.1, 27.7, 39.9 δ

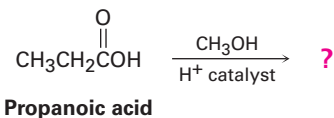
- 11.65** 3-Methylbutan-2-ol has five signals in its ^{13}C NMR spectrum at 17.90, 18.15, 20.00, 35.05, and 72.75 δ . Why are the two methyl groups attached to C3 nonequivalent? Making a molecular model should be helpful.



- 11.66 A ^{13}C NMR spectrum of commercially available pentane-2,4-diol shows *five* peaks at 23.3, 23.9, 46.5, 64.8, and 68.1 δ . Explain.



- 11.67 Carboxylic acids (RCO_2H) react with alcohols ($\text{R}'\text{OH}$) in the presence of an acid catalyst. The reaction product of propanoic acid with methanol has the following spectroscopic properties. Propose a structure.



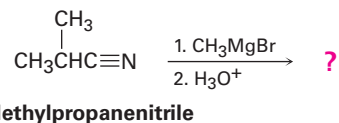
MS: $\text{M}^+ = 88$

IR: 1735 cm^{-1}

^1H NMR: 1.11 δ (3 H, triplet, $J = 7$ Hz); 2.32 δ (2 H, quartet, $J = 7$ Hz);
3.65 δ (3 H, singlet)

^{13}C NMR: 9.3, 27.6, 51.4, 174.6 δ

- 11.68 Nitriles ($\text{RC}\equiv\text{N}$) react with Grignard reagents ($\text{R}'\text{MgBr}$). The reaction product from 2-methylpropanenitrile with methylmagnesium bromide has the following spectroscopic properties. Propose a structure.



MS: $\text{M}^+ = 86$

IR: 1715 cm^{-1}

^1H NMR: 1.05 δ (6 H, doublet, $J = 7$ Hz); 2.12 δ (3 H, singlet); 2.67 δ
(1 H, septet, $J = 7$ Hz)

^{13}C NMR: 18.2, 27.2, 41.6, 211.2 δ

12

Organohalides: Nucleophilic Substitutions and Eliminations

CONTENTS

- 12-1** Names and Structures of Alkyl Halides
- 12-2** Preparing Alkyl Halides from Alkenes: Allylic Bromination
- 12-3** Preparing Alkyl Halides from Alcohols
- 12-4** Reactions of Alkyl Halides: Grignard Reagents
- 12-5** Organometallic Coupling Reactions
- 12-6** Discovery of the Nucleophilic Substitution Reaction
- 12-7** The S_N2 Reaction
- 12-8** Characteristics of the S_N2 Reaction
- 12-9** The S_N1 Reaction
- 12-10** Characteristics of the S_N1 Reaction
- 12-11** Biological Substitution Reactions
- 12-12** Elimination Reactions: Zaitsev's Rule
- 12-13** The E2 Reaction and the Deuterium Isotope Effect
- 12-14** The E1 and E1cB Reactions
- 12-15** Biological Elimination Reactions
- 12-16** A Summary of Reactivity: S_N1 , S_N2 , E1, E1cB, and E2

SOMETHING EXTRA

Naturally Occurring Organohalides



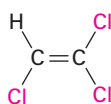
N⁶-Adenine methyltransferase catalyzes the methylation of pyrimidine nucleotides in DNA.

WHY THIS CHAPTER?

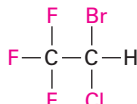
Alkyl halides themselves are not often involved in the biochemical pathways of terrestrial organisms, but some of the *kinds* of reactions they undergo—nucleophilic substitutions and eliminations—are frequently involved. Thus, alkyl halide chemistry acts as a relatively simple model for many mechanistically similar but structurally more complex reactions found in biomolecules. We'll begin with a look at how to name and prepare alkyl halides, and we'll then make a detailed study of their substitution and elimination reactions—two of the most important and well-studied reaction types in organic chemistry.

Now that we've covered the chemistry of hydrocarbons, it's time to start looking at more complex substances that contain elements in addition to C and H. We'll begin by discussing the chemistry of **organohalides**, compounds that contain one or more halogen atoms.

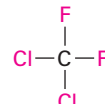
Halogen-substituted organic compounds are widespread in nature, and more than 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for instance, is released in large amounts by ocean kelp, as well as by forest fires and volcanoes. Halogen-containing compounds also have a vast array of industrial applications, including their use as solvents, inhaled anesthetics, refrigerants, and pesticides.



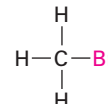
Trichloroethylene
(a solvent)



Halothane
(an inhaled anesthetic)



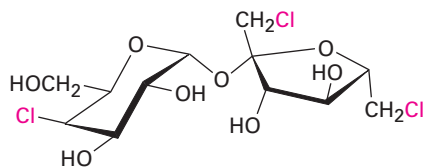
Dichlorodifluoromethane
(a refrigerant)



Bromomethane
(a fumigant)

Other halo-substituted compounds are used as medicines and food additives. The nonnutritive sweetener sucralose, marketed as Splenda,

contains three chlorine atoms, for instance. Sucralose is about 600 times as sweet as sucrose, so only 1 mg is equivalent to an entire teaspoon of table sugar.



Sucralose

A large variety of organohalides are known. The halogen might be bonded to an alkynyl group ($C\equiv C-X$), a vinylic group ($C=C-X$), an aromatic ring ($Ar-X$), or an alkyl group. We'll be concerned in this chapter, however, primarily with **alkyl halides**, compounds with a halogen atom bonded to a saturated, sp^3 -hybridized carbon atom.

12-1 Names and Structures of Alkyl Halides

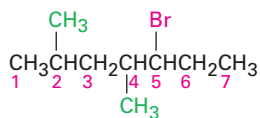
Although commonly called *alkyl halides*, halogen-substituted alkanes are named systematically as *haloalkanes* (Section 3-4), treating the halogen as a substituent on a parent alkane chain. There are three steps:

Step 1

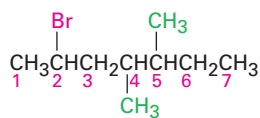
Find the longest chain, and name it as the parent. If a double or triple bond is present, the parent chain must contain it.

Step 2

Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo. Assign each substituent a number according to its position on the chain.

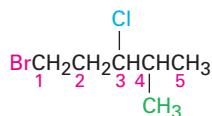


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

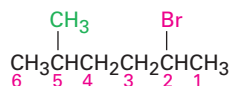
If different halogens are present, number all and list them in alphabetical order when writing the name.



1-Bromo-3-chloro-4-methylpentane

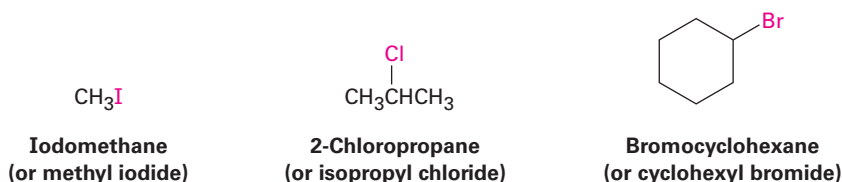
Step 3

If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.



2-Bromo-5-methylhexane
(Not 5-bromo-2-methylhexane)

In addition to their systematic names, many simple alkyl halides can also be named by identifying first the alkyl group and then the halogen. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.



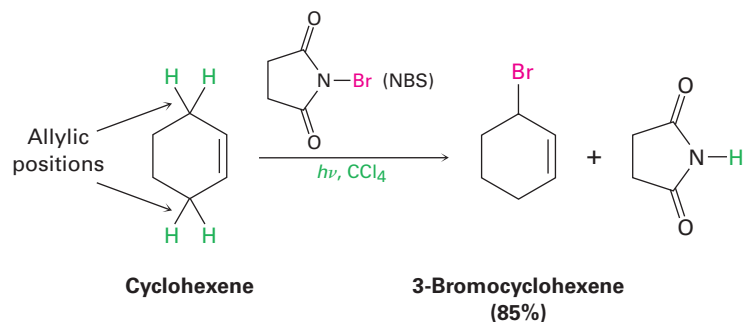
Halogens increase in size going down the periodic table, so the lengths of the corresponding carbon–halogen bonds increase accordingly (TABLE 12.1). In addition, C–X bond strengths decrease going down the periodic table. As we've been doing thus far, we'll continue to use the abbreviation X to represent any of the halogens F, Cl, Br, or I.

TABLE 12.1 A Comparison of the Halomethanes

Halomethane	Bond length (pm)	Bond strength		Dipole moment (D)
		(kJ/mol)	(kcal/mol)	
CH_3F	139	460	110	1.85
CH_3Cl	178	350	84	1.87
CH_3Br	193	294	70	1.81
CH_3I	214	239	57	1.62

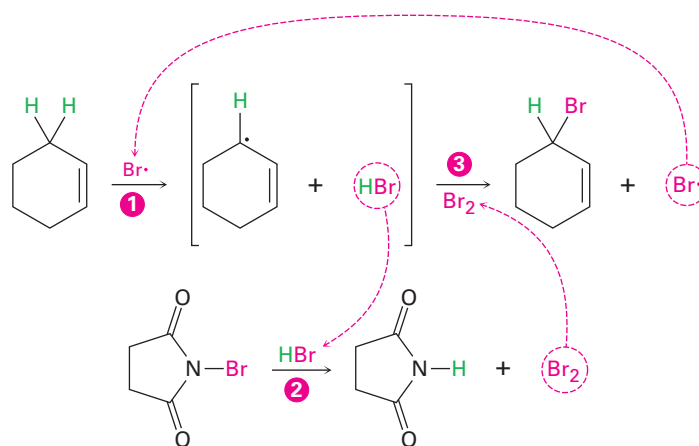
In our discussion of bond polarity in functional groups in Section 6-4, we noted that halogens are more electronegative than carbon. The C–X bond is therefore polar, with the carbon atom bearing a slight positive charge (δ^+) and the halogen a slight negative charge (δ^-). This polarity results in a substantial dipole moment for halomethanes (Table 12.1) and implies that the alkyl halide C–X carbon atom should behave as an electrophile in polar reactions. We'll soon see that this is indeed the case.

Another laboratory method for preparing alkyl halides from alkenes is by reaction with *N*-bromosuccinimide (abbreviated NBS) in the presence of light to give products resulting from substitution of hydrogen by bromine at the position next to the double bond—the allylic position (Section 8-13). Cyclohexene, for example, gives 3-bromocyclohexene.



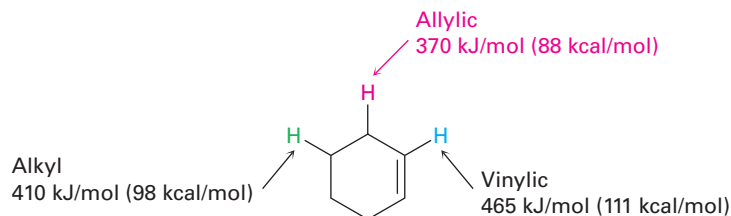
This allylic bromination with NBS is analogous to the methane chlorination reaction discussed in Section 6-3 and occurs by a similar radical chain reaction mechanism. As in methane halogenation, $\text{Br}\cdot$ radical abstracts an allylic hydrogen atom, forming an allylic radical plus HBr . The HBr then reacts with NBS to form Br_2 , which reacts with the allylic radical to yield the brominated product and a $\text{Br}\cdot$ radical that cycles back into the first step and carries on the chain (FIGURE 12.1).

FIGURE 12.1 Mechanism of allylic bromination of an alkene with NBS. The process is a radical chain reaction in which **1** a $\text{Br}\cdot$ radical abstracts an allylic hydrogen atom of the alkene and gives an allylic radical plus HBr . **2** The HBr then reacts with NBS to form Br_2 , which **3** reacts with the allylic radical to yield the bromoalkene product and a $\text{Br}\cdot$ radical that carries on the chain.



Why does bromination with NBS occur exclusively at an allylic position rather than elsewhere in the molecule? The answer has to do with the relative stabilities of various kinds of radicals. There are three sorts of C–H bonds in cyclohexene, and Table 6.3 on page 166 gives an estimate of their relative strengths. Although a typical secondary alkyl C–H bond has a strength of about 410 kJ/mol (98 kcal/mol) and a typical vinylic C–H bond has a strength

of 465 kJ/mol (111 kcal/mol), an allylic C–H bond has a strength of only about 370 kJ/mol (88 kcal/mol). An allylic radical is therefore more stable than a related alkyl radical by about 40 kJ/mol (9 kcal/mol) and, according to the Hammond postulate (Section 7-9), should form faster.



Allylic *radicals* are stable for the same reason that allylic *carbocations* are stable (Section 8-13). Like an allylic carbocation, an allylic radical has two resonance forms. One form has the unpaired electron on the left and the double bond on the right, and one form has the unpaired electron on the right and the double bond on the left (**FIGURE 12.2**). Neither structure is correct by itself; the true structure of the allyl radical is a resonance hybrid of the two. In molecular orbital terms, the unpaired electron is delocalized, or spread out, over an extended π orbital network rather than localized at only one site. Thus, the two terminal carbons share the unpaired electron.

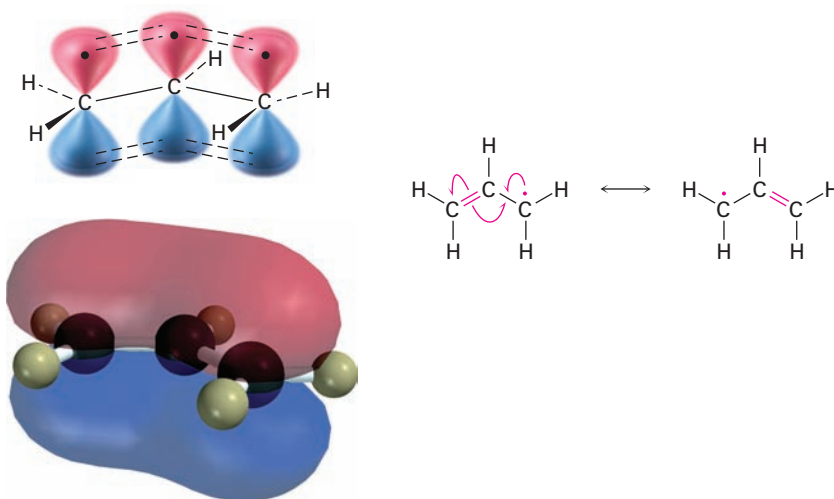
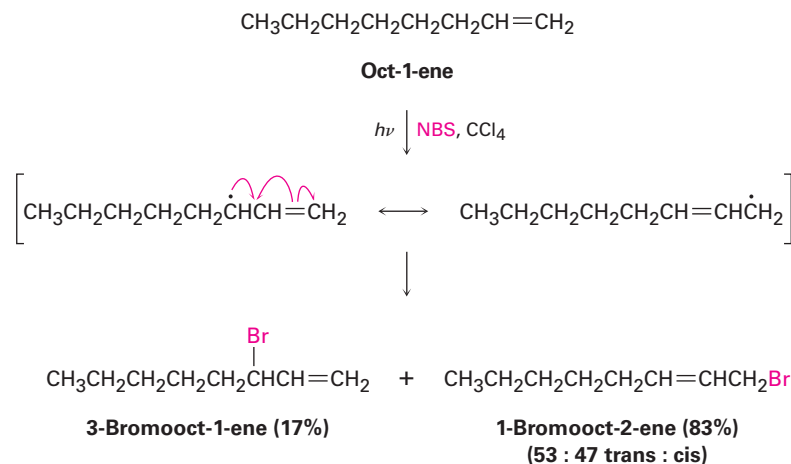


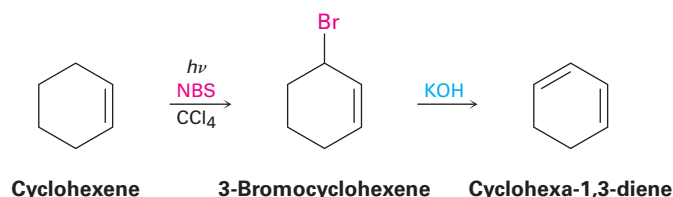
FIGURE 12.2 Orbital view of the allyl radical. The p orbital on the central carbon can overlap equally well with a p orbital on either neighboring carbon, giving rise to two resonance structures.

Because the unpaired electron in an allylic radical is delocalized over both ends of the π orbital system, reaction with Br_2 can occur at either end. As a result, allylic bromination of an unsymmetrical alkene often leads to a mixture of products. For example, bromination of oct-1-ene gives a mixture of 3-bromooct-1-ene and 1-bromooct-2-ene. The two products are not formed in equal amounts, however, because the intermediate allylic radical is not

symmetrical and reaction at the two ends is not equally likely. Reaction at the less hindered, primary end is favored.



The products of allylic bromination reactions are useful for conversion into conjugated dienes by dehydrohalogenation with base. Cyclohexene can be converted into cyclohexa-1,3-diene, for example.



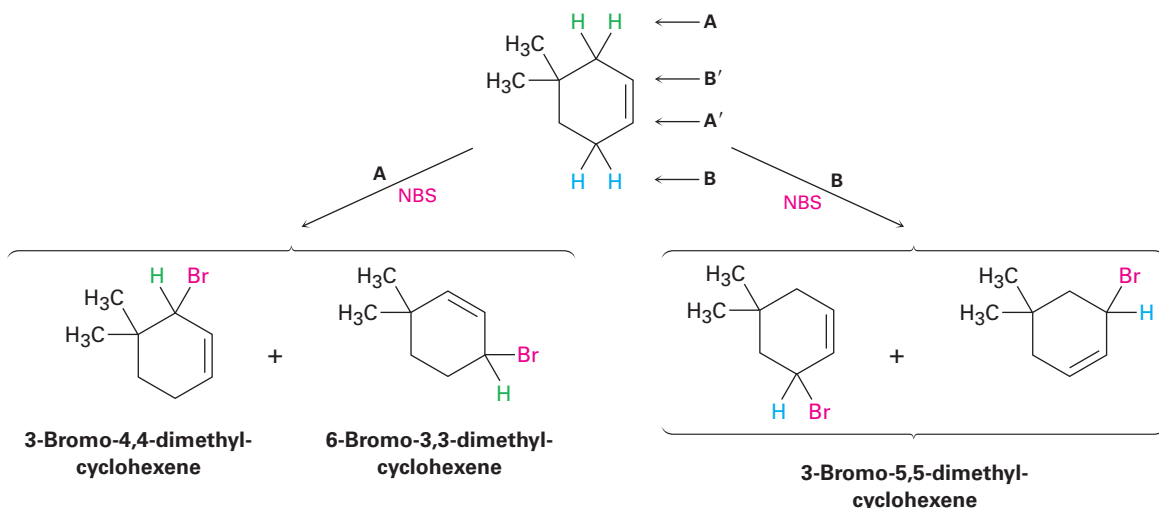
WORKED EXAMPLE 12.1

Predicting the Product of an Allylic Bromination Reaction

What products would you expect from reaction of 4,4-dimethylcyclohexene with NBS?

Strategy

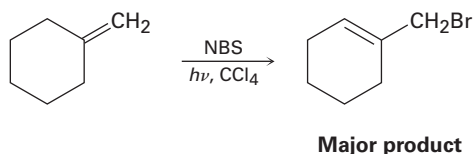
Draw the alkene reactant, and identify the allylic positions. In this case, there are two different allylic positions; we'll label them **A** and **B**. Now abstract an allylic hydrogen from each position to generate the two corresponding allylic radicals. Each of the two allylic radicals can add a Br atom at either end (**A** or **A'**; **B** or **B'**), to give a mixture of up to four products. Draw and name the products. In the present instance, the "two" products from reaction at positions **B** and **B'** are identical, so a total of only three products are formed in this reaction.

Solution**PROBLEM 12.3**

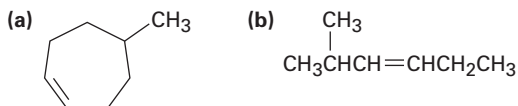
Draw three resonance forms for the cyclohexadienyl radical.

**PROBLEM 12.4**

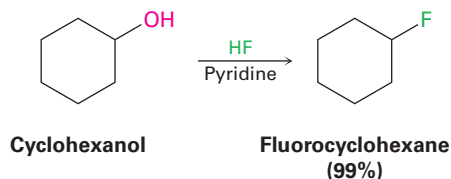
The major product of the reaction of methylenecyclohexane with *N*-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.

**PROBLEM 12.5**

What products would you expect from reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

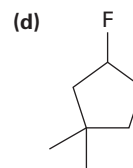
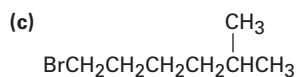
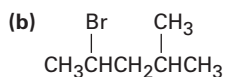
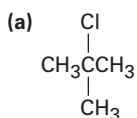


Alkyl fluorides can also be prepared from alcohols. Numerous alternative reagents are used for the reaction, including diethylaminosulfur trifluoride $[(\text{CH}_3\text{CH}_2)_2\text{NSF}_3]$ and HF in pyridine solvent.



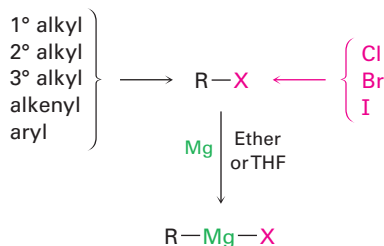
PROBLEM 12.6

How would you prepare the following alkyl halides from the corresponding alcohols?



12-4 Reactions of Alkyl Halides: Grignard Reagents

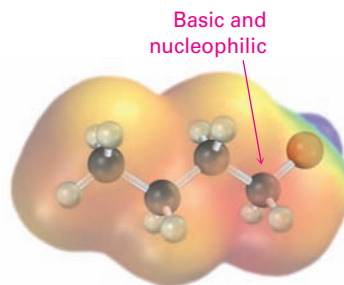
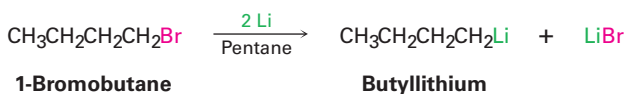
Alkyl halides, RX , react with magnesium metal in ether or tetrahydrofuran (THF; Section 8-1) solvent to yield alkylmagnesium halides, RMgX . The products, called **Grignard reagents** after their discoverer, Victor Grignard, are examples of *organometallic* compounds because they contain a carbon–metal bond. In addition to alkyl halides, Grignard reagents can also be made from alkenyl (vinylic) and aryl (aromatic) halides. The halogen can be Cl, Br, or I, although chlorides are less reactive than bromides and iodides. Organofluorides rarely react with magnesium.



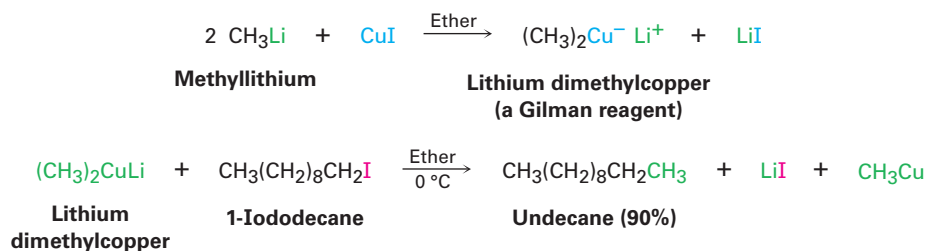
As you might expect from the discussion of electronegativity and bond polarity in Section 6-4, the carbon–magnesium bond is polarized, making the carbon atom of Grignard reagents both nucleophilic and basic. An electrostatic

12-5 Organometallic Coupling Reactions

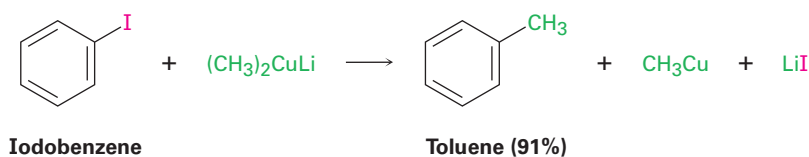
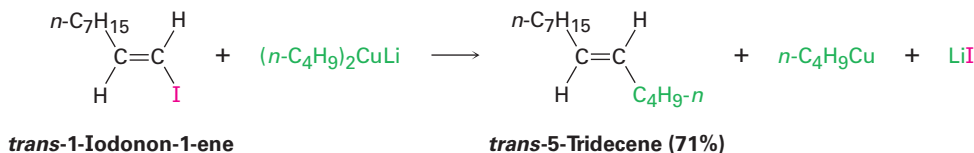
Many other kinds of organometallic compounds can be prepared in a manner similar to that of Grignard reagents. For instance, alkyl lithium reagents, RLi, can be prepared by the reaction of an alkyl halide with lithium metal. Alkyl lithiums are both nucleophiles and strong bases, and their chemistry is similar in many respects to that of alkylmagnesium halides.



One particularly valuable reaction of alkyl lithiums is in making lithium diorganocopper compounds, R_2CuLi , by reaction with copper(I) iodide in diethyl ether as solvent. Called **Gilman reagents**, lithium diorganocopper compounds are useful because they undergo a *coupling* reaction with organochlorides, bromides, and iodides (but not fluorides). One of the alkyl groups from the Gilman reagent replaces the halogen of the organohalide, forming a new carbon-carbon bond and yielding a hydrocarbon product. Lithium dimethylcopper, for instance, reacts with 1-iododecane to give undecane.

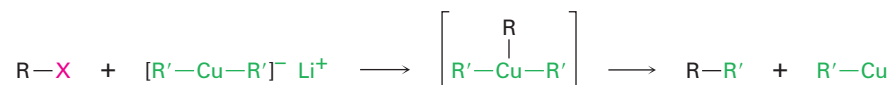


This organometallic coupling reaction is useful in organic synthesis because it forms carbon-carbon bonds, thereby making possible the preparation of larger molecules from smaller ones. As the following examples indicate, the coupling reaction can be carried out on aryl and vinylic halides as well as on alkyl halides.

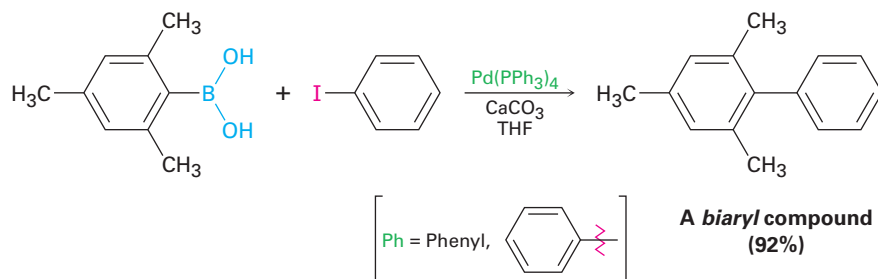


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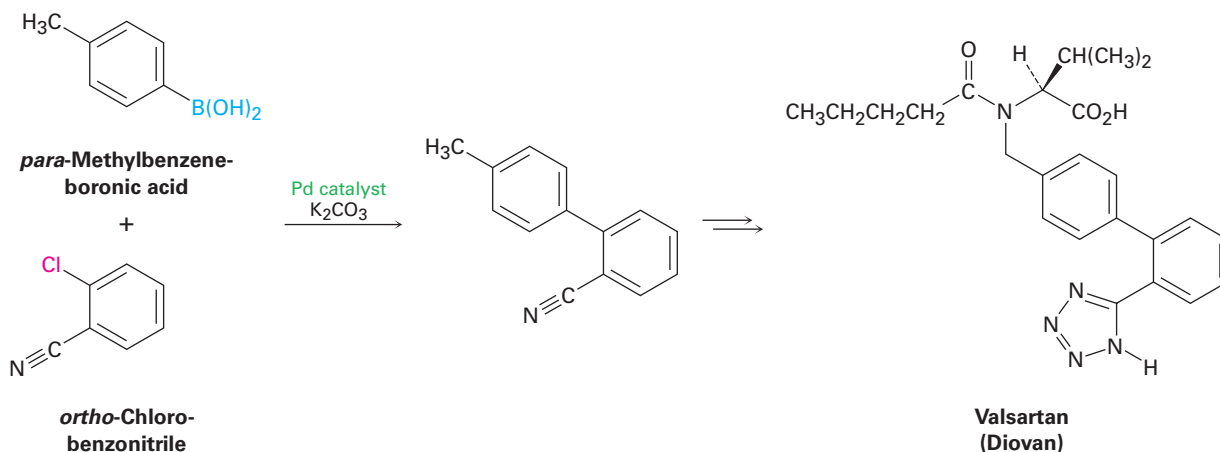
The mechanism of the coupling reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of RCu . The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the next section.



In addition to the coupling reaction of diorganocopper reagents with organohalides, related processes occur with other organometallic reagents, particularly organopalladium compounds. One of the most commonly used procedures is the coupling reaction of an aromatic or vinyl substituted boronic acid $[\text{R-B(OH)}_2]$ with an aromatic or vinyl substituted organohalide in the presence of a base and a palladium catalyst. The reaction is less general than the diorganocopper reaction because it does not work with alkyl substrates, but it is preferred when possible because it uses only a catalytic amount of metal rather than a full equivalent and because palladium compounds are less toxic than copper compounds. For example:



Called the *Suzuki-Miyaura reaction*, the process is particularly useful for preparing so-called biaryl compounds, which have two aromatic rings joined together. A large number of commonly used drugs fit this description, so the Suzuki-Miyaura reaction is much-used in the pharmaceutical industry. In fact it has been estimated that the reaction is used in the synthesis of up to 40% of new drug candidates. As an example, valsartan, marketed as Diovan, is a widely prescribed antihypertensive agent whose synthesis begins with a Suzuki-Miyaura coupling of *ortho*-chlorobenzonitrile with *para*-methylbenzeneboronic acid.



Shown in a simplified form in **FIGURE 12.3**, the mechanism of the Suzuki–Miyaura reaction involves initial reaction of the aromatic halide with the palladium catalyst to form an organopalladium intermediate, followed by reaction of that intermediate with the aromatic boronic acid. The resultant diorganopalladium complex then decomposes to the coupled biaryl product plus regenerated catalyst.

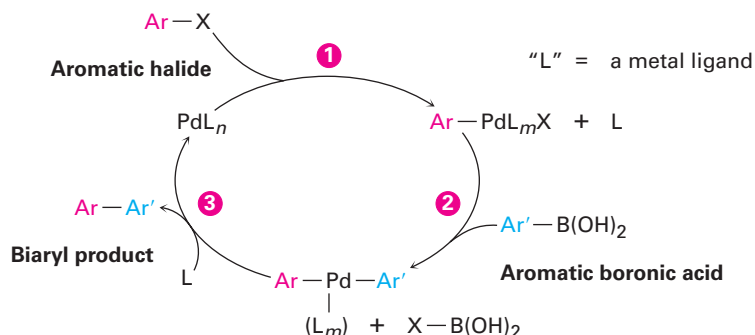
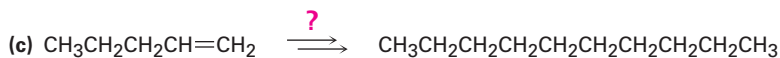
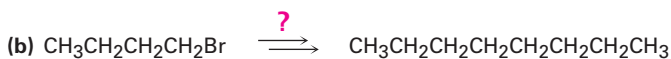
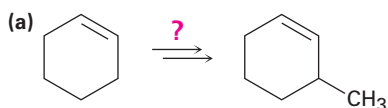


FIGURE 12.3 Mechanism of the Suzuki–Miyaura coupling reaction of an aromatic boronic acid with an aromatic halide to give a biaryl. The reaction takes place by **1** reaction of the aromatic halide, ArX, with the catalyst to form an organopalladium intermediate, followed by **2** reaction with the aromatic boronic acid. **3** Subsequent decomposition of the diarylpalladium intermediate gives the biaryl product.

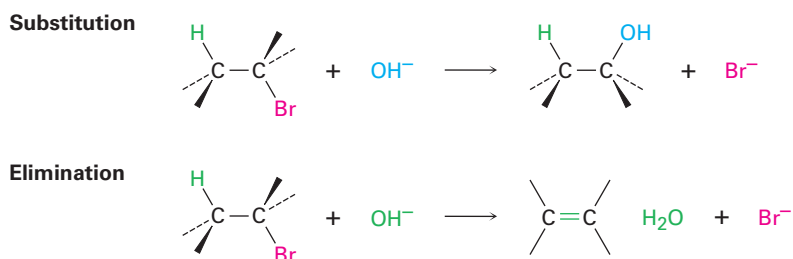
PROBLEM 12.9

How would you carry out the following transformations using an organocopper coupling reaction? More than one step is needed in each case.



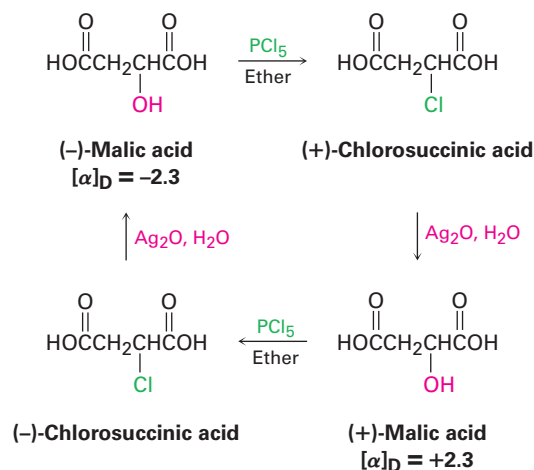
12-6 Discovery of the Nucleophilic Substitution Reaction

As we saw in Section 12-1, the carbon–halogen bond in an alkyl halide is polar and the carbon atom is electron-poor. Thus, alkyl halides are electrophiles, and much of their chemistry involves polar reactions with nucleophiles and bases. When they react with nucleophiles/bases, such as hydroxide ion, alkyl halides do one of two things: either they undergo *substitution* of the X group by the nucleophile, or they undergo *elimination* of HX to yield an alkene.



Let's look first at substitution reactions. The discovery of the nucleophilic substitution reaction of alkyl halides dates back to work carried out in 1896 by the German chemist Paul Walden. Walden found that the pure enantiomeric (+)- and (-)-malic acids could be interconverted through a series of simple substitution reactions. When Walden treated (-)-malic acid with PCl_5 , he isolated (+)-chlorosuccinic acid. This, on treatment with wet Ag_2O , gave (+)-malic acid. Similarly, reaction of (+)-malic acid with PCl_5 gave (-)-chlorosuccinic acid, which was converted into (-)-malic acid when treated with wet Ag_2O . The full cycle of reactions is shown in **FIGURE 12.4**.

FIGURE 12.4 Walden's cycle of reactions interconverting (+)- and (-)-malic acids.



At the time, the results were astonishing. The eminent chemist Emil Fischer called Walden's discovery "the most remarkable observation made in the field of optical activity since the fundamental observations of Pasteur." Because (-)-malic acid was converted into (+)-malic acid, *some reactions in the cycle must have occurred with a change, or inversion, in configuration at the chirality center*. But which ones, and how? (Remember from Section 5-5 that the direction of light rotation and the configuration of a chirality center aren't directly related. You can't tell by looking at the sign of rotation whether a change in configuration has occurred during a reaction.)

Today, we refer to the transformations taking place in Walden's cycle as **nucleophilic substitution reactions** because each step involves the substitution of one nucleophile (chloride ion, Cl^- , or hydroxide ion, HO^-) by another. Nucleophilic substitution reactions are one of the most common and versatile reaction types in organic chemistry.



Following the work of Walden, further investigations were undertaken during the 1920s and 1930s to clarify the mechanism of nucleophilic substitution reactions and to find out how inversions of configuration occur. Among the first series studied was one that interconverted the two enantiomers of 1-phenylpropan-2-ol (**FIGURE 12.5**). Although this particular series of reactions involves nucleophilic substitution of an alkyl *p*-toluenesulfonate (called a *tosylate*) rather than an alkyl halide, exactly the same type of reaction is involved as that studied by Walden. For all practical purposes, the entire tosylate group acts as

if it were simply a halogen substituent. (In fact, when you see a tosylate substituent in a molecule, do a mental substitution and tell yourself you're dealing with an alkyl halide.)

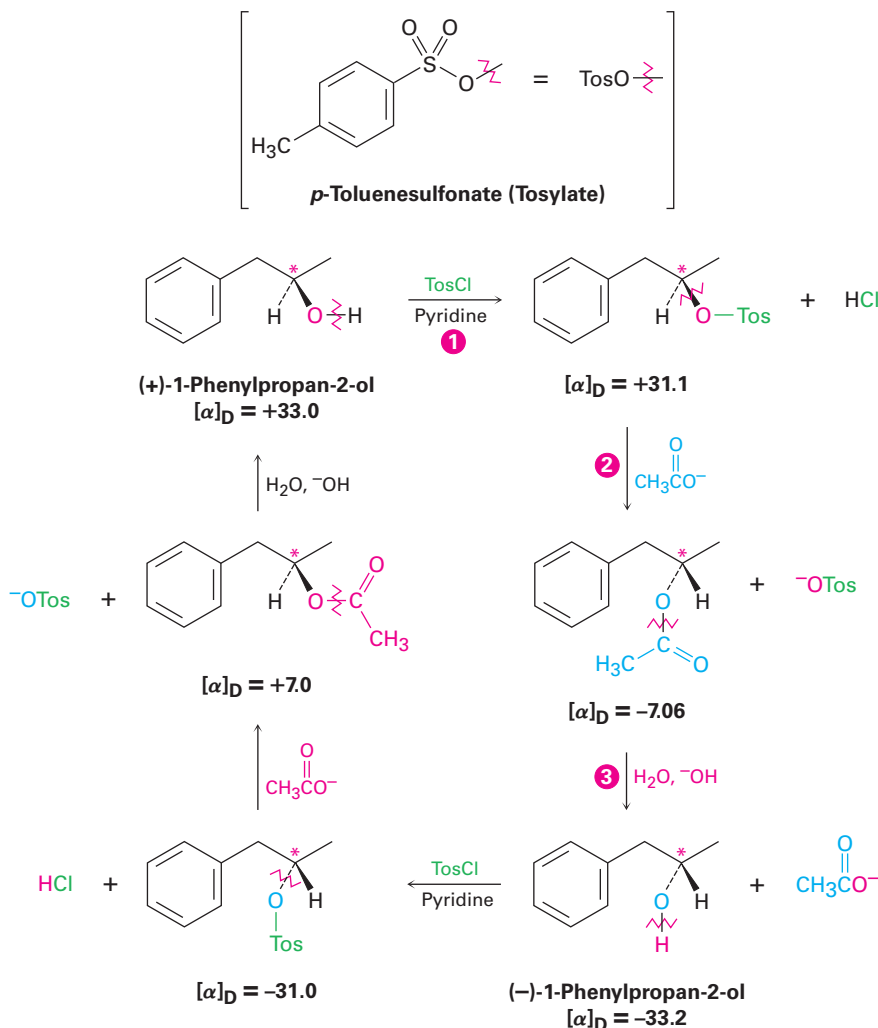
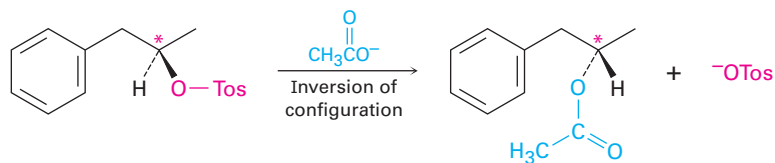


FIGURE 12.5 Walden cycle interconverting (+) and (-) enantiomers of 1-phenylpropan-2-ol. Chirality centers are marked by asterisks, and the bonds broken in each reaction are indicated by red wavy lines. The inversion of chirality occurs in step **2**, where acetate ion substitutes for tosylate ion.

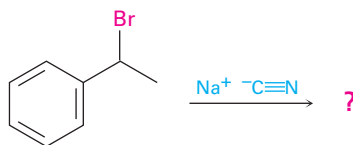
In the three-step reaction sequence shown in Figure 12.5, (+)-1-phenylpropan-2-ol is interconverted with its (-) enantiomer, so at least one of the three steps must involve an inversion of configuration at the chirality center. Step 1, formation of a tosylate, occurs by breaking the O–H bond of the alcohol rather than the C–O bond to the chiral carbon, so the configuration around carbon is unchanged. Similarly, step 3, hydroxide-ion cleavage of the acetate, takes place without breaking the C–O bond at the chirality center. *The inversion of stereochemical configuration must therefore take place in the step 2, the nucleophilic substitution of tosylate ion by acetate ion.*



From this and nearly a dozen other series of similar reactions, workers concluded that the nucleophilic substitution reaction of a primary or secondary alkyl halide or tosylate always proceeds with inversion of configuration. (Tertiary alkyl halides and tosylates, as we'll see shortly, give different stereochemical results and react by a different mechanism.)

WORKED EXAMPLE 12.2 Predicting the Stereochemistry of a Nucleophilic Substitution Reaction

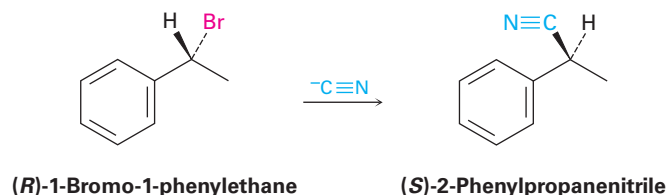
What product would you expect from a nucleophilic substitution reaction of (*R*)-1-bromo-1-phenylethane with cyanide ion, $\text{C}\equiv\text{N}^-$, as nucleophile? Show the stereochemistry of both reactant and product, assuming that inversion of configuration occurs.



Strategy

Draw the *R* enantiomer of the reactant, and then change the configuration of the chirality center while replacing the $-\text{Br}$ with a $-\text{CN}$.

Solution



PROBLEM 12.10

What product would you expect to obtain from a nucleophilic substitution reaction of (*S*)-2-bromohexane with acetate ion, CH_3CO_2^- ? Assume that inversion of configuration occurs, and show the stereochemistry of both reactant and product.

12-7 The $\text{S}_{\text{N}}2$ Reaction

In every chemical reaction, there is a direct relationship between the rate at which the reaction occurs and the concentrations of the reactants. When we measure this relationship, we measure the **kinetics** of the reaction. For example, let's look at the kinetics of a simple nucleophilic substitution—the reaction of CH_3Br with OH^- to yield CH_3OH plus Br^- .



At a given temperature, solvent, and concentration of reactants, the substitution occurs at a certain rate. If we double the concentration of OH^- , the frequency of encounter between the reaction partners doubles, and we find that

the reaction rate also doubles. Similarly, if we double the concentration of CH₃Br, the reaction rate again doubles. We call such a reaction, in which the rate is linearly dependent on the concentrations of two species, a **second-order reaction**. Mathematically, we can express this second-order dependence of the nucleophilic substitution reaction by setting up a *rate equation*. As either [RX] or [OH⁻] changes, the rate of the reaction changes proportionately.

$$\begin{aligned}\text{Reaction rate} &= \text{Rate of disappearance of reactant} \\ &= k \times [\text{RX}] \times [\text{OH}^-]\end{aligned}$$

where

[RX] = CH₃Br concentration in molarity

[OH⁻] = OH⁻ concentration in molarity

k = A constant value (the rate constant)

A mechanism that accounts for both the inversion of configuration and the second-order kinetics that are observed with nucleophilic substitution reactions was suggested in 1937 by the British chemists E. D. Hughes and Christopher Ingold, who formulated what they called the **S_N2 reaction**—short for *substitution, nucleophilic, bimolecular*. (*Bimolecular* means that two molecules, nucleophile and alkyl halide, take part in the step whose kinetics are measured.)

The essential feature of the S_N2 mechanism is that it takes place in a single step without intermediates when the incoming nucleophile reacts with the alkyl halide or tosylate (the *substrate*) from a direction opposite the group that is displaced (the *leaving group*). As the nucleophile comes in on one side of the substrate and bonds to the carbon, the halide or tosylate departs from the other side, thereby inverting the stereochemical configuration. The process is shown in **FIGURE 12.6** for the reaction of (*S*)-2-bromobutane with HO⁻ to give (*R*)-butan-2-ol.

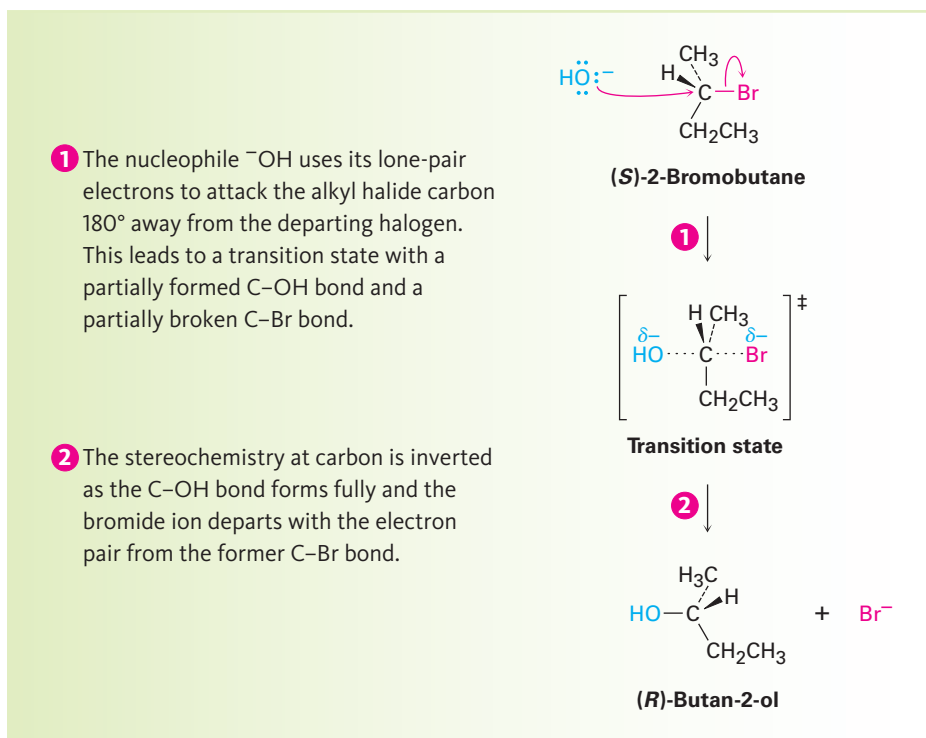
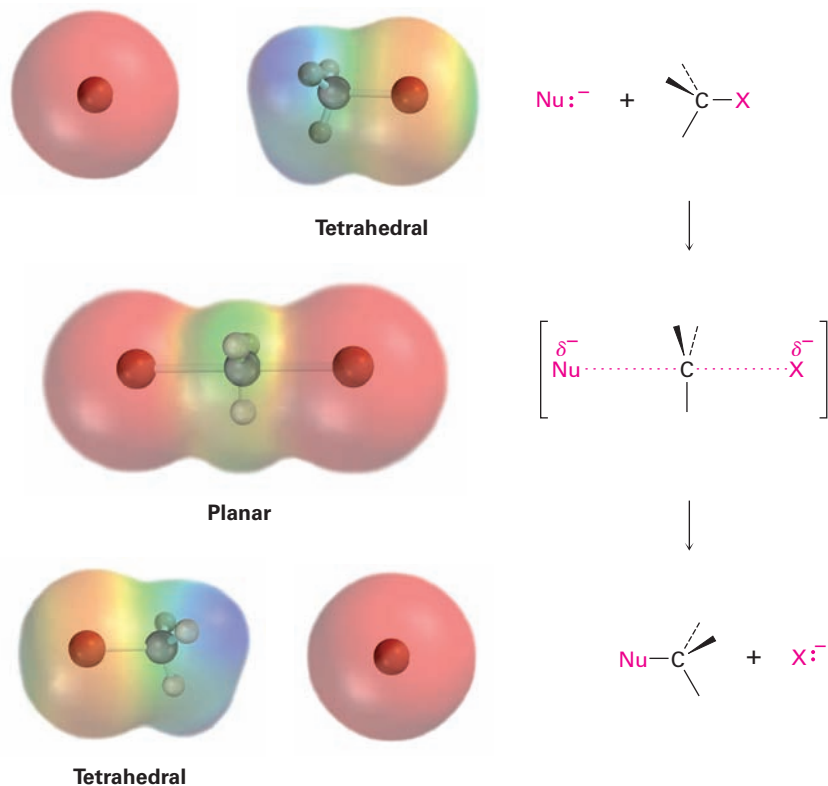


FIGURE 12.6 Mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

As shown in Figure 12.6, the S_N2 reaction occurs when an electron pair on the nucleophile Nu^- forces out the group X^- , which takes with it the electron pair from the former C-X bond. This occurs through a transition state in which the new Nu-C bond is partially forming at the same time that the old C-X bond is partially breaking, and in which the negative charge is shared by both the incoming nucleophile and the outgoing halide ion. The transition state for this inversion has the remaining three bonds to carbon in a planar arrangement (FIGURE 12.7).

FIGURE 12.7 Transition state of an S_N2 reaction. The carbon atom and the remaining three groups have a planar arrangement. Electrostatic potential maps show that negative charge is delocalized in the transition state.



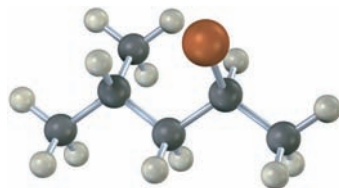
The mechanism proposed by Hughes and Ingold is fully consistent with experimental results, explaining both stereochemical and kinetic data. Thus, the requirement for backside approach of the entering nucleophile from a direction 180° away from the leaving group causes the stereochemistry of the substrate to invert, much like an umbrella turning inside out in the wind. The Hughes-Ingold mechanism also explains why second-order kinetics are found: the S_N2 reaction occurs in a single step that involves both alkyl halide and nucleophile. Two molecules are involved in the step whose rate is measured.

PROBLEM 12.11

What product would you expect to obtain from S_N2 reaction of OH^- with (*R*)-2-bromobutane? Show the stereochemistry of both reactant and product.

PROBLEM 12.12

Assign configuration to the following substance, and draw the structure of the product that would result on nucleophilic substitution reaction with HS⁻ (red-brown = Br):



12-8 Characteristics of the S_N2 Reaction

Now that we know how S_N2 reactions occur, we need to see how they can be used and what variables affect them. Some S_N2 reactions are fast and some are slow; some take place in high yield and others, in low yield. Understanding the factors involved can be of tremendous value. Let's begin by recalling a few things about reaction rates in general.

The rate of a chemical reaction is determined by the activation energy ΔG^\ddagger , the energy difference between reactant ground state and transition state. A change in reaction conditions can affect ΔG^\ddagger either by changing the reactant energy level or by changing the transition-state energy level. Lowering the reactant energy or raising the transition-state energy increases ΔG^\ddagger and decreases the reaction rate; raising the reactant energy or decreasing the transition-state energy decreases ΔG^\ddagger and increases the reaction rate (FIGURE 12.8). We'll see examples of all these effects as we look at S_N2 reaction variables.

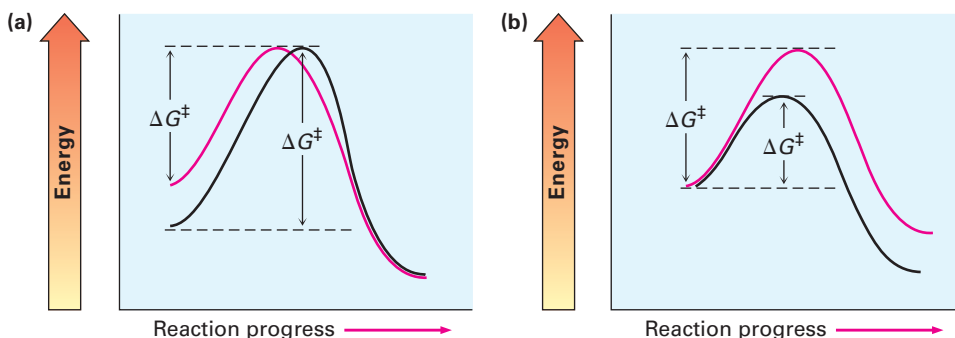


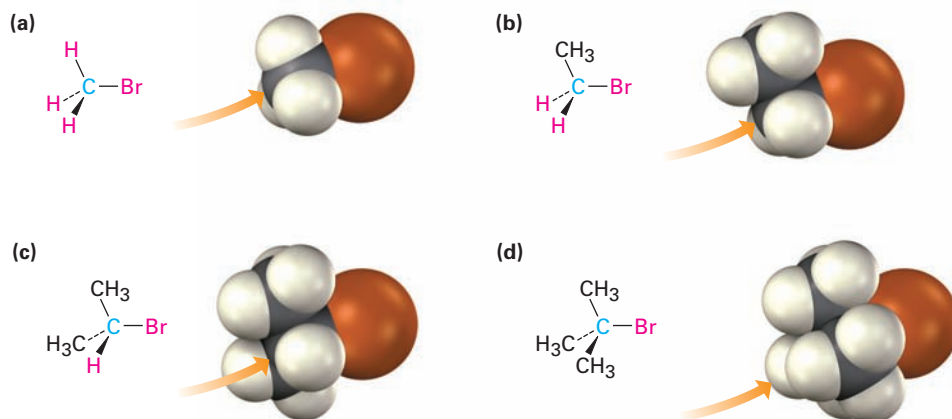
FIGURE 12.8 Effects of changes in reactant and transition-state energy levels on reaction rate. **(a)** A higher reactant energy level (red curve) corresponds to a faster reaction (smaller ΔG^\ddagger). **(b)** A higher transition-state energy level (red curve) corresponds to a slower reaction (larger ΔG^\ddagger).

The Substrate: Steric Effects in the S_N2 Reaction

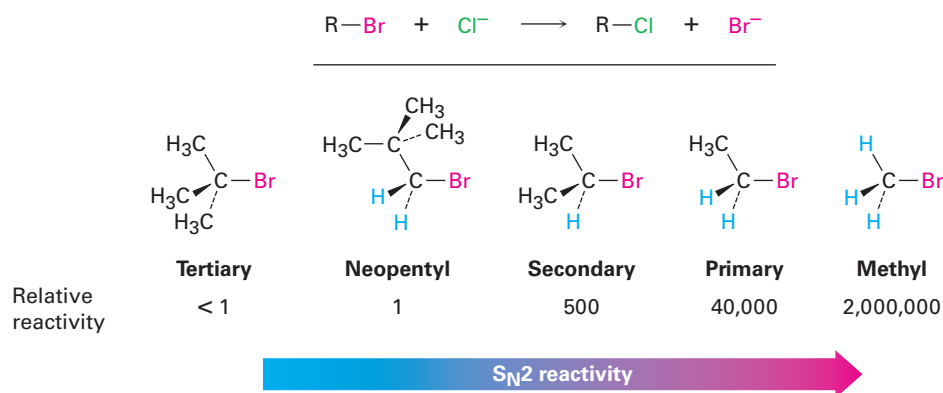
The first S_N2 reaction variable to look at is the structure of the substrate. Because the S_N2 transition state involves partial bond formation between the incoming nucleophile and the alkyl halide carbon atom, it seems reasonable that a hindered, bulky substrate should prevent easy approach of the nucleophile, making bond formation difficult. In other words, the transition state for

reaction of a sterically hindered substrate, whose carbon atom is shielded from approach of the incoming nucleophile, is higher in energy and forms more slowly than the corresponding transition state for a less hindered substrate (FIGURE 12.9).

FIGURE 12.9 Steric hindrance to the S_N2 reaction. The carbon atom in (a) bromomethane is readily accessible, resulting in a fast S_N2 reaction. The carbon atoms in (b) bromoethane (primary), (c) 2-bromopropane (secondary), and (d) 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.



As Figure 12.9 shows, the difficulty of nucleophile approach increases as the three substituents bonded to the halo-substituted carbon atom increase in size. Methyl halides are by far the most reactive substrates in S_N2 reactions, followed by primary alkyl halides such as ethyl and propyl. Alkyl branching at the reacting center, as in isopropyl halides (2°), slows the reaction greatly, and further branching, as in *tert*-butyl halides (3°), effectively halts the reaction. Even branching one carbon removed from the reacting center, as in 2,2-dimethylpropyl (*neopentyl*) halides, greatly slows nucleophilic displacement. As a result, S_N2 reactions occur only at relatively unhindered sites and are normally useful only with methyl halides, primary halides, and a few simple secondary halides. Relative reactivities for some different substrates are as follows:



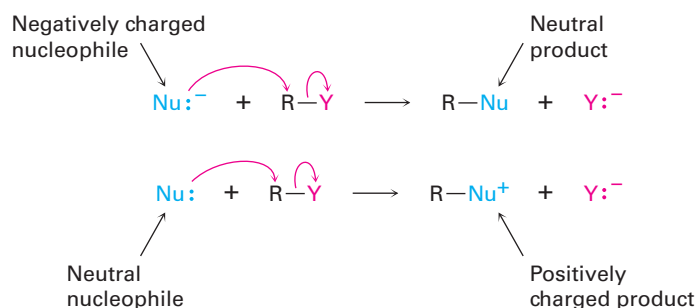
Vinyl halides ($R_2C=CRX$) and aryl halides are not shown on this reactivity list because they are unreactive toward S_N2 displacement. This lack of reactivity is due to steric factors: the incoming nucleophile would have to

approach in the plane of the carbon–carbon double bond and burrow through part of the molecule to carry out a backside displacement.

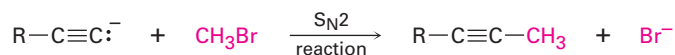


The Nucleophile

Another variable that has a major effect on the S_N2 reaction is the nature of the nucleophile. Any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons; that is, as long as it is a Lewis base. If the nucleophile is negatively charged, the product is neutral; if the nucleophile is neutral, the product is positively charged.



A wide array of substances can be prepared using nucleophilic substitution reactions. In fact, we've already seen an example: the reaction of an acetylide anion with an alkyl halide discussed in Section 8-15 is an S_N2 reaction in which the acetylide nucleophile replaces a halide leaving group.



An acetylide anion

TABLE 12.2 lists some nucleophiles in the order of their reactivity, shows the products of their reactions with bromomethane, and gives the relative rates of their reactions.

The data in Table 12.2 show that there are large differences in the rates at which various nucleophiles react. Detailed explanations for the observed reactivities aren't always simple, but some trends can be detected.

- **Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same reacting atom.** Thus, OH[−] is both more basic and more nucleophilic than acetate ion, CH₃CO₂[−], which in turn is more basic and more nucleophilic than H₂O. Since “nucleophilicity” is usually taken as the affinity of a Lewis base for a carbon atom in the S_N2 reaction and “basicity” is the affinity of a base for a proton, it's easy to see why there might be a correlation between the two kinds of behavior.

TABLE 12.2 Some S_N2 Reactions with Bromomethane in Protic Solvents

$\text{Nu}^- + \text{CH}_3\text{Br} \rightarrow \text{CH}_3\text{Nu} + \text{Br}^-$				
Nucleophile		Product		Relative rate of reaction
Formula	Name	Formula	Name	
H ₂ O	Water	CH ₃ OH ₂ ⁺	Methylhydronium ion	1
CH ₃ CO ₂ ⁻	Acetate	CH ₃ CO ₂ CH ₃	Methyl acetate	500
NH ₃	Ammonia	CH ₃ NH ₃ ⁺	Methylammonium ion	700
Cl ⁻	Chloride	CH ₃ Cl	Chloromethane	1,000
HO ⁻	Hydroxide	CH ₃ OH	Methanol	10,000
CH ₃ O ⁻	Methoxide	CH ₃ OCH ₃	Dimethyl ether	25,000
I ⁻	Iodide	CH ₃ I	Iodomethane	100,000
⁻ CN	Cyanide	CH ₃ CN	Acetonitrile	125,000
HS ⁻	Hydrosulfide	CH ₃ SH	Methanethiol	125,000

- **Nucleophilicity usually increases going down a column of the periodic table.** Thus, HS⁻ is more nucleophilic than HO⁻, and the halide reactivity order is I⁻ > Br⁻ > Cl⁻. Going down the periodic table, elements have their valence electrons in successively larger shells, where they are successively farther from the nucleus, less tightly held, and consequently more reactive. The matter is complex, though, and the nucleophilicity order can change depending on the solvent.
- **Negatively charged nucleophiles are usually more reactive than neutral ones.** As a result, S_N2 reactions are often carried out under basic conditions rather than neutral or acidic conditions.

PROBLEM 12.13

What product would you expect from S_N2 reaction of 1-bromobutane with each of the following?

- (a) NaI (b) KOH (c) H-C≡C-Li (d) NH₃

PROBLEM 12.14

Which substance in each of the following pairs is more reactive as a nucleophile? Explain.

- (a) (CH₃)₂N⁻ or (CH₃)₂NH (b) (CH₃)₃B or (CH₃)₃N (c) H₂O or H₂S

The Leaving Group

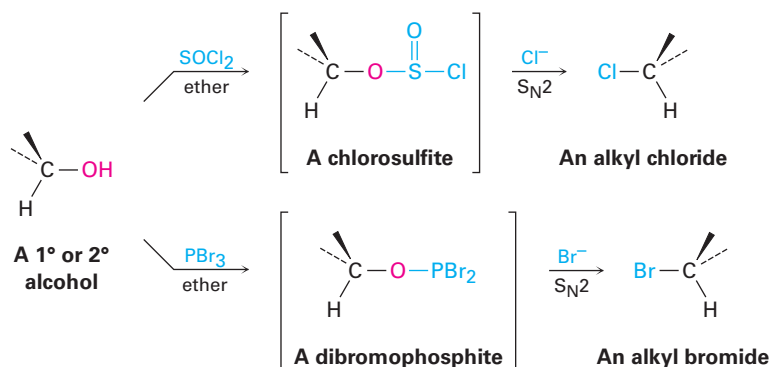
Still another variable that can affect the S_N2 reaction is the nature of the group displaced by the incoming nucleophile. Because the leaving group is expelled with a negative charge in most S_N2 reactions, the best leaving groups are those that best stabilize the negative charge in the transition state. The greater the extent of charge stabilization by the leaving group, the lower the energy of the

transition state and the more rapid the reaction. But as we saw in Section 2-8, those groups that best stabilize a negative charge are also the weakest bases. Thus, weak bases such as Cl⁻ and tosylate ion make good leaving groups, while strong bases such as OH⁻ and NH₂⁻ make poor leaving groups.

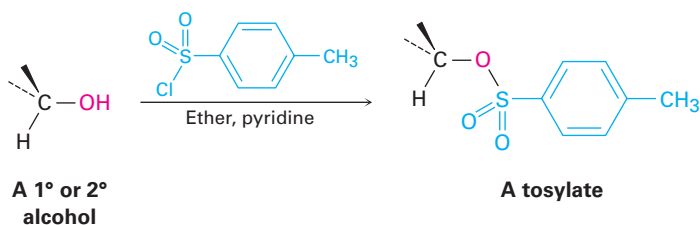
Relative reactivity	$\underbrace{\text{OH}^-, \text{NH}_2^-, \text{OR}^-}_{\ll 1}$	F ⁻	Cl ⁻	Br ⁻	I ⁻	TosO ⁻
		1	200	10,000	30,000	60,000



It's just as important to know which are poor leaving groups as to know which are good, and the preceding data clearly indicate that F⁻, HO⁻, RO⁻, and H₂N⁻ are not displaced by nucleophiles. In other words, alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions. To carry out an S_N2 reaction with an alcohol, it's necessary to convert the -OH into a better leaving group. This, in fact, is just what happens when a primary or secondary alcohol is converted into either an alkyl chloride by reaction with SOCl₂ or an alkyl bromide by reaction with PBr₃ (Section 12-3).

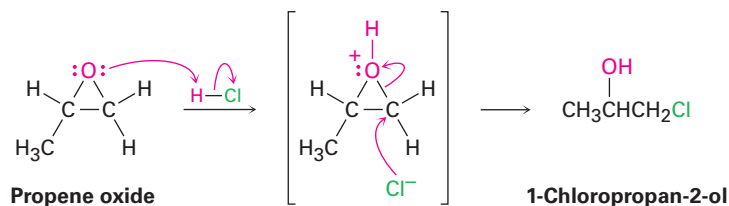


Alternatively, an alcohol can be made more reactive toward nucleophilic substitution by treating it with *p*-toluenesulfonyl chloride to form a tosylate. As noted previously, tosylates are even more reactive than halides in nucleophilic substitutions. Note that tosylate formation does not change the configuration of the oxygen-bearing carbon because the C-O bond is not broken.



The one general exception to the rule that ethers don't typically undergo S_N2 reactions occurs with epoxides, the three-membered cyclic ethers that we saw in Section 8-6. Epoxides, because of the angle strain in the three-membered

ring, are much more reactive than other ethers. They react with aqueous acid to give 1,2-diols and they react readily with many other nucleophiles as well. Propene oxide, for instance, reacts with HCl to give 1-chloropropan-2-ol by S_N2 backside attack on the less hindered primary carbon atom.



PROBLEM 12.15

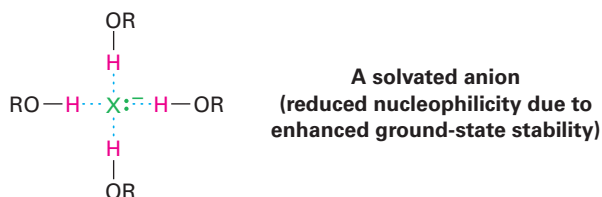
Rank the following compounds in order of their expected reactivity toward S_N2 reaction:



The Solvent

The rates of S_N2 reactions are strongly affected by the solvent. Protic solvents—those that contain an $-\text{OH}$ or $-\text{NH}$ group—are generally the worst for S_N2 reactions, while polar aprotic solvents, which are polar but don't have an $-\text{OH}$ or $-\text{NH}$ group, are the best.

Protic solvents, such as methanol and ethanol, slow down S_N2 reactions by **solvation** of the reactant nucleophile. The solvent molecules hydrogen bond to the nucleophile and form a cage around it, thereby lowering its energy and reactivity.




In contrast with protic solvents, which decrease the rates of S_N2 reactions by lowering the ground-state energy of the nucleophile, polar aprotic solvents increase the rates of S_N2 reactions by raising the ground-state energy of the nucleophile. Acetonitrile (CH_3CN), dimethylformamide [$(\text{CH}_3)_2\text{NCHO}$, abbreviated DMF], dimethyl sulfoxide [$(\text{CH}_3)_2\text{SO}$, abbreviated DMSO], and hexamethylphosphoramide [$(\text{CH}_3)_3\text{NPO}$, abbreviated HMPA] are particularly

useful. These solvents can dissolve many salts because of their high polarity, but they solvate metal cations rather than nucleophilic anions. As a result, the relatively unsolvated anions have a greater nucleophilicity and S_N2 reactions take place at correspondingly faster rates. For instance, a rate increase of 200,000 has been observed on changing from methanol to HMPA for the reaction of azide ion with 1-bromobutane.

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{-Br} + \text{N}_3^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{-N}_3 + \text{Br}^-$$

Solvent	CH ₃ OH	H ₂ O	DMSO	DMF	CH ₃ CN	HMPA
Relative reactivity	1	7	1300	2800	5000	200,000



PROBLEM 12.16

Organic solvents such as ether and chloroform are neither protic nor strongly polar. What effect would you expect these solvents to have on the reactivity of a nucleophile in S_N2 reactions?

A Summary of S_N2 Reaction Characteristics

The effects on S_N2 reactions of the four variables—substrate structure, nucleophile, leaving group, and solvent—are summarized in the following statements and in the energy diagrams of **FIGURE 12.10**:

Substrate	Steric hindrance raises the energy of the S _N 2 transition state, increasing ΔG^\ddagger and decreasing the reaction rate (FIGURE 12.10a). As a result, S _N 2 reactions are best for methyl and primary substrates. Secondary substrates react slowly, and tertiary substrates do not react by an S _N 2 mechanism.
Nucleophile	Basic, negatively charged nucleophiles are less stable and have a higher ground-state energy than neutral ones, decreasing ΔG^\ddagger and increasing the S _N 2 reaction rate (FIGURE 12.10b).
Leaving group	Good leaving groups (more stable anions) lower the energy of the transition state, decreasing ΔG^\ddagger and increasing the S _N 2 reaction rate (FIGURE 12.10c).
Solvent	Protic solvents solvate the nucleophile, thereby lowering its ground-state energy, increasing ΔG^\ddagger , and decreasing the S _N 2 reaction rate. Polar aprotic solvents surround the accompanying cation but not the nucleophilic anion, thereby raising the ground-state energy of the nucleophile, decreasing ΔG^\ddagger , and increasing the reaction rate (FIGURE 12.10d).

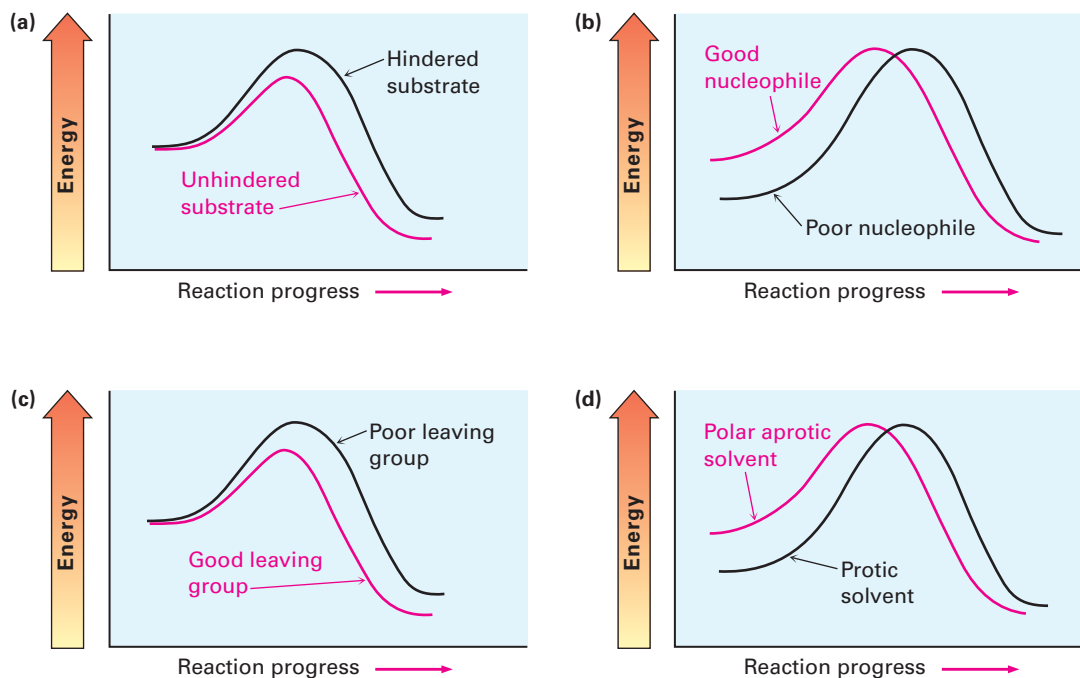
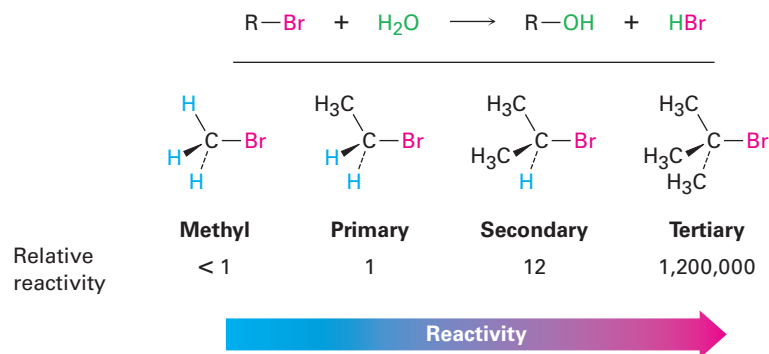


FIGURE 12.10 Energy diagrams showing the effects of (a) substrate, (b) nucleophile, (c) leaving group, and (d) solvent on S_N2 reaction rates. Substrate and leaving group effects are felt primarily in the transition state. Nucleophile and solvent effects are felt primarily in the reactant ground state.

12-9 The S_N1 Reaction

Most nucleophilic substitutions take place by the S_N2 pathway just discussed. The reaction is favored when carried out with an unhindered substrate and a negatively charged nucleophile in a polar aprotic solvent, but is disfavored when carried out with a hindered substrate and a neutral nucleophile in a protic solvent. You might therefore expect the reaction of a tertiary substrate (hindered) with water (neutral, protic) to be among the slowest of substitution reactions. Remarkably, however, the opposite is true. Reaction of the tertiary halide $(\text{CH}_3)_3\text{CBr}$ with H_2O to give the alcohol 2-methylpropan-2-ol is more than *1 million times* as fast as the corresponding reaction of CH_3Br to give methanol.



What's going on here? Clearly, a nucleophilic substitution reaction is occurring—a halogen is replacing a hydroxyl group—yet the reactivity order

seems backward. These reactions can't be taking place by the S_N2 mechanism we've been discussing, and we must therefore conclude that they are occurring by an alternative substitution mechanism. This alternative mechanism is called the **S_N1 reaction**, for *substitution, nucleophilic, unimolecular*.

In contrast to the S_N2 reaction of CH₃Br with OH⁻, the S_N1 reaction of (CH₃)₃CBr with H₂O has a rate that depends only on the alkyl halide concentration and is independent of the H₂O concentration. In other words, the reaction is a **first-order process**; the concentration of the nucleophile does not appear in the rate equation.

$$\begin{aligned}\text{Reaction rate} &= \text{Rate of disappearance of alkyl halide} \\ &= k \times [\text{RX}]\end{aligned}$$

To explain this result, we need to know more about kinetics measurements. Many organic reactions occur in several steps, one of which usually has a higher-energy transition state than the others and is therefore slower. We call this step with the highest transition-state energy the *rate-limiting step*, or *rate-determining step*. No reaction can proceed faster than its rate-limiting step, which acts as a kind of traffic jam, or bottleneck. In the S_N1 reaction of (CH₃)₃CBr with H₂O, the fact that the nucleophile concentration does not appear in the first-order rate equation means that it is not involved in the rate-limiting step and must therefore be involved in some other, non-rate-limiting step. The mechanism shown in **FIGURE 12.11** accounts for these observations.

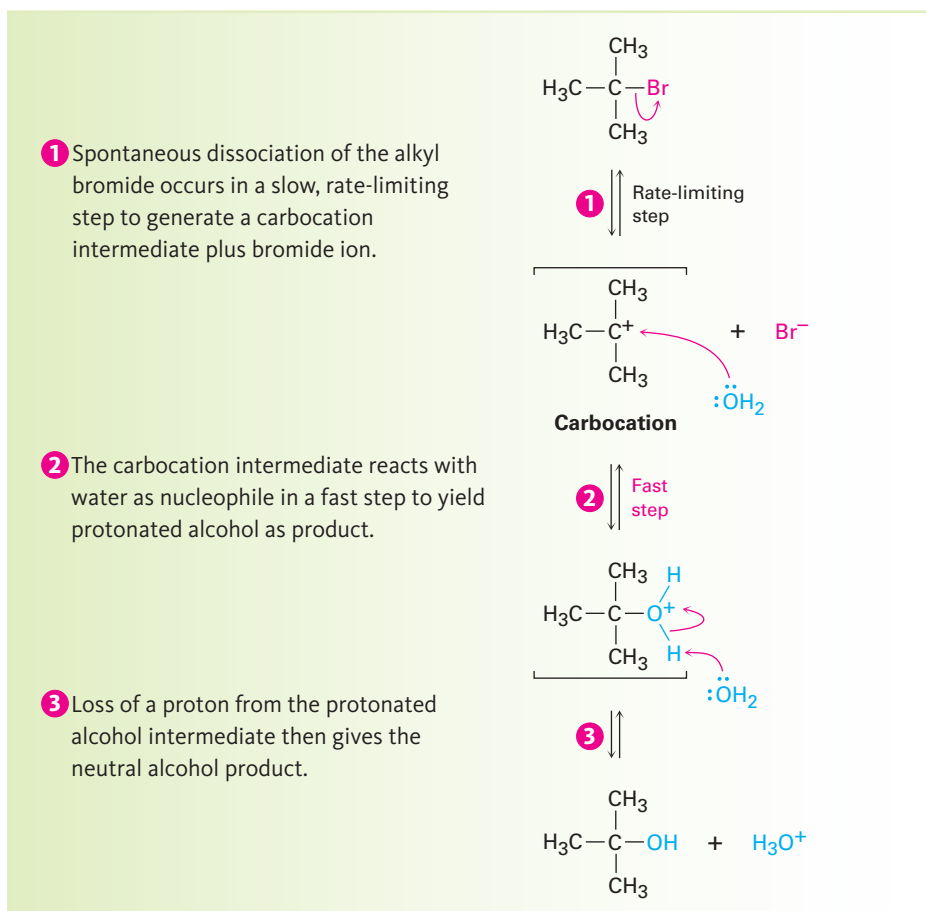
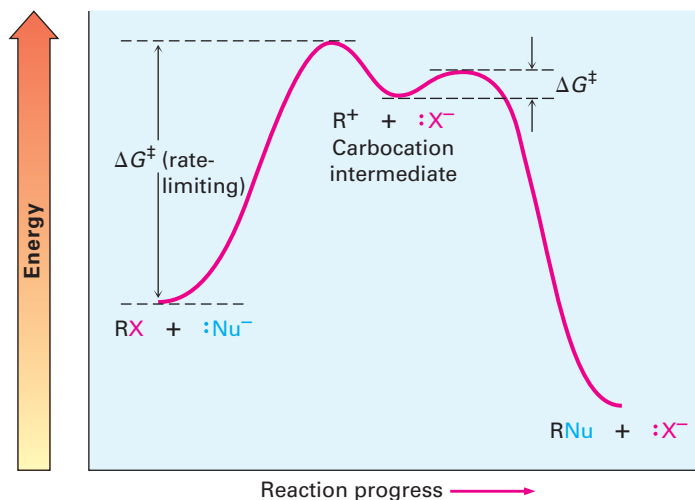


FIGURE 12.11 Mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H₂O. Three steps are involved: Step **1**, the spontaneous unimolecular dissociation of the alkyl bromide to yield a carbocation, is rate-limiting.

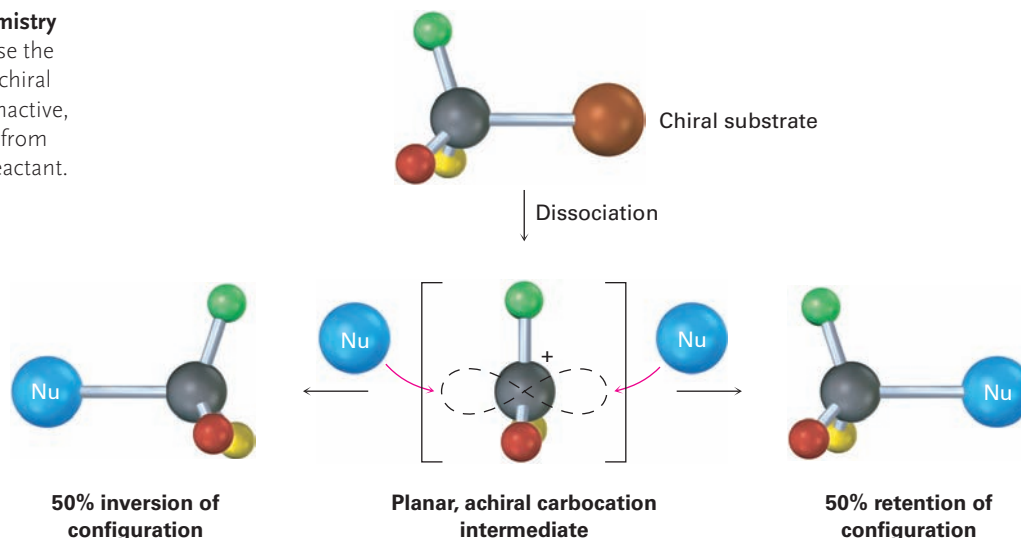
Unlike what happens in an S_N2 reaction, where the leaving group is displaced at the same time the incoming nucleophile approaches, an S_N1 reaction takes place by loss of the leaving group *before* the nucleophile approaches. 2-Bromo-2-methylpropane spontaneously dissociates to the *tert*-butyl carbocation plus Br^- in a slow, rate-limiting step, and the intermediate carbocation is then immediately trapped by the nucleophile water in a faster second step. Water is not a reactant in the step whose rate is measured. The energy diagram is shown in **FIGURE 12.12**.

FIGURE 12.12 Energy diagram for an S_N1 reaction. The rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

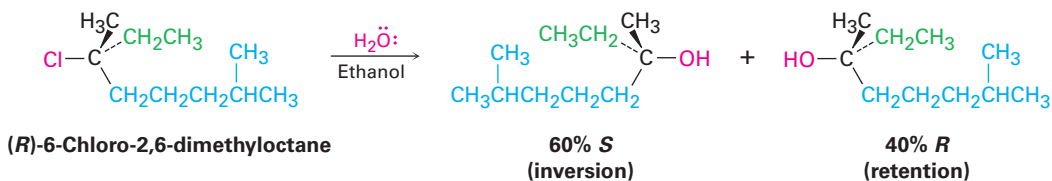


Because an S_N1 reaction occurs through a carbocation intermediate, its stereochemical outcome is different from that of an S_N2 reaction. Carbocations, as we've seen, are planar, sp^2 -hybridized, and achiral. Thus, if we carry out an S_N1 reaction on one enantiomer of a chiral reactant and go through an achiral carbocation intermediate, the molecule loses its chirality so the product must lose its optical activity. That is, the symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic, 50:50 mixture of enantiomers (**FIGURE 12.13**).

FIGURE 12.13 Stereochemistry of the S_N1 reaction. Because the reaction goes through an achiral intermediate, an optically inactive, racemic product is formed from an enantiomerically pure reactant.



The conclusion that S_N1 reactions on enantiomerically pure substrates should give racemic products is nearly, but not exactly, what is found. In fact, few S_N1 displacements occur with complete racemization. Most give a minor (0–20%) excess of inversion. The reaction of (*R*)-6-chloro-2,6-dimethyloctane with H₂O, for example, leads to an alcohol product that is approximately 80% racemized and 20% inverted (80% *R,S* + 20% *S* is equivalent to 40% *R* + 60% *S*):



This lack of complete racemization in S_N1 reactions is due to the fact that *ion pairs* are involved. Dissociation of the substrate occurs to give a structure in which the two ions are still loosely associated and in which the carbocation is effectively shielded from reaction on one side by the departing anion. If a certain amount of substitution occurs before the two ions fully diffuse apart, then a net inversion of configuration will be observed (FIGURE 12.14).

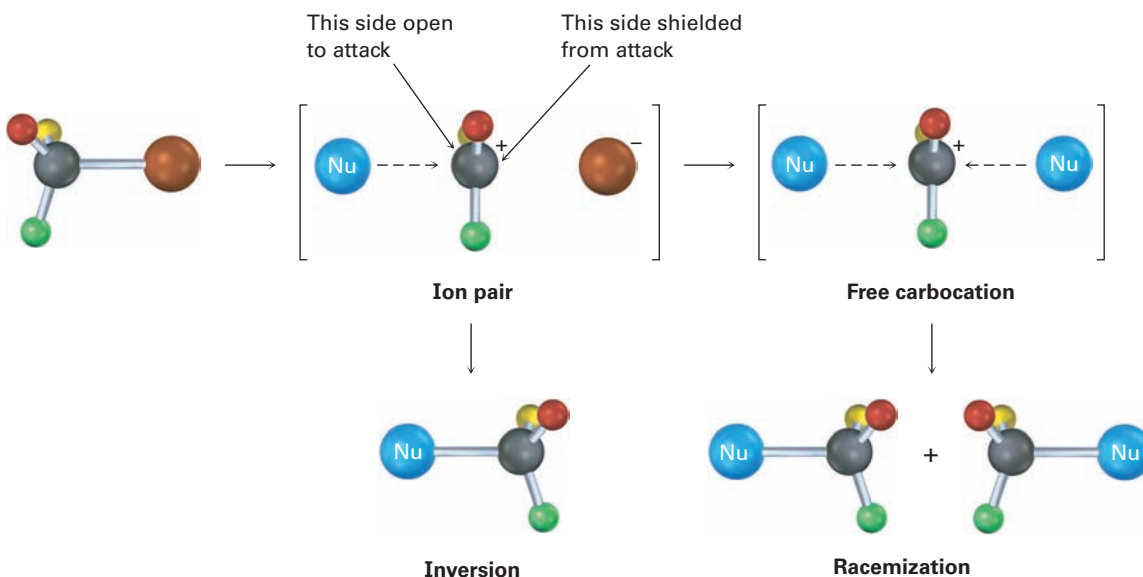


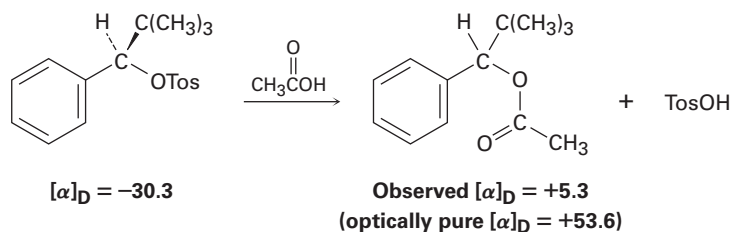
FIGURE 12.14 Ion pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.

PROBLEM 12.17

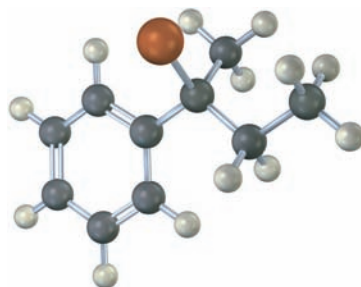
What product(s) would you expect from reaction of (*S*)-3-chloro-3-methyloctane with acetic acid? Show the stereochemistry of both reactant and product.

PROBLEM 12.18

Among the many examples of S_N1 reactions that occur with incomplete racemization, the optically pure tosylate of 2,2-dimethyl-1-phenylpropan-1-ol ($[\alpha]_D = -30.3$) gives the corresponding acetate ($[\alpha]_D = +5.3$) when heated in acetic acid. If complete inversion had occurred, the optically pure acetate would have had $[\alpha]_D = +53.6$. What percentage racemization and what percentage inversion occurred in this reaction?

**PROBLEM 12.19**

Assign configuration to the following substrate, and show the stereochemistry and identity of the product you would obtain by S_N1 reaction with water (red brown = Br):



12-10 Characteristics of the S_N1 Reaction

Just as the S_N2 reaction is strongly influenced by the structure of the substrate, the leaving group, the nucleophile, and the solvent, the S_N1 reaction is similarly influenced. Factors that lower ΔG^\ddagger , either by lowering the energy level of the transition state or by raising the energy level of the ground state, favor faster S_N1 reactions. Conversely, factors that raise ΔG^\ddagger , either by raising the energy level of the transition state or by lowering the energy level of the reactant, slow down the S_N1 reaction.

The Substrate

According to the Hammond postulate (Section 7-9), any factor that stabilizes a high-energy intermediate also stabilizes the transition state leading to that intermediate. Since the rate-limiting step in an S_N1 reaction is the spontaneous, unimolecular dissociation of the substrate to yield a carbocation, the

reaction is favored whenever a stabilized carbocation intermediate is formed. The more stable the carbocation intermediate, the faster the S_N1 reaction.

We saw in Section 7-8 that the stability order of alkyl carbocations is 3° > 2° > 1° > -CH₃. To this list we must also add the resonance-stabilized allylic and benzylic cations. Just as allylic radicals are unusually stable because the unpaired electron can be delocalized over an extended π orbital system (Section 12-2), so allylic and benzylic carbocations are unusually stable. As **FIGURE 12.15** indicates, an allylic cation has two resonance forms. In one form the double bond is on the “left”; in the other form it’s on the “right.” A benzylic cation has five resonance forms, all of which contribute to the overall resonance hybrid.

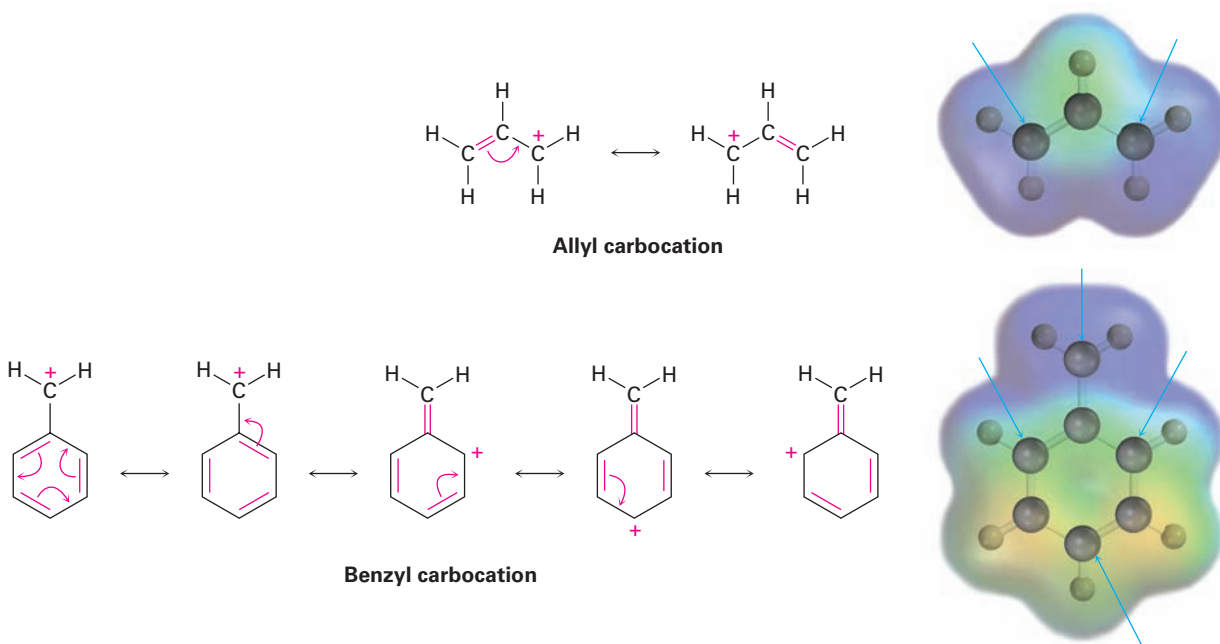
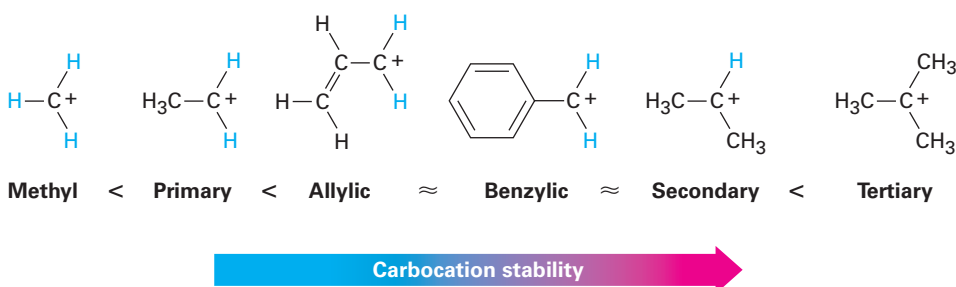
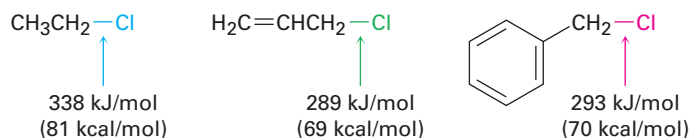


FIGURE 12.15 Resonance forms of allylic and benzylic carbocations. The positive charge (blue) is delocalized over the π system in both. **Electron-poor atoms** are indicated by blue arrows.

Because of resonance stabilization, a *primary* allylic or benzylic carbocation is about as stable as a *secondary* alkyl carbocation and a *secondary* allylic or benzylic carbocation is about as stable as a *tertiary* alkyl carbocation. This stability order of carbocations is the same as the order of S_N1 reactivity for alkyl halides and tosylates.

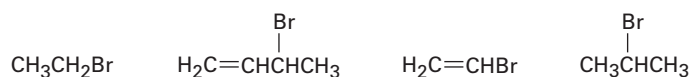


We should also note parenthetically that primary allylic and benzylic substrates are particularly reactive in S_N2 reactions as well as in S_N1 reactions. Allylic and benzylic C–X bonds are about 50 kJ/mol (12 kcal/mol) weaker than the corresponding saturated bonds and are therefore more easily broken.



PROBLEM 12.20

Rank the following substances in order of their expected S_N1 reactivity:



PROBLEM 12.21

3-Bromobut-1-ene and 1-bromobut-2-ene undergo S_N1 reaction at nearly the same rate even though one is a secondary halide and the other is primary. Explain.

The Leaving Group

We said during the discussion of S_N2 reactivity that the best leaving groups are those that are most stable, that is, those that are the conjugate bases of strong acids. An identical reactivity order is found for the S_N1 reaction because the leaving group is directly involved in the rate-limiting step. Thus, the S_N1 reactivity order is



Leaving group reactivity

Note that in the S_N1 reaction, which is often carried out under acidic conditions, neutral water is sometimes the leaving group. This occurs, for example, when an alkyl halide is prepared from a tertiary alcohol by reaction with HBr or HCl (Section 12-3). As shown in **FIGURE 12.16**, the alcohol is first protonated and then spontaneously loses H_2O to generate a carbocation, which reacts with halide ion to give the alkyl halide. Knowing that an S_N1 reaction is involved in the conversion of alcohols to alkyl halides explains why the reaction works well only for tertiary alcohols: tertiary alcohols react fastest because they give the most stable carbocation intermediates.

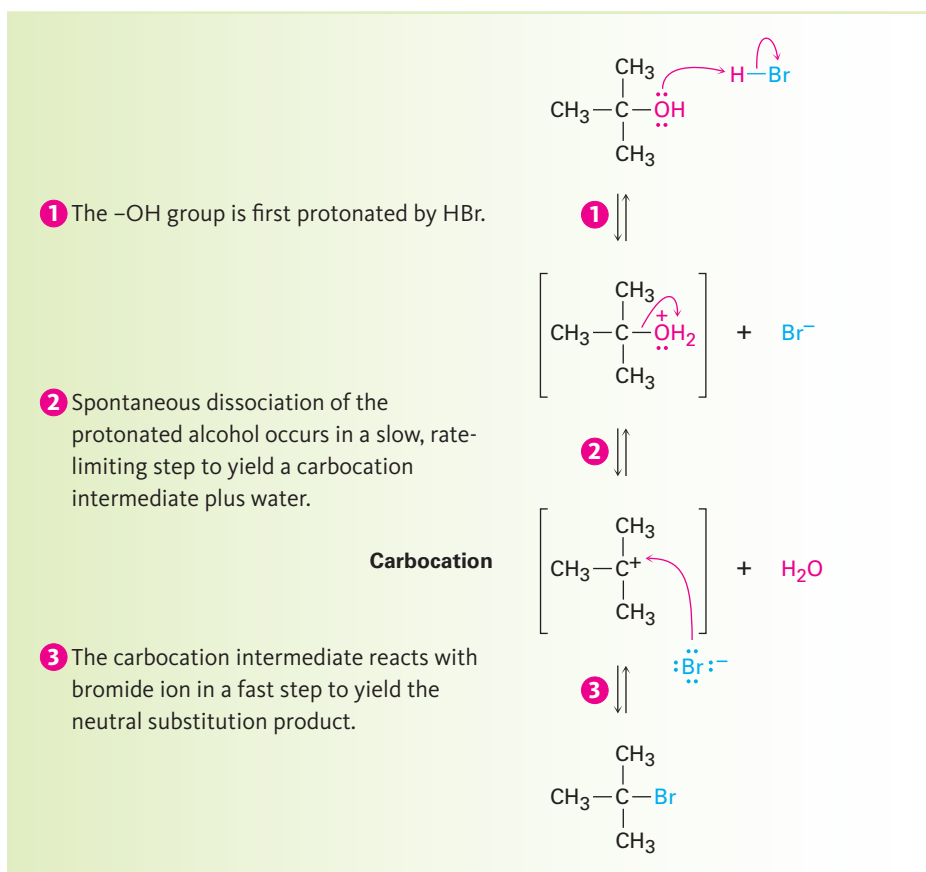
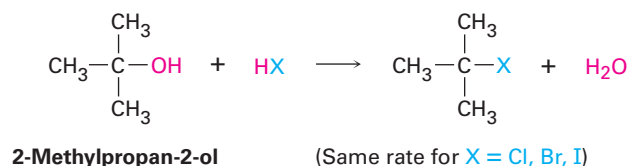


FIGURE 12.16 Mechanism of the S_N1 reaction of a tertiary alcohol with HBr to yield an alkyl halide. Neutral water is the leaving group (step 2).

© John McMurry

The Nucleophile

The nature of the nucleophile plays a major role in the S_N2 reaction but does not affect an S_N1 reaction. Because the S_N1 reaction occurs through a rate-limiting step in which the added nucleophile has no part, the nucleophile can't affect the reaction rate. The reaction of 2-methylpropan-2-ol with HX, for instance, occurs at the same rate regardless of whether X is Cl, Br, or I. Furthermore, neutral nucleophiles are just as effective as negatively charged ones, so S_N1 reactions frequently occur under neutral or acidic conditions.



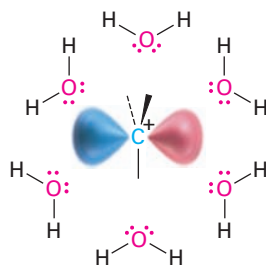
The Solvent

What about the solvent? Do solvents have the same effect in S_N1 reactions that they have in S_N2 reactions? The answer is both yes and no. Yes, solvents have a large effect on S_N1 reactions, but no, the reasons for the effects on S_N1 and S_N2 reactions are not the same. Solvent effects in the S_N2 reaction are due

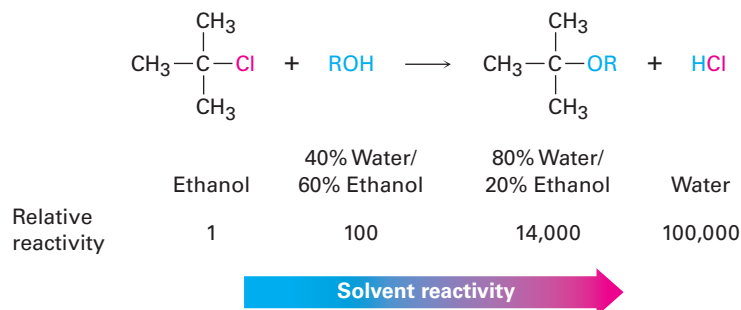
largely to stabilization or destabilization of the nucleophile *reactant*. Solvent effects in the S_N1 reaction, however, are due largely to stabilization or destabilization of the *transition state*.

The Hammond postulate says that any factor stabilizing the intermediate carbocation should increase the rate of an S_N1 reaction. Solvation of the carbocation—the interaction of the ion with solvent molecules—has just such an effect. Solvent molecules orient around the carbocation so that the electron-rich ends of the solvent dipoles face the positive charge (FIGURE 12.17), thereby lowering the energy of the ion and favoring its formation.

FIGURE 12.17 Solvation of a carbocation by water. The electron-rich oxygen atoms of solvent molecules orient around the positively charged carbocation and thereby stabilize it.



The properties of a solvent that contribute to its ability to stabilize ions by solvation are related to the solvent's polarity. S_N1 reactions take place much more rapidly in strongly polar solvents, such as water and methanol, than in less polar solvents, such as ether and chloroform. In the reaction of 2-chloro-2-methylpropane, for example, a rate increase of 100,000 is observed on going from ethanol (less polar) to water (more polar). The rate increases on going from a hydrocarbon solvent to water are so large they can't be measured accurately.



A Summary of S_N1 Reaction Characteristics

The effects on S_N1 reactions of the four variables—substrate, leaving group, nucleophile, and solvent—are summarized in the following statements:

Substrate The best substrates yield the most stable carbocations. As a result, S_N1 reactions are best for tertiary, allylic, and benzylic halides.

Leaving group Good leaving groups increase the reaction rate by lowering the energy level of the transition state for carbocation formation.

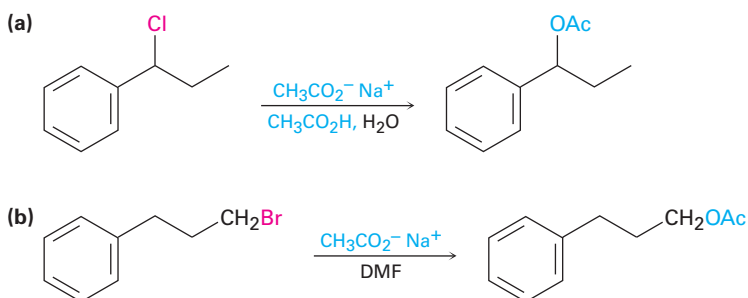
Nucleophile The nucleophile must be nonbasic to prevent a competitive elimination of HX (Section 12-13), but otherwise does not affect the reaction rate. Neutral nucleophiles work well.

Solvent Polar solvents stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate.

Predicting the Mechanism of a Nucleophilic Substitution Reaction

WORKED EXAMPLE 12.3

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:



Strategy

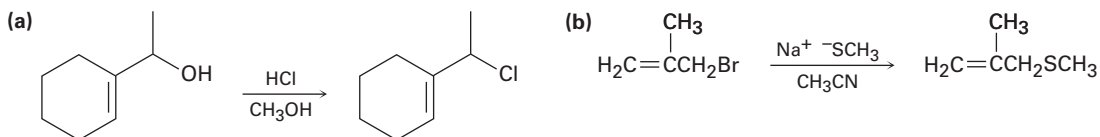
Look at the substrate, leaving group, nucleophile, and solvent. Then decide from the summaries at the ends of Sections 12-7 and 12-9 whether an S_N1 or an S_N2 reaction is favored. S_N1 reactions are favored by tertiary, allylic, or benzylic substrates, by good leaving groups, by nonbasic nucleophiles, and by protic solvents. S_N2 reactions are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents.

Solution

- (a) This is likely to be an S_N1 reaction because the substrate is secondary and benzylic, the nucleophile is weakly basic, and the solvent is protic.
- (b) This is likely to be an S_N2 reaction because the substrate is primary, the nucleophile is a reasonably good one, and the solvent is polar aprotic.

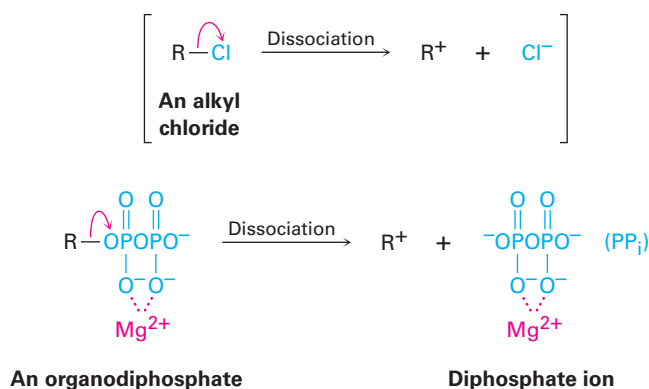
PROBLEM 12.22

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:



12-11 Biological Substitution Reactions

Both S_N1 and S_N2 reactions are well known in biological chemistry, particularly in the pathways for biosynthesis of the many thousands of terpenes (Chapter 7 *Something Extra*). Unlike what typically happens in the laboratory, however, the substrate in a biological substitution reaction is usually an organodiphosphate rather than an alkyl halide. Thus, the leaving group is the diphosphate ion, abbreviated PP_i , rather than a halide ion. In fact, it's useful to think of the diphosphate group as the “biological equivalent” of a halogen. You might recall from Section 9-7, for instance, that organodiphosphates can react with aromatic compounds in Friedel–Crafts-like alkylation reactions much as alkyl halides do. You might also recall from Section 9-7 that the dissociation of an organodiphosphate in a biological reaction is typically assisted by complexation to a divalent metal cation such as Mg^{2+} to help neutralize charge and make the diphosphate a better leaving group.



As examples of biological substitution reactions, two S_N1 reactions occur during the biosynthesis of geraniol, a fragrant alcohol found in roses and used in perfumery. Geraniol biosynthesis begins with dissociation of dimethylallyl diphosphate to give an allylic carbocation, which reacts with isopentenyl diphosphate (FIGURE 12.18). From the viewpoint of isopentenyl diphosphate, the reaction is an electrophilic alkene addition of the dimethylallyl carbocation. From the viewpoint of dimethylallyl diphosphate, however, the process is an S_N1 reaction in which the carbocation intermediate produced by dissociation of diphosphate ion reacts with a double bond as the nucleophile.

Following this initial S_N1 reaction, loss of the *pro-R* hydrogen gives geranyl diphosphate, itself an allylic diphosphate that dissociates a second time. Reaction of the geranyl carbocation with water in a second S_N1 reaction, followed by loss of a proton, yields geraniol.

S_N2 reactions are involved in almost all biological methylations, which transfer a $-\text{CH}_3$ group from an electrophilic donor to a nucleophile. The donor is usually *S*-adenosylmethionine (abbreviated SAM), which contains a positively charged sulfur (a sulfonium ion; Section 5-10), and the leaving group is the neutral *S*-adenosylhomocysteine molecule. In the biosynthesis of epinephrine (adrenaline) from norepinephrine, for instance, the nucleophilic

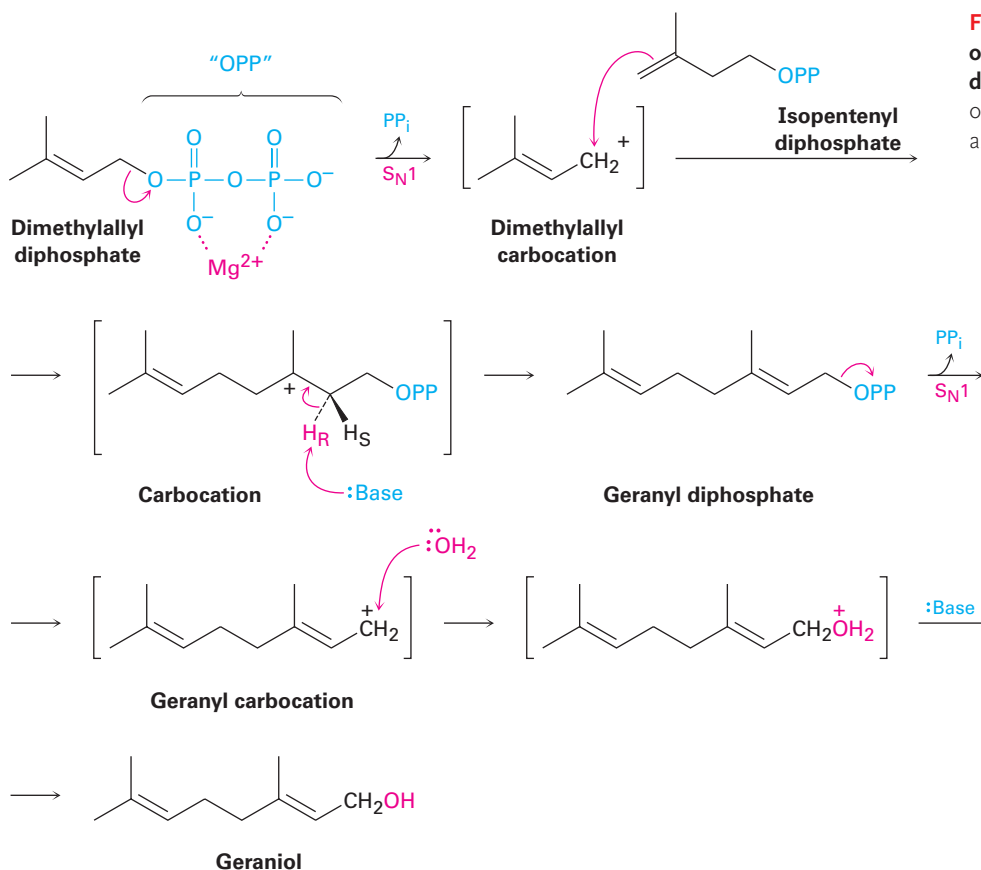


FIGURE 12.18 Biosynthesis of geraniol from dimethylallyl diphosphate. Two S_N1 reactions occur, both with diphosphate ion as the leaving group.

nitrogen atom of norepinephrine attacks the electrophilic methyl carbon atom of *S*-adenosylmethionine in an S_N2 reaction, displacing *S*-adenosylhomocysteine (FIGURE 12.19). In effect, *S*-adenosylmethionine is simply a biological equivalent of CH_3Cl .

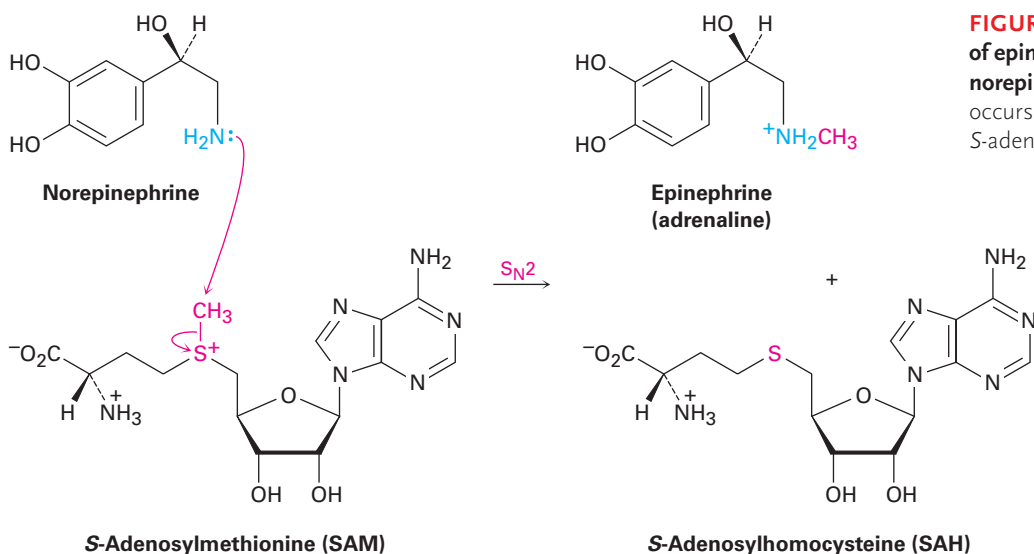
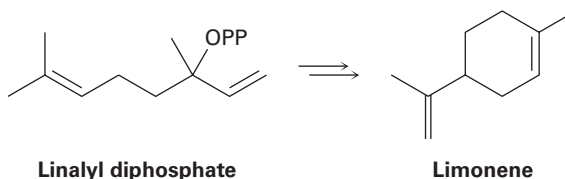


FIGURE 12.19 Biosynthesis of epinephrine from norepinephrine. The process occurs by an S_N2 reaction with *S*-adenosylmethionine.

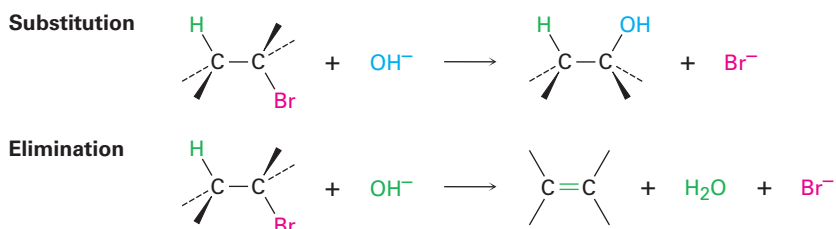
PROBLEM 12.23

Review the mechanism of geraniol biosynthesis shown in Figure 12.18, and propose a mechanism for the biosynthesis of limonene from linalyl diphosphate. What kind of reaction is occurring?



12-12 Elimination Reactions: Zaitsev's Rule

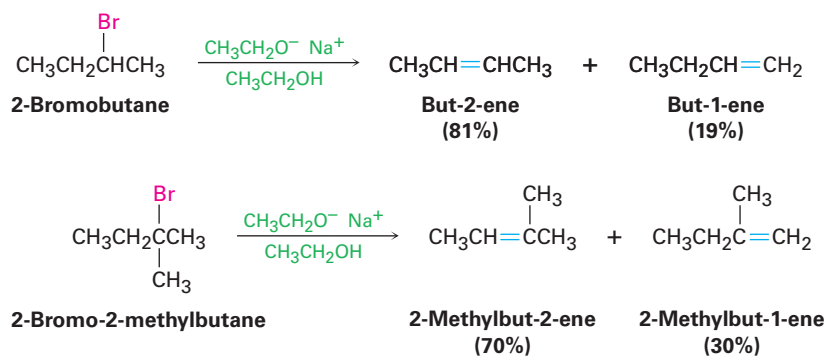
We began this chapter by saying that two kinds of reactions can take place when a nucleophile/Lewis base reacts with an alkyl halide. The nucleophile can either substitute for the halide by reaction at carbon, or it can cause elimination of HX by reaction at a neighboring hydrogen:



Elimination reactions are more complex than substitution reactions for several reasons. One is the problem of regiochemistry. What products result by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

According to **Zaitsev's rule**, formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.

Zaitsev's rule In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

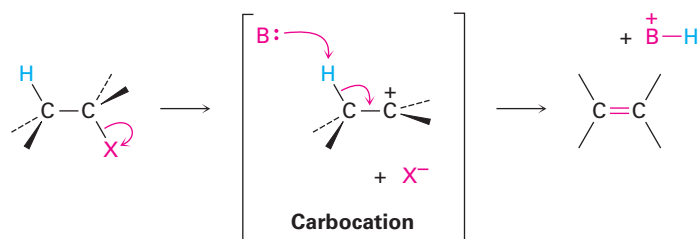


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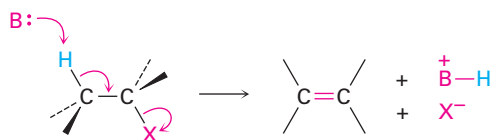
Another factor that complicates a study of elimination reactions is that they can take place by different mechanisms, just as substitutions can. We'll consider three of the most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C–H and C–X bond-breaking.

In the E1 reaction, the C–X bond breaks first to give a carbocation intermediate that undergoes subsequent base abstraction of H⁺ to yield the alkene. In the E2 reaction, base-induced C–H bond cleavage is simultaneous with C–X bond cleavage, giving the alkene in a single step. In the E1cB reaction (cB for “conjugate base”), base abstraction of the proton occurs first, giving a carbanion (R:[−]) intermediate. This anion, the conjugate base of the reactant “acid,” then undergoes loss of X[−] in a subsequent step to give the alkene. All three mechanisms occur frequently in the laboratory, but the E1cB mechanism predominates in biological pathways.

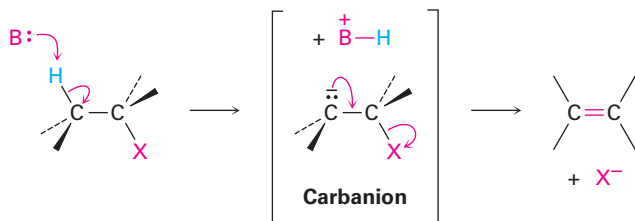
E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



E2 Reaction: C–H and C–X bonds break simultaneously, giving the alkene in a single step without intermediates.



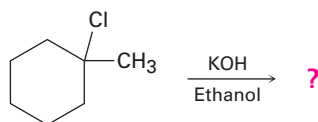
E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X[−] to form the alkene.



Predicting the Product of an Elimination Reaction

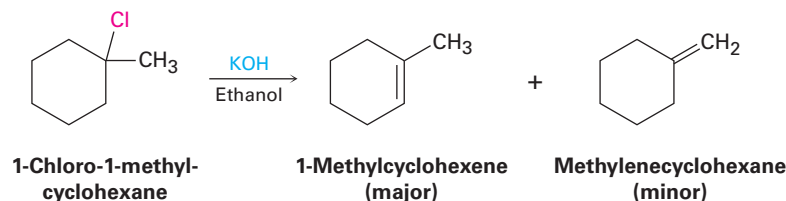
WORKED EXAMPLE 12.4

What product would you expect from reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?

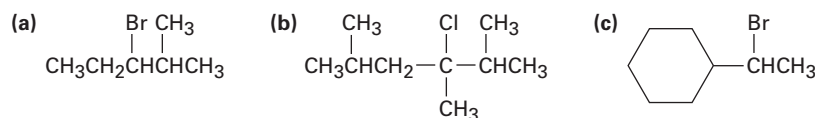


Strategy

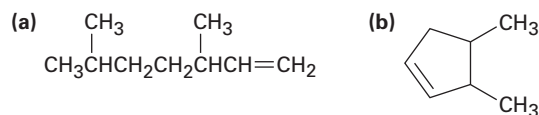
Treatment of an alkyl halide with a strong base such as KOH yields an alkene. To find the products in a specific case, locate the hydrogen atoms on each carbon next to the leaving group, and then generate the potential alkene products by removing HX in as many ways as possible. The major product will be the one that has the most highly substituted double bond—in this case, 1-methylcyclohexene.

Solution**PROBLEM 12.24**

Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides? Which product will be major in each case?

**PROBLEM 12.25**

What alkyl halides might the following alkenes have been made from?

**12-13 The E2 Reaction and the Deuterium Isotope Effect**

The **E2 reaction** (for *elimination, bimolecular*) occurs when an alkyl halide is treated with a strong base, such as hydroxide ion or alkoxide ion (RO^-). It is the most commonly occurring pathway for elimination in the laboratory and can be formulated as shown in **FIGURE 12.20**.

Like the $\text{S}_{\text{N}}2$ reaction, the E2 reaction takes place in one step without intermediates. As the base begins to abstract H^+ from a carbon next to the leaving group, the C–H bond begins to break, a C=C bond begins to form, and the leaving group begins to depart, taking with it the electron pair from the C–X bond. Among the pieces of evidence supporting this mechanism is that E2 reactions show second-order kinetics and follow the rate law: $\text{rate} = k \times [\text{RX}] \times [\text{Base}]$. That is, both base and alkyl halide take part in the rate-limiting step.

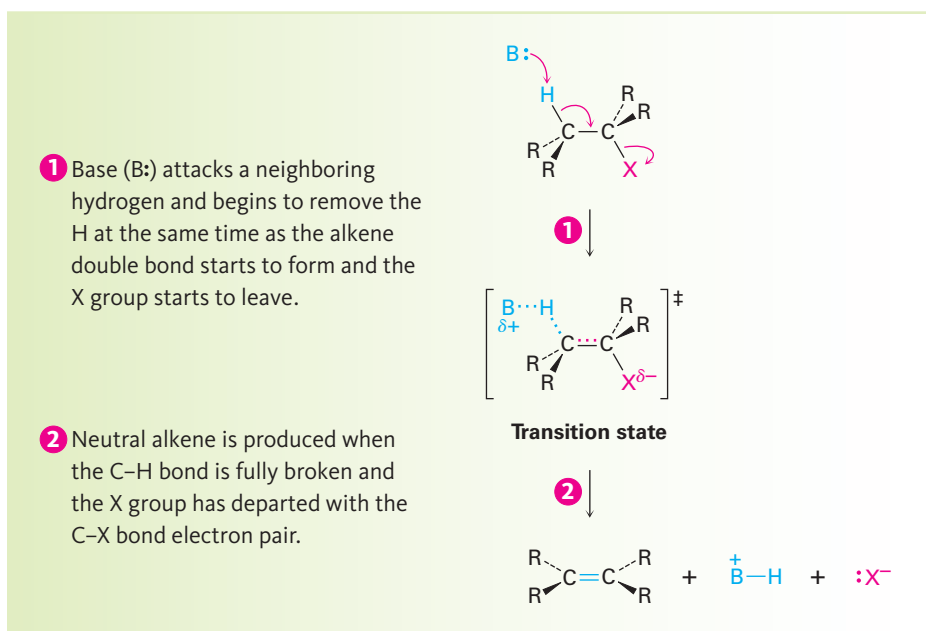
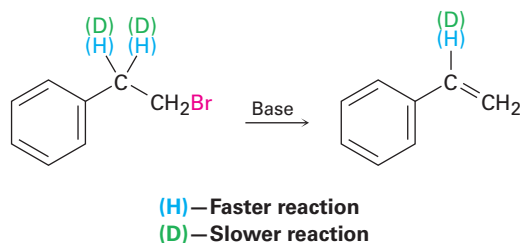


FIGURE 12.20 Mechanism of the E2 reaction of an alkyl halide.

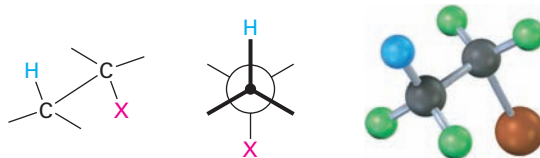
The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.

A second piece of evidence in support of the E2 mechanism is provided by a phenomenon known as the **deuterium isotope effect**. For reasons that we won't go into, a carbon-hydrogen bond is weaker by about 5 kJ/mol (1.2 kcal/mol) than the corresponding carbon-deuterium bond. Thus, a C-H bond is more easily broken than an equivalent C-D bond, and the rate of C-H bond cleavage is faster. For instance, the base-induced elimination of HBr from 1-bromo-2-phenylethane proceeds 7.11 times as fast as the corresponding elimination of DBr from 1-bromo-2,2-dideuterio-2-phenylethane. This result tells us that the C-H (or C-D) bond is broken in the rate-limiting step, consistent with our picture of the E2 reaction as a one-step process. If it were otherwise, we couldn't measure a rate difference.

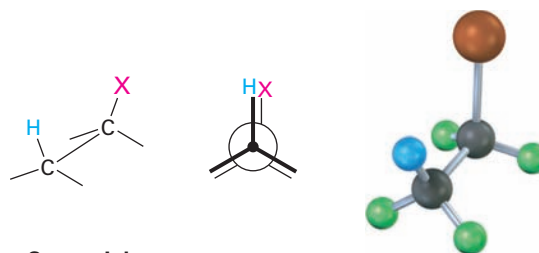


Yet a third piece of mechanistic evidence involves the stereochemistry of E2 eliminations. As shown by a large number of experiments, E2 reactions occur with *periplanar* geometry, meaning that all four reacting atoms—the hydrogen, the two carbons, and the leaving group—lie in the same plane. Two such geometries are possible: **syn periplanar** geometry, in which the H and the X are on the same side of the molecule, and **anti periplanar** geometry, in which the H and the X are on opposite sides of the molecule. Of the two, anti periplanar geometry is energetically preferred because it allows the

substituents on the two carbons to adopt a staggered relationship, whereas syn geometry requires that the substituents be eclipsed.

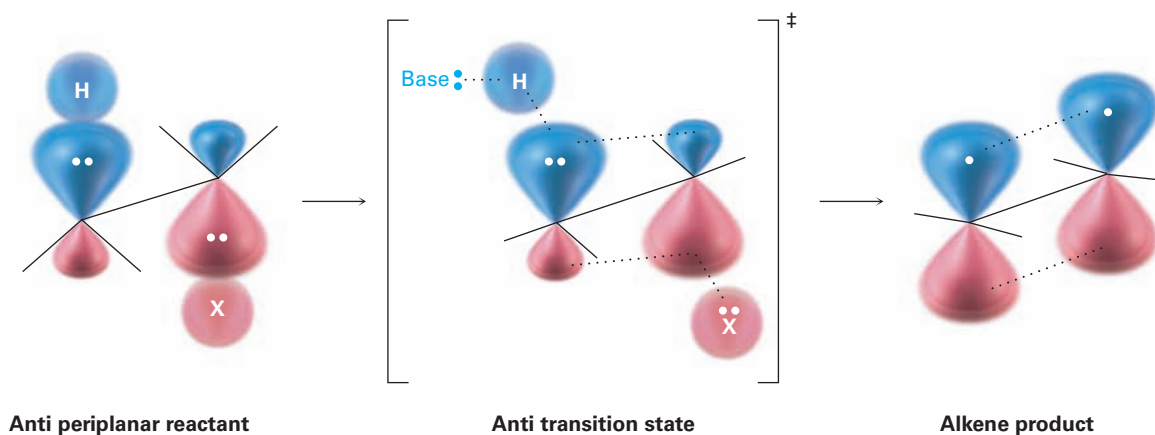


**Anti periplanar geometry
(staggered, lower energy)**



**Syn periplanar geometry
(eclipsed, higher energy)**

What's so special about periplanar geometry? Because the sp^3 σ orbitals in the reactant C–H and C–X bonds must overlap and become p π orbitals in the alkene product, there must also be some overlap in the transition state. This can occur most easily if all the orbitals are in the same plane to begin with—that is, if they're periplanar (**FIGURE 12.21**).



Anti periplanar reactant

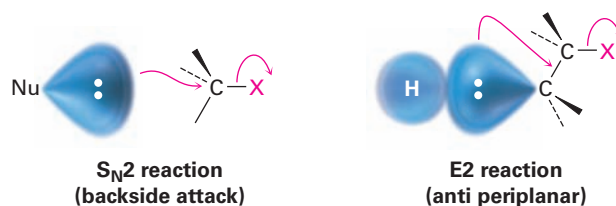
Anti transition state

Alkene product

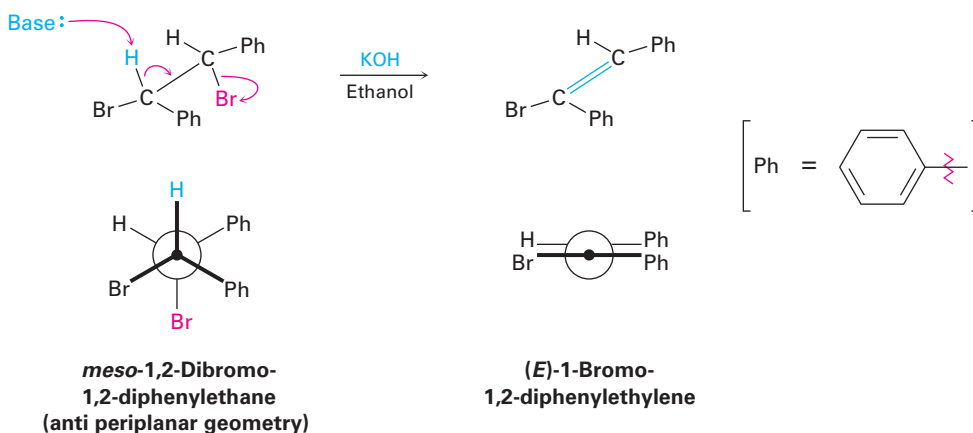
FIGURE 12.21 Transition state for the E2 reaction of an alkyl halide with base. Overlap of the developing p orbitals in the transition state requires periplanar geometry of the reactant.

You might think of E2 elimination reactions with periplanar geometry as being similar to S_N2 reactions with 180° geometry. In an S_N2 reaction, an electron pair from the incoming nucleophile pushes out the leaving group on the opposite side of the molecule. In an E2 reaction, an electron pair from a

neighboring C–H bond pushes out the leaving group on the opposite side of the molecule.

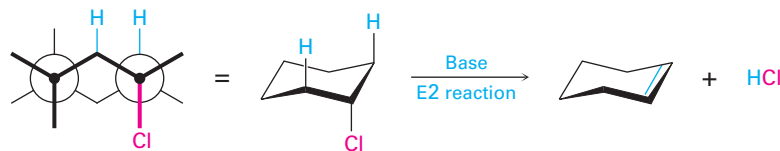


Anti periplanar geometry for E2 eliminations has specific stereochemical consequences that provide strong evidence for the proposed mechanism. To take just one example, *meso*-1,2-dibromo-1,2-diphenylethane undergoes E2 elimination on treatment with base to give only the *E* alkene. None of the isomeric *Z* alkene is formed because the transition state leading to the *Z* alkene would have to have syn periplanar geometry and thus be higher in energy.



Anti periplanar geometry is particularly important in cyclohexane rings, where chair geometry forces a rigid relationship between substituents on adjacent carbon atoms (Section 4-6). Only if the hydrogen and the leaving group are trans diaxial can an E2 reaction occur (FIGURE 12.22). If either the leaving group or the hydrogen is equatorial, E2 elimination can't occur.

Axial chlorine: H and Cl are anti periplanar



Equatorial chlorine: H and Cl are not anti periplanar

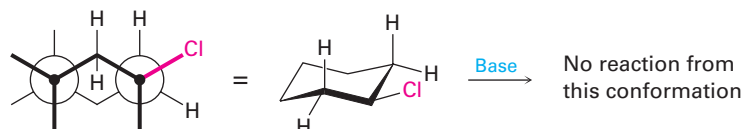


FIGURE 12.22 Geometric requirement for an E2 reaction in a substituted cyclohexane.

The hydrogen and the leaving group must both be axial for anti periplanar elimination to occur.

WORKED EXAMPLE 12.5 Predicting the Stereochemistry of an E2 Reaction

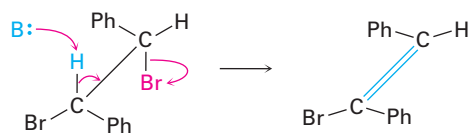
What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane?

Strategy

Draw (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane so that you can see its stereochemistry and so that the –H and –Br groups to be eliminated are anti periplanar. Then carry out the elimination while keeping all substituents in approximately their same positions, and see what alkene results.

Solution

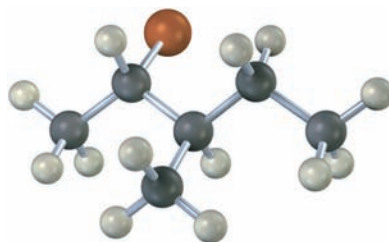
Anti periplanar elimination of HBr gives (*Z*)-1-bromo-1,2-diphenylethylene.

**PROBLEM 12.26**

What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

PROBLEM 12.27

The following alkyl halide undergoes E2 elimination on treatment with KOH to give a mixture of two alkenes, one monosubstituted and one trisubstituted. What stereochemistry do you expect for the trisubstituted alkene? (Red-brown = Br.)

**PROBLEM 12.28**

Which would you expect to undergo E2 elimination faster, *trans*-1-bromo-4-*tert*-butylcyclohexane or *cis*-1-bromo-4-*tert*-butylcyclohexane? Draw each molecule in its more stable chair conformation, and explain your answer.

12-14 The E1 and E1cB Reactions

The E1 Reaction

Just as the E2 reaction is analogous to the S_N2 reaction, the S_N1 reaction has a close analog called the **E1 reaction** (for *elimination, unimolecular*). The E1 reaction can be formulated as shown in **FIGURE 12.23** for the elimination of HCl from 2-chloro-2-methylpropane.

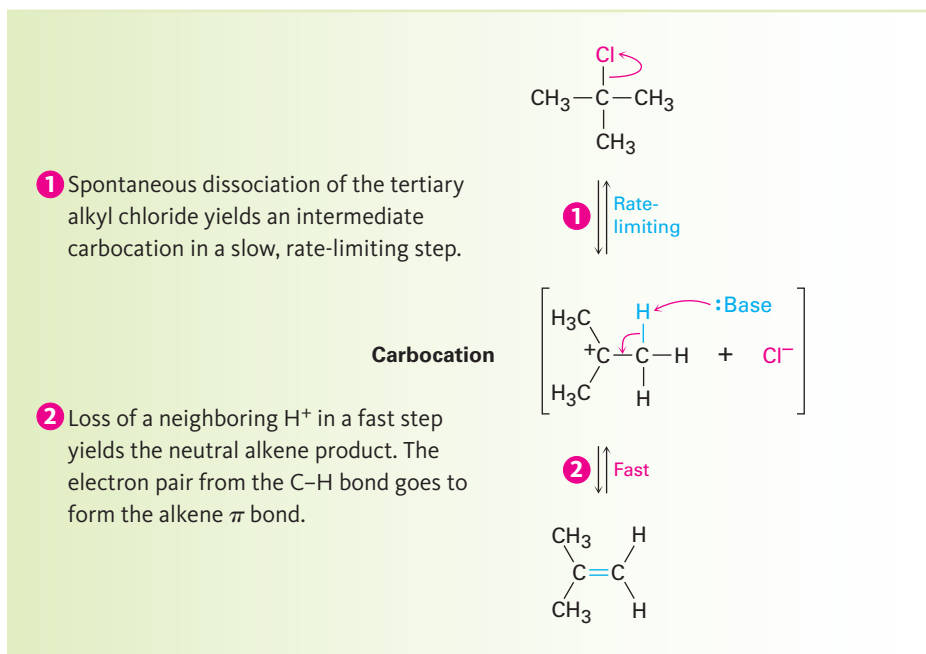
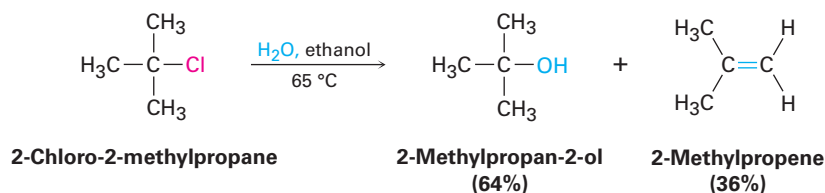


FIGURE 12.23 Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.

E1 eliminations begin with the same unimolecular dissociation to give a carbocation that we saw in the S_N1 reaction, but the dissociation is followed by loss of H⁺ from the adjacent carbon rather than by substitution. In fact, the E1 and S_N1 reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a nonbasic nucleophile. Thus, the best E1 substrates are also the best S_N1 substrates, and mixtures of substitution and elimination products are usually obtained. For example, when 2-chloro-2-methylpropane is warmed to 65 °C in 80% aqueous ethanol, a 64:36 mixture of 2-methylpropan-2-ol (S_N1) and 2-methylpropene (E1) results:

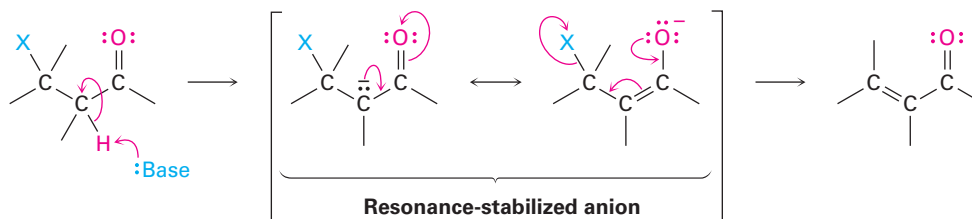


Much evidence has been obtained in support of the E1 mechanism. For example, E1 reactions show first-order kinetics, consistent with a rate-limiting, unimolecular dissociation process. Furthermore, E1 reactions show

no deuterium isotope effect. Because rupture of the C–H (or C–D) bond occurs after the rate-limiting step rather than during it, we can't measure a rate difference between a deuterated and nondeuterated substrate. A final piece of evidence is that there is no geometric requirement on the E1 reaction because the halide and the hydrogen are lost in separate steps, unlike the E2 reaction, where anti periplanar geometry is required.

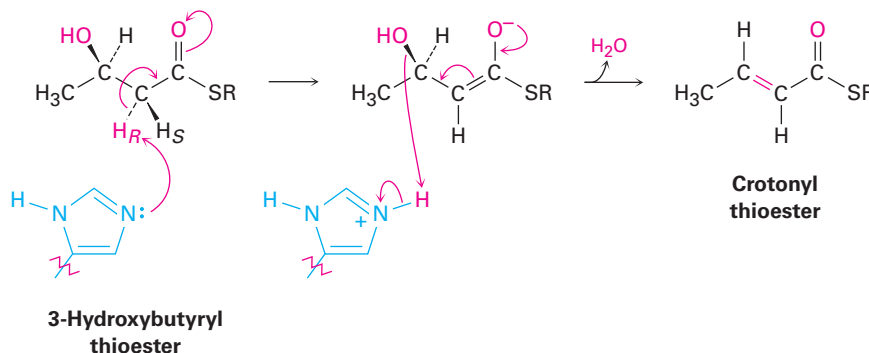
The E1cB Reaction

In contrast to the E1 reaction, which involves a *carbocation* intermediate, the **E1cB reaction** takes place through a *carbanion* intermediate. Base-induced abstraction of a proton in a slow, rate-limiting step gives an anion, which expels a leaving group on the adjacent carbon. The reaction is particularly common in substrates that have a poor leaving group, such as –OH, two carbons removed from a carbonyl group, HO–C–CH–C=O. The poor leaving group disfavors the alternative E1 and E2 possibilities, and the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of the anion intermediate. We'll look at this acidifying effect of a carbonyl group in Section 17-4. Note that the carbon–carbon double bond in the product is conjugated to the carbonyl, C=C–C=O, a situation similar to that in conjugated dienes (Section 8-12).



12-15 Biological Elimination Reactions

All three elimination reactions—E2, E1, and E1cB—occur in biological pathways, but the E1cB mechanism is particularly common. The substrate is usually an alcohol rather than an alkyl halide, and the H atom removed is usually adjacent to a carbonyl group, just as in laboratory reactions. Thus, 3-hydroxy carbonyl compounds are frequently converted to conjugated unsaturated carbonyl compounds by elimination reactions. A typical example occurs during the biosynthesis of fats when a 3-hydroxybutyryl thioester is dehydrated to the corresponding unsaturated (crotonyl) thioester. The base in this reaction is the imidazole ring (Section 9-4) of a histidine amino acid in the enzyme, and loss of the hydroxyl group is assisted by simultaneous protonation.



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12-16 A Summary of Reactivity: S_N1, S_N2, E1, E1cB, and E2

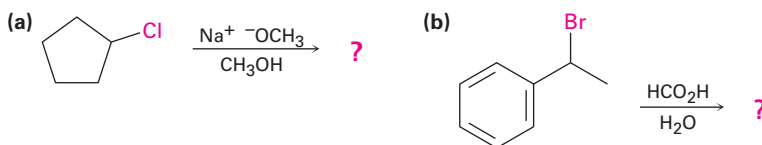
S_N1, S_N2, E1, E1cB, E2—how can you keep it all straight and predict what will happen in any given case? Will substitution or elimination occur? Will the reaction be bimolecular or unimolecular? There are no rigid answers to these questions, but it's possible to recognize some trends and make some generalizations.

- **Primary alkyl halides** S_N2 substitution occurs if a good nucleophile is used, E2 elimination occurs if a strong, sterically hindered base is used, and E1cB elimination occurs if the leaving group is two carbons away from a carbonyl group.
- **Secondary alkyl halides** S_N2 substitution occurs if a weakly basic nucleophile is used in a polar aprotic solvent, E2 elimination predominates if a strong base is used, and E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group. Secondary allylic and benzylic alkyl halides can also undergo S_N1 and E1 reactions if a weakly basic nucleophile is used in a protic solvent.
- **Tertiary alkyl halides** E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral conditions, such as in pure ethanol or water. E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group.

Predicting the Product and Mechanism of a Reaction

WORKED EXAMPLE 12.6

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2, and predict the product of each:

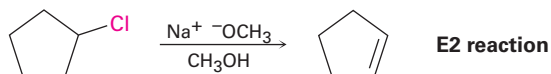


Strategy

Look carefully in each reaction at the substrate, leaving group, nucleophile, and solvent. Then decide from the preceding summary which kind of reaction is likely to be favored.

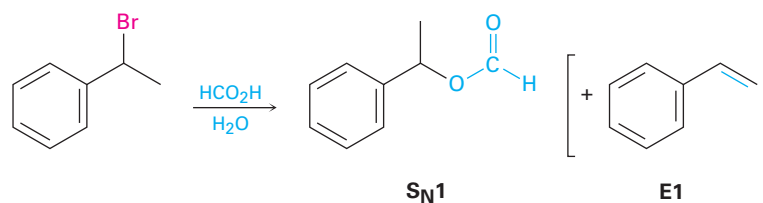
Solution

- (a) A secondary, nonallylic substrate can undergo an S_N2 reaction with a good nucleophile in a polar aprotic solvent but will undergo an E2 reaction on treatment with a strong base in a protic solvent. In this case, E2 reaction is likely to predominate.



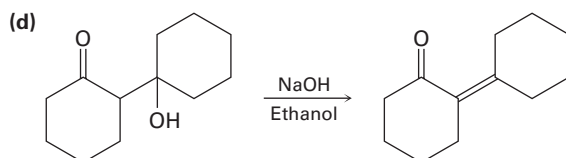
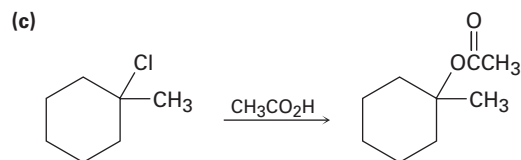
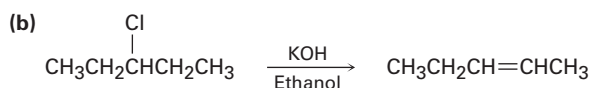
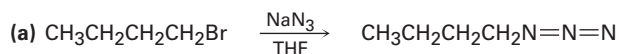
- (b) A secondary benzylic substrate can undergo an S_N2 reaction on treatment with a nonbasic nucleophile in a polar aprotic solvent and will undergo an E2 reaction on treatment with a base. Under protic conditions, such as

aqueous formic acid (HCO_2H), an $\text{S}_{\text{N}}1$ reaction is likely, along with some $\text{E}1$ reaction.



PROBLEM 12.29

Tell whether each of the following reactions is likely to be $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, $\text{E}1$, $\text{E}1\text{cB}$, or $\text{E}2$:



SOMETHING EXTRA

Naturally Occurring Organohalides

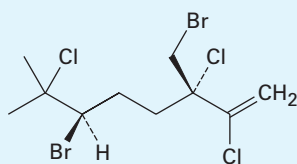
As recently as 1970, only about 30 naturally occurring organohalides were known. It was simply assumed that chloroform, halogenated phenols, chlorinated aromatic compounds called PCBs, and other such substances found in the environment were industrial pollutants. Now, a bit more than a third of a century later, the situation is quite different. More than 5000 organohalides

Marine corals secrete organohalogen compounds that act as a feeding deterrent to fish.



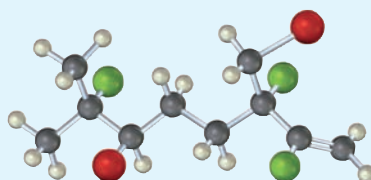
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have been found to occur naturally, and tens of thousands more surely exist. From a simple compound like chloromethane to an extremely complex one like the antibiotic vancomycin, a remarkably diverse range of organohalides exists in plants, bacteria, and animals. Many even have valuable physiological activity. The pentahalogenated alkene halomon, for instance, has been isolated from the red alga *Portieria hornemannii* and found to have anticancer activity against several human tumor cell lines.



Halomon

Some naturally occurring organohalides are produced in massive quantities. Forest fires, volcanoes, and marine kelp release up to 5 million tons of CH_3Cl per year, for example, while annual industrial emissions total about 26,000 tons. Termites are thought to release as much as 10^8 kg of chloroform per year. A detailed examination of the Okinawan acorn worm *Ptychodera flava* found that the 64 million worms living in a 1 km^2



study area excreted nearly 8000 pounds per year of bromophenols and bromoindoles, compounds previously thought to be nonnatural pollutants.

Why do organisms produce organohalides, many of which are undoubtedly toxic? The answer seems to be that many organisms use organohalogen compounds for self-defense, either as feeding deterrents, as irritants to predators, or as natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalides that deter fish, starfish, and other predators from eating them. Even humans appear to produce halogenated compounds as part of their defense against infection. The human immune system contains a peroxidase enzyme capable of carrying out halogenation reactions on fungi and bacteria, thereby killing the pathogen. And most remarkable of all, even free chlorine— Cl_2 —has been found to be present in humans.

Much remains to be learned—only a few hundred of the more than 500,000 known species of marine organisms have been examined—but it is clear that organohalides are an integral part of the world around us.



SUMMARY

Alkyl halides are not often found in terrestrial organisms, but the kinds of reactions they undergo are among the most important and well-studied reaction types in organic chemistry. In this chapter, we saw how to name and prepare alkyl halides, and we made a detailed study of their substitution and elimination reactions.

Alkyl halides contain a halogen bonded to a saturated, sp^3 -hybridized carbon atom. The C–X bond is polar, and alkyl halides can therefore behave as electrophiles. Alkyl halides can be prepared from alkenes by reaction with *N*-bromosuccinimide (NBS) to give the product of allylic bromination. The NBS bromination of an alkene takes place through an intermediate allylic radical, which is stabilized by resonance. Alkyl halides are also prepared from alcohols by reaction with HX, but the process works well only for tertiary alcohols, R_3COH . Primary and secondary alkyl halides are normally prepared from alcohols using either SOCl_2 , PBr_3 , or HF in pyridine.

Alkyl halides react with magnesium in ether solution to form alkyl-magnesium halides, called **Grignard reagents (RMgX)**. Because Grignard

KEY WORDS

- alkyl halide, 383
- anti periplanar, 423
- carbanion, 392
- deuterium isotope effect, 423
- E1 reaction, 427
- E1cB reaction, 428
- E2 reaction, 422
- first-order reaction, 409
- Gilman reagent, 393
- Grignard reagent (RMgX), 391
- kinetics, 398

nucleophilic substitution reaction,	396
organohalide,	382
second-order reaction,	399
S _N 1 reaction,	409
S _N 2 reaction,	399
solvation,	406
syn periplanar,	423
Zaitsev's rule,	420

reagents are both nucleophilic and basic, they react with acids to yield hydrocarbons. Alkyl halides also react with lithium metal to form organolithium reagents, RLi. In the presence of CuI, these form diorganocoppers, or **Gilman reagents (LiR₂Cu)**. Gilman reagents react with organohalides to yield coupled hydrocarbon products.

The reaction of an alkyl halide or tosylate with a nucleophile/base results either in substitution or in elimination. Nucleophilic substitutions are of two types: **S_N2 reactions** and **S_N1 reactions**. In the S_N2 reaction, the entering nucleophile approaches the halide from a direction 180° away from the leaving group, resulting in an umbrella-like inversion of configuration at the carbon atom. The reaction is kinetically **second-order** and is strongly inhibited by increasing steric bulk of the substrate. Thus, S_N2 reactions are favored for primary and simple secondary substrates.

The S_N1 reaction occurs when the substrate dissociates to a carbocation in a slow rate-limiting step, followed by a rapid reaction with the nucleophile. As a result, S_N1 reactions are kinetically **first-order** and take place with substantial racemization of configuration at the carbon atom. They are most favored for tertiary substrates. Both S_N1 and S_N2 reactions occur in biological pathways, although the leaving group is typically a diphosphate ion rather than a halide.

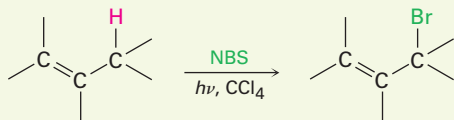
Eliminations of alkyl halides to yield alkenes commonly occur by three mechanisms, **E2 reactions**, **E1 reactions**, and **E1cB reactions**, which differ in the timing of C–H and C–X bond-breaking. In the E2 reaction, C–H and C–X bond-breaking occur simultaneously when a base abstracts H⁺ from one carbon at the same time the leaving group departs from the neighboring carbon. The reaction takes place preferentially through an **anti periplanar** transition state in which the four reacting atoms—hydrogen, two carbons, and leaving group—are in the same plane. The reaction shows second-order kinetics and a deuterium isotope effect, and occurs when a secondary or tertiary substrate is treated with a strong base. These elimination reactions usually give a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev's rule**).

In the E1 reaction, C–X bond-breaking occurs first. The substrate dissociates to yield a carbocation in the slow rate-limiting step before losing H⁺ from an adjacent carbon in a second step. The reaction shows first-order kinetics and no deuterium isotope effect and occurs when a tertiary substrate reacts in polar, nonbasic solution.

In the E1cB reaction, C–H bond-breaking occurs first. A base abstracts a proton to give an anion, followed by loss of the leaving group from the adjacent carbon in a second step. The reaction is favored when the leaving group is two carbons removed from a carbonyl, which stabilizes the intermediate anion by resonance. Biological elimination reactions typically occur by this E1cB mechanism.

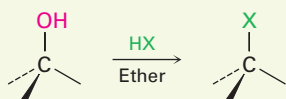
SUMMARY OF REACTIONS

1. Preparation of allylic bromides from alkenes (Section 12-2)



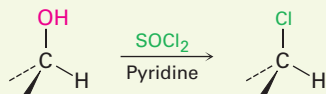
2. Preparation of alkyl halides from alcohols (Section 12-3)

- (a) Reaction with HCl and HBr

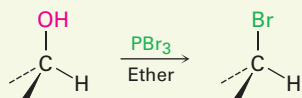


Reactivity order: $3^\circ > 2^\circ > 1^\circ$

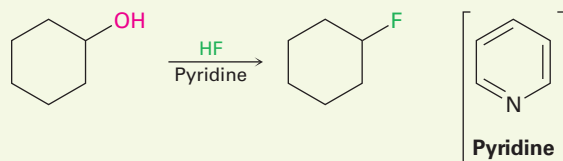
- (b) Reaction of 1° and 2° alcohols with SOCl_2



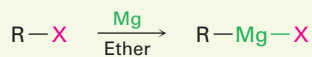
- (c) Reaction of 1° and 2° alcohols with PBr_3



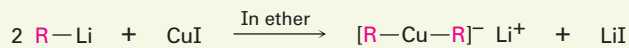
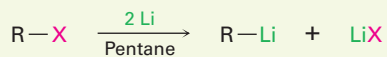
- (d) Reaction of 1° and 2° alcohols with HF–pyridine



3. Formation of Grignard reagents from alkyl halides (Section 12-4)

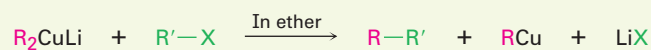


Formation of Gilman (diorganocopper) reagents (Section 12-4)

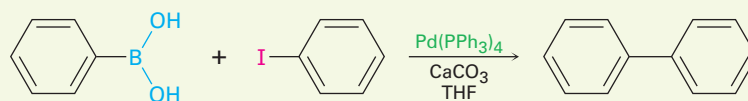


4. Organometallic coupling (Section 12-5)

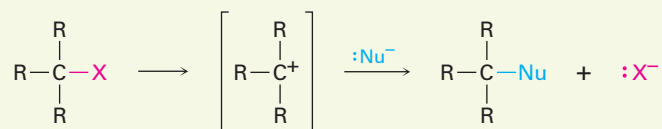
(a) Diorganocopper reaction



(b) Palladium-catalyzed Suzuki–Miyaura reaction

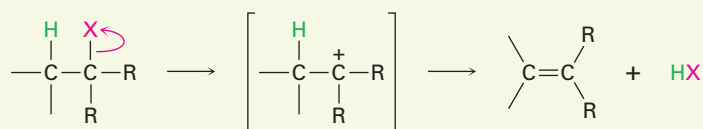


5. Nucleophilic substitutions

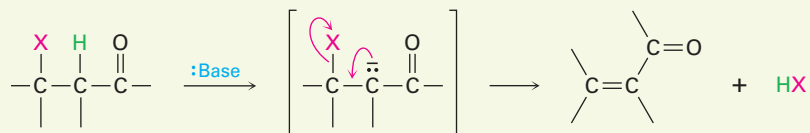
(a) S_N1 reaction of 3°, allylic, and benzylic halides (Sections 12-9 and 12-10)(b) S_N2 reaction of 1° and simple 2° halides (Sections 12-7 and 12-8)

6. Eliminations

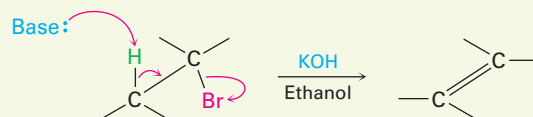
(a) E1 reaction (Section 12-15)



(b) E1cB reaction (Section 12-15)



(c) E2 reaction (Section 12-14)

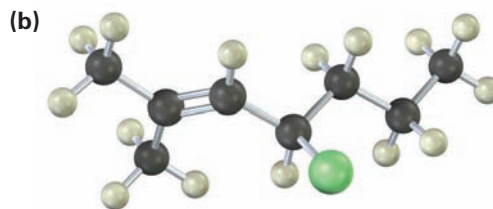
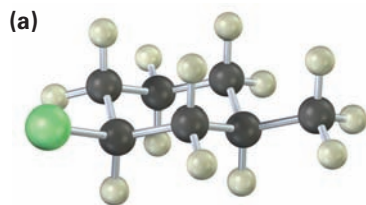


EXERCISES

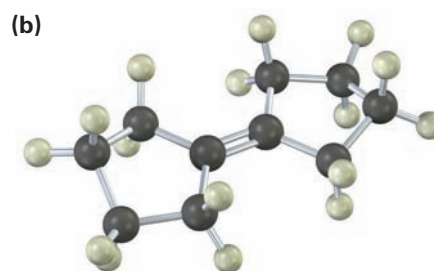
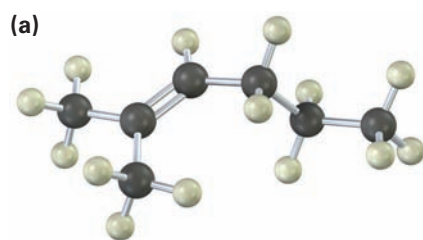
VISUALIZING CHEMISTRY

(Problems 12.1–12.29 appear within the chapter.)

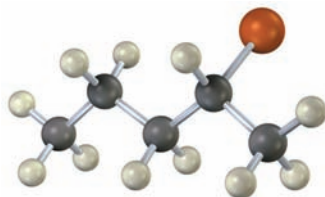
12.30 Give IUPAC names for the following alkyl halides (green = Cl):



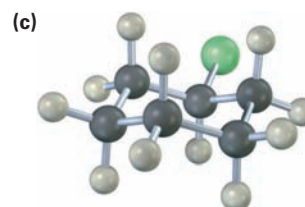
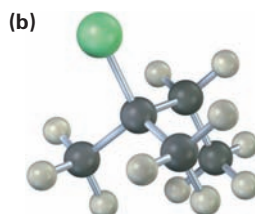
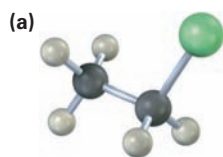
12.31 Show the product(s) of reaction of the following alkenes with NBS:



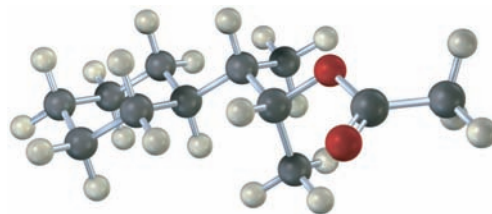
12.32 The following alkyl bromide can be prepared by reaction of the alcohol (*S*)-pentan-2-ol with PBr_3 . Name the compound, assign (*R*) or (*S*) stereochemistry, and tell whether the reaction of the alcohol occurs with retention or inversion of configuration (red-brown = Br).



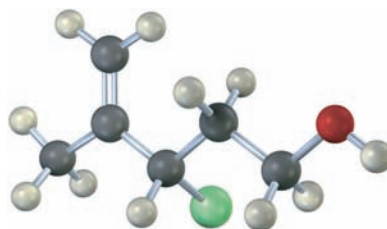
12.33 Write the product you would expect from reaction of each of the following alkyl chlorides with (i) $\text{Na}^+ \text{SCH}_3^-$ and (ii) $\text{Na}^+ \text{OH}^-$:



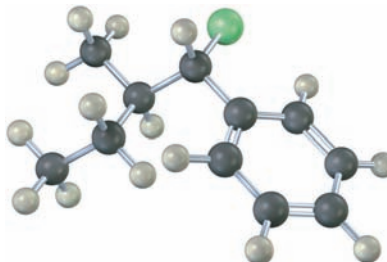
- 12.34 From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing the stereochemistry.



- 12.35 Assign *R* or *S* configuration to the following chloro alcohol, write the product from S_N2 reaction with NaCN, and assign *R* or *S* configuration to the product:



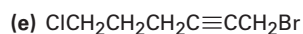
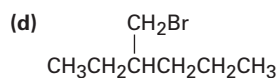
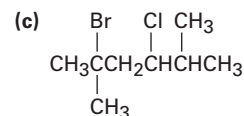
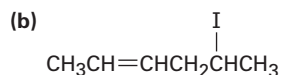
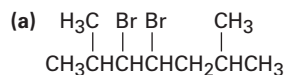
- 12.36 Draw the structure and assign *Z* or *E* stereochemistry to the product you expect from E2 reaction of the following molecule with NaOH:



ADDITIONAL PROBLEMS

Naming Alkyl Halides

- 12.37 Name the following alkyl halides:



12.38 Draw structures corresponding to the following IUPAC names:

- (a) 2,3-Dichloro-4-methylhexane
 (b) 4-Bromo-4-ethyl-2-methylhexane
 (c) 3-Iodo-2,2,4,4-tetramethylpentane
 (d) *cis*-1-Bromo-2-ethylcyclopentane

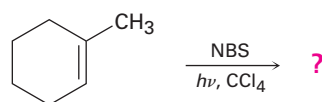
12.39 Draw and name all monochloro derivatives of 2-methylbutane. Which are chiral?

Synthesis and Reactions of Alkyl Halides

12.40 How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

- (a) Chlorocyclopentane (b) Methylcyclopentane
 (c) 3-Bromocyclopentene (d) Cyclopentanol
 (e) Cyclopentylcyclopentane (f) Cyclopenta-1,3-diene

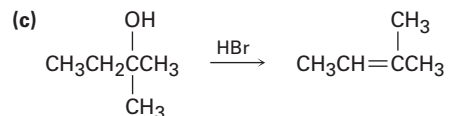
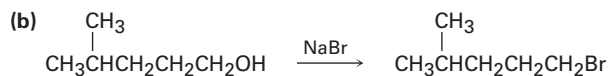
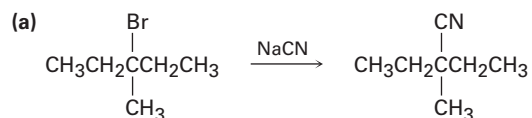
12.41 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS?



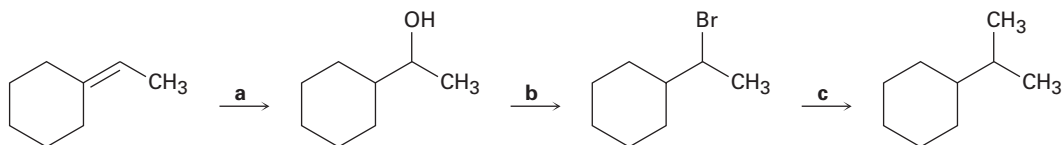
12.42 Predict the product(s) of the following reactions:

- (a) CC1(O)CCCCC1
 $\xrightarrow[\text{Ether}]{\text{HBr}}$
?
- (b) CCCCO
 $\xrightarrow{\text{SOCl}_2}$
?
- (c) C1=CCCCC1
 $\xrightarrow[h\nu, \text{CCl}_4]{\text{NBS}}$
?
- (d) OC1CCCCC1
 $\xrightarrow[\text{Ether}]{\text{PBr}_3}$
?
- (e) CC(C)CBr
 $\xrightarrow[\text{Ether}]{\text{Mg}}$
A?
 $\xrightarrow{\text{H}_2\text{O}}$
B?
- (f) CCCCBr
 $\xrightarrow[\text{Pentane}]{\text{Li}}$
A?
 $\xrightarrow{\text{CuI}}$
B?
- (g) CCCCBr + (CH3)2CuLi
 $\xrightarrow{\text{Ether}}$
?

12.43 None of the following reactions take place as written. What is wrong with each?



12.44 Identify the reagents **a–c** in the following scheme:



Nucleophilic Substitution Reactions

12.45 Which compound in each of the following pairs will react faster in an S_N2 reaction with OH^- ?

- (a) CH_3Br or CH_3I
 (b) $\text{CH}_3\text{CH}_2\text{I}$ in ethanol or in dimethyl sulfoxide
 (c) $(\text{CH}_3)_3\text{CCl}$ or CH_3Cl
 (d) $\text{H}_2\text{C}=\text{CHBr}$ or $\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$

12.46 What effect would you expect the following changes to have on the rate of the S_N2 reaction of 1-iodo-2-methylbutane with cyanide ion?

- (a) The CN^- concentration is halved, and the 1-iodo-2-methylbutane concentration is doubled.
 (b) Both the CN^- and the 1-iodo-2-methylbutane concentrations are tripled.

12.47 What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?

- (a) The concentration of the halide is tripled.
 (b) The concentration of the ethanol is halved by adding diethyl ether as an inert solvent.

12.48 How might you prepare each of the following molecules using a nucleophilic substitution reaction at some step?



12.49 Which reaction in each of the following pairs would you expect to be faster?

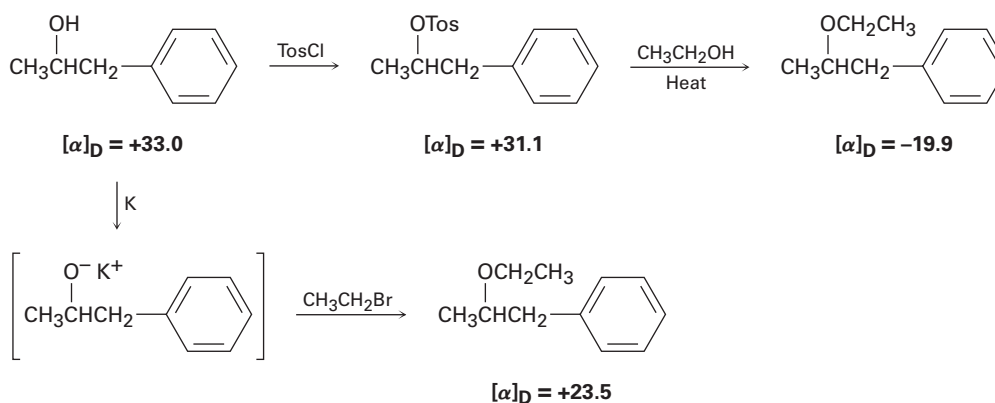
(a) The $\text{S}_{\text{N}}2$ displacement by I^- on CH_3Cl or on CH_3OTos

(b) The $\text{S}_{\text{N}}2$ displacement by CH_3CO_2^- on bromoethane or on bromocyclohexane

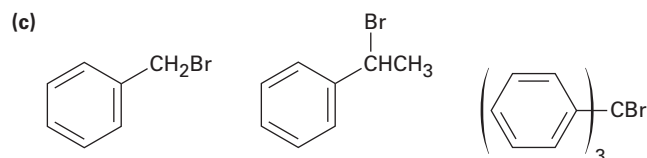
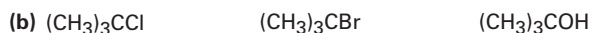
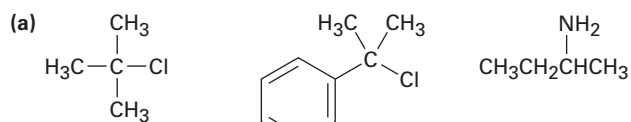
(c) The $\text{S}_{\text{N}}2$ displacement on 2-bromopropane by $\text{CH}_3\text{CH}_2\text{O}^-$ or by CN^-

(d) The $\text{S}_{\text{N}}2$ displacement by HS^- on bromomethane in toluene or in acetonitrile

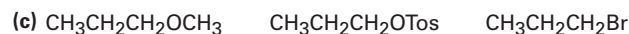
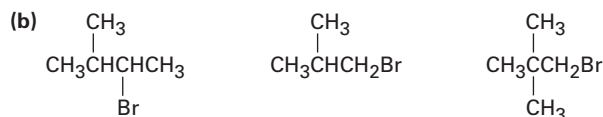
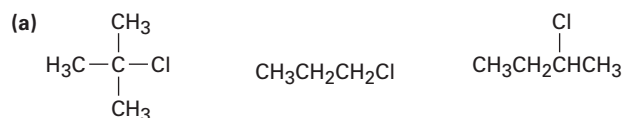
12.50 The following Walden cycle has been carried out. Explain the results, and indicate where Walden inversion is occurring.



12.51 Order each of the following sets of compounds with respect to $\text{S}_{\text{N}}1$ reactivity:



12.52 Order each of the following sets of compounds with respect to S_N2 reactivity:

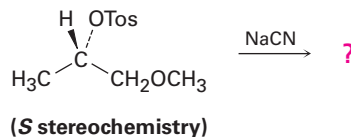


12.53 Predict the product and give the stereochemistry resulting from reaction of each of the following nucleophiles with (*R*)-2-bromooctane:



12.54 (*R*)-2-Bromooctane undergoes racemization to give (\pm)-2-bromooctane when treated with NaBr in dimethyl sulfoxide. Explain.

12.55 Reaction of the following *S* tosylate with cyanide ion yields a nitrile product that also has *S* stereochemistry. Explain.



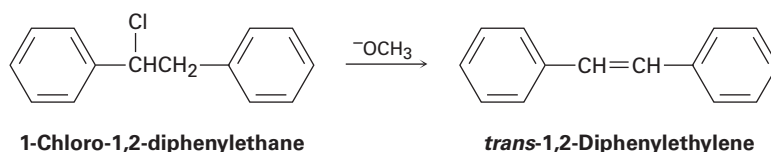
12.56 The S_N2 reaction can occur *intramolecularly* (within the same molecule). What product would you expect from treatment of 4-bromobutan-1-ol with base?

Elimination Reactions

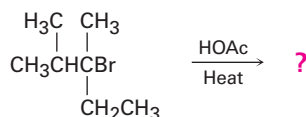
12.57 Propose structures for compounds that fit the following descriptions:

- An alkyl halide that gives a mixture of three alkenes on E2 reaction
- An organic halide that will not undergo nucleophilic substitution
- An alkyl halide that gives the non-Zaitsev product on E2 reaction
- An alcohol that reacts rapidly with HCl at 0 °C

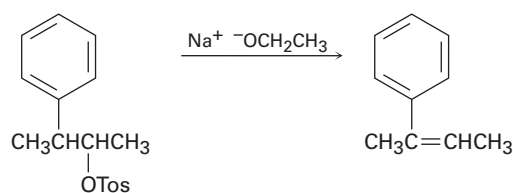
- 12.58 1-Chloro-1,2-diphenylethane can undergo E2 elimination to give either *cis*- or *trans*-1,2-diphenylethylene (stilbene). Draw Newman projections of the reactive conformations leading to both possible products, and suggest a reason why the *trans* alkene is the major product.



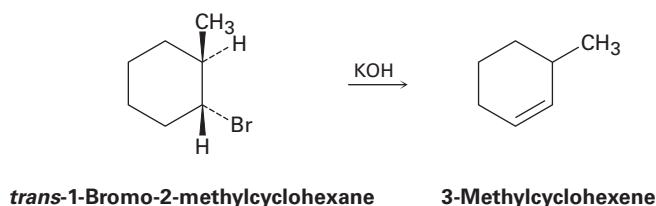
- 12.59 Predict the major alkene product of the following E1 reaction:



- 12.60 The tosylate of (2*R*,3*S*)-3-phenylbutan-2-ol undergoes E2 elimination on treatment with sodium ethoxide to yield (*Z*)-2-phenylbut-2-ene. Explain, using Newman projections.



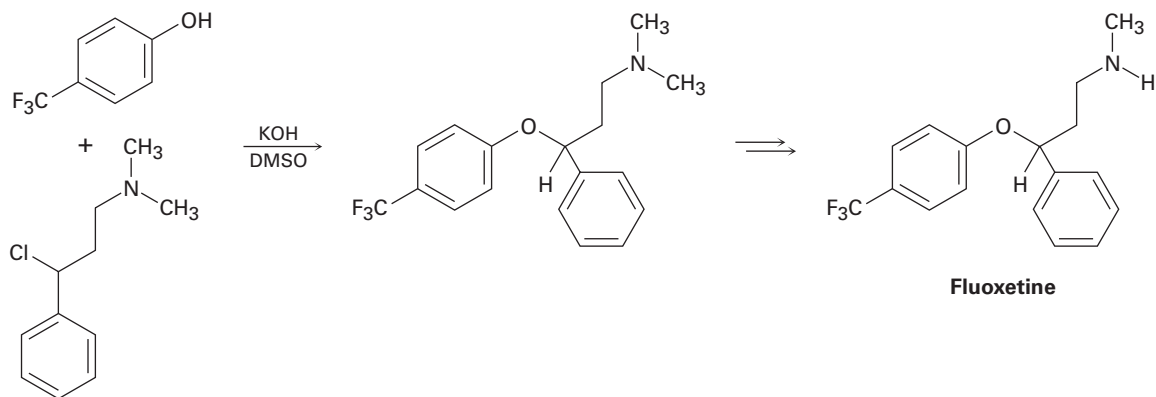
- 12.61 In light of your answer to Problem 12.60, which alkene, *E* or *Z*, would you expect from an E2 reaction on the tosylate of (2*R*,3*R*)-3-phenylbutan-2-ol? Which alkene would result from E2 reaction on the (2*S*,3*R*) and (2*S*,3*S*) tosylates? Explain.
- 12.62 How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?



- 12.63 There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

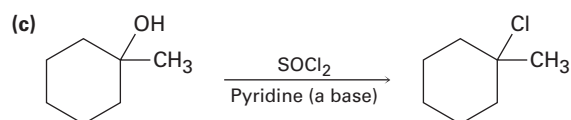
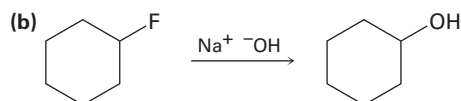
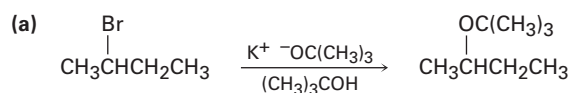
General Problems

12.64 The antidepressant fluoxetine, marketed as Prozac, can be prepared by a sequence of steps that involves the substitution reaction of an alkyl chloride with a phenol, using a base to convert the phenol into its phenoxide anion.

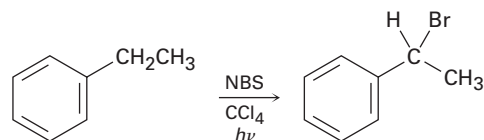


- (a) Identify the nucleophile and electrophile in the reaction.
- (b) The rate of the substitution reaction depends on concentrations of both the alkyl chloride and phenol. Is this an S_N1 or an S_N2 reaction?
- (c) The physiologically active enantiomer of fluoxetine has (*S*) stereochemistry. Based on your answer in part (b), draw the structure of the alkyl chloride showing the correct stereochemistry.

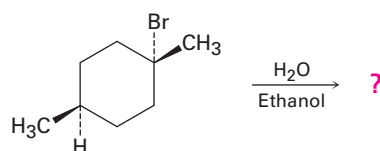
12.65 The following reactions are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.



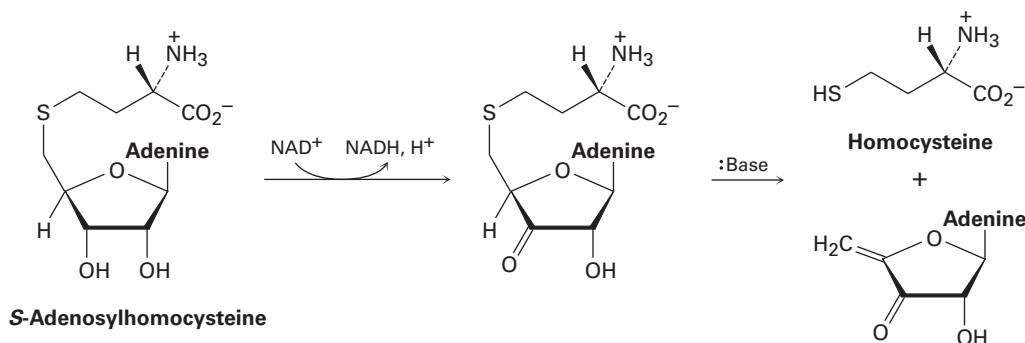
12.66 Arenes such as ethylbenzene react with NBS to give products in which bromine substitution has occurred at the benzylic position. Explain the result, and propose a mechanism.



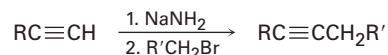
- 12.67 Predict the product(s) of the following reaction, indicating stereochemistry:



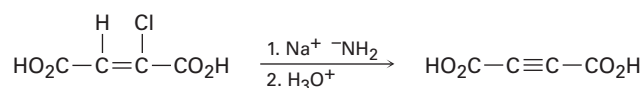
- 12.68 Metabolism of *S*-adenosylhomocysteine (Section 12-11) involves the following steps. Propose mechanisms for both.



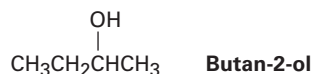
- 12.69 Reaction of iodoethane with CN^- yields a small amount of *isonitrile*, $\text{CH}_3\text{CH}_2\text{N}\equiv\text{C}$, along with the nitrile $\text{CH}_3\text{CH}_2\text{C}\equiv\text{N}$ as the major product. Write electron-dot structures for both products, and propose mechanisms to account for their formation.
- 12.70 Internal alkynes can be made from terminal alkynes by converting the terminal alkyne to an acetylide anion and then treating the anion with a primary alkyl halide. Propose a mechanism for the alkylation. (See Section 8-15.)



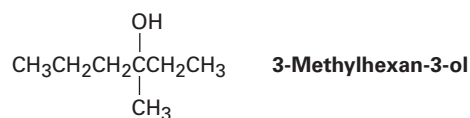
- 12.71 Alkynes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (*Z*)-2-chlorobut-2-enedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?



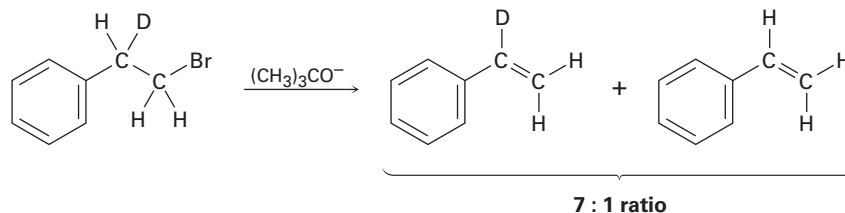
- 12.72 (*S*)-Butan-2-ol slowly racemizes on standing in dilute sulfuric acid. Explain.



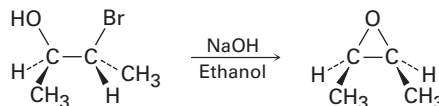
- 12.73** Reaction of HBr with (*R*)-3-methylhexan-3-ol leads to racemic 3-bromo-3-methylhexane. Explain.



- 12.74** Treatment of 1-bromo-2-deuterio-2-phenylethane with strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in a ratio of approximately 7 : 1. Explain.

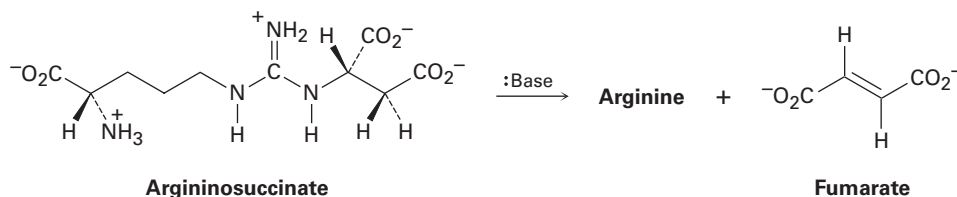


- 12.75** We saw in Section 8-3 that an alkene can be converted into a bromohydrin on treatment with Br₂ in the presence of water. When the bromohydrin is then treated with base, an epoxide is formed. Propose a mechanism for the epoxide formation, using curved arrows to show the electron flow.



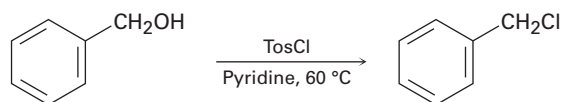
- 12.76** Show the stereochemistry of the epoxide (Problem 12.75) you would obtain by formation of a bromohydrin from *trans*-but-2-ene, followed by treatment with base.

- 12.77** One step in the urea cycle for ridding the body of ammonia is the conversion of argininosuccinate to the amino acid arginine plus fumarate. Propose a mechanism for the reaction, and show the structure of arginine.

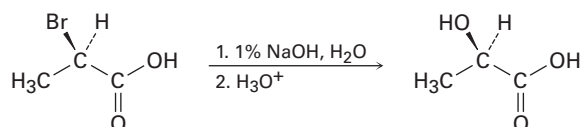


- 12.78** Propose a structure, including stereochemistry, for an alkyl halide that gives only (*E*)-3-methyl-2-phenylpent-2-ene on E2 elimination.

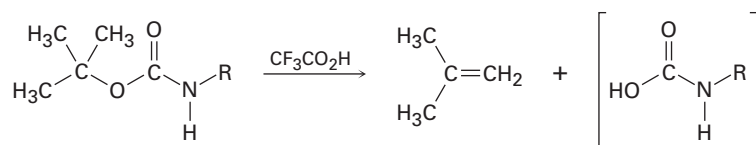
- 12.79 When a primary alcohol is treated with *p*-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at higher temperature, an alkyl chloride is often formed. Explain.



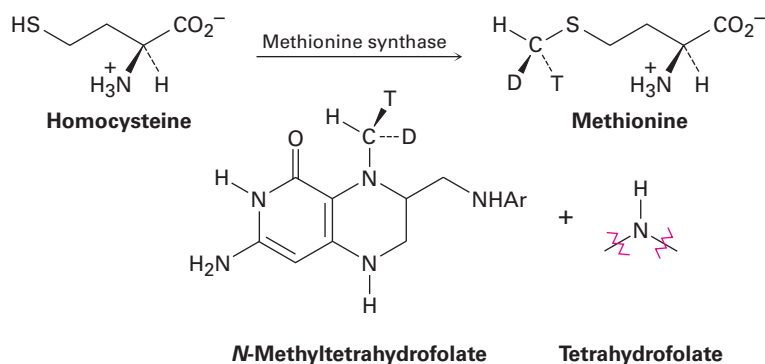
- 12.80 S_N2 reactions take place with inversion of configuration, and S_N1 reactions take place with racemization. The following substitution reaction, however, occurs with complete *retention* of configuration. Propose a mechanism.



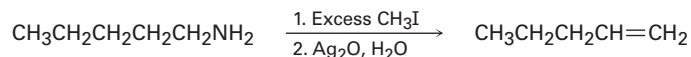
- 12.81 Propose a mechanism for the following reaction, an important step in the laboratory synthesis of proteins:



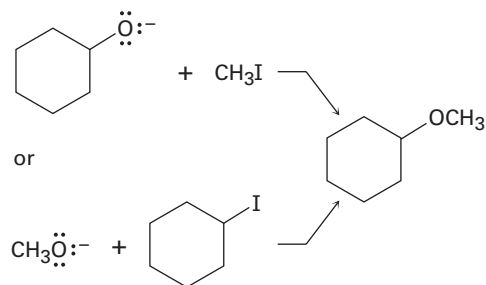
- 12.82 The amino acid methionine is formed by a methylation reaction of homocysteine with *N*-methyltetrahydrofolate. The stereochemistry of the reaction has been probed by carrying out the transformation using a donor with a “chiral methyl group” that contains protium (H), deuterium (D), and tritium (T) isotopes of hydrogen. Does the methylation reaction occur with inversion or retention of configuration? How might you explain this result?



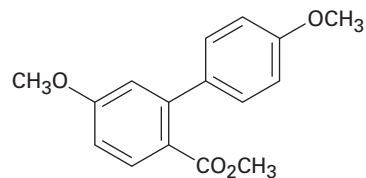
- 12.83** Amines are converted into alkenes by a two-step process called the *Hofmann elimination*. Reaction of the amine with excess CH_3I in the first step yields an intermediate that undergoes E2 reaction when treated with basic silver oxide. Pentylamine, for example, yields pent-1-ene. Propose a structure for the intermediate, and explain why it undergoes ready elimination.



- 12.84** Ethers can often be prepared by $\text{S}_{\text{N}}2$ reaction of alkoxide ions, RO^- , with alkyl halides. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the two possible routes shown below would you choose?



- 12.85** How might you use a Suzuki–Miyaura coupling to prepare the following biaryl compound? Show the two potential reaction routes.



Alcohols, Phenols, and Thiols; Ethers and Sulfides

13



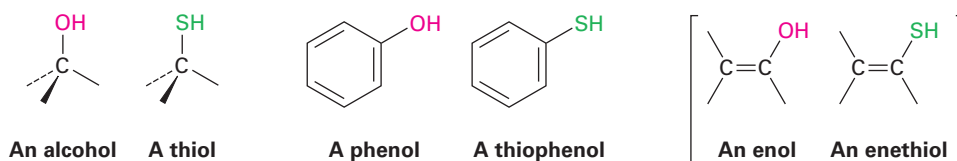
Liver alcohol dehydrogenase catalyzes the oxidation of ethanol to acetaldehyde.

WHY THIS CHAPTER?

Up to this point, we've focused on developing some general ideas about organic reactivity, on looking at the chemistry of hydrocarbons and alkyl halides, and on seeing some of the tools used in structural studies. With that background, it's now time to begin a study of the oxygen-containing functional groups that lie at the heart of organic and biological chemistry. To understand the chemistry of living organisms, it's necessary to understand oxygen-containing functional groups. We'll look at compounds with C–O and C–S single bonds in this chapter and then move on to carbonyl (C=O) compounds in Chapters 14–17.

Alcohols, phenols, and ethers can be thought of as organic derivatives of water in which one or both of the water hydrogens is replaced by an organic group: H–O–H versus R–O–H, Ar–O–H, and R–O–R'. **Thiols and sulfides** are the corresponding sulfur analogs, R–S–H and R–S–R', respectively.

In practice, the names *alcohol* and *thiol* are restricted to compounds that have their –OH or –SH group bonded to a saturated, sp^3 -hybridized carbon atom. Compounds with their –OH or –SH bonded to an aromatic ring are called *phenols* (Section 9-1) and *thiophenols*, while compounds with the –OH or –SH group bonded to a vinylic, sp^2 -hybridized carbon are called *enols* and *enethiols*. We'll look in detail at the chemistry of enols in Chapter 17.



Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 40 million metric tons (13 billion gallons) of methanol is

CONTENTS

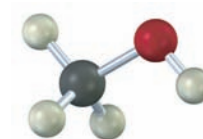
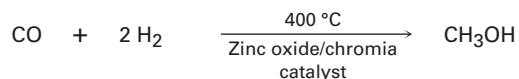
- 13-1** Naming Alcohols, Phenols, and Thiols
- 13-2** Properties of Alcohols, Phenols, and Thiols
- 13-3** Preparing Alcohols from Carbonyl Compounds
- 13-4** Reactions of Alcohols
- 13-5** Oxidation of Alcohols and Phenols
- 13-6** Protection of Alcohols
- 13-7** Preparation and Reactions of Thiols
- 13-8** Ethers and Sulfides
- 13-9** Preparing Ethers
- 13-10** Reactions of Ethers
- 13-11** Crown Ethers and Ionophores
- 13-12** Preparation and Reactions of Sulfides
- 13-13** Spectroscopy of Alcohols, Phenols, and Ethers

SOMETHING EXTRA

Ethanol: Chemical, Drug, Poison



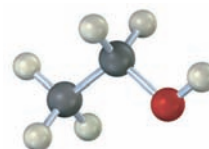
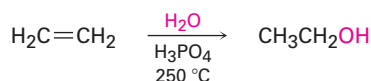
manufactured worldwide each year, most of it by catalytic reduction of carbon monoxide with hydrogen.



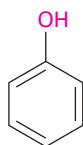
Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid ($\text{CH}_3\text{CO}_2\text{H}$).

Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Approximately 67 million metric tons (22 billion gallons) of ethanol is now produced worldwide each year, most of it by fermentation of corn, barley, sorghum, and other plant materials. Essentially the entire amount is used for automobile fuel.

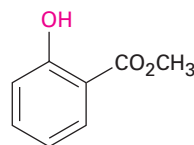
Ethanol for industrial use as a solvent or chemical intermediate is largely obtained by acid-catalyzed hydration of ethylene at high temperature.



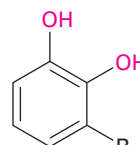
Phenols occur widely in living organisms and are intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar, methyl salicylate is a flavoring agent found in oil of wintergreen, and the urushiols are the allergenic constituents of poison oak and poison ivy. Note that the word *phenol* is the name both of the specific compound (hydroxybenzene) and of a class of compounds.



Phenol
(also known as
carbolic acid)



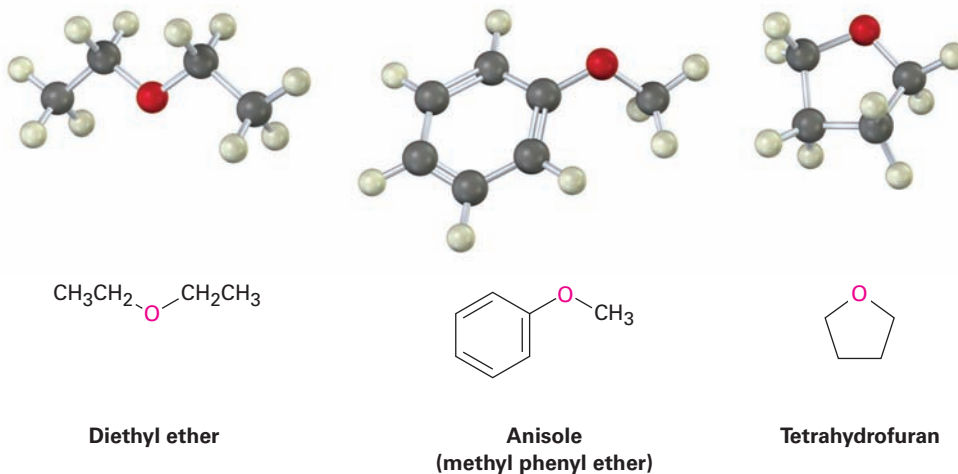
Methyl salicylate



Urushiols
(R = different C_{15} alkyl
and alkenyl chains)

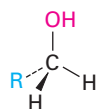
Perhaps the most well-known ether is diethyl ether, which has a long history of medical use as an anesthetic and industrial use as a solvent. Other useful ethers include anisole, a pleasant-smelling aromatic ether used in perfumery, and tetrahydrofuran (THF), a cyclic ether often used as a solvent.

Thiols and sulfides are found in various biomolecules, although not as commonly as their oxygen-containing relatives.

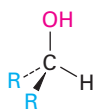


13-1 Naming Alcohols, Phenols, and Thiols

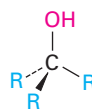
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol



A tertiary (3°) alcohol

Simple alcohols are named in the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*:

Rule 1

Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

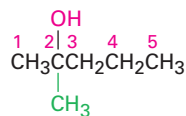
Rule 2

Number the alkane chain beginning at the end nearer the hydroxyl group.

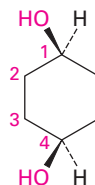
Rule 3

Number the substituents according to their position on the chain and write the name, listing the substituents in alphabetical order and identifying the position to which the -OH is bonded. Note that in naming *cis*-cyclohexane-1,4-diol, the final *-e* of cyclohexane is not deleted because the next letter, *d*, is not a vowel; that is, cyclohexanediol rather than cyclohexandiol. As with

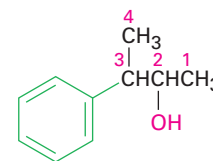
alkenes (Section 7-2), newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.



2-Methylpentan-2-ol
(Old: **2-Methyl-2-pentanol**)

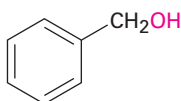


cis-Cyclohexane-1,4-diol
(Old: **cis-1,4-cyclohexanediol**)



3-Phenylbutan-2-ol
(Old: **3-Phenyl-2-butanol**)

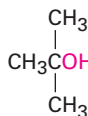
Some simple and widely occurring alcohols also have common names that are accepted by IUPAC. For example:



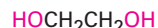
Benzyl alcohol
(phenylmethanol)



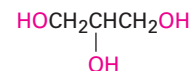
Allyl alcohol
(prop-2-en-1-ol)



tert-Butyl alcohol
(2-methylpropan-2-ol)

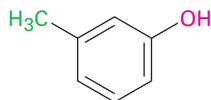


Ethylene glycol
(ethane-1,2-diol)



Glycerol
(propane-1,2,3-triol)

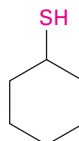
Phenols are named as described previously in Section 9-1 for aromatic compounds. Thiols are named by the same system used for alcohols, with the suffix *-thiol* in place of *-ol*. The $-\text{SH}$ group itself is sometimes referred to as a **mercapto group**, and thiols are sometimes called *mercaptans*.



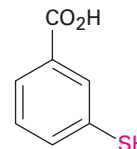
m-Methylphenol
(*m*-Cresol)



Ethanethiol



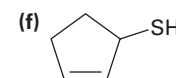
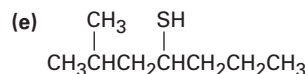
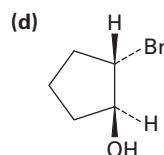
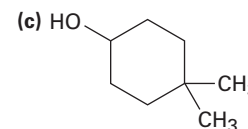
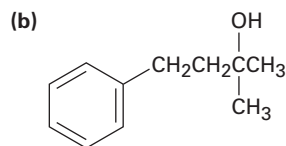
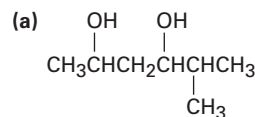
Cyclohexanethiol



m-Mercaptobenzoic acid

PROBLEM 13.1

Give IUPAC names for the following compounds:



PROBLEM 13.2

Draw structures corresponding to the following IUPAC names:

- (a) 2-Ethylbut-2-en-1-ol (b) Cyclohex-3-en-1-ol
 (c) *trans*-3-Chlorocycloheptanol (d) Pentane-1,4-dithiol
 (e) 2,4-Dimethylphenol (f) *o*-(2-Hydroxyethyl)phenol

13-2 Properties of Alcohols, Phenols, and Thiols

Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The C–O–H bond angle has an approximately tetrahedral value (108.5° in methanol, for instance), and the oxygen atom is sp^3 -hybridized. Thiols have a more compressed C–S–H bond angle (96.5° in methanethiol).

Also like water, alcohols and phenols have higher boiling points than might be expected because of hydrogen-bonding (Section 2-12). A positively polarized –OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together (FIGURE 13.1). These intermolecular attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. Thiols do not typically form hydrogen bonds because sulfur is not sufficiently electronegative.

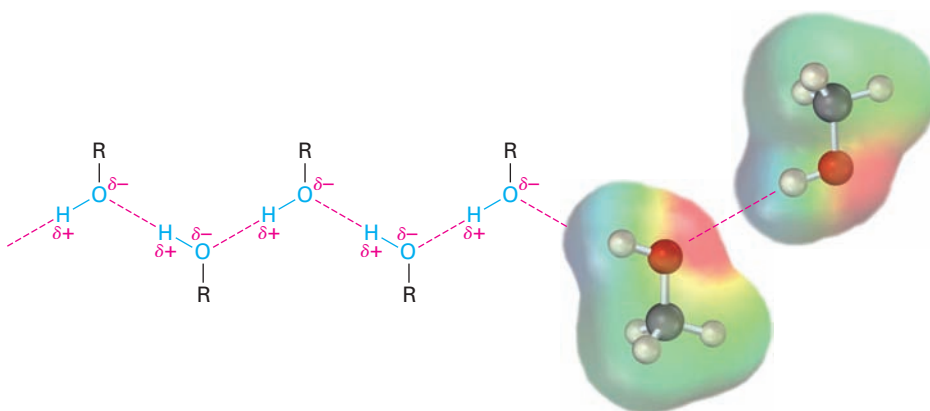
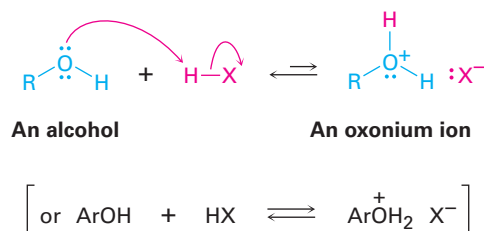


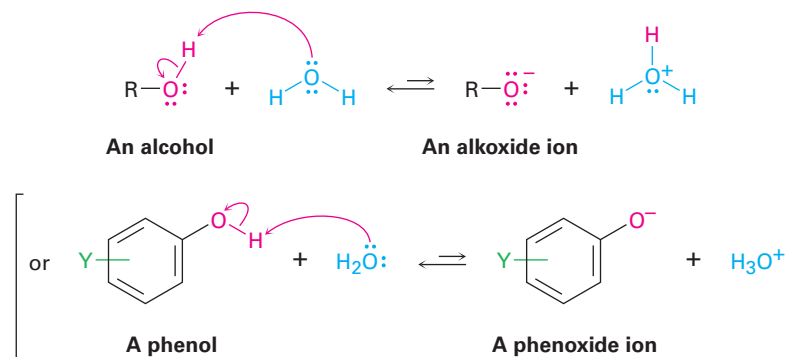
FIGURE 13.1 Hydrogen-bonding in alcohols and phenols.

Attraction between a positively polarized OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the **positively polarized O–H hydrogen** and the **negatively polarized oxygen**.

Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+ :



As weak acids, they dissociate slightly in dilute aqueous solution by donating a proton to water, generating H_3O^+ and an **alkoxide ion**, RO^- , or a **phenoxide ion**, ArO^- .



Recall from the earlier discussion of acidity in Sections 2-8-2-10 that the strength of any acid HA in water can be expressed by an acidity constant, K_a :

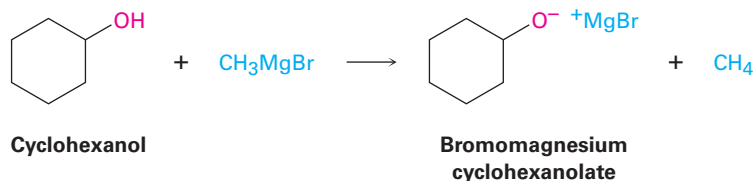
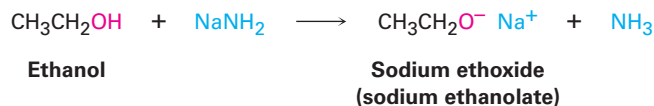
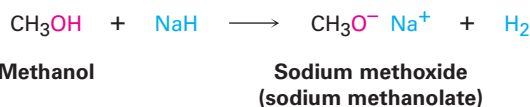
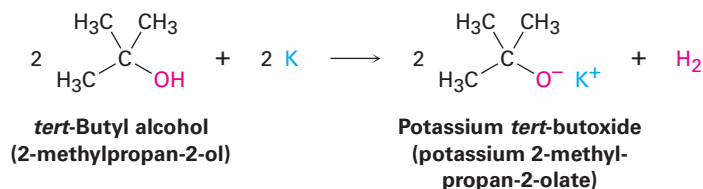
$$K_a = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]} \quad \text{p}K_a = -\log K_a$$

Compounds with a smaller K_a and larger $\text{p}K_a$ are less acidic, whereas compounds with a larger K_a and smaller $\text{p}K_a$ are more acidic. As shown by the data in **TABLE 13.1**, simple alcohols like methanol and ethanol are very close to water in acidity, but the more highly substituted *tert*-butyl alcohol is somewhat weaker. Both phenols and thiols are substantially more acidic than water.

TABLE 13.1 Acidity Constants of Some Alcohols, Phenols, and Thiols			
Compound	$\text{p}K_a$		
$(\text{CH}_3)_3\text{COH}$	18.00	Weaker acid	
$\text{CH}_3\text{CH}_2\text{OH}$	16.00		
H_2O	15.74		
CH_3OH	15.54		
CH_3SH	10.3		
<i>p</i> -Methylphenol	10.17		
Phenol	9.89		
<i>p</i> -Chlorophenol	9.38		
<i>p</i> -Nitrophenol	7.15		Stronger acid

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Because alcohols are weak acids, they don't react with weak bases, such as amines or bicarbonate ion, and they react to only a limited extent with metal hydroxides, such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide (NaNH₂), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.



Phenols and thiols are about a million times more acidic than alcohols (Table 13.1). Both are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture by basic extraction into aqueous solution, followed by reacidification. Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. Delocalization of the negative charge over the ortho and para positions of the aromatic ring results in increased stability of the phenoxide anion relative to undissociated phenol and in a consequently lower ΔG° for dissociation.

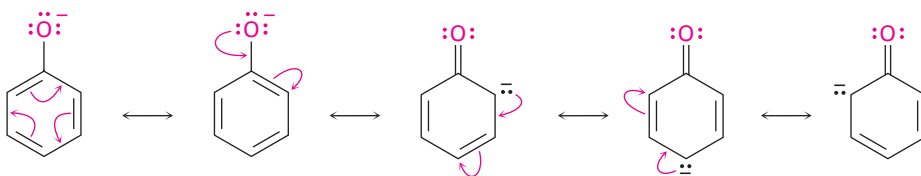
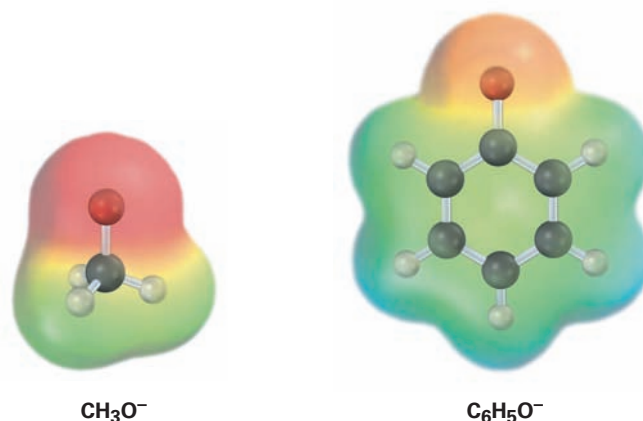
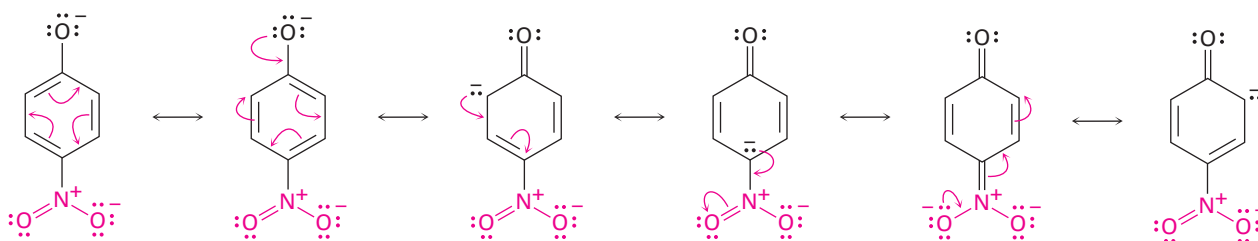


FIGURE 13.2 compares electrostatic potential maps of an alkoxide ion (CH₃O⁻) with phenoxide ion and shows how the negative charge in phenoxide ion is delocalized from oxygen to the ring.

FIGURE 13.2 Comparison of the resonance-stabilized phenoxide ion and an alkoxide ion. Electrostatic potential maps show how the **negative charge** is concentrated on oxygen in the methoxide ion but is spread over the aromatic ring in the phenoxide ion. As a result, the phenoxide ion is more stable.



Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-withdrawing or electron-donating (Section 9-8). Phenols with an electron-withdrawing substituent are more acidic because these substituents delocalize the negative charge; phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge. The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.



WORKED EXAMPLE 13.1

Predicting the Relative Acidity of a Substituted Phenol

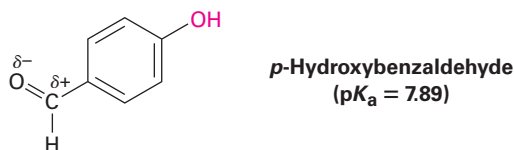
Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy

Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution

We saw in Section 9-8 that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde ($\text{p}K_{\text{a}} = 7.89$) is more acidic than phenol ($\text{p}K_{\text{a}} = 9.89$).



PROBLEM 13.3

Rank the following substances in order of increasing acidity:

- (a) Phenol, *p*-methylphenol, *p*-(trifluoromethyl)phenol
 (b) Benzyl alcohol, phenol, *p*-hydroxybenzoic acid

PROBLEM 13.4

p-Nitrobenzyl alcohol is more acidic than benzyl alcohol, but *p*-methoxybenzyl alcohol is less acidic. Explain.

PROBLEM 13.5

Which would you expect to be more acidic, methanethiol or thiophenol, C₆H₅SH? Explain.

13-3 Preparing Alcohols from Carbonyl Compounds

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of products (FIGURE 13.3).

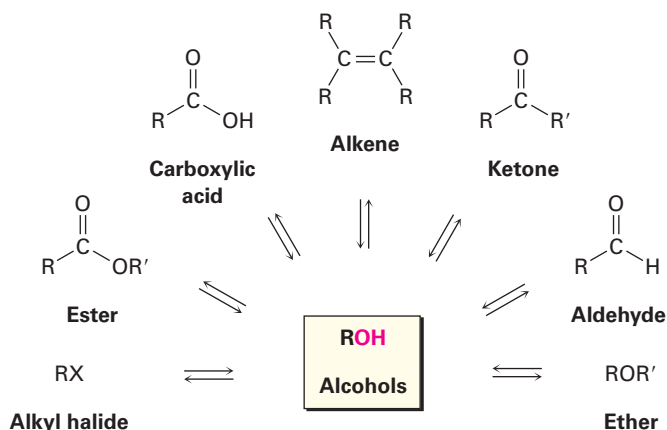
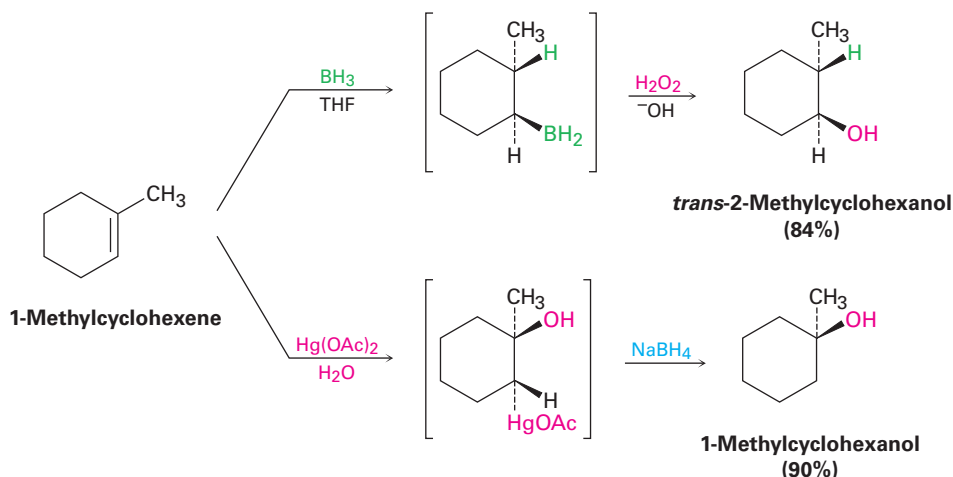


FIGURE 13.3 The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

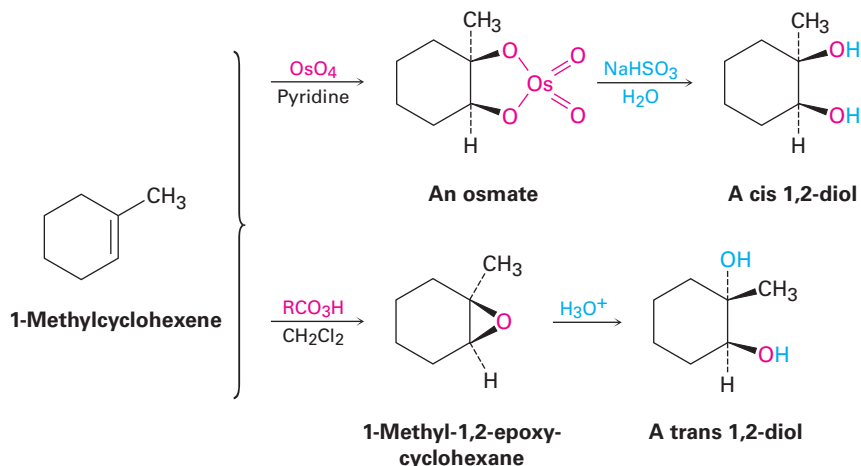
We've already seen several methods of alcohol synthesis:

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration-oxidation yields the product of syn, non-Markovnikov hydration, whereas

oxymercuration–demercuration yields the product of Markovnikov hydration (Section 8-4).

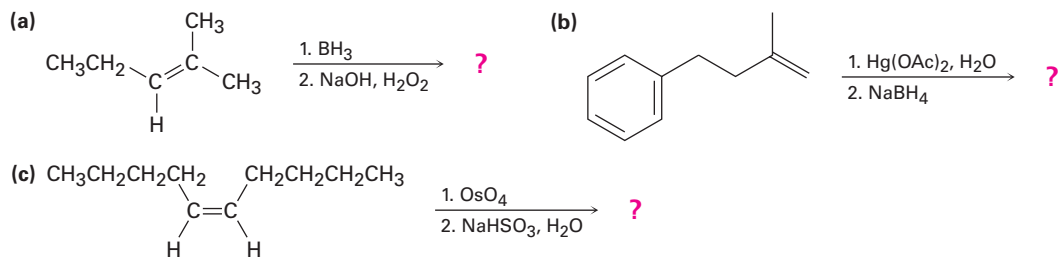


- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with NaHSO_3 or by acid-catalyzed hydrolysis of an epoxide (Section 8-7). The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.



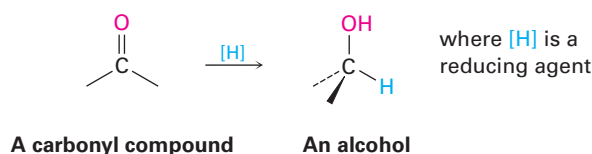
PROBLEM 13.6

Predict the products of the following reactions:

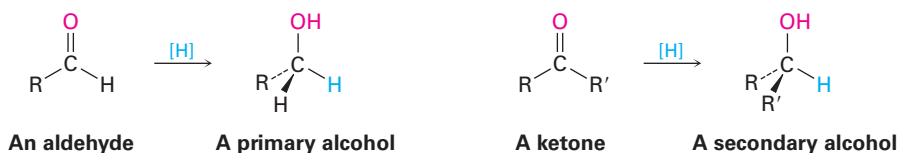


Reduction of Carbonyl Compounds

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane (Section 8-5), reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.

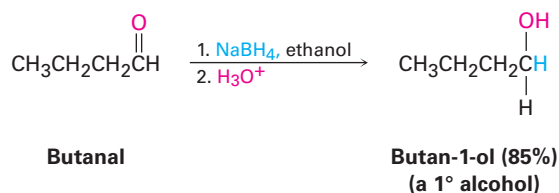


REDUCTION OF ALDEHYDES AND KETONES Aldehydes are reduced to give primary alcohols, and ketones are reduced to give secondary alcohols:

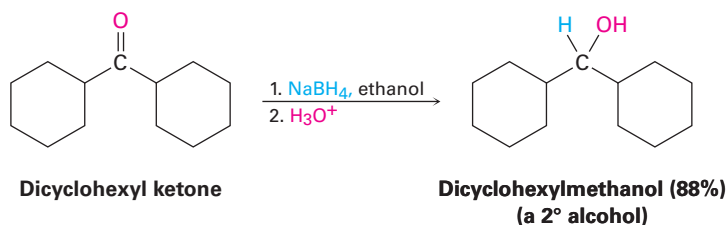


Dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, NaBH₄, is usually chosen because of its safety and ease of handling. Sodium borohydride is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

Aldehyde reduction

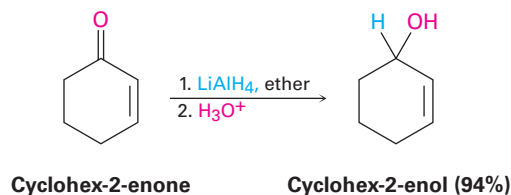


Ketone reduction

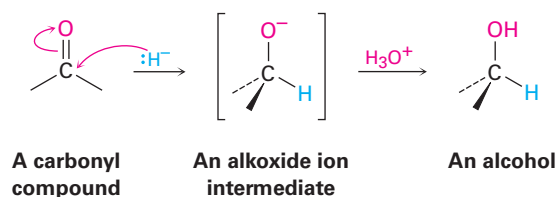


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Lithium aluminum hydride, LiAlH_4 , is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, LiAlH_4 is much more reactive than NaBH_4 but also more dangerous. It reacts violently with water and decomposes explosively when heated above 120°C .

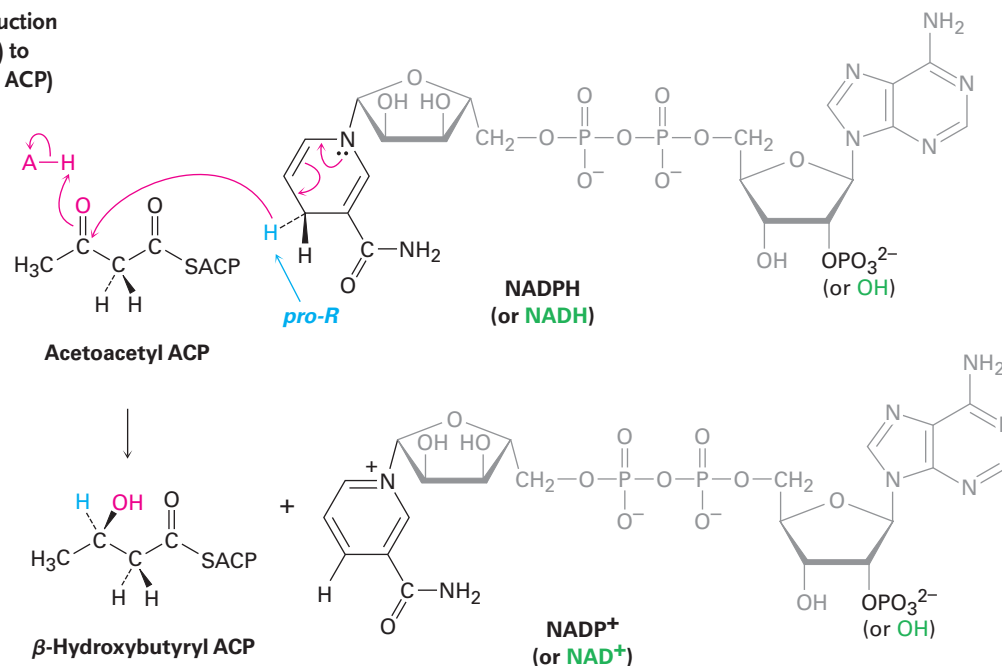


We'll defer a detailed discussion of the mechanisms of these reductions until Section 14-6. For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion ($:\text{H}^-$) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



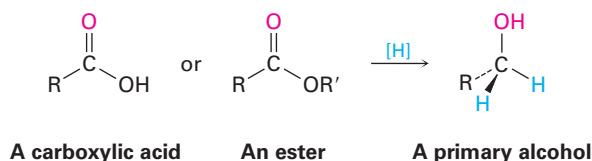
In living organisms, aldehyde and ketone reductions are often carried out by either of the coenzymes NADH (reduced nicotinamide adenine dinucleotide) or NADPH (reduced nicotinamide adenine dinucleotide phosphate) (**FIGURE 13.4**).

FIGURE 13.4 Biological reduction of a ketone (acetoacetyl ACP) to an alcohol (β -hydroxybutyryl ACP) by NADPH.



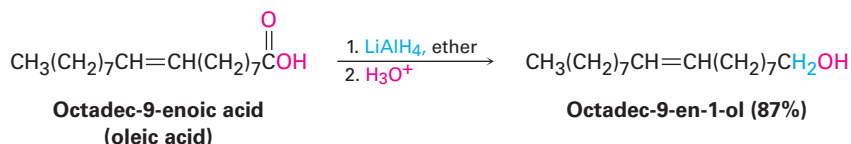
Although these biological “reagents” are substantially more complex than NaBH_4 or LiAlH_4 , the mechanisms of laboratory and biological reactions are similar. The coenzyme acts as a hydride-ion donor to give an alkoxide anion, and the intermediate anion is then protonated by acid. An example is the reduction of acetoacetyl ACP to β -hydroxybutyryl ACP, a step in the biological synthesis of fats. Note that the *pro-R* hydrogen of NADPH is the one transferred in this example. Enzyme-catalyzed reactions usually occur with high specificity, although it’s not usually possible to predict the stereochemical result before the fact.

REDUCTION OF CARBOXYLIC ACIDS AND ESTERS Carboxylic acids and esters are reduced to give primary alcohols.

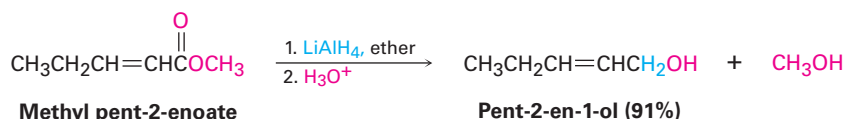


These reactions aren’t as rapid as the reductions of aldehydes and ketones. NaBH_4 reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent LiAlH_4 . All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by LiAlH_4 . Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions. We’ll defer a discussion of the mechanisms of these reactions until Chapter 16.

Carboxylic acid reduction



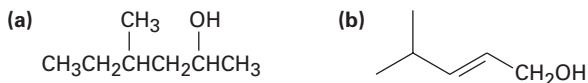
Ester reduction



Identifying a Reactant, Given the Product

WORKED EXAMPLE 13.2

What carbonyl compounds would you reduce to obtain the following alcohols?

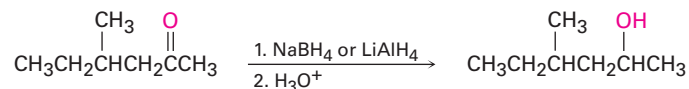


Strategy

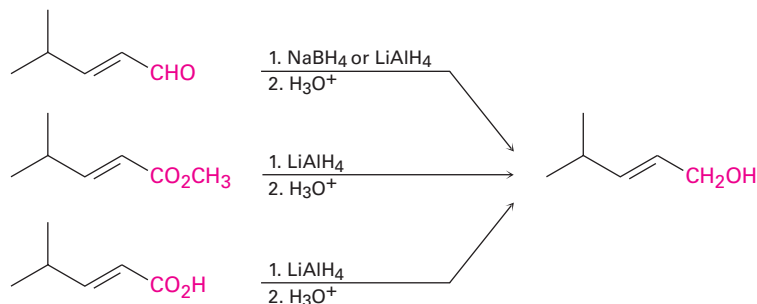
Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

Solution

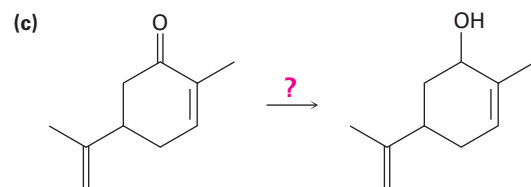
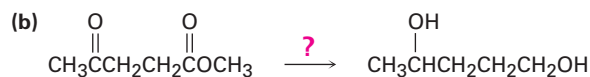
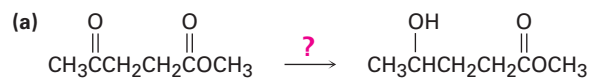
- (a) The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either NaBH_4 or LiAlH_4 can be used.



- (b) The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. LiAlH_4 rather than NaBH_4 is needed for the ester and carboxylic acid reductions.

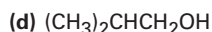
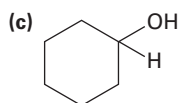
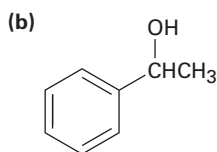
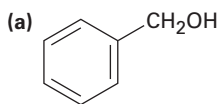
**PROBLEM 13.7**

What reagent would you use to accomplish each of the following reactions?



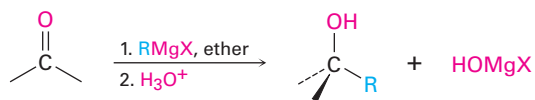
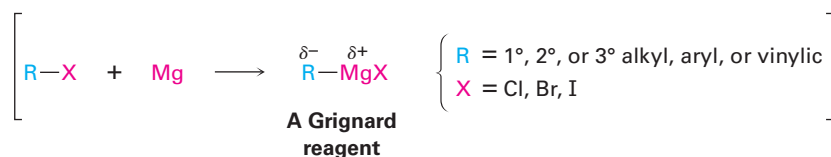
PROBLEM 13.8

What carbonyl compounds give the following alcohols on reduction with LiAlH_4 ? Show all possibilities.



Grignard Reactions of Carbonyl Compounds

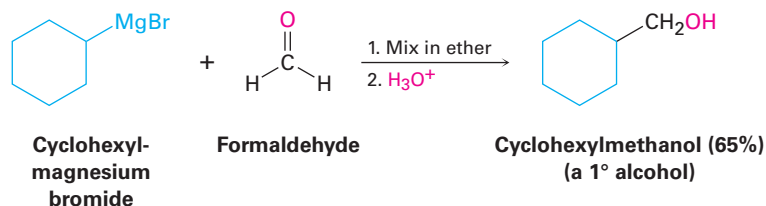
Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 12-4), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the $\text{C}=\text{O}$ bond, Grignard reaction involves addition of a carbanion nucleophile ($\text{R}^- + \text{MgX}$).



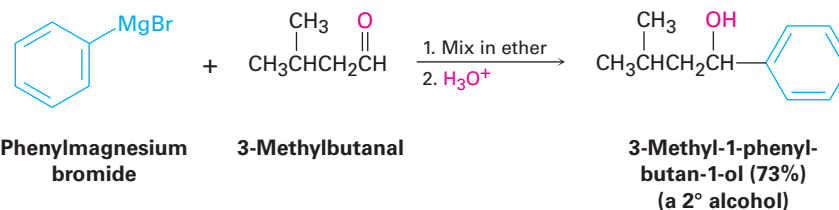
The reaction of Grignard reagents with carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth knowing about for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction *does* have an *indirect* biological counterpart, for we'll see in Chapter 17 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon-carbon bonds.

As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $\text{H}_2\text{C}=\text{O}$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols:

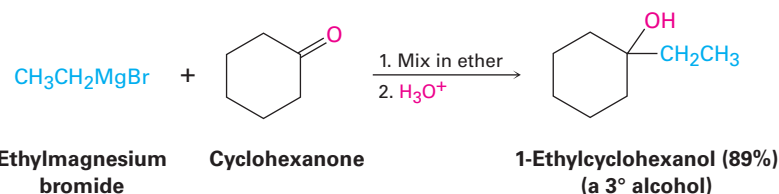
Formaldehyde reaction



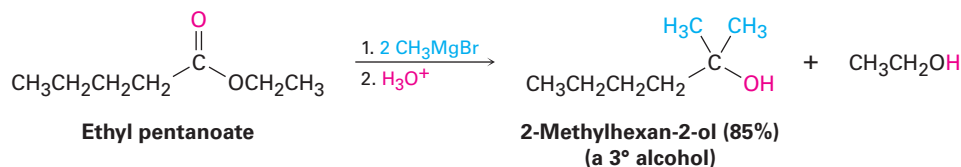
Aldehyde reaction



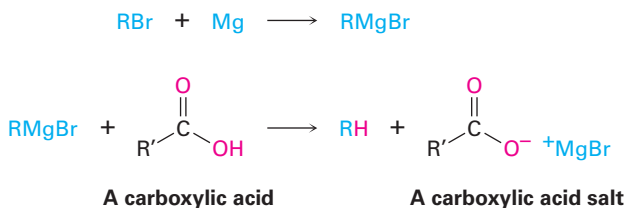
Ketone reaction



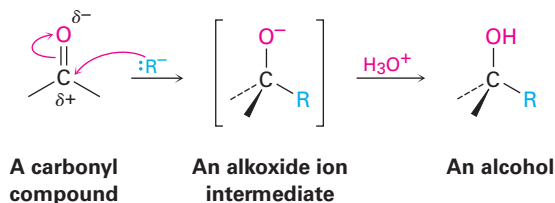
Esters react with Grignard reagents to yield tertiary alcohols in which *two* of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as LiAlH_4 reduction of an ester adds two hydrogens.



Carboxylic acids don't give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.



As with the reduction of carbonyl compounds, we'll defer a discussion of the mechanism of Grignard reactions until Section 14-6. For the moment, it's sufficient to note that Grignard reagents act as nucleophilic carbanions (R^-) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step.



Using a Grignard Reaction to Synthesize an Alcohol

WORKED EXAMPLE 13.3

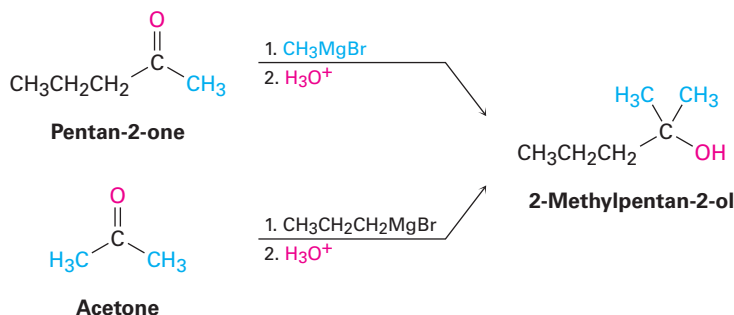
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methylpentan-2-ol?

Strategy

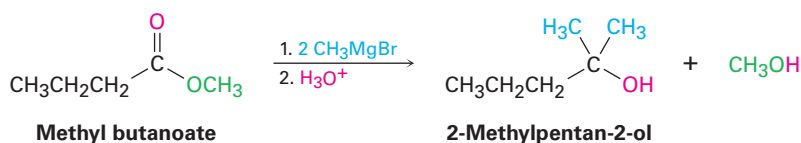
Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound might be either a ketone or an ester.

Solution

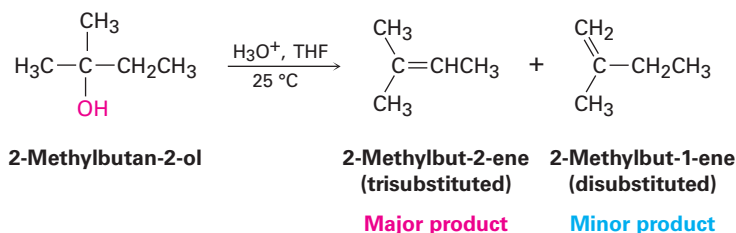
In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to pentan-2-one and addition of propylmagnesium bromide to acetone:



Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate:



usually follows Zaitsev's rule (Section 12-12) and yields the more stable alkene as the major product. Thus, 2-methylbutan-2-ol gives primarily 2-methylbut-2-ene (trisubstituted double bond) rather than 2-methylbut-1-ene (disubstituted double bond).



The reaction is an E1 process (Section 12-14) and occurs by a three-step mechanism involving protonation of the alcohol oxygen, unimolecular loss of water to generate a carbocation intermediate, and final loss of a proton from the neighboring carbon atom (FIGURE 13.5). As usual for E1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates. Primary and secondary alcohols are much less reactive and require much higher temperatures for reaction.

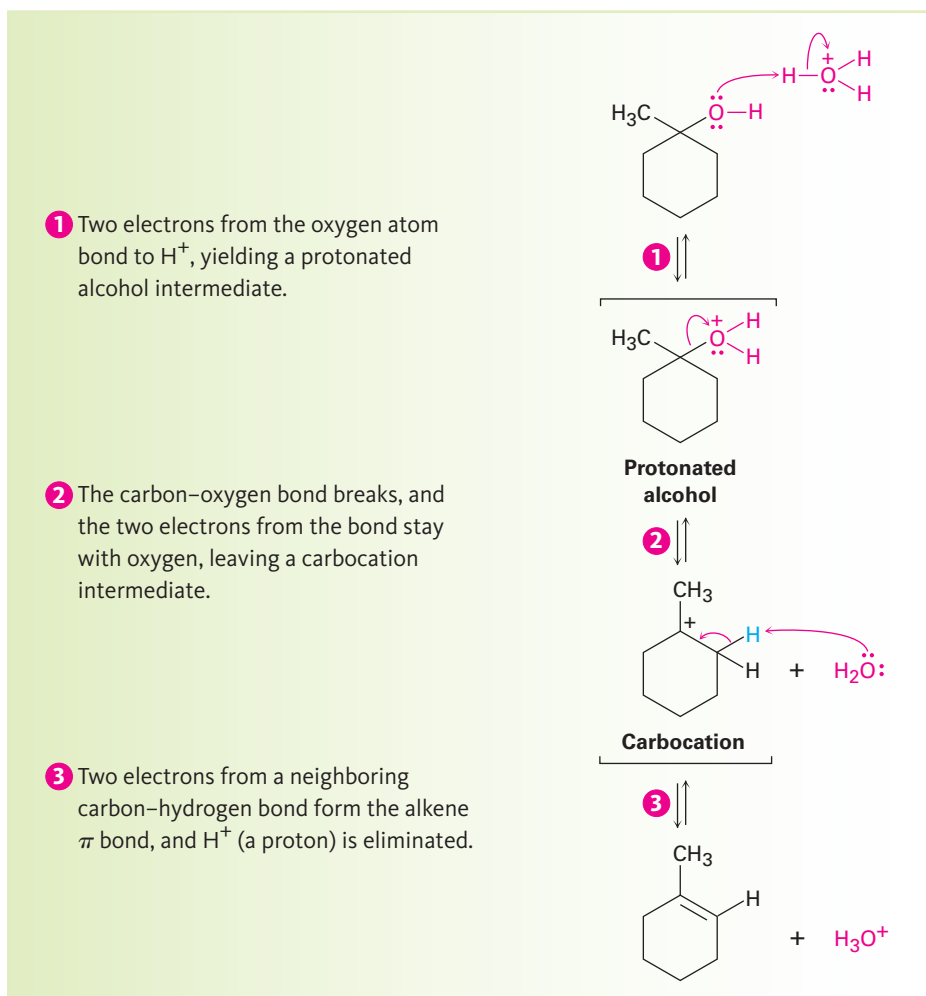
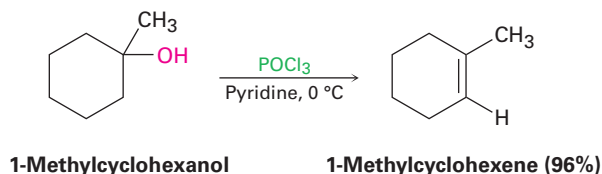


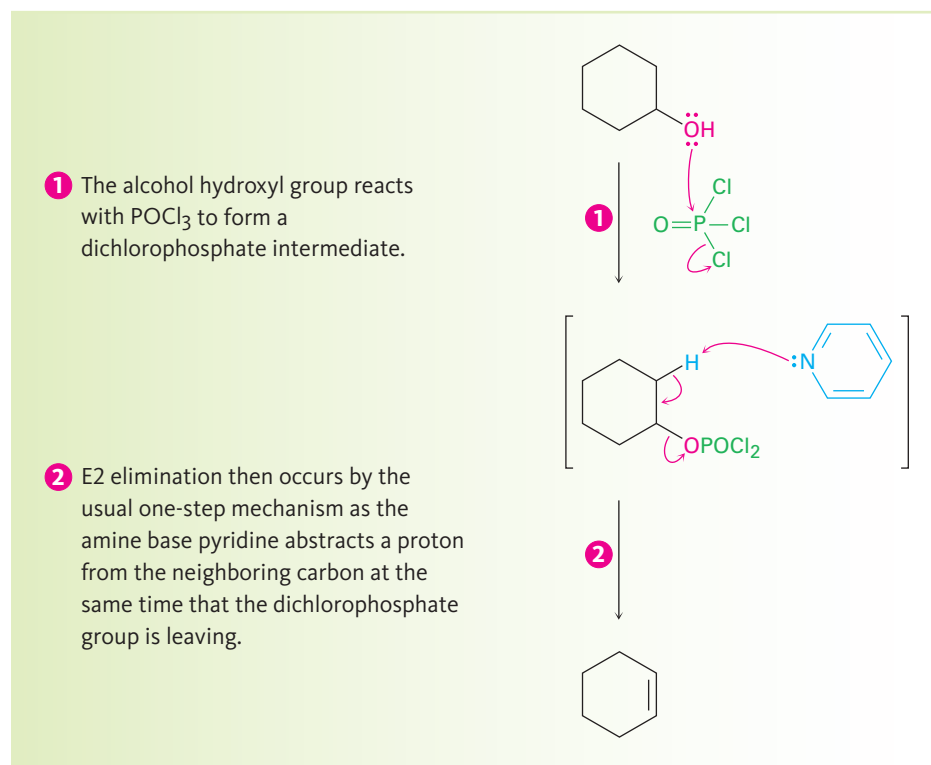
FIGURE 13.5 Mechanism of the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride (POCl_3) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0°C .



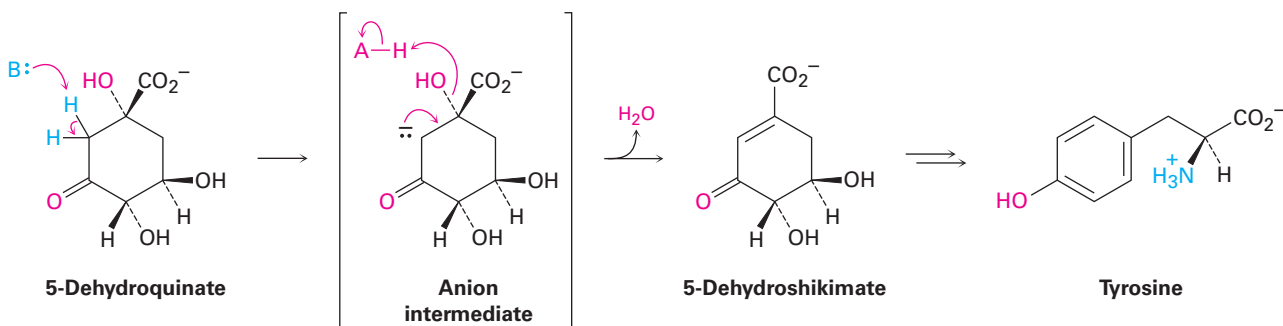
Alcohol dehydrations carried out with POCl_3 in pyridine take place by an E_2 mechanism, as shown in **FIGURE 13.6**. Because hydroxide ion is a poor leaving group (Section 12-8), direct E_2 elimination of water from an alcohol does not occur. On reaction with POCl_3 , however, the $-\text{OH}$ group is converted into a dichlorophosphate ($-\text{OPOCl}_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E_2 elimination step.

FIGURE 13.6 Mechanism of the dehydration of secondary and tertiary alcohols by reaction with POCl_3 in pyridine. The reaction is an E_2 process.



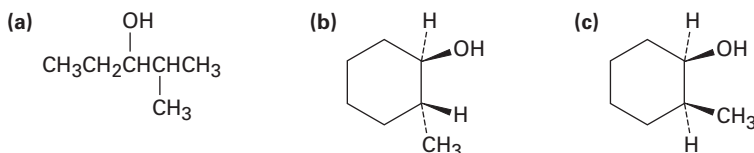
As noted previously in Section 12-15, biological dehydrations are also common and usually occur by an E_1cB mechanism on a substrate in which the $-\text{OH}$ group is two carbons away from a carbonyl group. An example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base ($:\text{B}$) first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion

intermediate then expels the -OH group with simultaneous protonation by an acid (HA) to form water.



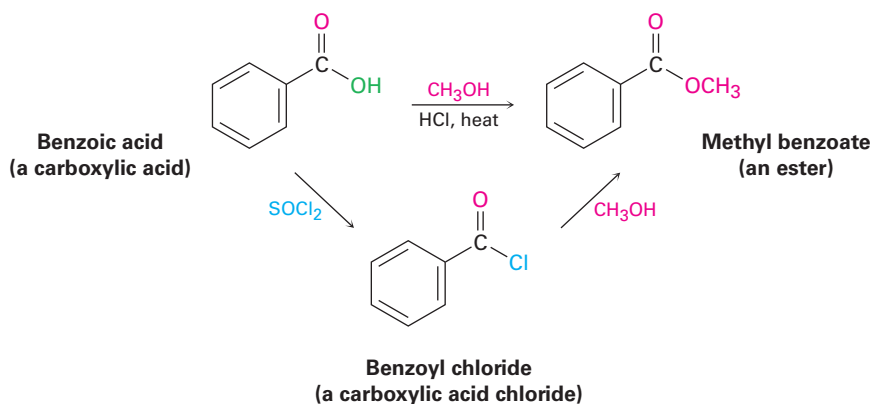
PROBLEM 13.12

What product(s) would you expect from dehydration of the following alcohols with POCl_3 in pyridine? Indicate the major product in each case.

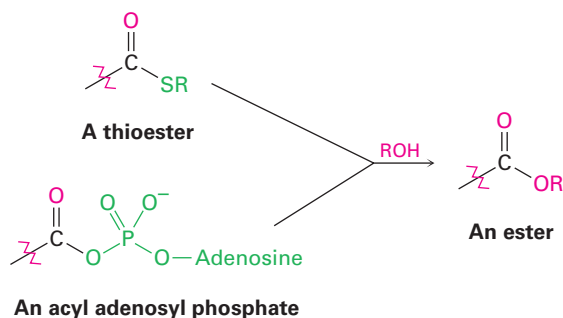


Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol. For example:



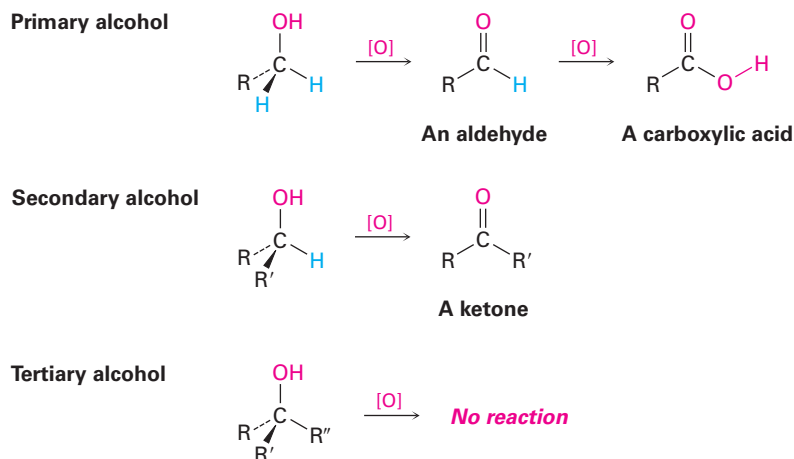
In living organisms, a similar process occurs, although a thioester or acyl adenosyl phosphate is the substrate rather than a carboxylic acid chloride. We'll look at the mechanisms of these reactions in Chapter 16.



13-5 Oxidation of Alcohols and Phenols

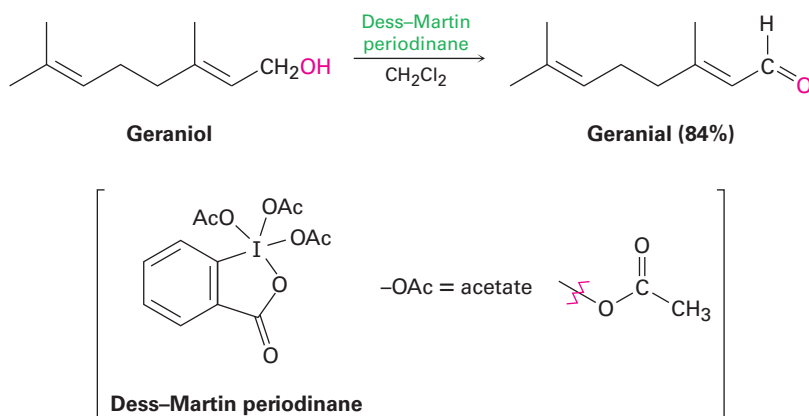
Oxidation of Alcohols

Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds—the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don't normally react with most oxidizing agents.

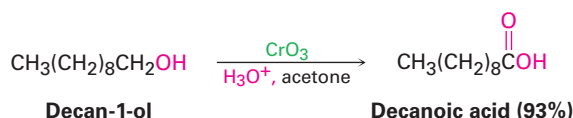


Primary alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagents chosen and the conditions used. Older methods were often based on Cr(VI) reagents, such as CrO_3 or $\text{Na}_2\text{Cr}_2\text{O}_7$, but a more common current choice for preparing an aldehyde from a primary alcohol in the

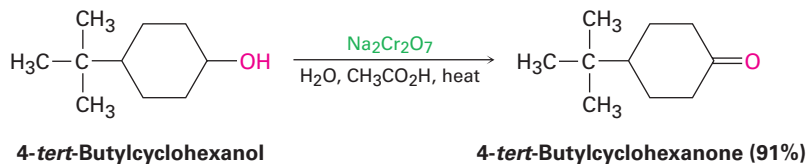
laboratory is to use the I(V)-containing *Dess–Martin periodinane* in dichloromethane solvent.



Most other commonly used oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can't usually be isolated because it is further oxidized too rapidly.

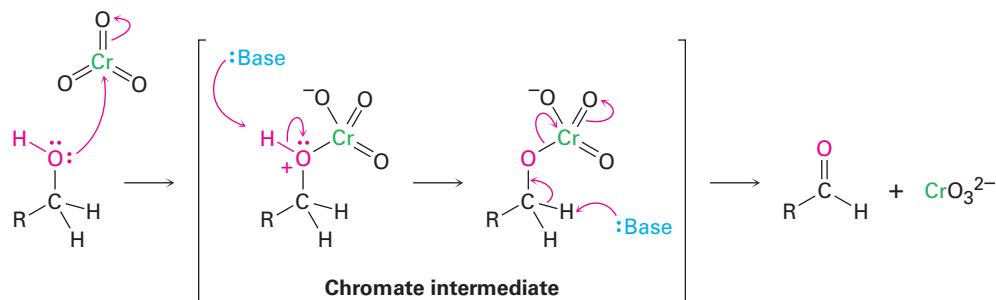
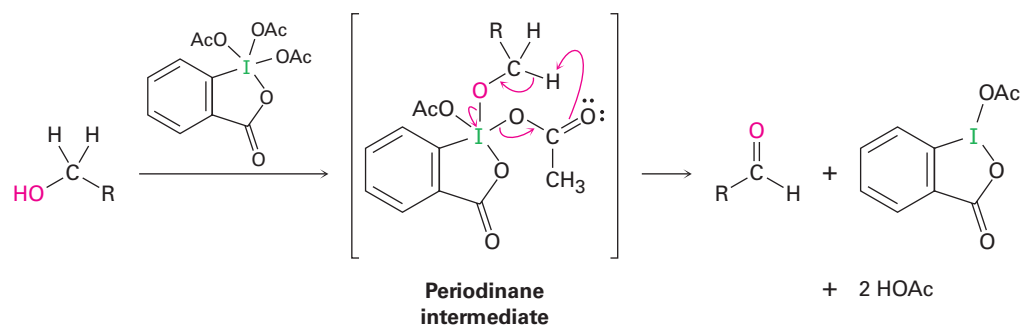


Secondary alcohols are easily oxidized to give ketones. For a sensitive or costly alcohol, the Dess–Martin procedure is often used because the reaction is nonacidic and occurs at lower temperatures. For a large-scale oxidation, however, an inexpensive reagent such as $\text{Na}_2\text{Cr}_2\text{O}_7$ in aqueous acetic acid might be used.



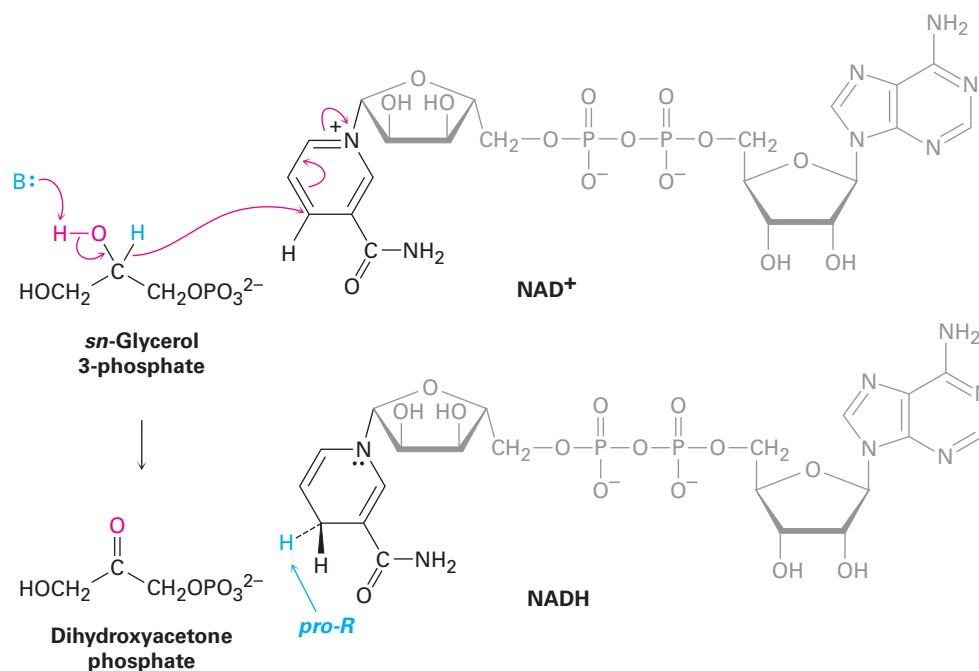
All these oxidations occur by a mechanism that is closely related to the E2 reaction (Section 12-13). In the Dess–Martin oxidation, for instance, the first step involves a substitution reaction between the alcohol and the I(V) reagent to form a new periodinane intermediate, followed by expulsion of reduced I(III) as the leaving group. Similarly, when a Cr(VI) reagent, such as CrO_3 , is the oxidant, reaction with the alcohol gives a chromate intermediate followed by expulsion of a reduced Cr(IV) species. Although we usually think of the E2 reaction as a means of generating a carbon–carbon double bond by elimination of a halide leaving group, the reaction is also useful for generating

a carbon–oxygen double bond by elimination of a reduced iodine or metal as the leaving group.



Biological alcohol oxidations are the opposite of biological carbonyl reductions and are carried by the coenzymes NAD^+ and NADP^+ . A base removes the $-\text{OH}$ proton, and the alkoxide ion transfers a hydride ion to the coenzyme. An example is the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate, a step in the biological metabolism of fats (**FIGURE 13.7**). Note that addition occurs exclusively on the *Re* face of the NAD^+ ring (Section 5-11), adding a hydrogen with *pro-R* stereochemistry.

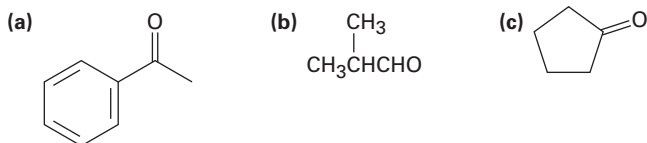
FIGURE 13.7 Biological oxidation of an alcohol (*sn*-glycerol 3-phosphate) to give a ketone (dihydroxyacetone phosphate). This mechanism is the exact opposite of the ketone reduction shown previously in Figure 13.4.



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PROBLEM 13.13

What alcohols would give the following products on oxidation?

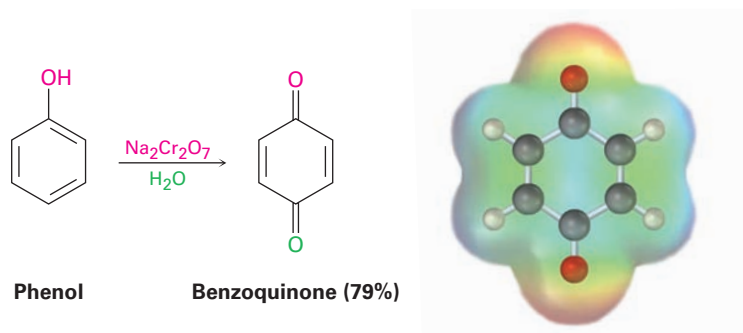
**PROBLEM 13.14**

What products would you expect from oxidation of the following compounds with CrO_3 in aqueous acid? With the Dess–Martin periodinane?

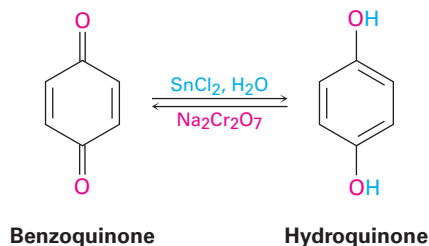
(a) Hexan-1-ol (b) Hexan-2-ol (c) Hexanal

Oxidation of Phenols: Quinones

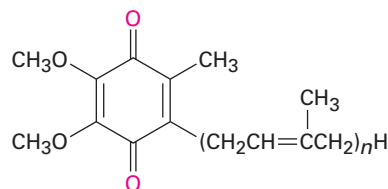
Phenols don't undergo oxidation in the same way that alcohols do because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, oxidation of a phenol yields a cyclohexa-2,5-diene-1,4-dione, or **quinone**. Many different oxidizing agents will accomplish the transformation, with $\text{Na}_2\text{Cr}_2\text{O}_7$ a common choice.



Quinones are a valuable class of compounds because of their oxidation–reduction, or redox, properties. They can be easily reduced to **hydroquinones** (*p*-dihydroxybenzenes) by reagents such as NaBH_4 and SnCl_2 , and hydroquinones can be easily reoxidized back to quinones by $\text{Na}_2\text{Cr}_2\text{O}_7$.



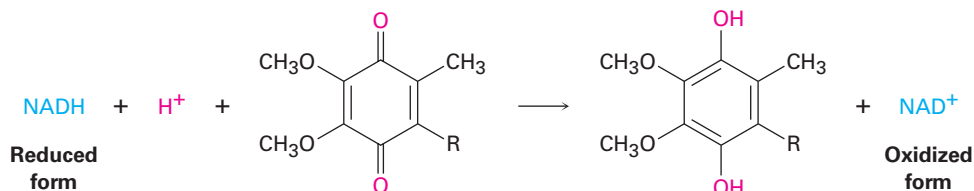
The redox properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q*, are components of the cells of all aerobic organisms, from the simplest bacterium to humans. They are so named because of their ubiquitous occurrence in nature.



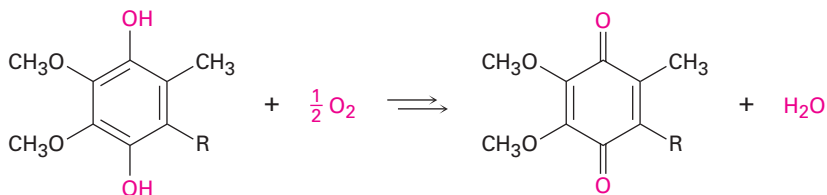
Ubiquinones ($n = 1-10$)

Ubiquinones function within the mitochondria of cells to mediate the respiration process in which electrons are transported from the biological reducing agent NADH to molecular oxygen. Through a complex series of steps, the ultimate result is a cycle whereby NADH is oxidized to NAD^+ , O_2 is reduced to water, and energy is produced. Ubiquinone acts only as an intermediary and is itself unchanged.

Step 1



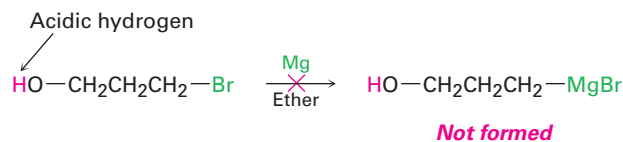
Step 2



13-6 Protection of Alcohols

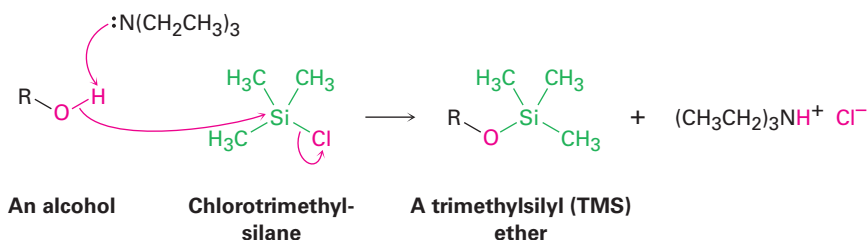
It often happens, particularly during the preparation of complex molecules, that one functional group in a molecule interferes with an intended

reaction on another functional group elsewhere in the same molecule. For example, a Grignard reagent can't be prepared from a halo alcohol because the C–Mg bond is not compatible with the presence of an acidic –OH group in the same molecule.

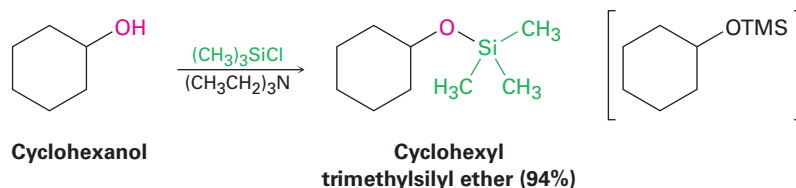


When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (1) introducing a **protecting group** to block the interfering function, (2) carrying out the desired reaction, and (3) removing the protecting group.

One of the more common methods of alcohol protection is by reaction with a chlorotrialkylsilane, Cl–SiR₃, to yield a trialkylsilyl ether, R'–O–SiR₃. Chlorotrimethylsilane is often used, and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.

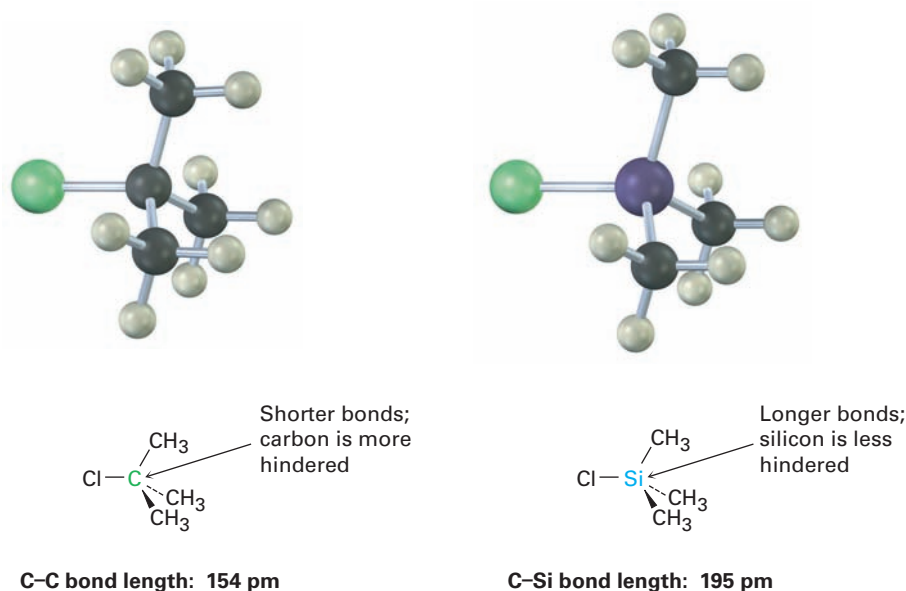


For example:

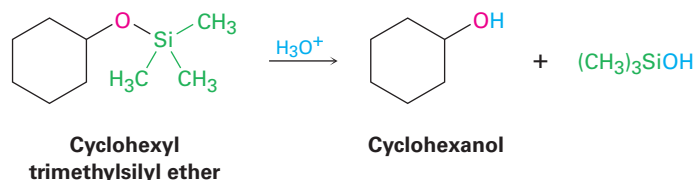


The ether-forming step is an S_N2-like reaction of the alkoxide ion on the silicon atom, with concurrent loss of the leaving chloride anion. Unlike most S_N2 reactions, though, this reaction takes place at a *tertiary* center—a trialkyl-substituted silicon atom. The reaction occurs because silicon, a third-row atom, is larger than carbon and forms longer bonds. The three methyl substituents

attached to silicon thus offer less steric hindrance to reaction than they do in the analogous *tert*-butyl chloride.



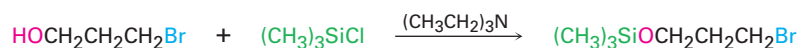
Like most other ethers, which we'll study later in this chapter, TMS ethers are relatively unreactive. They have no acidic hydrogens and don't react with oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol.



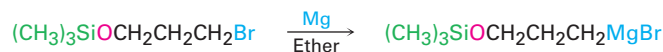
To now solve the problem posed at the beginning of this section, it's possible to use a halo alcohol in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromopropan-1-ol to acetaldehyde by the route shown in **FIGURE 13.8**.

FIGURE 13.8 Use of a TMS-protected alcohol during a Grignard reaction.

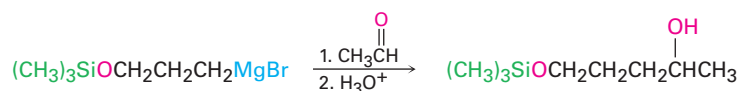
Step 1 Protect alcohol:



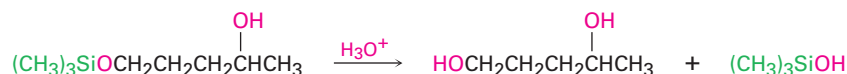
Step 2a Form Grignard reagent:



Step 2b Do Grignard reaction:



Step 3 Remove protecting group:



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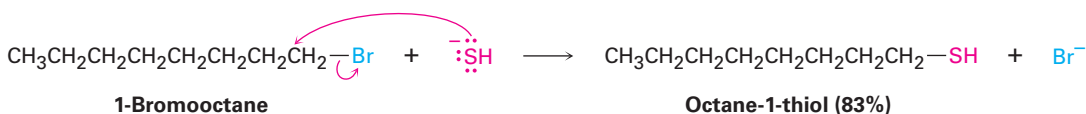
PROBLEM 13.15

TMS ethers can be removed by treatment with fluoride ion as well as by acid-catalyzed hydrolysis. Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF. Fluorotrimethylsilane is a product.

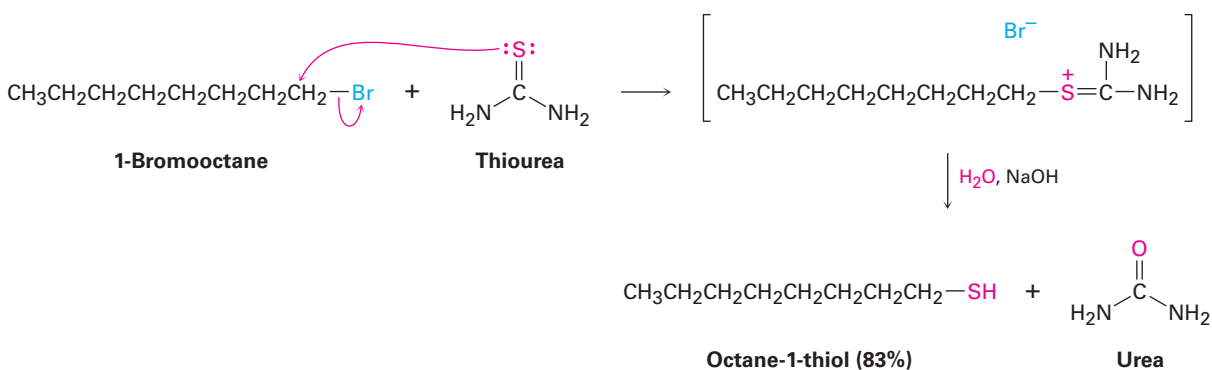
13-7 Preparation and Reactions of Thiols

The most striking characteristic of thiols is their appalling odor. Skunk scent, for instance, is caused primarily by the simple thiols 3-methylbutane-1-thiol and but-2-ene-1-thiol. Volatile thiols, such as ethanethiol, are also added to natural gas and liquefied propane to serve as an easily detectable warning in case of a leak.

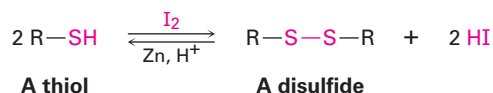
Thiols are usually prepared from alkyl halides by S_N2 displacement with a sulfur nucleophile such as hydrosulfide anion, ^-SH .



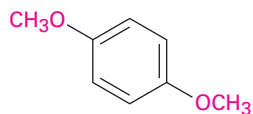
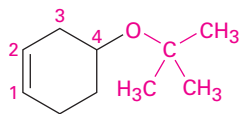
The reaction often works poorly unless an excess of the nucleophile is used because the product thiol can undergo a second S_N2 reaction with alkyl halide to give a sulfide as a by-product. To circumvent this problem, thiourea, $(\text{NH}_2)_2\text{C}=\text{S}$, is often used as the nucleophile in the preparation of a thiol from an alkyl halide. The reaction occurs by displacement of the halide ion to yield an intermediate alkylisothiurea salt, which is hydrolyzed by subsequent reaction with aqueous base.



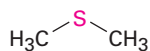
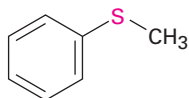
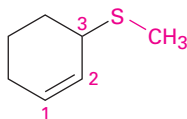
Thiols can be oxidized by Br_2 or I_2 to yield **disulfides** (RSSR'). The reaction is easily reversed, and a disulfide can be reduced back to a thiol by treatment with zinc and acid:



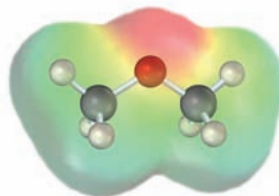
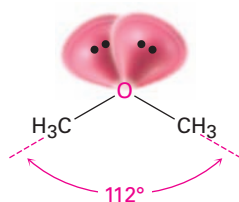
If other functional groups are present, the ether part is considered an *alkoxy* substituent. For example:

**p-Dimethoxybenzene****4-tert-Butoxy-1-cyclohexene**

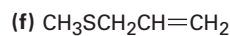
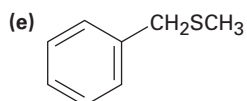
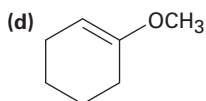
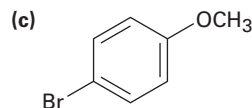
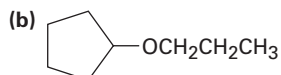
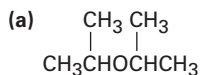
Sulfides are named by following the same rules used for ethers, with *sulfide* used in place of *ether* for simple compounds and *alkylthio* used in place of *alkoxy* for more complex substances.

**Dimethyl sulfide****Methyl phenyl sulfide****3-(Methylthio)cyclohexene**

Like alcohols, ethers have nearly the same geometry as water. The R–O–R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is sp^3 -hybridized.

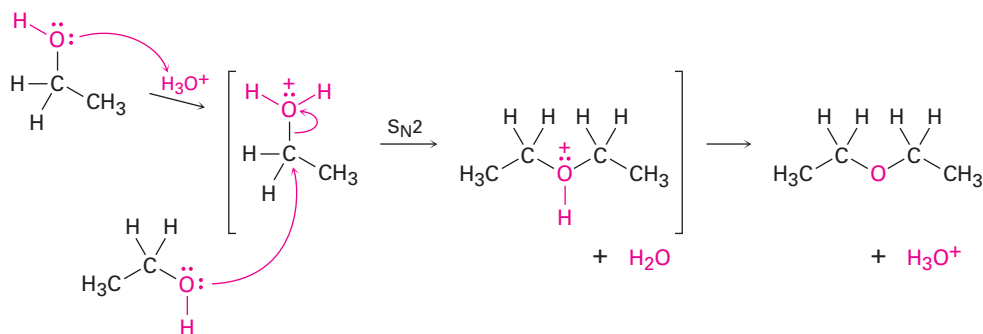
**PROBLEM 13.17**

Name the following ethers and sulfides according to IUPAC rules:

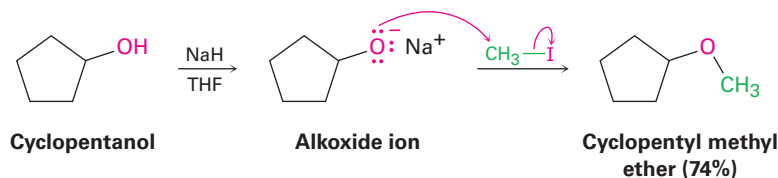


13-9 Preparing Ethers

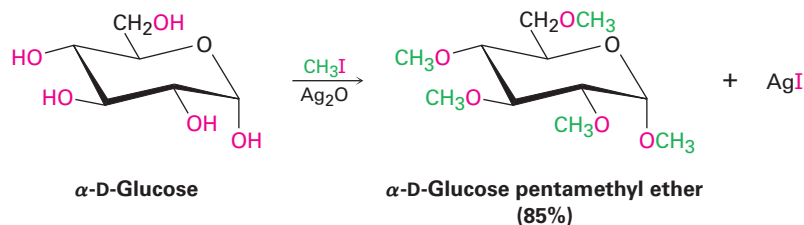
Diethyl ether and other simple symmetrical ethers are prepared industrially by the sulfuric acid-catalyzed reaction of alcohols. The process occurs by S_N2 displacement of water from a protonated ethanol molecule by the oxygen atom of a second ethanol. Unfortunately, the method is limited to use with primary alcohols because secondary and tertiary alcohols dehydrate by an $E1$ mechanism to yield alkenes.



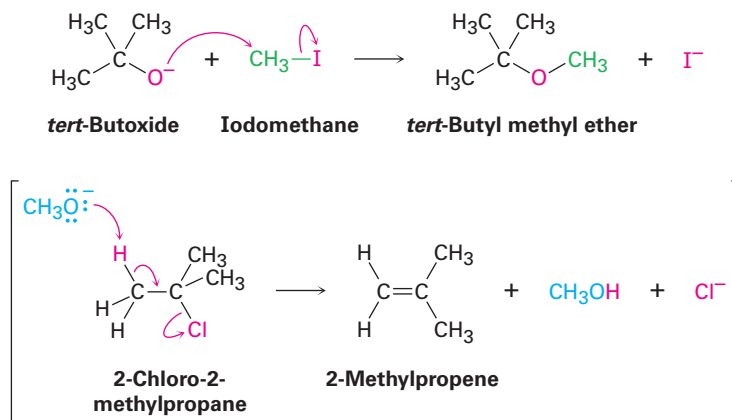
The most generally useful method of preparing ethers is by the *Williamson ether synthesis*, in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an S_N2 reaction. As we saw earlier in Section 13-2, the alkoxide ion is normally prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH .



A useful variation of the Williamson synthesis involves using silver oxide, Ag_2O , as a mild base rather than NaH . Under these conditions, the free alcohol reacts directly with alkyl halide, so there is no need to preform the metal alkoxide intermediate. Sugars react particularly well; glucose, for example, reacts with excess iodomethane in the presence of Ag_2O to generate a *pentaether* in 85% yield.



Because the Williamson synthesis is an S_N2 reaction, it is subject to all the usual constraints, as discussed in Section 12-8. Primary halides and tosylates work best because competitive $E2$ elimination can occur with more hindered substrates. Unsymmetrical ethers should therefore be synthesized by reaction between the more hindered alkoxide partner and less hindered halide partner rather than vice versa. For example, *tert*-butyl methyl ether, a substance used in the 1990s as an octane booster in gasoline, is best prepared by reaction of *tert*-butoxide ion with iodomethane rather than by reaction of methoxide ion with 2-chloro-2-methylpropane.



PROBLEM 13.18

Why do you suppose only symmetrical ethers are prepared by the sulfuric acid-catalyzed dehydration procedure? What product(s) would you expect if ethanol and propan-1-ol were allowed to react together? In what ratio would the products be formed if the two alcohols were of equal reactivity?

PROBLEM 13.19

How would you prepare the following ethers using a Williamson synthesis?

- (a) Methyl propyl ether (b) Anisole (methyl phenyl ether)
 (c) Benzyl isopropyl ether (d) Ethyl 2,2-dimethylpropyl ether

PROBLEM 13.20

Rank the following halides in order of their reactivity in the Williamson synthesis:

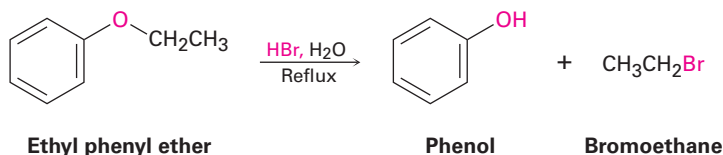
- (a) Bromoethane, 2-bromopropane, bromobenzene
 (b) Chloroethane, bromoethane, 1-iodopropene

13-10 Reactions of Ethers

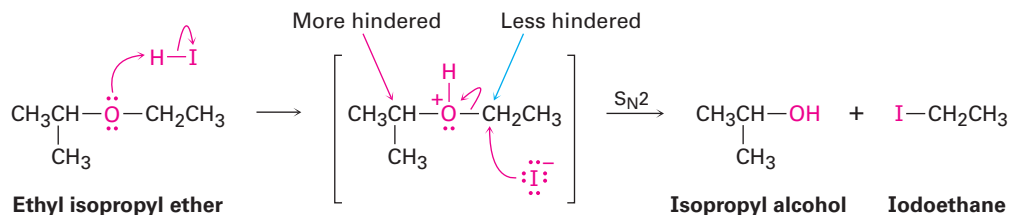
Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents. Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers.

Cleavage of Ethers

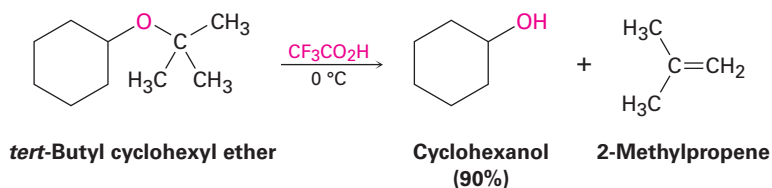
Ethers undergo only one truly general reaction—they are cleaved by strong acids. Aqueous HBr and HI both work well, but HCl does not cleave ethers.



Acidic ether cleavages are typical nucleophilic substitution reactions and take place by either S_N1 or S_N2 mechanisms depending on the structure of the substrate. Ethers with only primary and secondary alkyl groups react by an S_N2 mechanism, in which I[−] or Br[−] attacks the protonated ether at the less hindered site. This usually results in a selective cleavage into a single alcohol and a single alkyl halide. For example, ethyl isopropyl ether yields exclusively isopropyl alcohol and iodoethane on cleavage by HI because nucleophilic attack by iodide ion occurs at the less hindered primary site rather than at the more hindered secondary site.



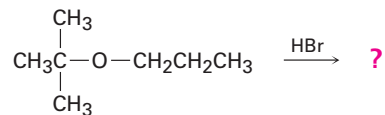
Ethers with a tertiary, benzylic, or allylic group cleave by either an S_N1 or E1 mechanism because these substrates can produce stable intermediate carbocations. These reactions are often fast and take place at moderate temperatures. *tert*-Butyl ethers, for example, react by an E1 mechanism on treatment with trifluoroacetic acid at 0 °C. We'll see in Section 19-7 that the reaction is often used in the laboratory synthesis of peptides.



WORKED EXAMPLE 13.4

Predicting the Product of an Ether Cleavage Reaction

Predict the products of the following reaction:

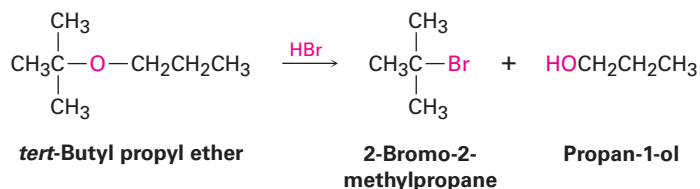


Strategy

Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl

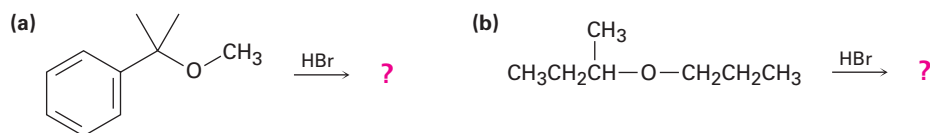
groups usually undergoes cleavage by S_N2 attack of a nucleophile on the less hindered alkyl group, but an ether with a tertiary alkyl group usually undergoes cleavage by an S_N1 mechanism. In this case, an S_N1 cleavage of the tertiary C–O bond will occur, giving propan-1-ol and a tertiary alkyl bromide.

Solution



PROBLEM 13.21

Predict the products of the following reactions:

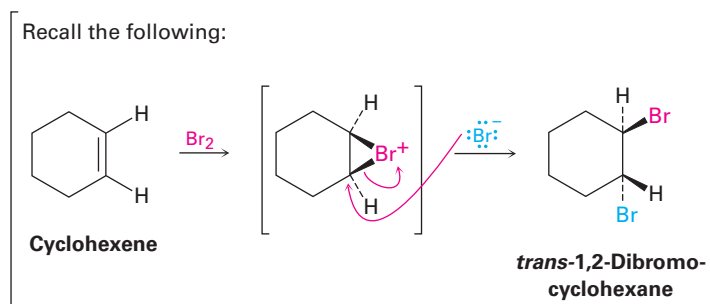
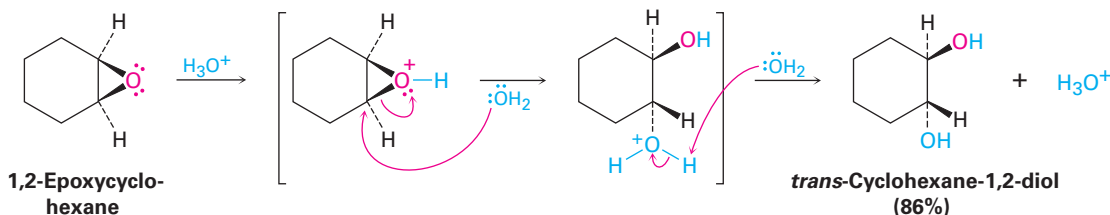


PROBLEM 13.22

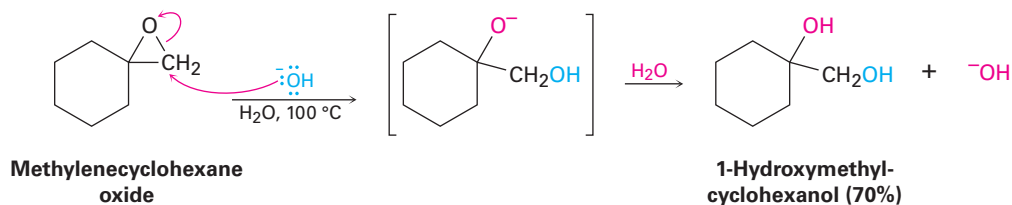
Write a mechanism for the acid-catalyzed cleavage of *tert*-butyl cyclohexyl ether with trifluoroacetic acid to yield cyclohexanol and 2-methylpropene.

Cleavage of Epoxides

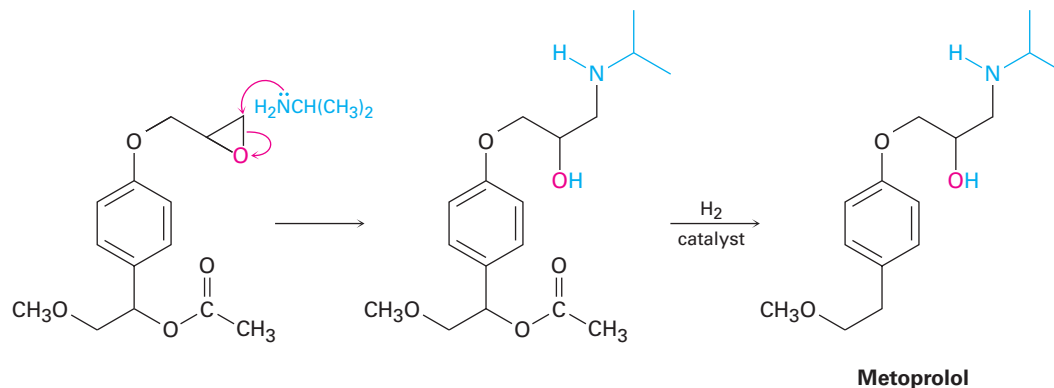
Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain. As we saw in Sections 8-7 and 12-7, dilute aqueous acid at room temperature is sufficient to cause the hydrolysis of an epoxide to give a 1,2-diol. The reaction takes place by S_N2 -like backside attack of water on the protonated epoxide, yielding a *trans*-1,2-diol as product:



Epoxides, in fact are so reactive in S_N2 processes because of angle strain that they also undergo a *base-induced* S_N2 ring-opening on treatment with hydroxide ion at 100 °C.

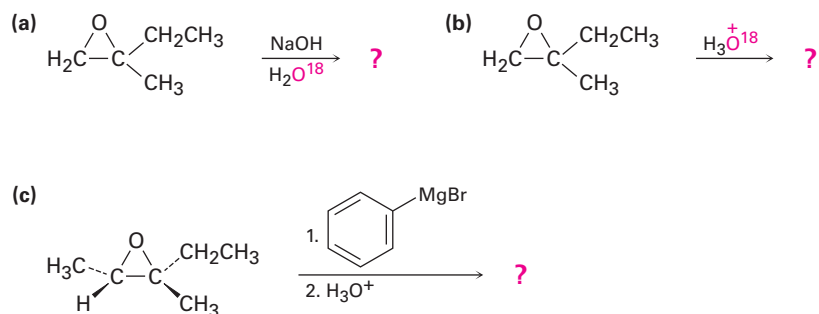


Many different nucleophiles can be used for epoxide opening in addition to OH^- , including amines (RNH_2 or R_2NH) and Grignard reagents ($RMgX$). An example of an amine reacting with an epoxide occurs in the commercial synthesis of metoprolol, a so-called beta-blocker that is used for treatment of cardiac arrhythmias, hypertension, and heart attacks. Beta-blockers are among the most widely prescribed drugs in the world.



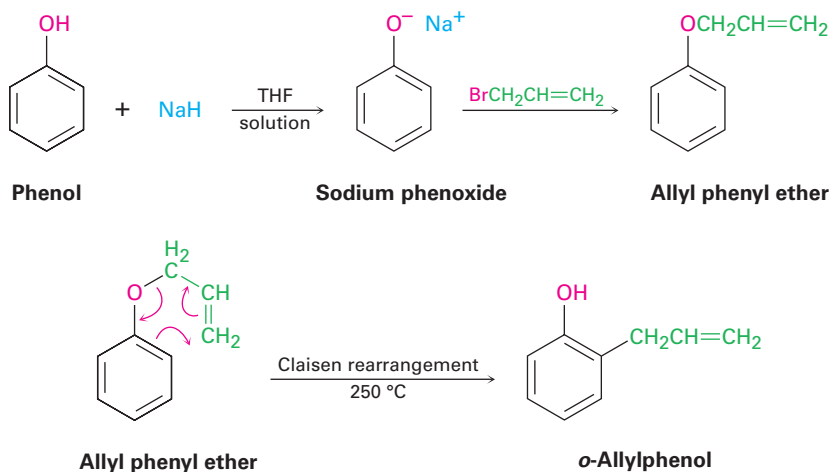
PROBLEM 13.23

Predict the major product of the following reactions:

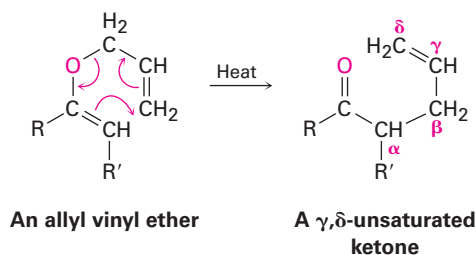


Claisen Rearrangement of Aryl Allyl Ethers

Unlike the acid-induced ether cleavage reaction, which is general for all ethers, the **Claisen rearrangement** is specific to aryl allyl ethers ($\text{Ar}-\text{O}-\text{CH}_2\text{CH}=\text{CH}_2$) and vinyl allyl ethers ($\text{H}_2\text{C}=\text{CH}-\text{O}-\text{CH}_2\text{CH}=\text{CH}_2$). Treatment of a phenoxide ion with 3-bromopropene (allyl bromide) results in a Williamson ether synthesis and formation of an allyl aryl ether. Heating the allyl aryl ether to 200–250 °C then effects Claisen rearrangement, leading to an *o*-allylphenol. The net result is alkylation of the phenol in an ortho position.



A similar rearrangement takes place with allyl vinyl ethers, leading to a so-called γ,δ -unsaturated ketone or aldehyde.



Like the Diels–Alder cycloaddition reaction discussed in Section 8-14, the Claisen rearrangement reaction takes place in a single step through a pericyclic mechanism in which a reorganization of bonding electrons occurs through a six-membered, cyclic transition state. The 6-allylcyclohexa-2,4-dienone intermediate then isomerizes to *o*-allylphenol (**FIGURE 13.9**).

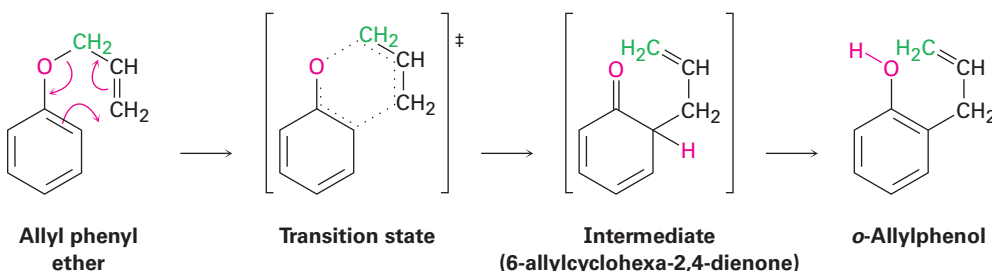
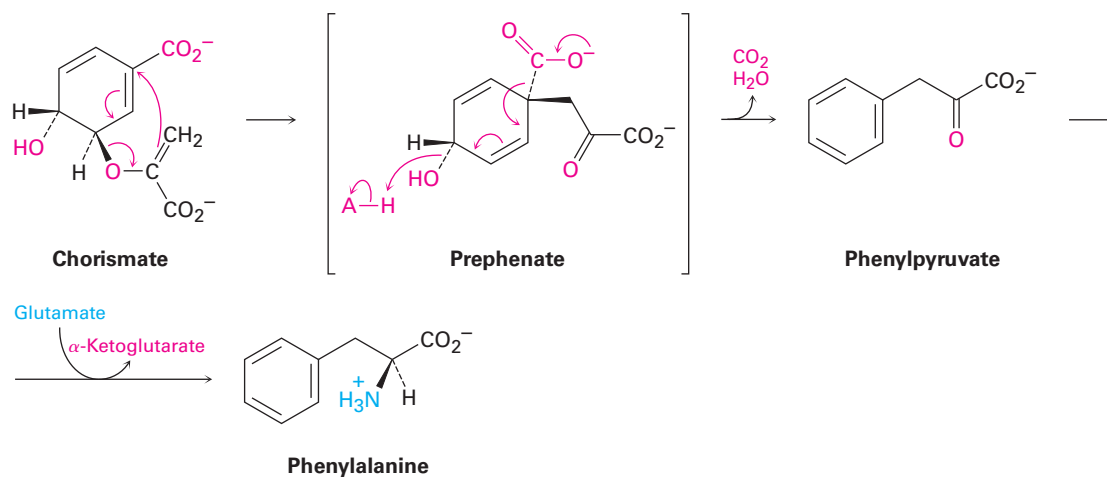


FIGURE 13.9
Mechanism of the Claisen rearrangement. The C–O bond-breaking and C–C bond-making occur simultaneously.

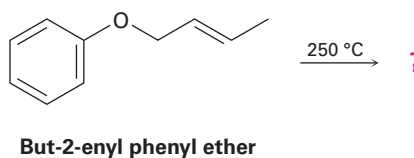
Evidence for this mechanism comes from the observation that the rearrangement takes place with an inversion of the allyl group. That is, allyl phenyl ether containing a ^{14}C label on the allyl *ether* carbon atom yields *o*-allylphenol in which the label is on the *terminal* vinylic carbon (green in Figure 13.9).

Claisen rearrangements are uncommon in biological pathways, but a well-studied example does occur during biosynthesis of the amino acids phenylalanine and tyrosine. Both phenylalanine and tyrosine arise from a precursor called prephenate, which is itself formed by a biological Claisen rearrangement of the allylic vinyl ether chorismate.



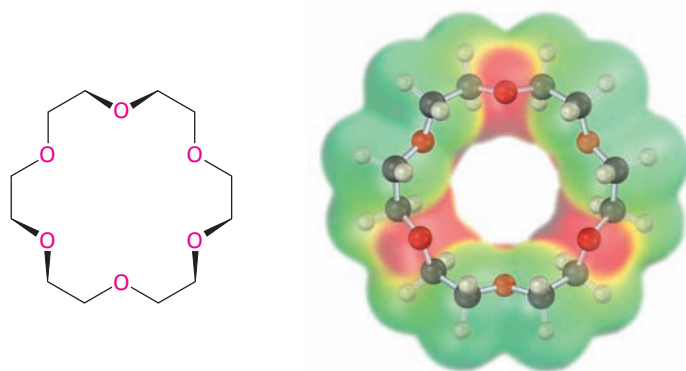
PROBLEM 13.24

What product would you expect from Claisen rearrangement of but-2-enyl phenyl ether?



13-11 Crown Ethers and Ionophores

Crown ethers, discovered in the early 1960s at the DuPont company, are a relatively recent addition to the ether family. They are named according to the general format *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. Thus, 18-crown-6 ether is an 18-membered ring containing 6 ether oxygen atoms. Note the size and negative (red) character of the crown ether cavity in the following electrostatic potential map.

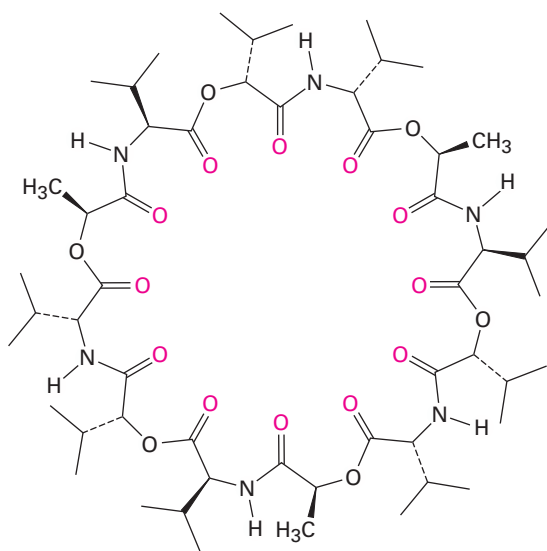


18-Crown-6 ether

The importance of crown ethers derives from their ability to sequester specific metal cations in the center of the polyether cavity while retaining their solubility in organic solvents. 18-Crown-6, for example, binds strongly with potassium ion. As a result, a solution of 18-crown-6 in a nonpolar organic solvent will dissolve many potassium salts. Potassium permanganate, KMnO_4 , dissolves in toluene in the presence of 18-crown-6, for instance, and the resulting solution is a valuable reagent for oxidizing alkenes.

The effect of using a crown ether to dissolve an inorganic salt in a hydrocarbon or ether solvent is similar to the effect of dissolving the salt in a polar aprotic solvent such as DMSO, DMF, or HMPA (Section 12-8). In both cases, the metal cation is strongly solvated, leaving the anion bare. Thus, the $\text{S}_{\text{N}}2$ reactivity of an anion is tremendously enhanced in the presence of a crown ether.

Although crown ethers do not occur naturally, a group of compounds called *ionophores* have similar ion-binding properties. Produced by various microorganisms, ionophores are fat-soluble molecules that bind to specific ions and facilitate transport of the ions through biological membranes. The antibiotic valinomycin, for instance, binds specifically to K^+ ions with a ten-thousandfold selectivity over Na^+ .



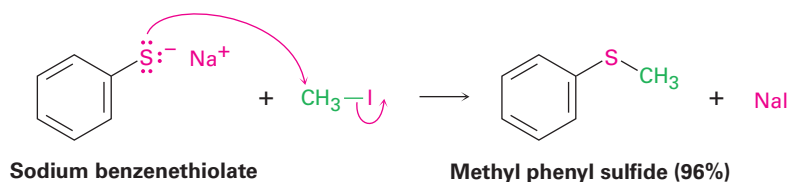
Valinomycin

PROBLEM 13.25

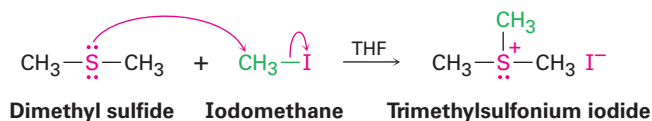
15-Crown-5 and 12-crown-4 ethers selectively complex Na^+ and Li^+ , respectively. Make models of these crown ethers, and compare the sizes of the cavities.

13-12 Preparation and Reactions of Sulfides

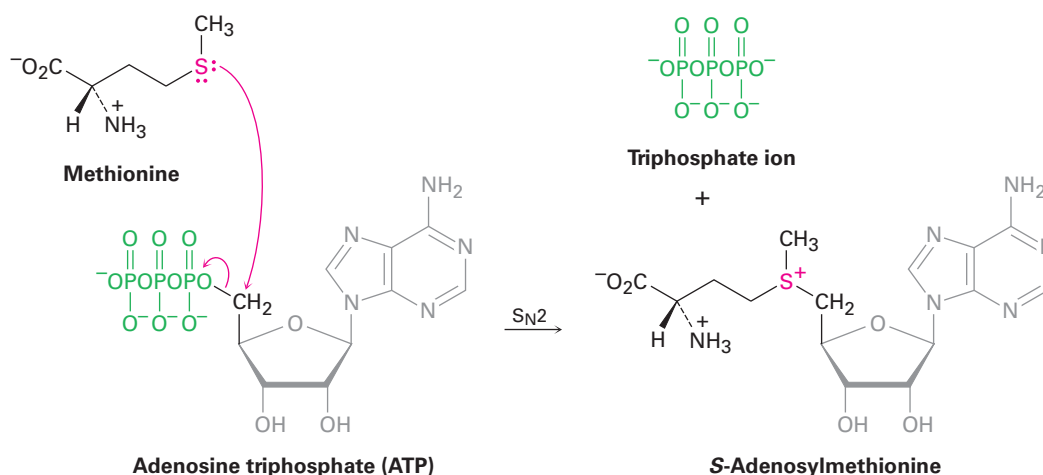
Just as ethers are generally prepared by $\text{S}_{\text{N}}2$ reaction of an alkoxide ion with an alkyl halide (Section 13-9), sulfides can be prepared by reaction of a thiolate ion (RS^-) with a primary or secondary alkyl halide. The thiolate ion is formed from the corresponding thiol by treatment with a base, such as NaH , and the reaction occurs by an $\text{S}_{\text{N}}2$ mechanism.



Despite their close structural similarity, sulfides and ethers differ substantially in their chemistry. Because the valence electrons on sulfur are farther from the nucleus and are less tightly held than those on oxygen ($3p$ electrons versus $2p$ electrons), sulfur compounds are more nucleophilic than their oxygen analogs. Unlike dialkyl ethers, dialkyl sulfides react rapidly with primary alkyl halides by an $\text{S}_{\text{N}}2$ mechanism to give *sulfonium ions* (R_3S^+).



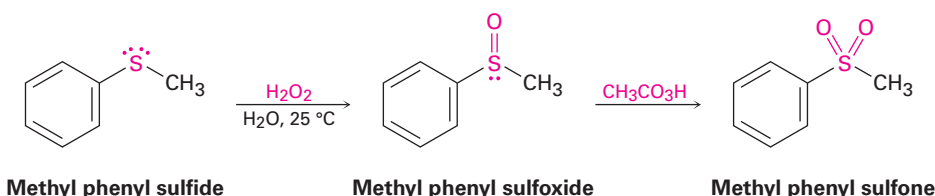
The most common example of this process in living organisms is the reaction of the amino acid methionine with adenosine triphosphate (ATP; Section 6-8) to give *S*-adenosylmethionine. The reaction is somewhat unusual in that the biological leaving group in this $\text{S}_{\text{N}}2$ process is the *triphosphate* ion rather than the more frequently seen *diphosphate* ion (Section 12-11).



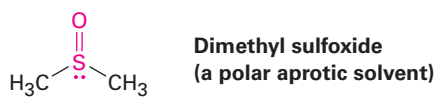
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Sulfonium ions are themselves useful alkylating agents because a nucleophile can attack one of the groups bonded to the positively charged sulfur, displacing a neutral sulfide as leaving group. We saw an example in Section 12-11 (Figure 12.19 on page 419) in which *S*-adenosylmethionine transferred a methyl group to norepinephrine to give adrenaline.

Another difference between sulfides and ethers is that sulfides are easily oxidized. Treatment of a sulfide with hydrogen peroxide, H_2O_2 , at room temperature yields the corresponding *sulfoxide* (R_2SO), and further oxidation of the sulfoxide with a peroxyacid yields a *sulfone* (R_2SO_2).



Dimethyl sulfoxide (DMSO) is a particularly well-known sulfoxide that is often used as a polar aprotic solvent. It must be handled with care, however, because it has a remarkable ability to penetrate the skin, carrying along whatever is dissolved in it.



13-13 Spectroscopy of Alcohols, Phenols, and Ethers

Infrared Spectroscopy

Alcohols have a strong C–O stretching absorption near 1050 cm^{-1} and a characteristic O–H stretching absorption at $3300\text{ to }3600\text{ cm}^{-1}$. The exact position of the O–H stretch depends on the extent of hydrogen-bonding in the molecule. Unassociated alcohols show a fairly sharp absorption near 3600 cm^{-1} , whereas hydrogen-bonded alcohols show a broader absorption in the $3300\text{ to }3400\text{ cm}^{-1}$ range. The hydrogen-bonded hydroxyl absorption appears at 3350 cm^{-1} in the IR spectrum of cyclohexanol (FIGURE 13.10).

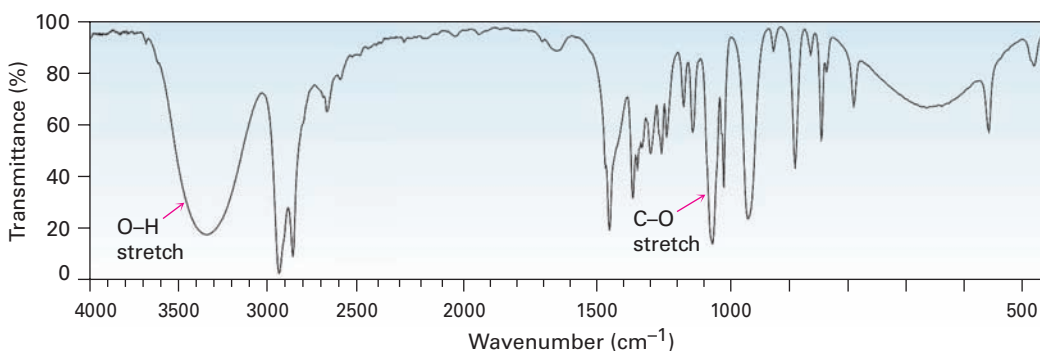
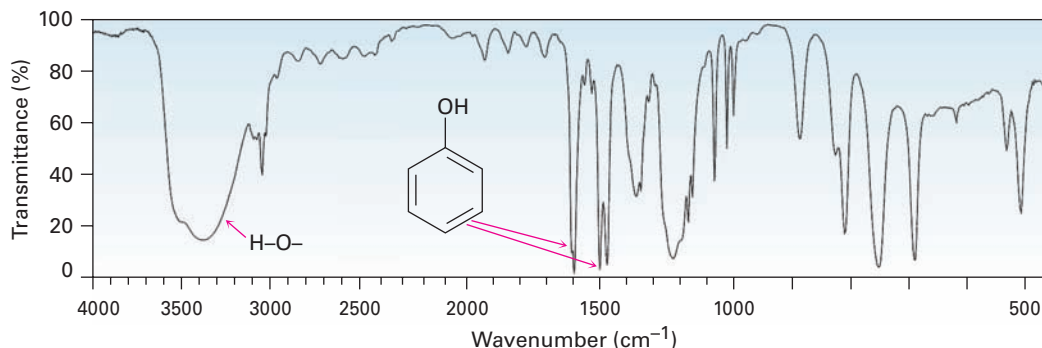


FIGURE 13.10
IR spectrum of cyclohexanol.
 Characteristic O–H and C–O stretching absorptions are indicated.

Phenols also show a characteristic broad absorption at 3500 cm^{-1} due to the -OH group, as well as the usual 1500 and 1600 cm^{-1} aromatic bands (FIGURE 13.11). In phenol itself, the monosubstituted aromatic-ring peaks at 690 and 760 cm^{-1} are visible.

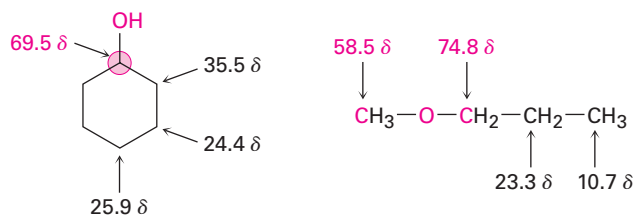
FIGURE 13.11
IR spectrum of phenol.



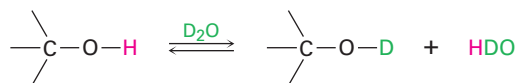
Ethers are difficult to identify by IR spectroscopy alone. Although they show an absorption due to C-O single-bond stretching in the range 1050 to 1150 cm^{-1} , many other kinds of absorptions occur in the same range.

Nuclear Magnetic Resonance Spectroscopy

Carbon atoms bonded to electron-withdrawing oxygen atoms are deshielded and absorb at a lower field in the ^{13}C NMR spectrum than do typical alkane carbons. Most alcohol and ether carbon absorptions fall in the range 50 to $80\text{ }\delta$.



Alcohols also show characteristic absorptions in the ^1H NMR spectrum. Hydrogens on the oxygen-bearing carbon atom are deshielded by the electron-withdrawing effect of the nearby oxygen, and their absorptions occur in the range 3.4 to $4.5\text{ }\delta$. Spin-spin splitting, however, is not usually observed between the O-H proton of an alcohol and the neighboring protons on carbon. Most samples contain small amounts of acidic impurities, which catalyze an exchange of the O-H proton on a timescale so rapid that the effect of spin-spin splitting is removed. It's often possible to take advantage of this rapid proton exchange to identify the position of the O-H absorption. If a small amount of deuterated water, D_2O , is added to the NMR sample tube, the O-H proton is rapidly exchanged for deuterium, and the hydroxyl absorption disappears from the spectrum.



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Typical spin–spin splitting is observed between protons on the oxygen-bearing carbon and other neighbors in both alcohols and ethers. **FIGURE 13.12** shows the ^1H NMR spectrum of propan-1-ol.

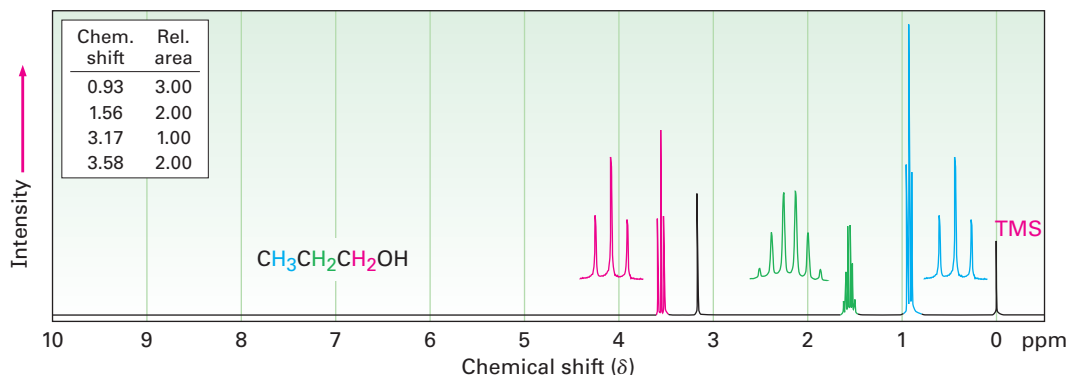


FIGURE 13.12 ^1H NMR spectrum of propan-1-ol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ .

Phenols, like all aromatic compounds, show ^1H NMR absorptions near 7 to 8 δ , the expected position for aromatic-ring protons (Section 11-9). In addition, phenol O–H protons absorb at 3 to 8 δ . In neither case are these absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

Mass Spectrometry

As noted previously in Section 10-3, alcohols undergo fragmentation in the mass spectrometer by two characteristic pathways, *alpha cleavage* and *dehydration*. In the alpha-cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a charged oxygen-containing fragment. In the dehydration pathway, water is eliminated, yielding an alkene radical cation. Both fragmentation modes are apparent in the mass spectrum of butan-1-ol (**FIGURE 13.13**). The peak at $m/z = 56$ is due to loss of water from the molecular ion, and the peak at $m/z = 31$ is due to an alpha cleavage.

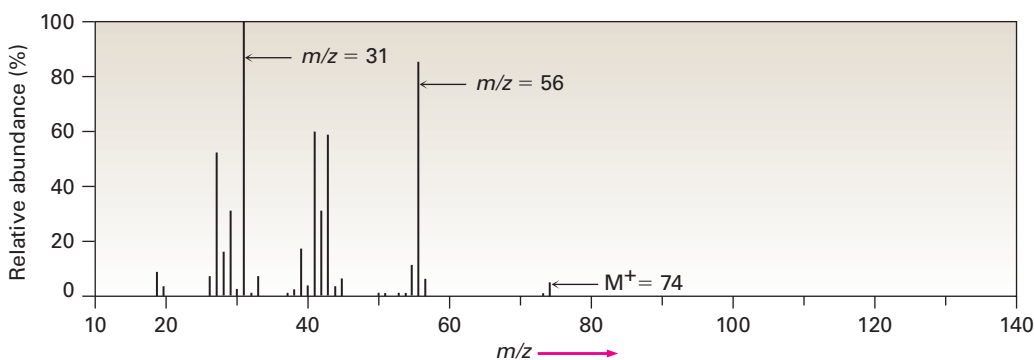
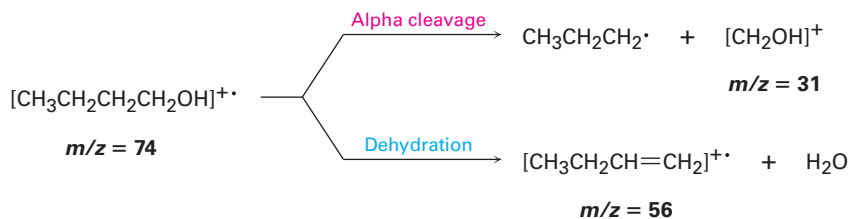


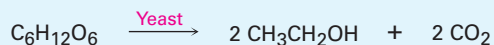
FIGURE 13.13 Mass spectrum of butan-1-ol ($M^+ = 74$). Dehydration gives a peak at $m/z = 56$, and fragmentation by alpha cleavage gives a peak at $m/z = 31$.



SOMETHING EXTRA

Ethanol: Chemical, Drug, Poison

The production of ethanol by fermentation of grains and sugars is one of the oldest known organic reactions, going back at least 8000 years in the Middle East and perhaps as many as 9000 years in China. Fermentation is carried out by adding yeast to an aqueous sugar solution, where enzymes break down carbohydrates into ethanol and CO_2 . Approximately 14 billion gallons of ethanol is produced annually in the United States by fermentation, with essentially the entire amount used to make E90 automobile fuel.



A carbohydrate

Ethanol is classified medically as a central nervous system (CNS) depressant. Its effects—that is, being drunk—resemble the human response to anesthetics. There is an initial excitability and increase in sociable behavior, but this results from depression of inhibition rather than from stimulation. At a blood alcohol concentration of 0.1% to 0.3%, motor coordination is affected, accompanied by loss of balance, slurred speech, and amnesia. When blood alcohol concentration rises to 0.3% to 0.4%, nausea and loss of consciousness occur. Above 0.6%, spontaneous respiration and cardiovascular regulation are affected, ultimately leading to death. The LD_{50} of ethanol is 10.6 g/kg (Chapter 1 *Something Extra*).

The passage of ethanol through the body begins with its absorption in the stomach and small intestine, followed by rapid distribution to all body fluids and organs. In the pituitary gland, ethanol inhibits the production of a hormone that regulates urine flow, causing increased urine production and dehydration. In the stomach, ethanol stimulates production of acid. Throughout the body, ethanol causes blood vessels to dilate, resulting in flushing of the skin and a sensation of warmth as blood moves into capillaries beneath the surface. The result is not a warming of the body, but an increased loss of heat at the surface.



Orlando / Three Lions/Getty Images

The Harger Drunkometer was the first breath analyzer, introduced in 1938 to help convict drunk drivers.

Ethanol metabolism occurs mainly in the liver and proceeds by oxidation in two steps, first to acetaldehyde (CH_3CHO) and then to acetic acid ($\text{CH}_3\text{CO}_2\text{H}$). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration seen in chronic alcoholics. The liver usually suffers the worst damage since it is the major site of alcohol metabolism.

Approximately 17,000 people are killed each year in the United States in alcohol-related automobile accidents. Thus, all 50 states—Massachusetts was the final holdout—have made it illegal to drive with a blood alcohol concentration (BAC) above 0.08%. Fortunately, simple tests have been devised for measuring blood alcohol concentration. The original breath analyzer test measured alcohol concentration in expired air by the color change that occurs when the bright orange oxidizing agent potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$) was reduced to blue-green chromium(III). Current consumer devices now use a conductivity sensor, and tests used by law-enforcement agencies use IR spectroscopy to measure blood alcohol levels in expired air. Just breathe into the machine, and let the spectrum tell the tale.

SUMMARY

In previous chapters, we focused on developing general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides, and seeing some of the tools used in structural studies. With that accomplished, we have now begun in this chapter to study the oxygen-containing functional groups that lie at the heart of organic and biological chemistry.

Alcohols are among the most versatile of all organic compounds. They occur widely in nature, are important industrially, and have an unusually rich chemistry. The most widely used methods of alcohol synthesis start with carbonyl compounds. Aldehydes, esters, and carboxylic acids are reduced by reaction with LiAlH_4 to give primary alcohols (RCH_2OH); ketones are reduced to yield secondary alcohols (R_2CHOH). Alcohols are also prepared by reaction of carbonyl compounds with Grignard reagents, RMgX . Addition of a Grignard reagent to formaldehyde yields a primary alcohol, addition to an aldehyde yields a secondary alcohol, and addition to a ketone or an ester yields a tertiary alcohol.

Alcohols undergo many reactions and can be converted into many other functional groups. They can be dehydrated to give alkenes by treatment with POCl_3 and can be transformed into alkyl halides by treatment with PBr_3 or SOCl_2 . Furthermore, alcohols are weakly acidic and react with strong bases to form **alkoxide anions**, which are used frequently in organic synthesis. Perhaps the most important reaction of alcohols is their oxidation to carbonyl compounds. Primary alcohols yield either aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols are not normally oxidized. An alcohol can be **protected** by formation of a trimethylsilyl (TMS) ether when the presence of the $-\text{OH}$ group might interfere with a reaction elsewhere in the molecule.

Phenols are aromatic counterparts of alcohols but are much more acidic ($\text{p}K_{\text{a}} \approx 10$) because their anions are resonance stabilized by delocalization of the negative charge into the aromatic ring. Phenols can be oxidized to **quinones** by reaction with $\text{Na}_2\text{Cr}_2\text{O}_7$, and quinones can be reduced to **hydroquinones** by reaction with NaBH_4 .

Ethers are compounds that have two organic groups bonded to the same oxygen atom, ROR' . They are often prepared by the Williamson ether synthesis, which involves $\text{S}_{\text{N}}2$ reaction of an alkoxide ion with a primary alkyl halide. Ethers are inert to most reagents but react with HI and HBr to give cleavage products. The cleavage reaction takes place by an $\text{S}_{\text{N}}2$ mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen but by an $\text{S}_{\text{N}}1$ or $\text{E}1$ mechanism if one of the alkyl groups bonded to oxygen is tertiary. Aryl allyl ethers undergo **Claisen rearrangement** to give *o*-allylphenols.

Thiols, the sulfur analogs of alcohols, are usually prepared by $\text{S}_{\text{N}}2$ reaction of an alkyl halide with thiourea. Mild oxidation of a thiol yields a **disulfide**, and mild reduction of a disulfide gives back the thiol. **Sulfides**, the sulfur analogs of ethers, are prepared by $\text{S}_{\text{N}}2$ reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are much more nucleophilic than ethers and can be oxidized to sulfoxides and to sulfones. Sulfides can also be alkylated by reaction with a primary alkyl halide to yield sulfonium ions.

KEY WORDS

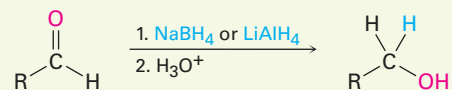
alcohol (ROH),	435
alkoxide ion (RO^-),	440
Claisen rearrangement,	471
crown ether,	472
disulfide (RSSR),	463
ether (ROR'),	435
hydroquinone,	459
mercapto group,	438
phenol (ArOH),	435
phenoxide ion (ArO^-),	440
protecting group,	461
quinone,	459
sulfide (RSR'),	435
thiol (RSH),	435

SUMMARY OF REACTIONS

1. Synthesis of alcohols (Section 13-3)

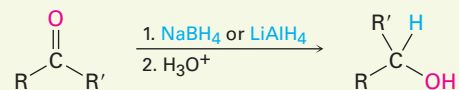
(a) Reduction of carbonyl compounds

(1) Aldehydes



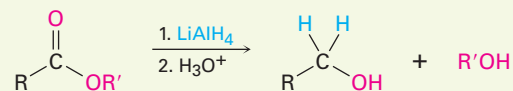
Primary alcohol

(2) Ketones



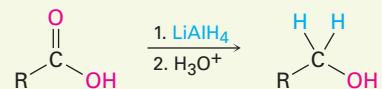
Secondary alcohol

(3) Esters



Primary alcohol

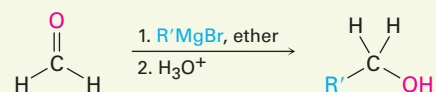
(4) Carboxylic acids



Primary alcohol

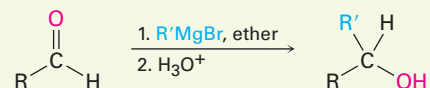
(b) Grignard addition to carbonyl compounds

(1) Formaldehyde



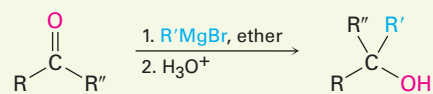
Primary alcohol

(2) Aldehydes

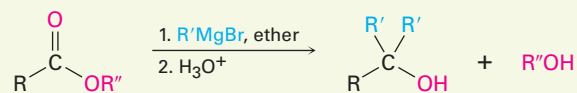


Secondary alcohol

(3) Ketones

**Tertiary alcohol**

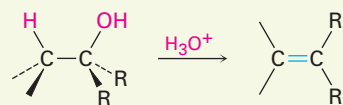
(4) Esters

**Tertiary alcohol**

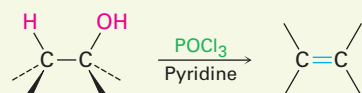
2. Reactions of alcohols

(a) Dehydration (Section 13-4)

(1) Tertiary alcohols

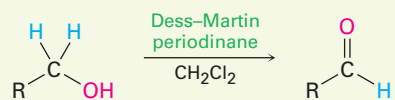
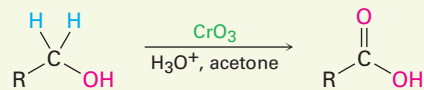


(2) Secondary and tertiary alcohols

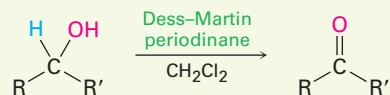


(b) Oxidation (Section 13-5)

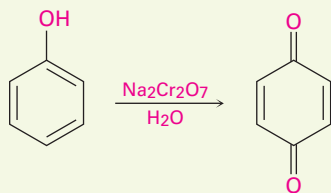
(1) Primary alcohols

**Aldehyde****Carboxylic acid**

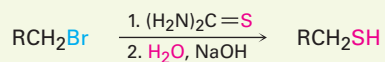
(2) Secondary alcohols

**Ketone**

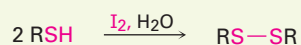
3. Oxidation of phenols to quinones (Section 13-5)



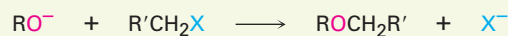
4. Synthesis of thiols (Section 13-7)



5. Oxidation of thiols to disulfides (Section 13-7)

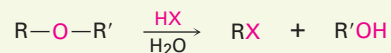


6. Synthesis of ethers (Section 13-9)

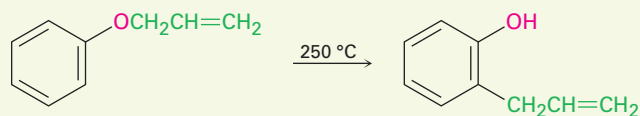


7. Reactions of ethers (Section 13-10)

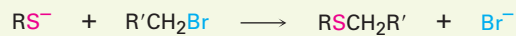
(a) Cleavage by HBr or HI



(b) Claisen rearrangement of allyl aryl ethers



8. Synthesis of sulfides (Section 13-11)

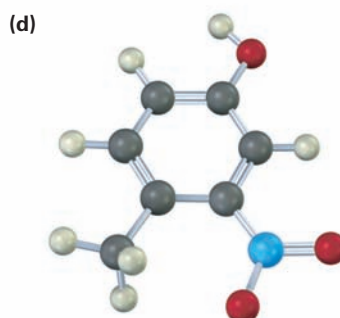
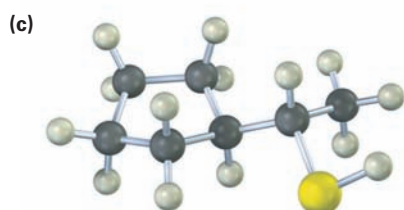
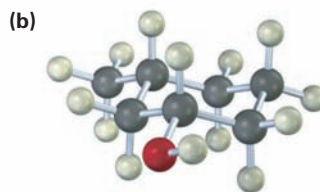
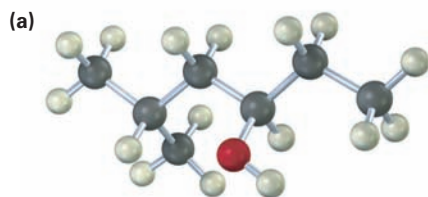


EXERCISES

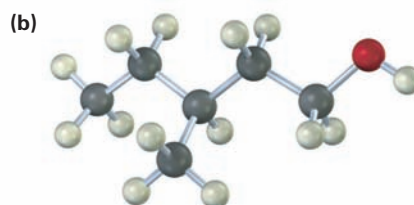
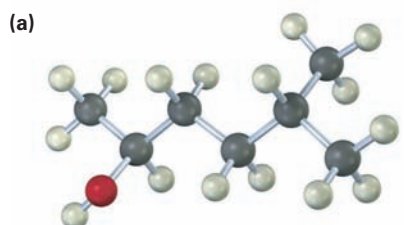
VISUALIZING CHEMISTRY

(Problems 13.1–13.25 appear within the chapter.)

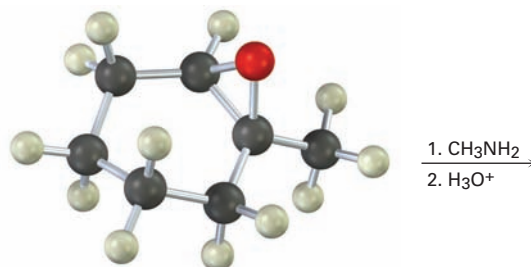
13.26 Give IUPAC names for the following compounds:



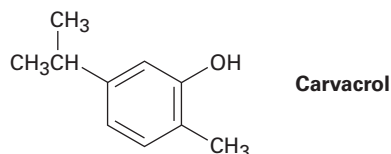
13.27 Draw the structure of the carbonyl compound(s) from which each of the following alcohols might have been prepared, and show the products you would obtain by treatment of each alcohol with (i) NaH, (ii) SOCl₂, and (iii) the Dess–Martin periodinane reagent:



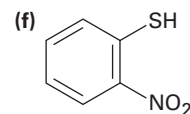
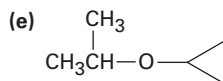
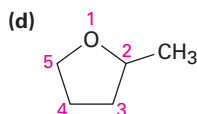
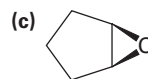
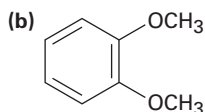
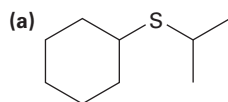
13.28 Show the product, including stereochemistry that would result from S_N2 reaction of the following epoxide with methylamine (CH₃NH₂):



- 13.32** Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$. Which are chiral?
- 13.33** Which of the eight alcohols you identified in Problem 13.32 react with CrO_3 in aqueous acid? Show the products you would expect from each reaction.
- 13.34** Named *bombykol*, the sex pheromone secreted by the female silkworm moth has the formula $C_{16}H_{30}O$ and the systematic name (10*E*,12*Z*)-hexadeca-10,12-dien-1-ol. Draw bombykol showing correct geometry for the two double bonds.
- 13.35** *Carvacrol* is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?

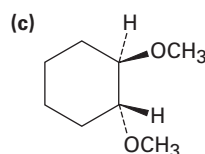
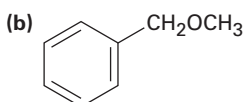
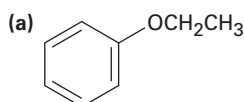


- 13.36** Give IUPAC names for the following compounds:

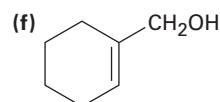
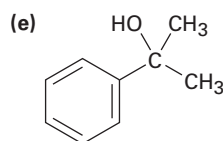
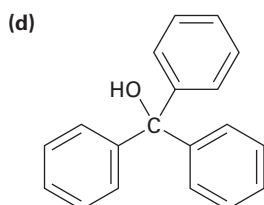
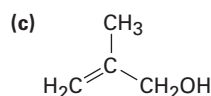
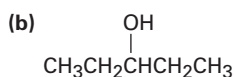
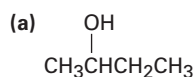


Synthesizing Alcohols, Ethers, Thiols, and Sulfides

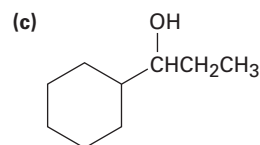
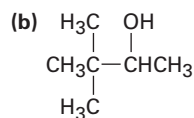
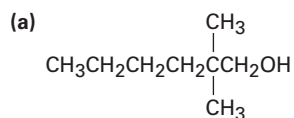
- 13.37** How would you prepare the following ethers?



- 13.38** What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols?



13.39 What carbonyl compounds would you reduce to prepare the following alcohols? List all possibilities.



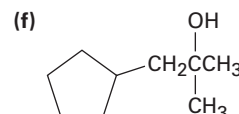
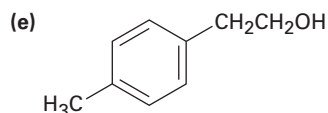
13.40 What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

(a) 2-Methylpropan-2-ol

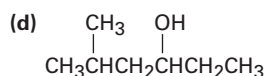
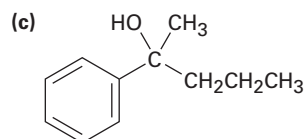
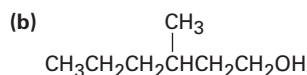
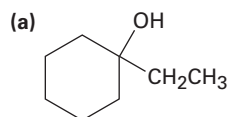
(b) 1-Ethylcyclohexanol

(c) 3-Phenylpentan-3-ol

(d) 2-Phenylpentan-2-ol

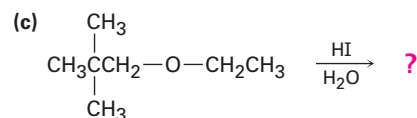
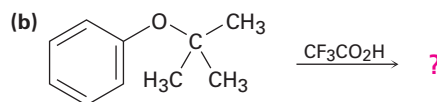
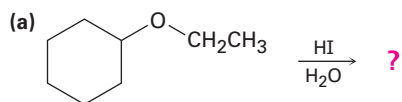


13.41 How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?



Reactions of Alcohols, Ethers, Phenols, Thiols, and Sulfides

13.42 Predict the products of the following ether cleavage reactions:



13.43 What products would you obtain from reaction of pentan-1-ol with the following reagents?

- (a) PBr_3 (b) SOCl_2
 (c) $\text{CrO}_3, \text{H}_2\text{O}, \text{H}_2\text{SO}_4$ (d) Dess–Martin reagent

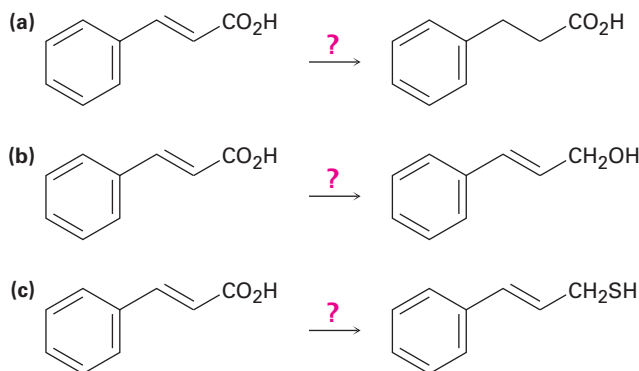
13.44 How would you prepare the following compounds from 2-phenylethanol? More than one step may be required.

- (a) Styrene ($\text{PhCH}=\text{CH}_2$)
 (b) Phenylacetaldehyde (PhCH_2CHO)
 (c) Phenylacetic acid ($\text{PhCH}_2\text{CO}_2\text{H}$)
 (d) Benzoic acid
 (e) Ethylbenzene
 (f) 1-Phenylethanol

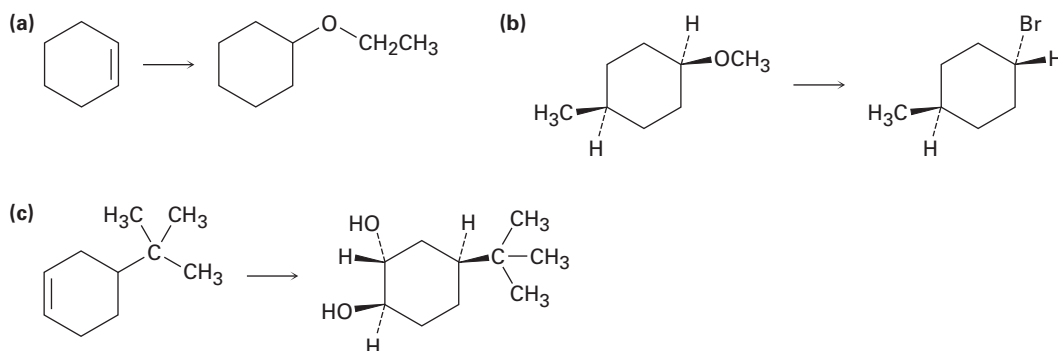
13.45 How would you prepare the following compounds from 1-phenylethanol? More than one step may be required.

- (a) Acetophenone (PhCOCH_3) (b) *m*-Bromobenzoic acid
 (c) *p*-Chloroethylbenzene (d) 2-Phenylpropan-2-ol
 (e) Methyl 1-phenylethyl ether (f) 1-Phenylethanol

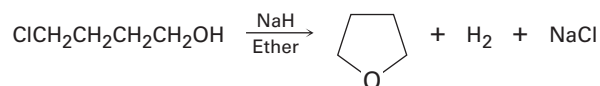
13.46 How would you carry out the following transformations?



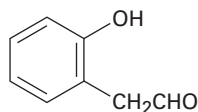
13.47 How would you carry out the following transformations? More than one step may be required.



- 13.48 When 4-chlorobutan-1-ol is treated with a strong base such as sodium hydride, NaH, tetrahydrofuran is produced. Suggest a mechanism.

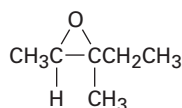


- 13.49 What product would you expect from cleavage of tetrahydrofuran with HI?
- 13.50 How would you prepare the following substances from cyclopentanol? More than one step may be required.
- (a) Cyclopentanone (b) Cyclopentene
- (c) 1-Methylcyclopentanol (d) *trans*-2-Methylcyclopentanol
- 13.51 What products would you expect to obtain from reaction of 1-methylcyclohexanol with the following reagents?
- (a) HBr (b) NaH (c) H₂SO₄ (d) Na₂Cr₂O₇
- 13.52 How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.



***o*-Hydroxyphenylacetaldehyde**

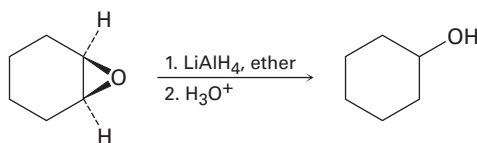
- 13.53 Imagine that you have treated (2*R*,3*R*)-2,3-epoxy-3-methylpentane with aqueous acid to carry out a ring-opening reaction.



2,3-Epoxy-3-methylpentane
(no stereochemistry implied)

- (a) Draw the epoxide showing stereochemistry.
- (b) Draw and name the product showing stereochemistry.
- (c) Is the product chiral? Explain.
- (d) Is the product optically active? Explain.

- 13.54 Epoxides are reduced by treatment with lithium aluminum hydride to yield alcohols. Propose a mechanism for this reaction.

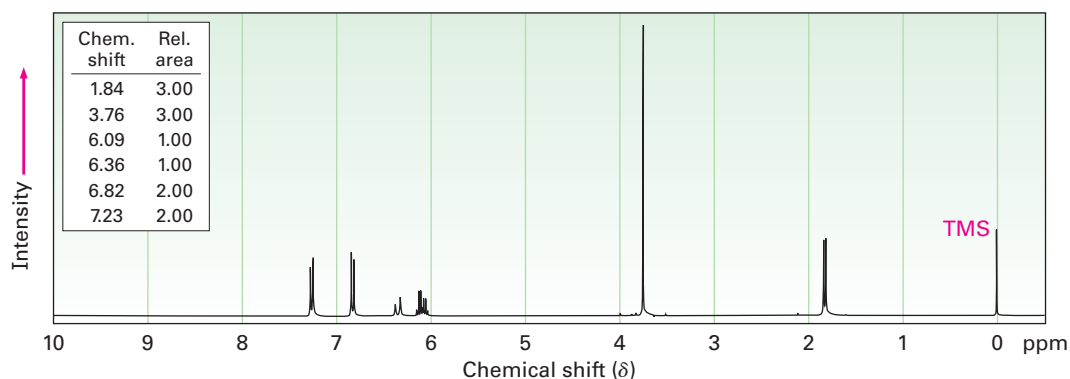


Spectroscopy of Alcohols, Ethers, Phenols, Thiols, and Sulfides

- 13.55 The red fox (*Vulpes vulpes*) uses a chemical communication system based on scent marks in urine. One component of fox urine is a sulfide. Mass spectral analysis of the pure scent-mark component shows $M^+ = 116$, IR spectroscopy shows an intense band at 890 cm^{-1} , and ^1H NMR spectroscopy reveals the following peaks. Propose a structure for the molecule. [Note: $(\text{CH}_3)_2\text{S}$ absorbs at 2.1δ .]

1.74 δ (3 H, singlet); 2.11 δ (3 H, singlet); 2.27 δ (2 H, triplet, $J = 4.2 \text{ Hz}$);
2.57 δ (2 H, triplet, $J = 4.2 \text{ Hz}$); 4.73 δ (2 H, broad)

- 13.56 Anethole, $\text{C}_{10}\text{H}_{12}\text{O}$, a major constituent of the oil of anise, has the ^1H NMR spectrum shown. On oxidation with $\text{Na}_2\text{Cr}_2\text{O}_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.

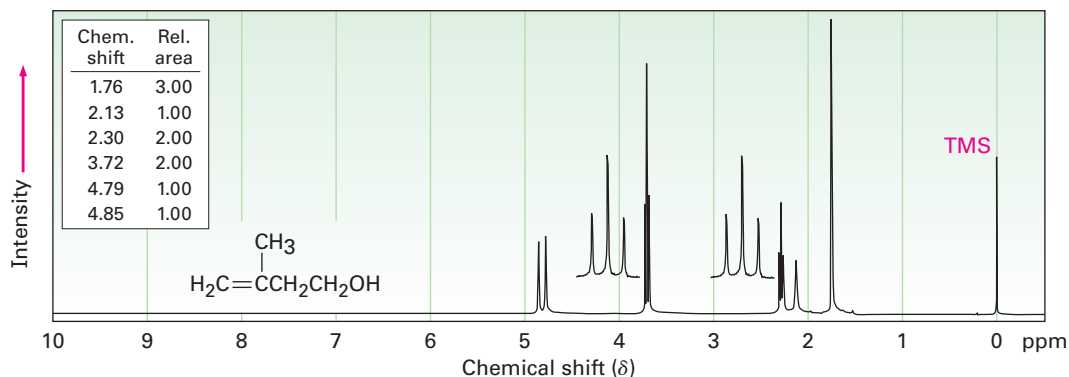


- 13.57 Propose a structure consistent with the following spectral data for a compound $\text{C}_8\text{H}_{18}\text{O}_2$:

IR: 3350 cm^{-1}

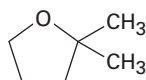
^1H NMR: 1.24 δ (12 H, singlet); 1.56 δ (4 H, singlet); 1.95 δ (2 H, singlet)

- 13.58** The ^1H NMR spectrum shown is that of 3-methylbut-3-en-1-ol. Assign all the observed resonance peaks to specific protons, and account for the splitting patterns.



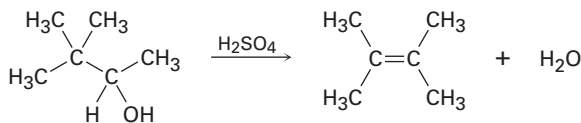
General Problems

- 13.59** When 2-methylpentane-2,5-diol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?

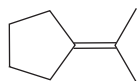


2,2-Dimethyltetrahydrofuran

- 13.60** Methyl aryl ethers, such as anisole, are cleaved to iodomethane and a phenoxide ion on heating with LiI in DMF. Propose a mechanism for this reaction.
- 13.61** *tert*-Butyl ethers can be prepared by the reaction of an alcohol with 2-methylpropene in the presence of an acid catalyst. Propose a mechanism.
- 13.62** Why do you suppose HI and HBr are more effective than HCl in cleaving ethers? (See Section 12-7.)
- 13.63** Evidence for carbocation intermediates in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethylbut-2-ene from 3,3-dimethylbutan-2-ol. (Review Section 7-10.)

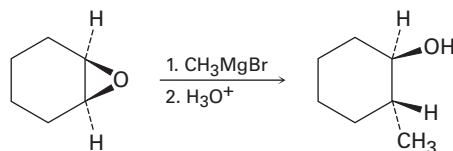


- 13.64** Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexene and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.

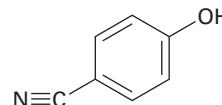
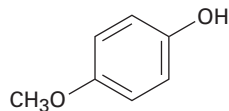
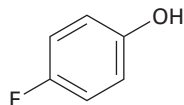
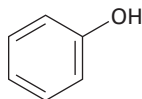


Isopropylidenecyclopentane

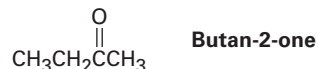
- 13.65** Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.



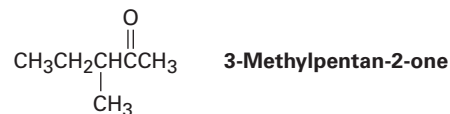
- 13.66** Rank the following substituted phenols in order of increasing acidity:



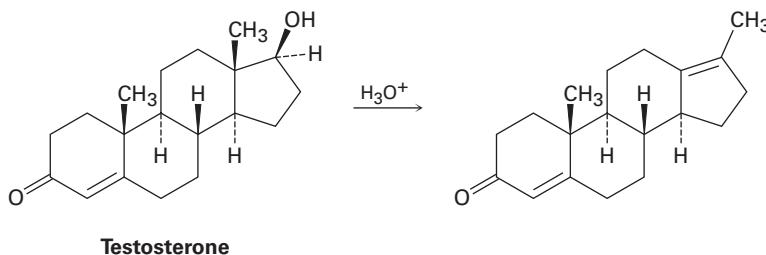
- 13.67** Reduction of butan-2-one with NaBH_4 yields butan-2-ol. Is the product chiral? Is it optically active? Explain.



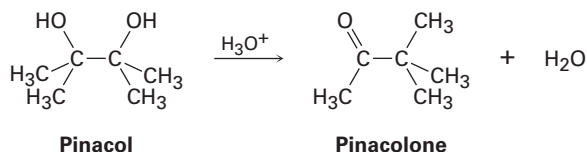
- 13.68** Reaction of (*S*)-3-methylpentan-2-one with methylmagnesium bromide followed by acidification yields 2,3-dimethylpentan-2-ol. What is the stereochemistry of the product? Is the product optically active?



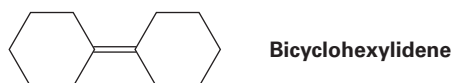
- 13.69** Testosterone is one of the most important male steroid hormones. When testosterone is dehydrated by treatment with acid, rearrangement occurs to yield the product shown. Propose a mechanism to account for this reaction.



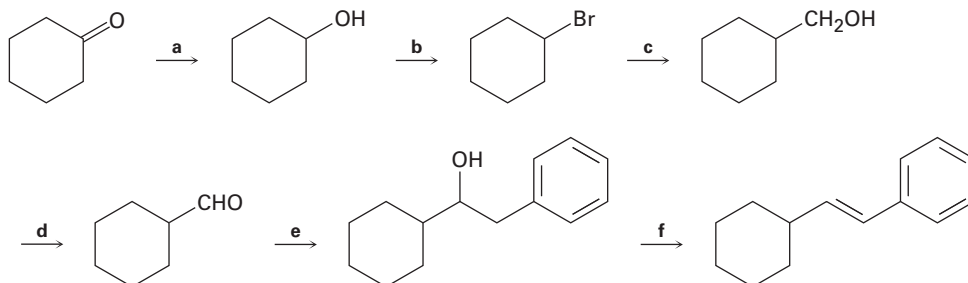
- 13.70** Dehydration of *trans*-2-methylcyclopentanol with POCl_3 in pyridine yields predominantly 3-methylcyclopentene. Is the stereochemistry of this dehydration syn or anti? Can you suggest a reason for formation of the observed product?
- 13.71** 2,3-Dimethylbutane-2,3-diol has the common name *pinacol*. On heating with aqueous acid, pinacol rearranges to *pinacolone*, 3,3-dimethylbutan-2-one. Suggest a mechanism.



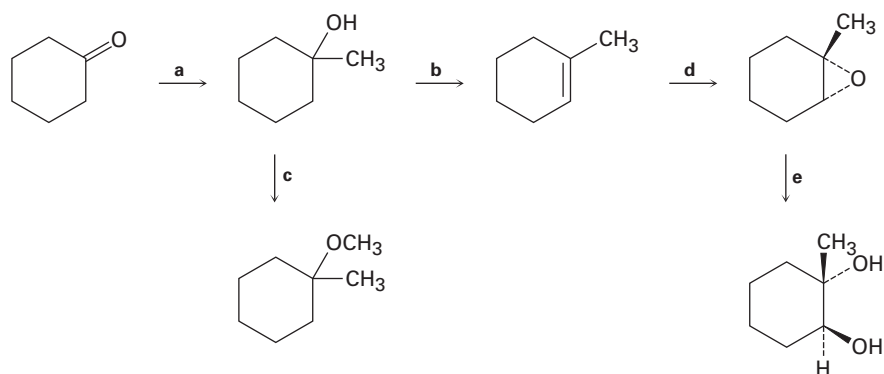
- 13.72** As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.
- 13.73** Propose a synthesis of bicyclohexylidene, starting from cyclohexanone as the only source of carbon.



- 13.74** Identify the reagents **a–f** in the following scheme:

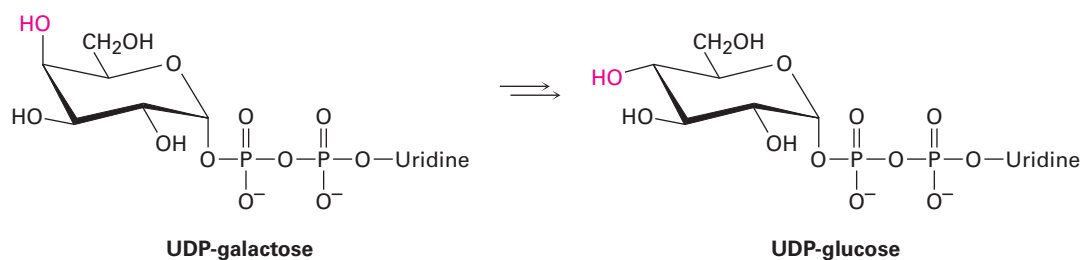


- 13.75** Identify the reagents **a–e** in the following scheme:



13.76 *Disparlure*, $C_{19}H_{38}O$, is a sex attractant released by the female gypsy moth, *Lymantria dispar*. The 1H NMR spectrum of *disparlure* shows a large absorption in the alkane region, 1 to 2 δ , and a triplet at 2.8 δ . Reaction of *disparlure*, first with aqueous acid and then with $KMnO_4$, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. ($KMnO_4$ cleaves 1,2-diols to yield carboxylic acids.) Neglecting stereochemistry, propose a structure for *disparlure*. The actual compound is a chiral molecule with $7R,8S$ stereochemistry. Draw *disparlure*, showing the correct stereochemistry.

13.77 Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the isomerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The enzyme responsible for the transformation uses NAD^+ as cofactor. Propose a mechanism.



13.78 Compound **A**, $C_5H_{10}O$, is one of the basic building blocks of nature. All steroids and many other naturally occurring compounds are built from compound **A**. Spectroscopic analysis of **A** yields the following information:

IR: 3400 cm^{-1} ; 1640 cm^{-1}

1H NMR: 1.63 δ (3 H, singlet); 1.70 δ (3 H, singlet);
 3.83 δ (1 H, broad singlet); 4.15 δ (2 H, doublet, $J = 7\text{ Hz}$);
 5.70 δ (1 H, triplet, $J = 7\text{ Hz}$)

- (a) From the IR spectrum, what is the nature of the oxygen-containing functional group?
- (b) What kinds of protons are responsible for the NMR absorptions listed?
- (c) Propose a structure for **A**.

13.79 A compound of unknown structure gave the following spectroscopic data:

Mass spectrum: $M^+ = 88.1$

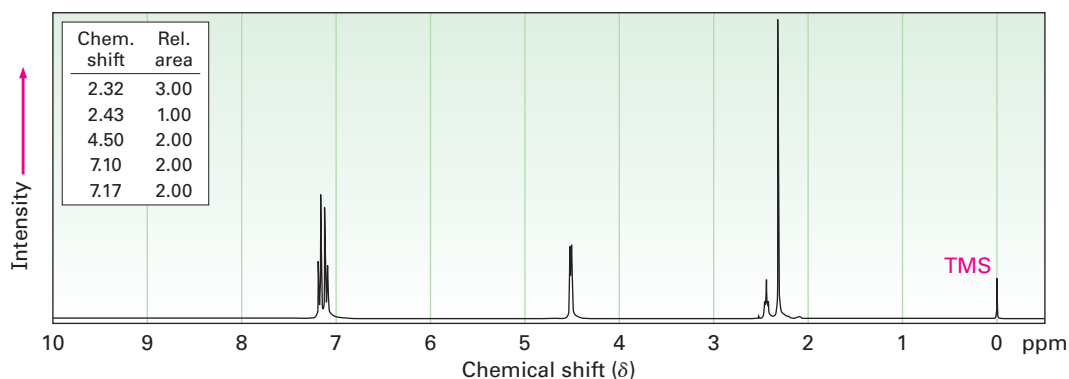
IR: 3600 cm^{-1}

$^1\text{H NMR}$: $1.4\ \delta$ (2 H, quartet, $J = 7\text{ Hz}$); $1.2\ \delta$ (6 H, singlet);
 $1.0\ \delta$ (1 H, singlet); $0.9\ \delta$ (3 H, triplet, $J = 7\text{ Hz}$)

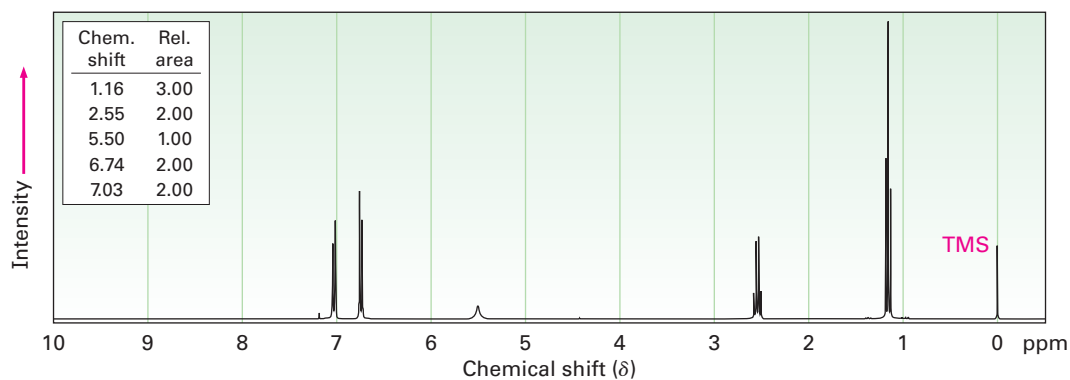
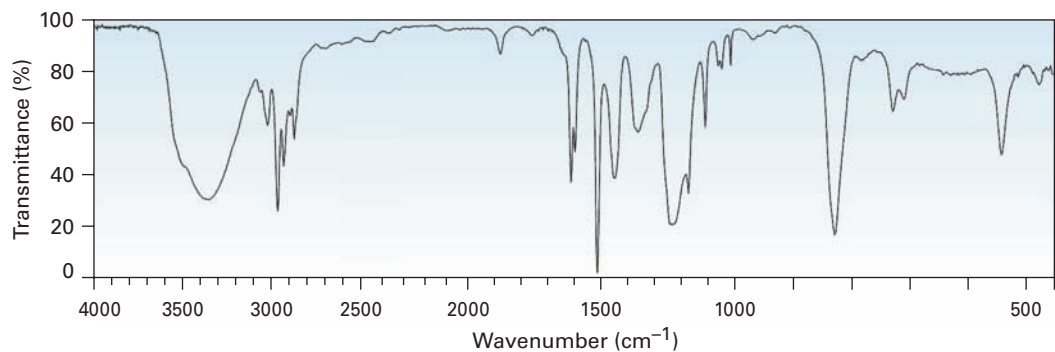
$^{13}\text{C NMR}$: $74, 35, 27, 9\ \delta$

- Assuming that the compound contains C and H but may or may not contain O, give three possible molecular formulas.
- How many protons (H) does the compound contain?
- What functional group(s) does the compound contain?
- How many carbons does the compound contain?
- What is the molecular formula of the compound?
- What is the structure of the compound?
- Assign the peaks in the $^1\text{H NMR}$ spectrum of the molecule to specific protons.

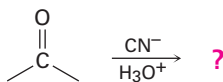
13.80 The following $^1\text{H NMR}$ spectrum is that of an alcohol, $\text{C}_8\text{H}_{10}\text{O}$. Propose a structure.



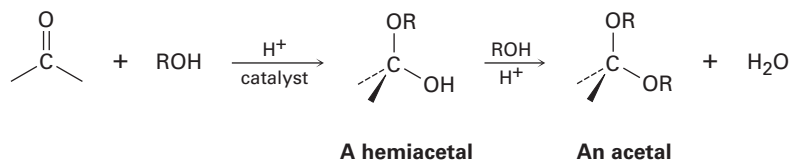
- 13.81 Compound A, $C_8H_{10}O$, has the IR and 1H NMR spectra shown. Propose a structure consistent with the observed spectra, and assign each peak in the NMR spectrum. Note that the absorption at 5.5δ disappears when D_2O is added.



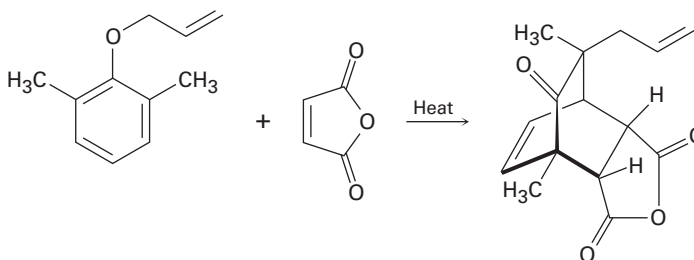
- 13.82 The reduction of carbonyl compounds by reaction with hydride reagents (H^-) and the Grignard addition by reaction with organo-magnesium halides ($R^- + MgBr$) are examples of *nucleophilic carbonyl addition reactions*. What analogous product do you think might result from reaction of cyanide ion with a ketone?



- 13.83** Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals*, compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further reaction of a hemiacetal with alcohol then yields an *acetal*, a compound that has two ether-like oxygens bonded to the same carbon.



- (a) Show the structures of the hemiacetal and acetal you would obtain by reaction of cyclohexanone with ethanol.
- (b) Propose a mechanism for the conversion of a hemiacetal into an acetal.
- 13.84** Propose a mechanism to account for the following transformation. What two kinds of reactions are occurring?

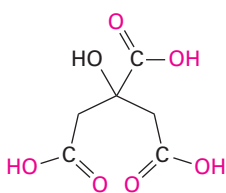


A Preview of Carbonyl Chemistry

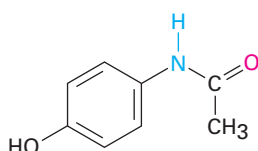
CONTENTS

- I Kinds of Carbonyl Compounds
- II Nature of the Carbonyl Group
- III General Reactions of Carbonyl Compounds
- IV Summary

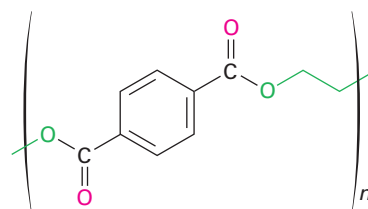
Carbonyl compounds are everywhere. Most biological molecules contain carbonyl groups, as do most pharmaceutical agents and many of the synthetic chemicals that touch our everyday lives. Citric acid, found in lemons and oranges; acetaminophen, the active ingredient in many over-the-counter headache remedies; and Dacron, the polyester material used in clothing, all contain different kinds of carbonyl groups.



Citric acid
(a carboxylic acid)



Acetaminophen
(an amide)



Dacron
(a polyester)

To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. Thus, we'll spend the next four chapters discussing the chemistry of the **carbonyl group**, $\text{C}=\text{O}$ (pronounced car-bo-neel). There are many different kinds of carbonyl compounds and many different reactions, but there are only a few fundamental principles that tie the entire field together. The purpose of this brief preview is not to show details of specific reactions but rather to provide a framework for learning carbonyl-group chemistry. Read through this preview now, and return to it on occasion to remind yourself of the larger picture.

I Kinds of Carbonyl Compounds

TABLE 1 shows some of the many different kinds of carbonyl compounds. All contain an **acyl group** ($\text{R}-\text{C}=\text{O}$) bonded to another substituent. The R part of the acyl group can be any practically organic part-structure, and the other substituent to which the acyl group is bonded might be a carbon, hydrogen, oxygen, halogen, nitrogen, or sulfur.

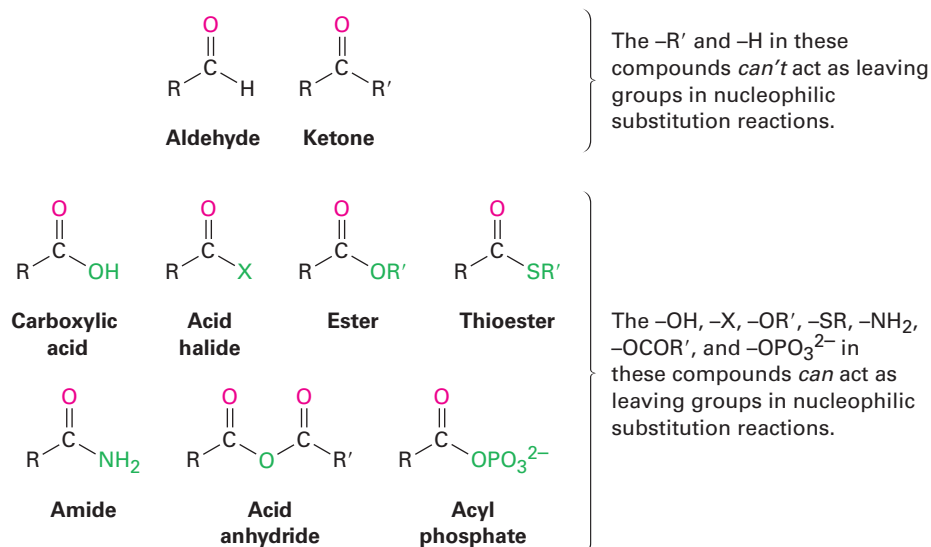
It's useful to classify carbonyl compounds into two categories based on the kinds of chemistry they undergo. In one category are aldehydes and ketones; in the other are carboxylic acids and their derivatives. The acyl group in an aldehyde or ketone is bonded to an atom (H or C, respectively) that can't stabilize a negative charge and therefore can't act as a leaving group in a



TABLE 1 Types of Carbonyl Compounds

Name	General formula	Name ending	Name	General formula	Name ending
Aldehyde		-al	Ester		-oate
Ketone		-one	Lactone (cyclic ester)		None
Carboxylic acid		-oic acid	Thioester		-thioate
Acid halide		-yl or -oyl halide	Amide		-amide
Acid anhydride		-oic anhydride	Lactam (cyclic amide)		None
Acyl phosphate		-yl phosphate			

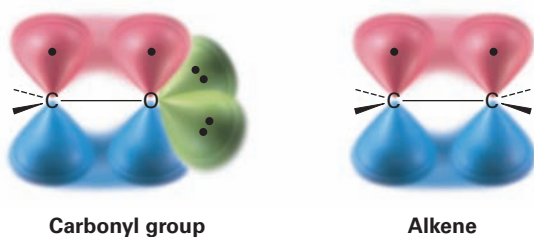
nucleophilic substitution reaction. The acyl group in a carboxylic acid or derivative, however, is bonded to an atom (oxygen, halogen, sulfur, or nitrogen) that *can* stabilize a negative charge and therefore *can* act as a leaving group in a nucleophilic substitution reaction.



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II Nature of the Carbonyl Group

The carbon–oxygen double bond of a carbonyl group is similar in many respects to the carbon–carbon double bond of an alkene. The carbonyl carbon atom is sp^2 -hybridized and forms three σ bonds. The fourth valence electron on carbon remains in a p orbital and forms a π bond to oxygen by overlap with an oxygen p orbital. The oxygen atom also has two nonbonding pairs of electrons, which occupy its remaining two orbitals.



Like alkenes, carbonyl compounds are planar about the double bond and have bond angles of approximately 120° . **FIGURE 1** shows the structure of acetaldehyde and indicates its bond lengths and angles. As you might expect, the carbon–oxygen double bond is both shorter (122 pm versus 143 pm) and stronger [732 kJ/mol (175 kcal/mol) versus 385 kJ/mol (92 kcal/mol)] than a C–O single bond.

Bond angle	($^\circ$)	Bond length	(pm)
H–C–C	118	C=O	122
C–C=O	121	C–C	150
H–C=O	121	OC–H	109

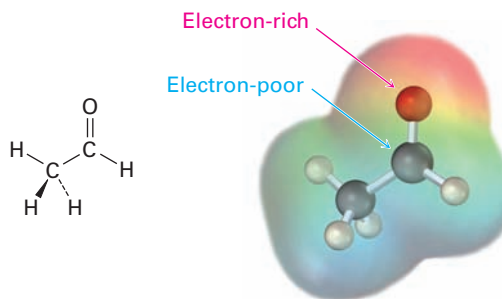


FIGURE 1 Structure of acetaldehyde.

As indicated by the electrostatic potential map in Figure 1, the carbon–oxygen double bond is strongly polarized because of the high electronegativity of oxygen relative to carbon. Thus, the carbonyl carbon atom carries a partial positive charge, is an electrophilic (Lewis acidic) site, and reacts with nucleophiles. Conversely, the carbonyl oxygen atom carries a partial negative charge, is a nucleophilic (Lewis basic) site, and reacts with electrophiles. We'll see in the next four chapters that the majority of carbonyl-group reactions can be rationalized by simple polarity arguments.

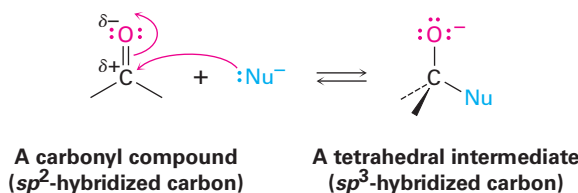
III General Reactions of Carbonyl Compounds

Both in the laboratory and in living organisms, most reactions of carbonyl compounds take place by one of four general mechanisms: *nucleophilic addition*, *nucleophilic acyl substitution*, *alpha substitution*, and *carbonyl condensation*.

These mechanisms have many variations, just as alkene electrophilic addition reactions and S_N2 reactions do, but the variations are much easier to learn when the fundamental similarities of their mechanisms are made clear. Let's see what the four mechanisms are and what kinds of chemistry carbonyl compounds undergo.

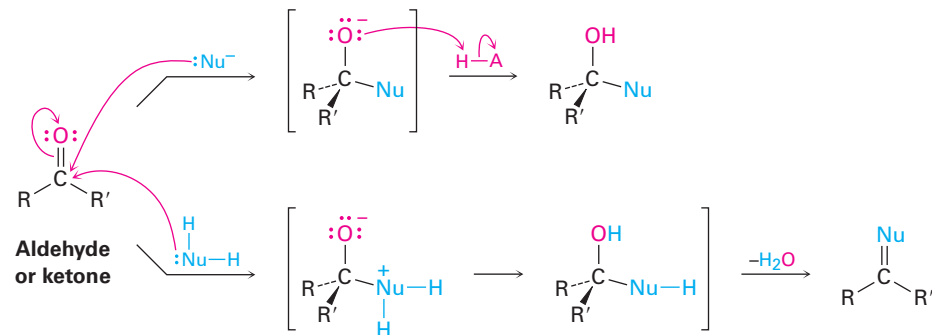
Nucleophilic Addition Reactions of Aldehydes and Ketones (Chapter 14)

The most common reaction of aldehydes and ketones is the **nucleophilic addition reaction**, in which a nucleophile, $:\text{Nu}^-$, adds to the electrophilic carbon of the carbonyl group. Because the nucleophile uses an electron pair to form a new bond to carbon, two electrons from the carbon–oxygen double bond must move toward the electronegative oxygen atom to give an alkoxide anion. The carbonyl carbon rehybridizes from sp^2 to sp^3 during the reaction, and the carbon atom of the alkoxide ion product therefore has tetrahedral geometry.



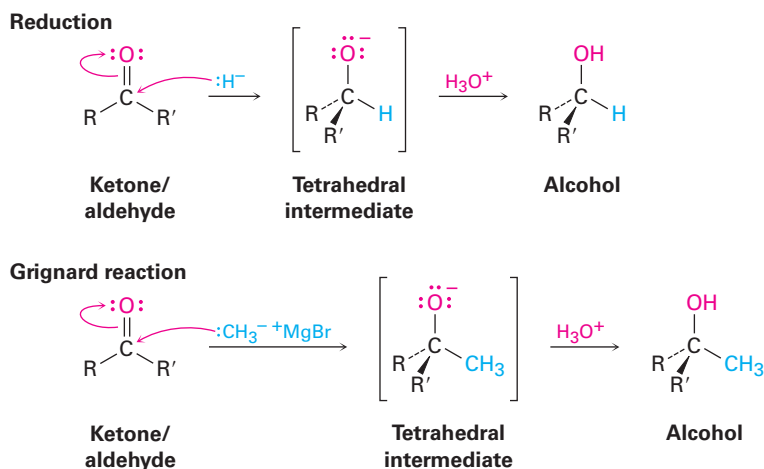
Once formed, and depending on the nature of the nucleophile, the tetrahedral alkoxide intermediate can undergo either of two further reactions, as shown in **FIGURE 2**. Often, the tetrahedral alkoxide intermediate is simply protonated by water or acid to form an alcohol product. Alternatively, the tetrahedral intermediate can be protonated and expel the oxygen to form a new double bond between the carbonyl carbon and the nucleophile. We'll study both processes in detail in Chapter 14.

FIGURE 2 The addition reaction of an aldehyde or a ketone with a nucleophile. Depending on the nucleophile, either an alcohol or a compound with a $\text{C}=\text{Nu}$ double bond is formed.



FORMATION OF AN ALCOHOL The simplest reaction of a tetrahedral alkoxide intermediate is protonation to yield an alcohol. We've already seen two examples of this kind of process during reduction of aldehydes and ketones with hydride reagents, such as NaBH_4 or LiAlH_4 , and during Grignard reactions (Section 13-3). During a reduction, the nucleophile that

adds to the carbonyl group is a hydride ion, H^- , while during a Grignard reaction, the nucleophile is a carbanion, R_3C^- .



FORMATION OF C=NU The second common mode of nucleophilic addition, which often occurs with amine nucleophiles, involves elimination of oxygen and formation of a $\text{C}=\text{Nu}$ double bond. For example, aldehydes and ketones react with primary amines, RNH_2 , to form *imines*, $\text{R}_2\text{C}=\text{NR}'$. These reactions proceed through exactly the same kind of tetrahedral intermediate as that formed during hydride reduction and Grignard reaction, but the initially formed alkoxide ion is not isolated. Instead, it is protonated and then loses water to form an imine, as shown in **FIGURE 3**.

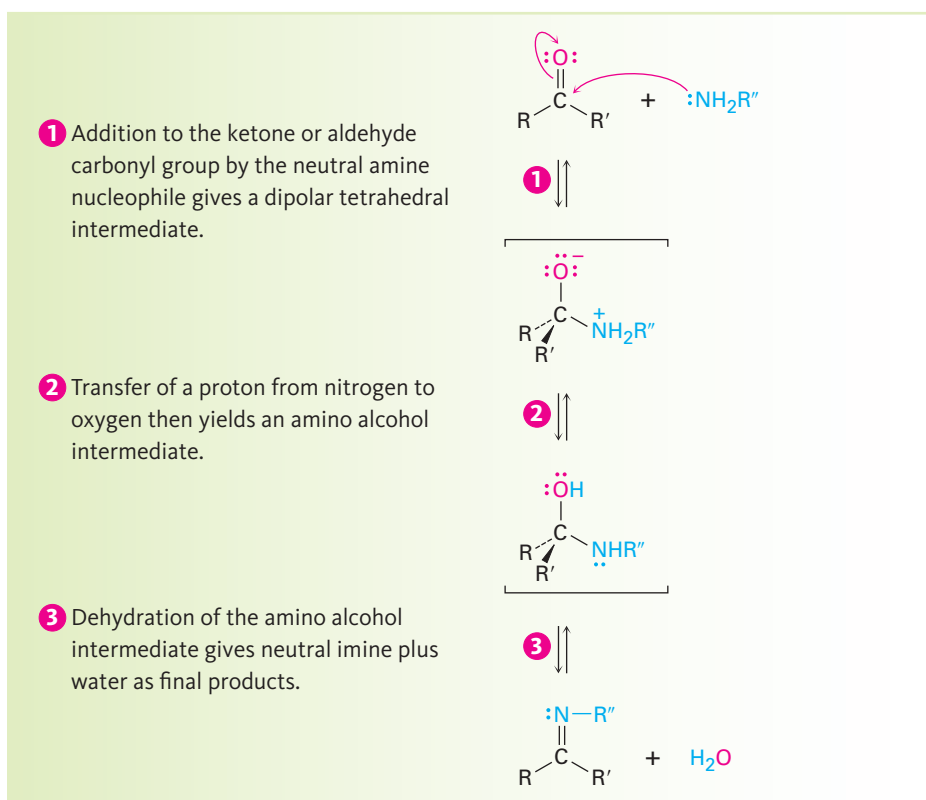
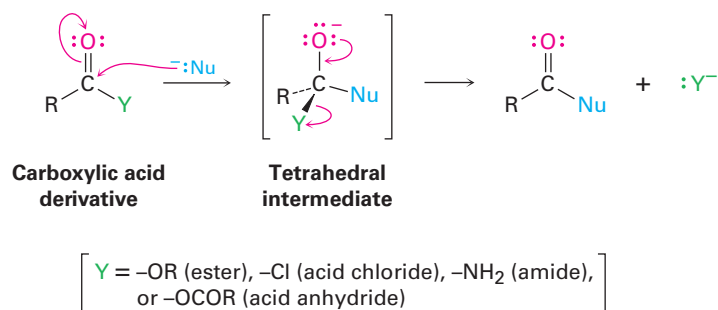


FIGURE 3 Mechanism of formation of an imine, $\text{R}_2\text{C}=\text{NR}'$, by reaction of an amine with an aldehyde or a ketone.

© John McMurry

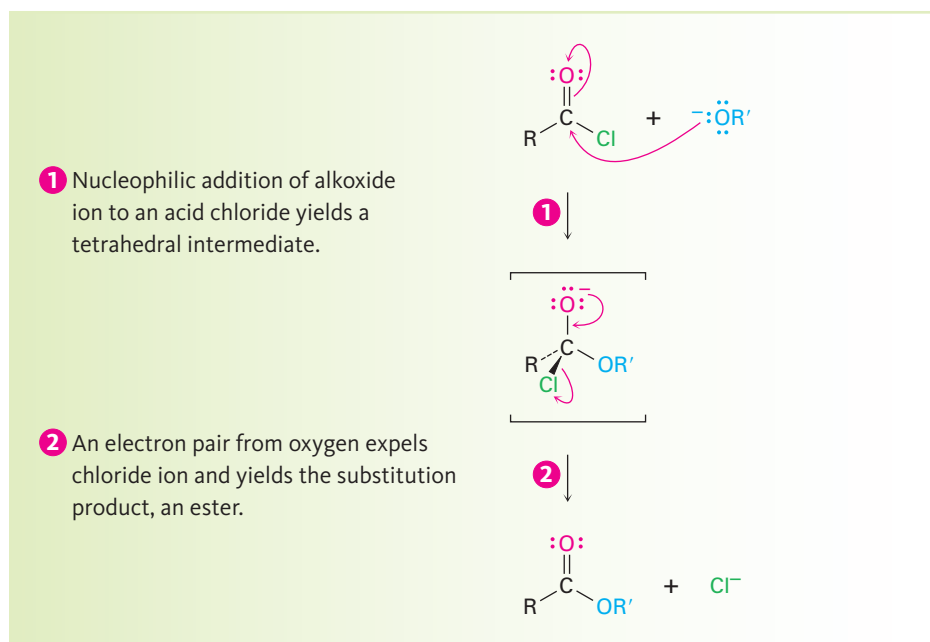
Nucleophilic Acyl Substitution Reactions of Carboxylic Acid Derivatives (Chapter 16)

The second fundamental reaction of carbonyl compounds, **nucleophilic acyl substitution**, is related to the nucleophilic addition reaction just discussed but occurs only with carboxylic acid derivatives rather than with aldehydes and ketones. When the carbonyl group of a carboxylic acid derivative reacts with a nucleophile, addition occurs in the usual way, but the initially formed tetrahedral alkoxide intermediate is not isolated. Because carboxylic acid derivatives have a leaving group bonded to the carbonyl-group carbon, the tetrahedral intermediate can react further by expelling the leaving group and forming a new carbonyl compound:



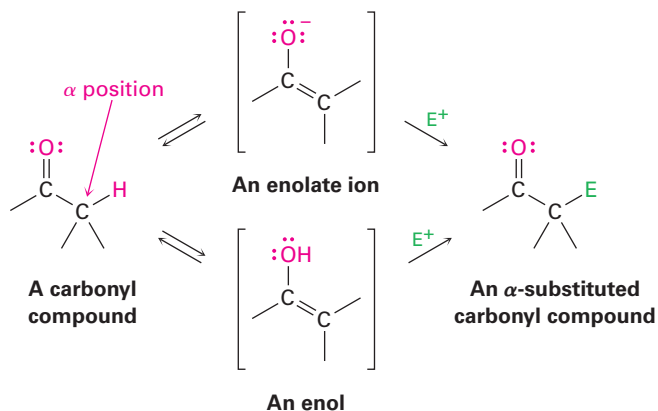
The net effect of nucleophilic acyl substitution is the replacement of the leaving group by the entering nucleophile. We'll see in Chapter 16, for instance, that acid chlorides are rapidly converted into esters by treatment with alkoxide ions (**FIGURE 4**).

FIGURE 4 Mechanism of the nucleophilic acyl substitution reaction of an acid chloride with an alkoxide ion. An ester product is formed.

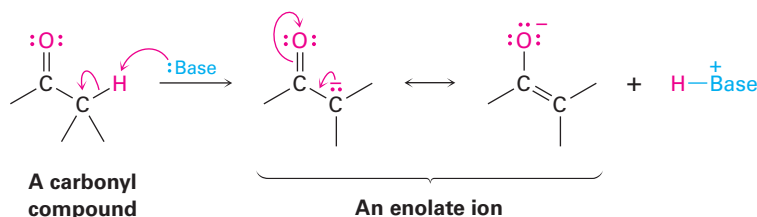


Alpha-Substitution Reactions (Chapter 17)

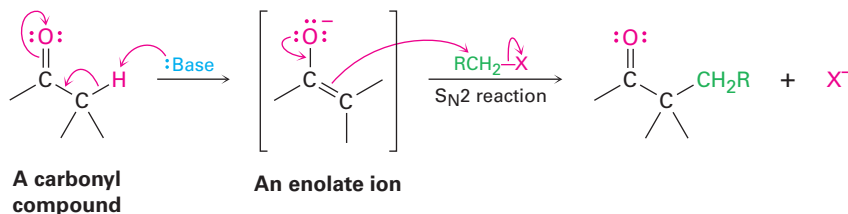
The third major reaction of carbonyl compounds, **alpha substitution**, occurs at the position next to the carbonyl group—the alpha (α) position. This reaction, which takes place with all carbonyl compounds regardless of structure, results in the substitution of an α hydrogen by an electrophile through the formation of an intermediate *enol* or *enolate ion*:



For reasons that we'll explore in Chapter 17, the presence of a carbonyl group renders the hydrogens on the α -carbon acidic. Carbonyl compounds therefore react with strong base to yield enolate ions.



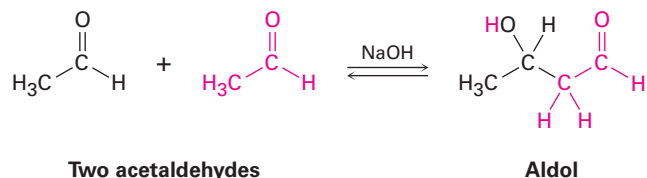
Because they're negatively charged, enolate ions act as nucleophiles and undergo many of the reactions we've already studied. For example, enolates react with primary alkyl halides in the S_N2 reaction. The nucleophilic enolate ion displaces halide ion, and a new C–C bond forms:



The S_N2 alkylation reaction between an enolate ion and an alkyl halide is a powerful method for making C–C bonds, thereby building up larger molecules from smaller precursors. We'll study the alkylation of many kinds of carbonyl compounds in Chapter 17.

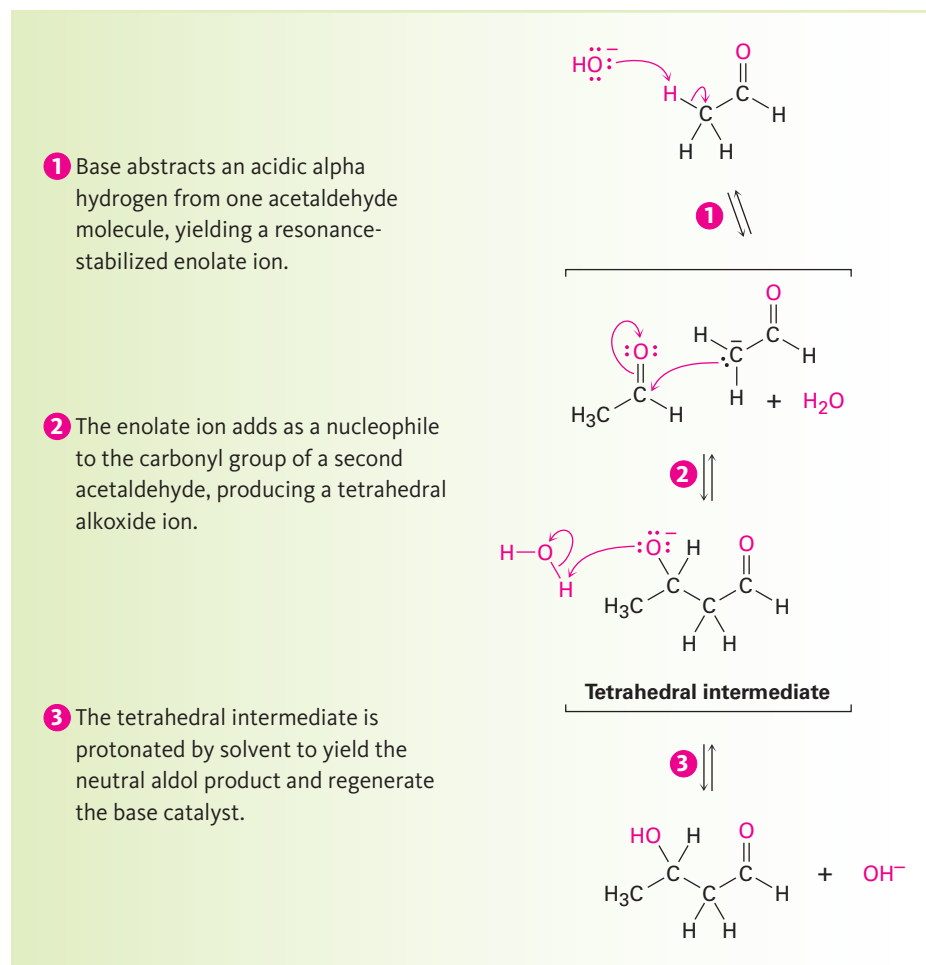
Carbonyl Condensation Reactions (Chapter 17)

The fourth and last fundamental reaction of carbonyl groups, **carbonyl condensation**, takes place when two carbonyl-containing molecules react with each other. When acetaldehyde is treated with base, for instance, two molecules combine to yield the hydroxy aldehyde product known as *aldol* (*aldehyde* + *alcohol*):



Although the carbonyl condensation reaction appears different from the three processes already discussed, it's actually quite similar. A carbonyl condensation reaction is simply a *combination* of an α -substitution step and a nucleophilic addition step. The initially formed enolate ion of one acetaldehyde molecule acts as a nucleophile and adds to the carbonyl group of a second acetaldehyde molecule, as shown in **FIGURE 5**. From the point of view of the first molecule, an α -substitution occurs; from the point of view of the second molecule, a nucleophilic addition occurs.

FIGURE 5 Mechanism of a carbonyl condensation reaction between two molecules of acetaldehyde. A hydroxy aldehyde product results.



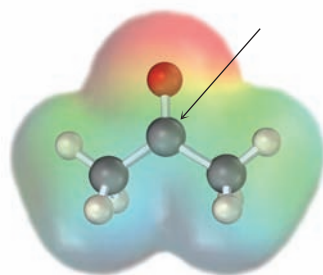
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IV Summary

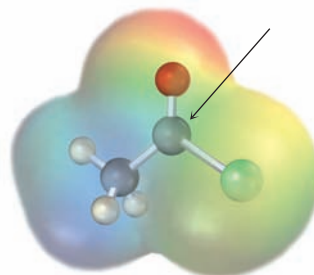
To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. We haven't looked at the details of specific carbonyl reactions in this short preview but rather have laid the groundwork for the next four chapters. All the carbonyl-group reactions we'll be studying in Chapters 14 through 17 fall into one of the four fundamental categories discussed in this preview. Knowing where you'll be heading should help you keep matters straight in understanding this most important of all functional groups.

EXERCISES

1. Judging from the following electrostatic potential maps, which kind of carbonyl compound has the more electrophilic carbonyl carbon atom, a ketone or an acid chloride? Which has the more nucleophilic carbonyl oxygen atom? Explain.



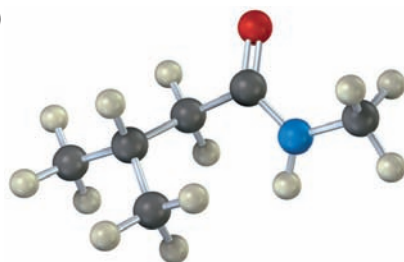
Acetone
(ketone)



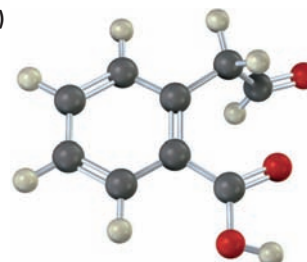
Acetyl chloride
(acid chloride)

2. Identify the kinds of carbonyl groups in the following molecules:

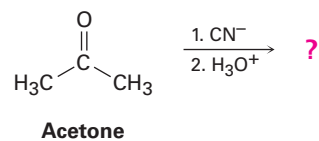
(a)



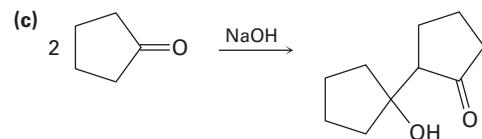
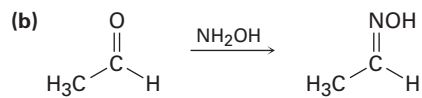
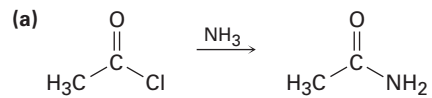
(b)



3. Predict the product formed by nucleophilic addition of cyanide ion (CN^-) to the carbonyl group of acetone, followed by protonation to give an alcohol:



4. Identify each of the following reactions as a nucleophilic addition, nucleophilic acyl substitution, an α substitution, or a carbonyl condensation:



14

Aldehydes and Ketones:
Nucleophilic Addition Reactions

CONTENTS

- 14-1** Naming Aldehydes and Ketones
- 14-2** Preparing Aldehydes and Ketones
- 14-3** Oxidation of Aldehydes
- 14-4** Nucleophilic Addition Reactions of Aldehydes and Ketones
- 14-5** Nucleophilic Addition of H_2O : Hydration
- 14-6** Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation
- 14-7** Nucleophilic Addition of Amines: Imine and Enamine Formation
- 14-8** Nucleophilic Addition of Alcohols: Acetal Formation
- 14-9** Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction
- 14-10** Biological Reductions
- 14-11** Conjugate Nucleophilic Addition to α,β -Unsaturated Aldehydes and Ketones
- 14-12** Spectroscopy of Aldehydes and Ketones

SOMETHING EXTRA

Enantioselective Synthesis

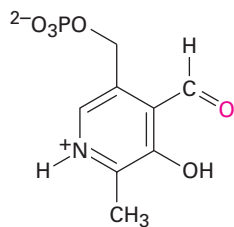


Phosphoglucose isomerase catalyzes the isomerization of glucose 6-phosphate to fructose 6-phosphate, the second step in glucose metabolism.

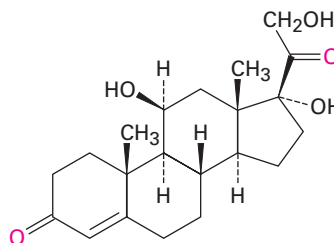
WHY THIS CHAPTER?

The chemistry of living organisms is, in many ways, the chemistry of carbonyl compounds. Aldehydes and ketones, in particular, are intermediates in the synthesis of many pharmaceutical agents, in almost all biological pathways, and in numerous industrial processes, so an understanding of their properties and reactions is essential. We'll look in this chapter at some of their most important reactions.

Aldehydes (RCHO) and ketones (R_2CO) are among the most widely occurring of all compounds. In nature, many substances required by living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions; the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.



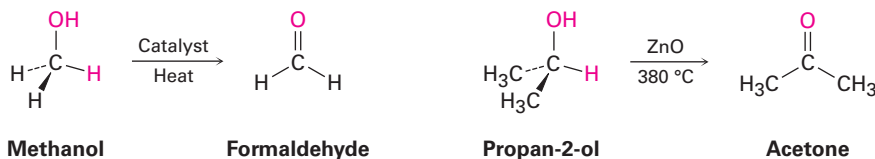
Pyridoxal phosphate (PLP)



Hydrocortisone

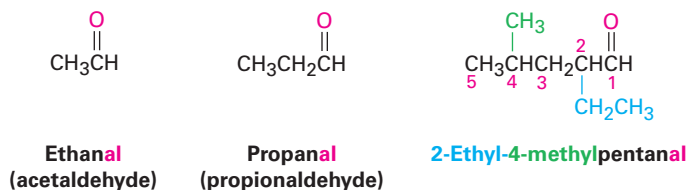
In the chemical industry, simple aldehydes and ketones are produced in large quantities for use as solvents and as starting materials to prepare a host of other compounds. For example, more than 23 million tons per year of formaldehyde, $\text{H}_2\text{C}=\text{O}$, is produced worldwide for use in building insulation

materials and in the adhesive resins that bind particle board and plywood. Acetone, $(\text{CH}_3)_2\text{C}=\text{O}$, is widely used as an industrial solvent; approximately 3.3 million tons per year is produced worldwide. Formaldehyde is synthesized industrially by catalytic oxidation of methanol, and one method of acetone preparation involves oxidation of propan-2-ol.

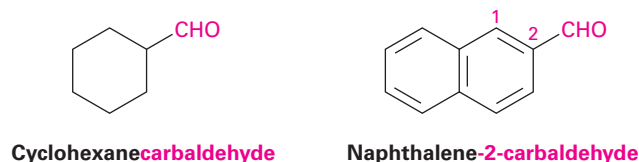


14-1 Naming Aldehydes and Ketones

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the $-\text{CHO}$ group, and the $-\text{CHO}$ carbon is numbered as C1. In the following examples, note that the longest chain in 2-ethyl-4-methylpentanal is actually a hexane, but this chain does not include the $-\text{CHO}$ group and thus is not the parent.




For cyclic aldehydes in which the $-\text{CHO}$ group is directly attached to a ring, the suffix *-carbaldehyde* is used:

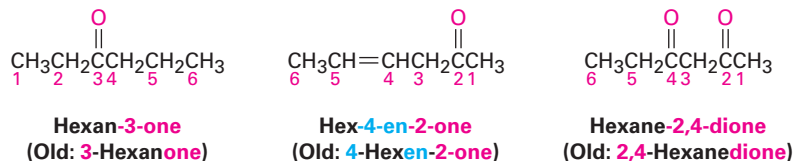


A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in [TABLE 14.1](#).

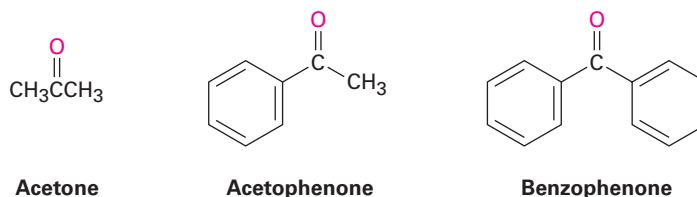
TABLE 14.1 Common Names of Some Simple Aldehydes

Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$\text{H}_2\text{C}=\text{CHCHO}$	Acrolein	Propenal
$\text{CH}_3\text{CH}=\text{CHCHO}$	Crotonaldehyde	But-2-enal
	Benzaldehyde	Benzenecarbaldehyde

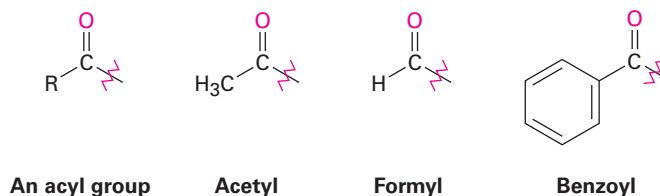
Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that contains the ketone group, and the numbering begins at the end nearer the carbonyl carbon. As with alkenes (Section 7-2) and alcohols (Section 13-1), the numerical locant is placed before the parent name in older rules but before the suffix in newer IUPAC recommendations. For example:



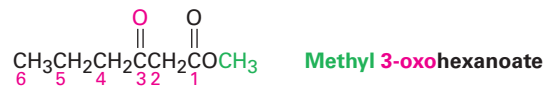
A few ketones are allowed by IUPAC to retain their common names:



When it's necessary to refer to the $\text{R}-\text{C}=\text{O}$ as a substituent, the name **acyl (a-sil) group** is used and the name ending *-yl* is attached. Thus, $\text{CH}_3\text{CO}-$ is an *acetyl* group, $-\text{CHO}$ is a *formyl* group, and $\text{C}_6\text{H}_5\text{CO}-$ is a *benzoyl* group.

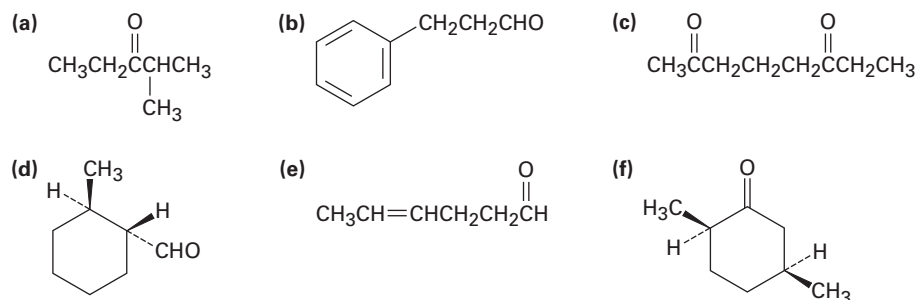


If other functional groups are present and the doubly bonded oxygen is considered a substituent on a parent chain, the prefix *oxo-* is used. For example:



PROBLEM 14.1

Name the following aldehydes and ketones:



PROBLEM 14.2

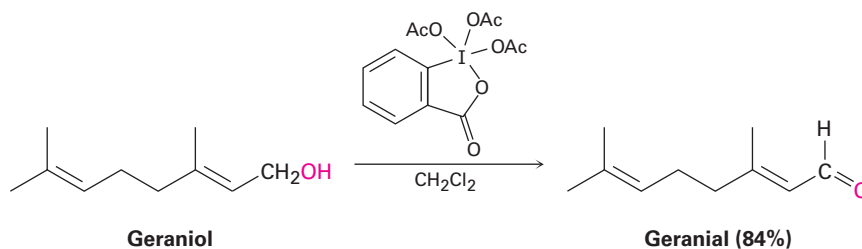
Draw structures corresponding to the following names:

- (a) 3-Methylbutanal (b) 4-Chloropentan-2-one
 (c) Phenylacetaldehyde (d) *cis*-3-*tert*-Butylcyclohexanecarbaldehyde
 (e) 3-Methylbut-3-enal (f) 2-(1-Chloroethyl)-5-methylheptanal

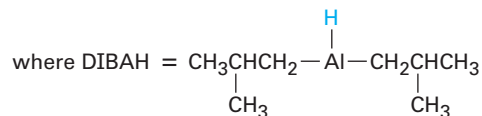
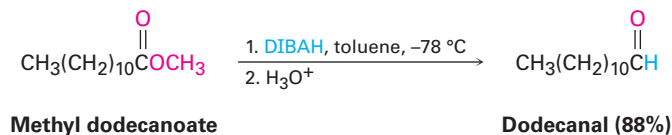
14-2 Preparing Aldehydes and Ketones

Preparing Aldehydes

One of the best methods of aldehyde synthesis is by oxidation of primary alcohols, as we saw in Section 13-5. The reaction is often carried out using the Dess–Martin periodinane reagent in dichloromethane solvent at room temperature:



A second method of aldehyde synthesis is one that we'll mention here just briefly and then return to in Section 16-6. Certain carboxylic acid derivatives can be *partially* reduced to yield aldehydes. The partial reduction of an ester by diisobutylaluminum hydride (DIBAH, or DIBAL-H), for instance, is an important laboratory-scale method of aldehyde synthesis, and mechanistically related processes also occur in biological pathways. The reaction is normally carried out at -78°C (dry-ice temperature) in toluene solution.



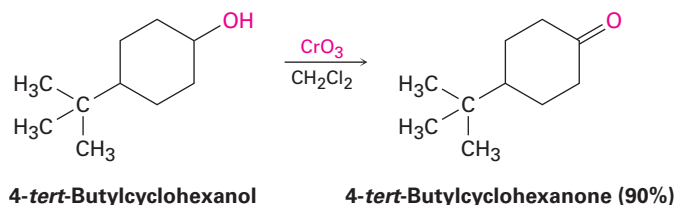
PROBLEM 14.3

How would you prepare pentanal from the following starting materials?

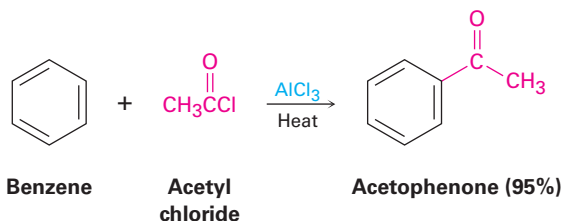
- (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$
 (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ (d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$

Preparing Ketones

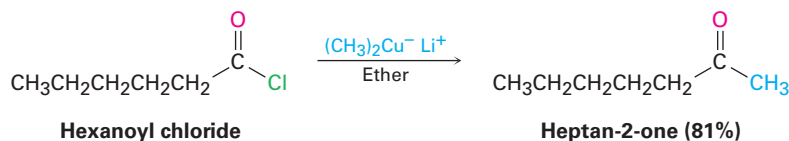
For the most part, methods of ketone synthesis are similar to those for aldehydes. Secondary alcohols are oxidized by a variety of reagents to give ketones (Section 13-5). The choice of oxidant depends on such factors as reaction scale, cost, and acid or base sensitivity of the alcohol, with either the Dess–Martin periodinane or a Cr(VI) reagent such as CrO_3 being a common choice.



Other methods include the ozonolysis of alkenes in which one of the unsaturated carbon atoms is disubstituted (Section 8-8) and Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of AlCl_3 catalyst (Section 9-7).



In addition, ketones can be prepared from certain carboxylic acid derivatives, just as aldehydes can. Among the most useful reactions of this type is that between an acid chloride and a lithium diorganocuprate reagent, R_2CuLi , such as we saw in Section 12-5. We'll look at this reaction in more detail in Section 16-4.



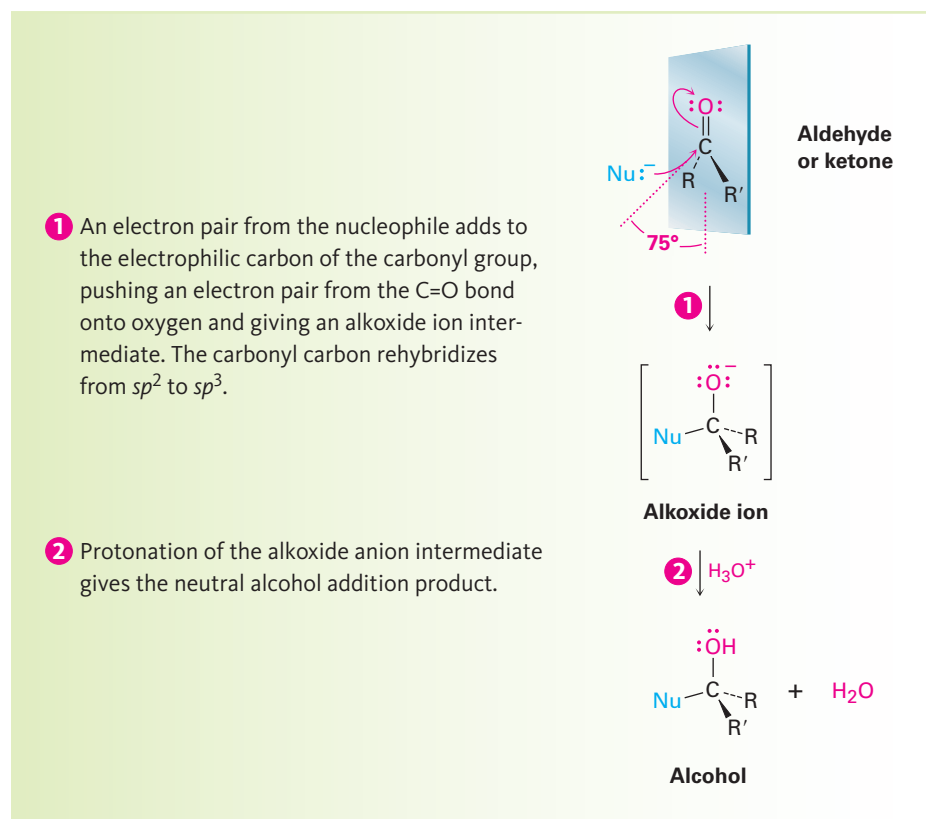
PROBLEM 14.4

How would you carry out the following reactions? More than one step may be required.

- Benzene \rightarrow *m*-Bromoacetophenone
- Bromobenzene \rightarrow Acetophenone
- 1-Methylcyclohexene \rightarrow 2-Methylcyclohexanone

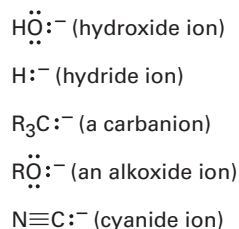
atom, and a tetrahedral alkoxide ion intermediate is produced (FIGURE 14.1). Protonation of the alkoxide by addition of acid then gives an alcohol.

FIGURE 14.1 Mechanism of a nucleophilic addition reaction to an aldehyde or ketone. The nucleophile approaches the carbonyl group from an angle of approximately 75° to the plane of the sp^2 orbitals, the carbonyl carbon rehybridizes from sp^2 to sp^3 , and an alkoxide ion is formed. Protonation by addition of acid then gives an alcohol.

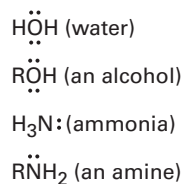


The nucleophile can be either negatively charged ($:\text{Nu}^-$) or neutral ($:\text{Nu}$). If it's neutral, however, it usually carries a hydrogen atom that can subsequently be eliminated, $:\text{Nu}-\text{H}$. For example:

Some negatively charged nucleophiles



Some neutral nucleophiles



Nucleophilic additions to aldehydes and ketones have two general variations, as shown in **FIGURE 14.2**. In one variation, the tetrahedral intermediate is protonated by water or acid to give an alcohol as the final product; in the second variation, the carbonyl oxygen atom is protonated and then eliminated as HO^- or H_2O to give a product with a $\text{C}=\text{Nu}$ bond.

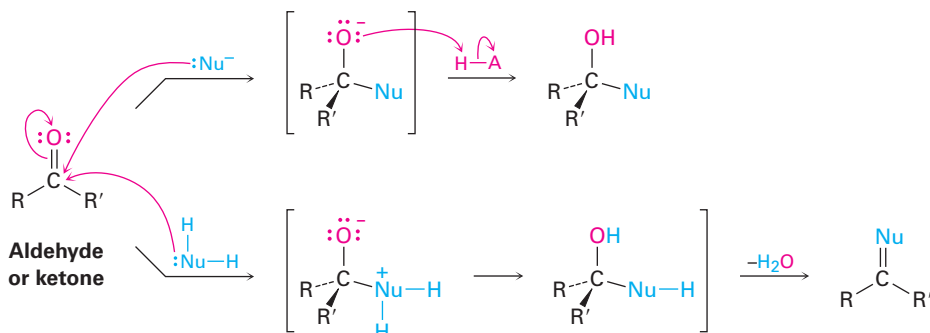


FIGURE 14.2 Two reaction pathways following addition of a nucleophile to an aldehyde or ketone. The top pathway leads to an alcohol product; the bottom pathway leads to a product with a $\text{C}=\text{Nu}$ bond.

Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons. Sterically, the presence of only one large substituent bonded to the $\text{C}=\text{O}$ carbon in an aldehyde versus two large substituents in a ketone means that a nucleophile is able to approach the aldehyde more readily. Thus, the transition state leading to the tetrahedral intermediate is less crowded and lower in energy for an aldehyde than for a ketone (**FIGURE 14.3**).

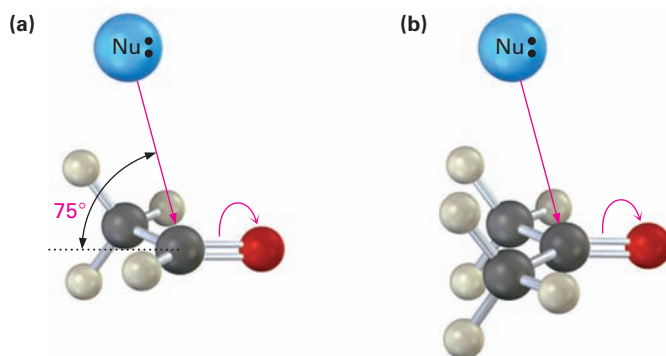
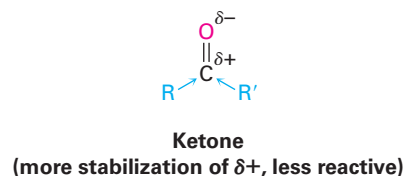
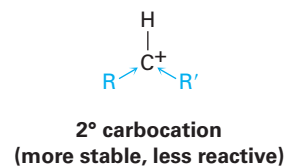
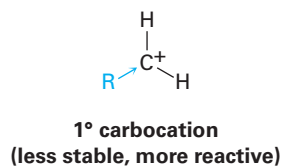


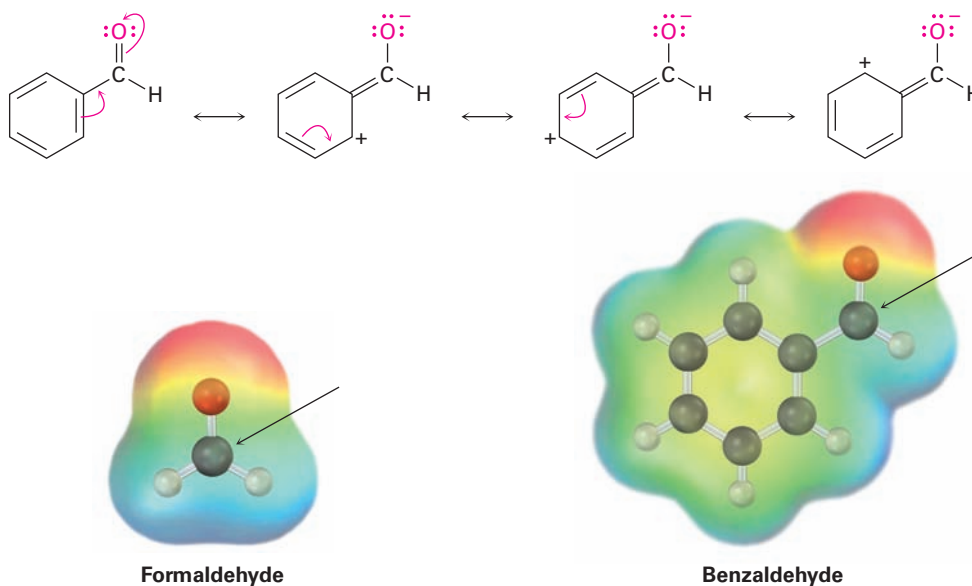
FIGURE 14.3 Steric hindrance in nucleophilic addition reactions. **(a)** Nucleophilic addition to an aldehyde is sterically less hindered because only one relatively large substituent is attached to the carbonyl-group carbon. **(b)** A ketone, however, has two large substituents and is more hindered. The approach of the nucleophile is along the $\text{C}=\text{O}$ bond at an angle of about 75° to the plane of the carbon sp^2 orbitals.

Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde carbonyl groups. To see this polarity difference, recall the stability order of carbocations (Section 7-8). A primary carbocation is higher in energy and thus more reactive than a secondary carbocation because it has only one alkyl group inductively stabilizing the positive charge rather than two. In the same way, an aldehyde has only one alkyl group inductively stabilizing the partial positive charge on the carbonyl carbon

rather than two, is a bit more electrophilic, and is therefore more reactive than a ketone.



One further comparison: aromatic aldehydes, such as benzaldehyde, are less reactive in nucleophilic addition reactions than aliphatic aldehydes because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic. Comparing electrostatic potential maps of formaldehyde and benzaldehyde, for instance, shows that the carbonyl carbon atom is less positive (less blue) in the aromatic aldehyde.



PROBLEM 14.5

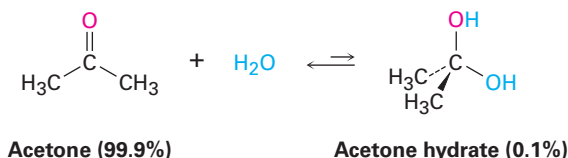
Treatment of an aldehyde or ketone with cyanide ion ($\text{:C}\equiv\text{N}^-$), followed by protonation of the tetrahedral alkoxide ion intermediate, gives a *cyanohydrin*. Show the structure of the cyanohydrin obtained from cyclohexanone.

PROBLEM 14.6

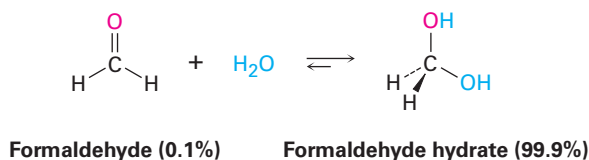
p-Nitrobenzaldehyde is more reactive toward nucleophilic additions than *p*-methoxybenzaldehyde. Explain.

14-5 Nucleophilic Addition of H₂O: Hydration

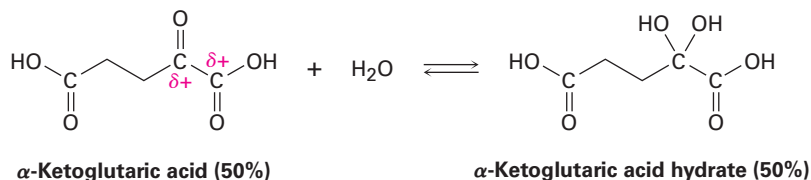
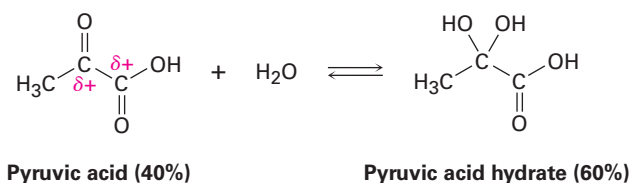
Aldehydes and ketones react with water to yield 1,1-diols, or *geminal (gem) diols*. The hydration reaction is reversible, and a gem diol can eliminate water to regenerate the aldehyde or ketone.



The position of the equilibrium between a gem diol and an aldehyde or ketone depends on the structure of the carbonyl compound. The equilibrium generally favors the carbonyl compound for steric reasons, but the gem diol is favored for a few simple aldehydes. For example, an aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde at equilibrium, whereas an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.



The hydrate is also favored for α -keto acids, difunctional compounds that have adjacent ketone and carboxylic acid groups. The presence of two adjacent positively polarized carbons destabilizes the keto form, thereby favoring the hydrate. Such compounds are particularly important in many biological pathways; pyruvic acid, which contains 60% hydrate at equilibrium, and α -ketoglutaric acid, which contains 50% hydrate, are examples.



Nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. Under basic conditions (FIGURE 14.4a), the nucleophile is negatively charged (OH⁻) and uses a pair of its electrons to form a bond to the electrophilic carbon atom of the

C=O group. At the same time, the C=O carbon atom rehybridizes from sp^2 to sp^3 and two electrons from the C=O π bond are pushed onto the oxygen atom, giving an alkoxide ion. Protonation of the alkoxide ion by water then yields a neutral addition product plus regenerated OH^- .

Under acidic conditions (FIGURE 14.4b), the carbonyl oxygen atom is first protonated by H_3O^+ to make the carbonyl group more strongly electrophilic. A neutral nucleophile, H_2O , then uses a pair of electrons to bond to the carbon atom of the C=O group, and two electrons from the C=O π bond move onto the oxygen atom. The positive charge on oxygen is thereby neutralized, while the nucleophile gains a positive charge. Finally, deprotonation by water gives the neutral addition product and regenerates the H_3O^+ catalyst.

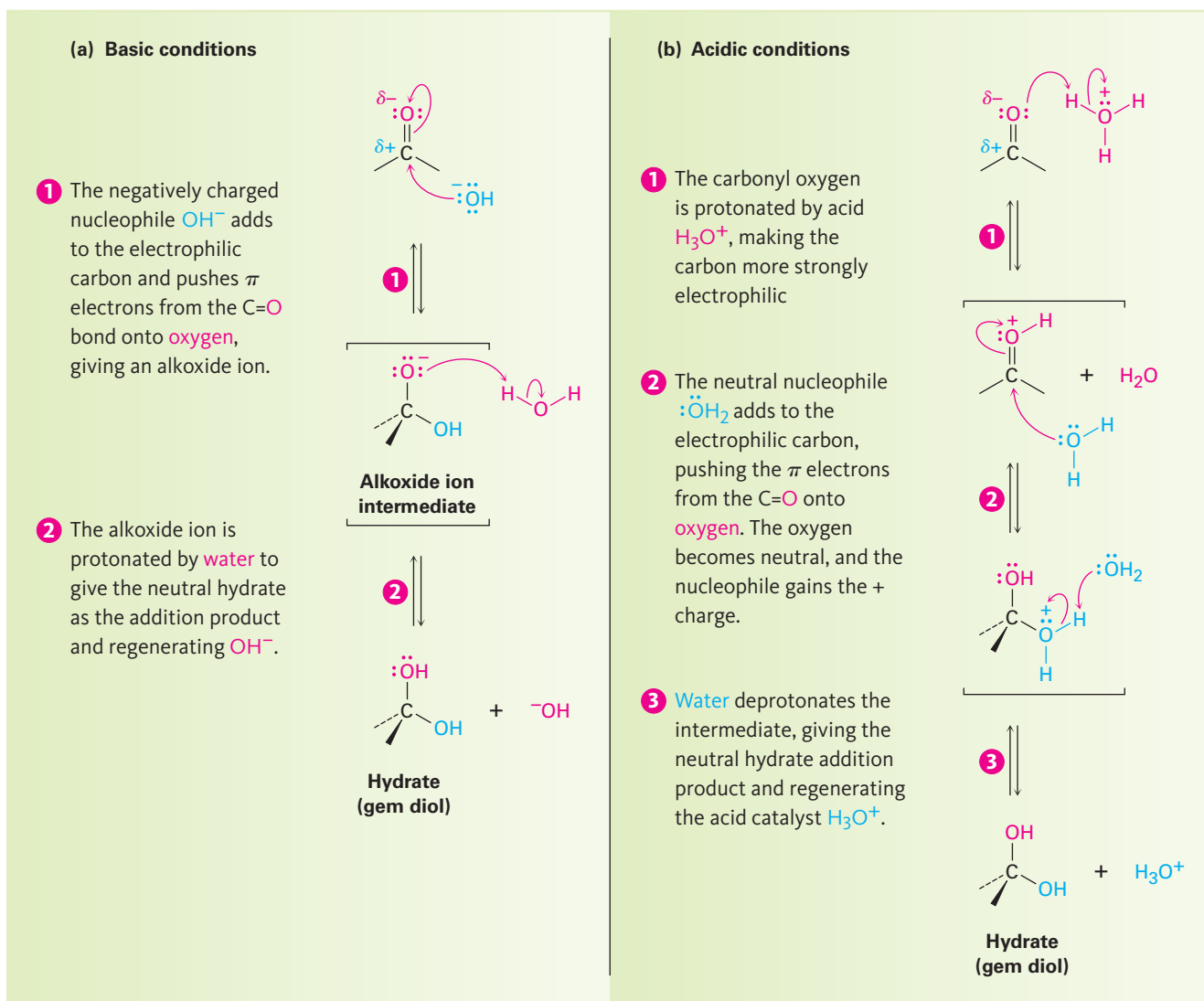
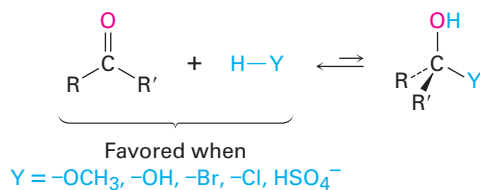


FIGURE 14.4 Mechanism of a nucleophilic addition reaction of aldehydes and ketones under basic and acidic conditions. (a) Under basic conditions, a negatively charged nucleophile adds to the carbonyl group to give an alkoxide ion intermediate, which is subsequently protonated. (b) Under acidic conditions, protonation of the carbonyl group occurs first, followed by addition of a neutral nucleophile and subsequent deprotonation.

Note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction takes place rapidly because water is converted into hydroxide ion, a much better *nucleophile*. The acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation into a much better *electrophile*.

The hydration reaction just described is typical of what happens when an aldehyde or ketone is treated with a nucleophile of the type H–Y, where the Y atom is electronegative and can stabilize a negative charge (oxygen, halogen, or sulfur, for instance). In such reactions, the nucleophilic addition is reversible, with the equilibrium generally favoring the carbonyl reactant rather than the tetrahedral addition product. In other words, treatment of an aldehyde or ketone with CH₃OH, H₂O, HCl, HBr, or H₂SO₄ does not normally lead to a stable alcohol addition product.



PROBLEM 14.7

When dissolved in water, trichloroacetaldehyde (chloral, CCl₃CHO) exists primarily as chloral hydrate, CCl₃CH(OH)₂. Show the structure of chloral hydrate.

PROBLEM 14.8

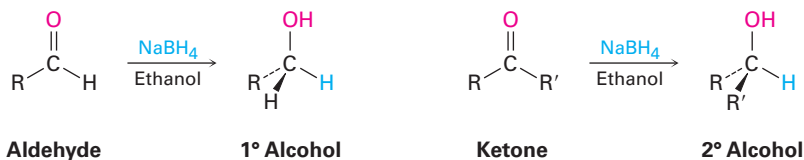
The oxygen in water is primarily (99.8%) ¹⁶O, but water enriched with the heavy isotope ¹⁸O is also available. When an aldehyde or ketone is dissolved in ¹⁸O-enriched water, the isotopic label becomes incorporated into the carbonyl group. Explain.



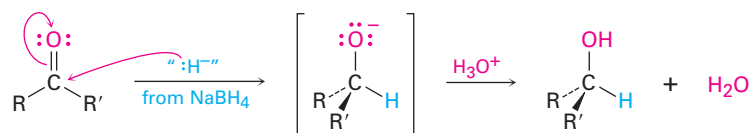
14-6 Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation

Addition of Hydride Reagents: Reduction

We saw in Section 13-3 that the most common method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of carbonyl compounds. Aldehydes are reduced with sodium borohydride (NaBH₄) to give primary alcohols, and ketones are reduced similarly to give secondary alcohols.



Carbonyl reduction occurs by a typical nucleophilic addition mechanism under basic conditions, as shown previously in Figure 14.4a. Although the details of carbonyl-group reductions are complex, LiAlH_4 and NaBH_4 act as if they were donors of hydride ion nucleophile, :H^- , and the initially formed alkoxide ion intermediate is then protonated by addition of aqueous acid. The reaction is effectively irreversible because the reverse process would require expulsion of a very poor leaving group.



Addition of Grignard Reagents

Just as aldehydes and ketones undergo nucleophilic addition with hydride ion to give alcohols, they undergo a similar addition with Grignard reagents, $\text{R}^- + \text{MgX}$ (FIGURE 14.5).

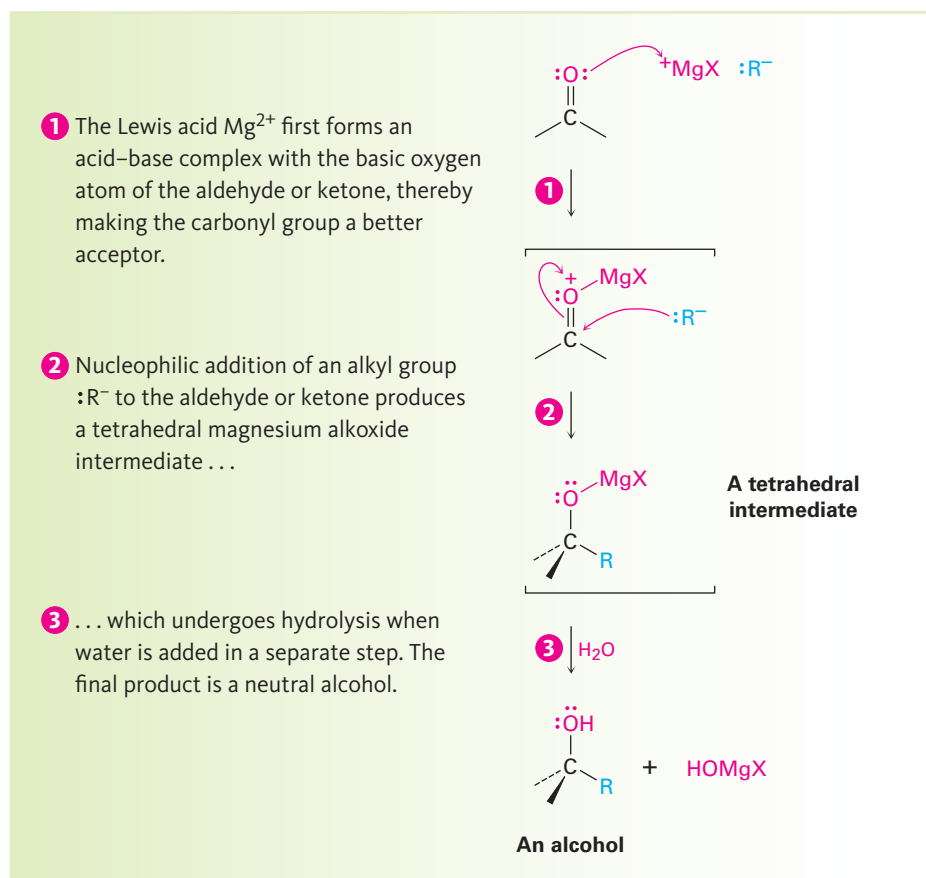
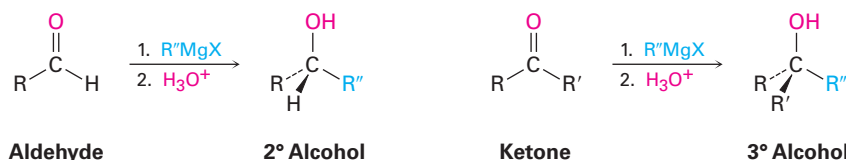


FIGURE 14.5 Mechanism of the Grignard reaction. Complexation of the carbonyl oxygen with the Lewis acid Mg^{2+} and subsequent nucleophilic addition of a carbanion to an aldehyde or ketone is followed by protonation of the alkoxide intermediate to yield an alcohol.

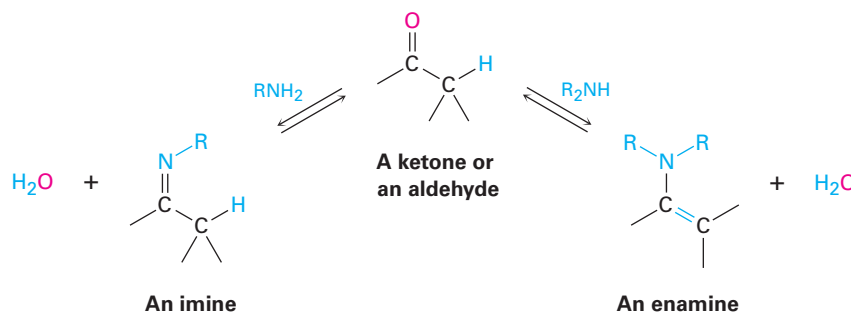
Aldehydes give secondary alcohols on reaction with Grignard reagents in ether solution, and ketones give tertiary alcohols.



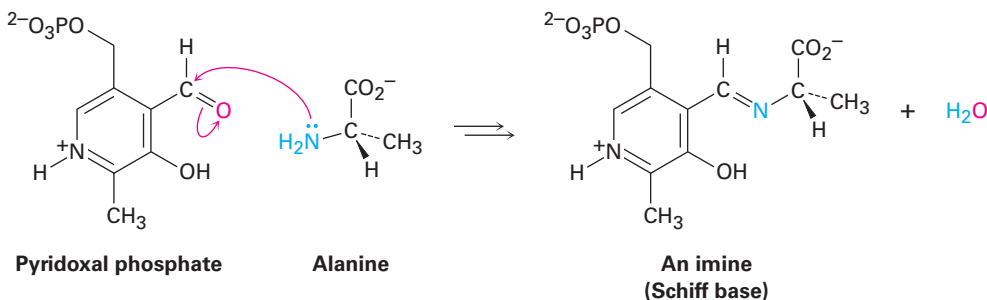
A Grignard reaction begins with an acid–base complexation of Mg^{2+} to the carbonyl oxygen atom of the aldehyde or ketone to make the carbonyl group a better electrophile. Nucleophilic addition of R^- then produces a tetrahedral magnesium alkoxide intermediate, and protonation by addition of water or dilute aqueous acid in a separate step yields the neutral alcohol. Like reduction, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

14-7 Nucleophilic Addition of Amines: Imine and Enamine Formation

Primary amines, RNH_2 , add to aldehydes and ketones to yield **imines**, $\text{R}_2\text{C}=\text{NR}$. Secondary amines, R_2NH , add similarly to yield **enamines**, $\text{R}_2\text{N}-\text{CR}=\text{CR}_2$ (*ene* + *amine* = unsaturated amine).



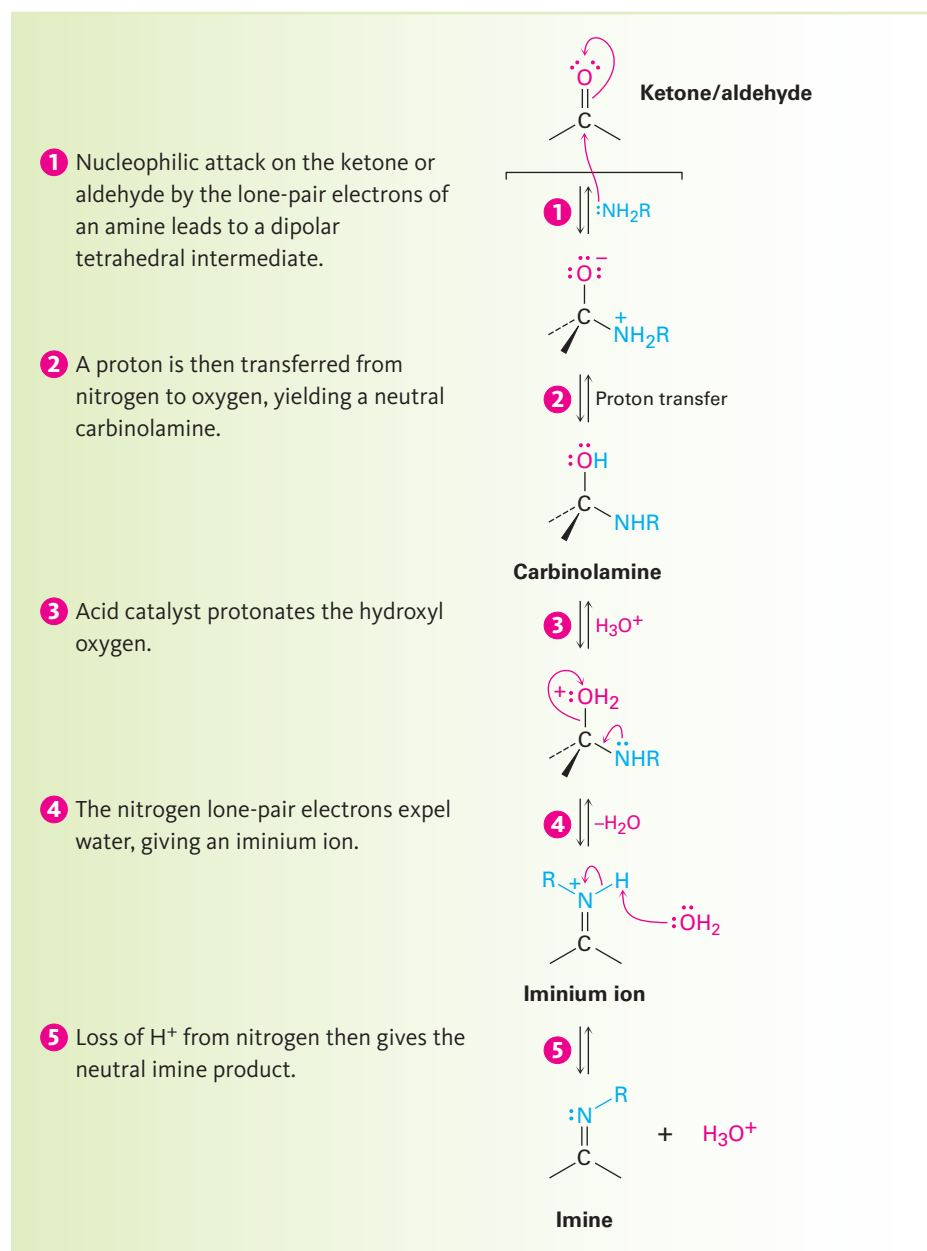
Imines are particularly common as intermediates in many biological pathways, where they are often called **Schiff bases**. The amino acid alanine, for instance, is metabolized in the body by reaction with the aldehyde pyridoxal phosphate (PLP), a derivative of vitamin B₆, to yield a Schiff base that is further degraded.



Imine formation and enamine formation appear different because one leads to a product with a C=N bond and the other leads to a product with a C=C bond. Actually, though, the reactions are closely related. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new C=Nu bond is formed.

An imine is formed in a reversible, acid-catalyzed process that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or *carbinolamine*. Protonation of the carbinolamine oxygen by an acid catalyst then converts the –OH into a better leaving group (–OH₂⁺), and E1-like loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst (FIGURE 14.6).

FIGURE 14.6 Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is nucleophilic addition to yield a carbinolamine intermediate, which loses water to give the imine.



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Reaction of an aldehyde or ketone with a secondary amine, R_2NH , rather than a primary amine yields an enamine. The process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the α carbon), yielding an enamine (FIGURE 14.7).

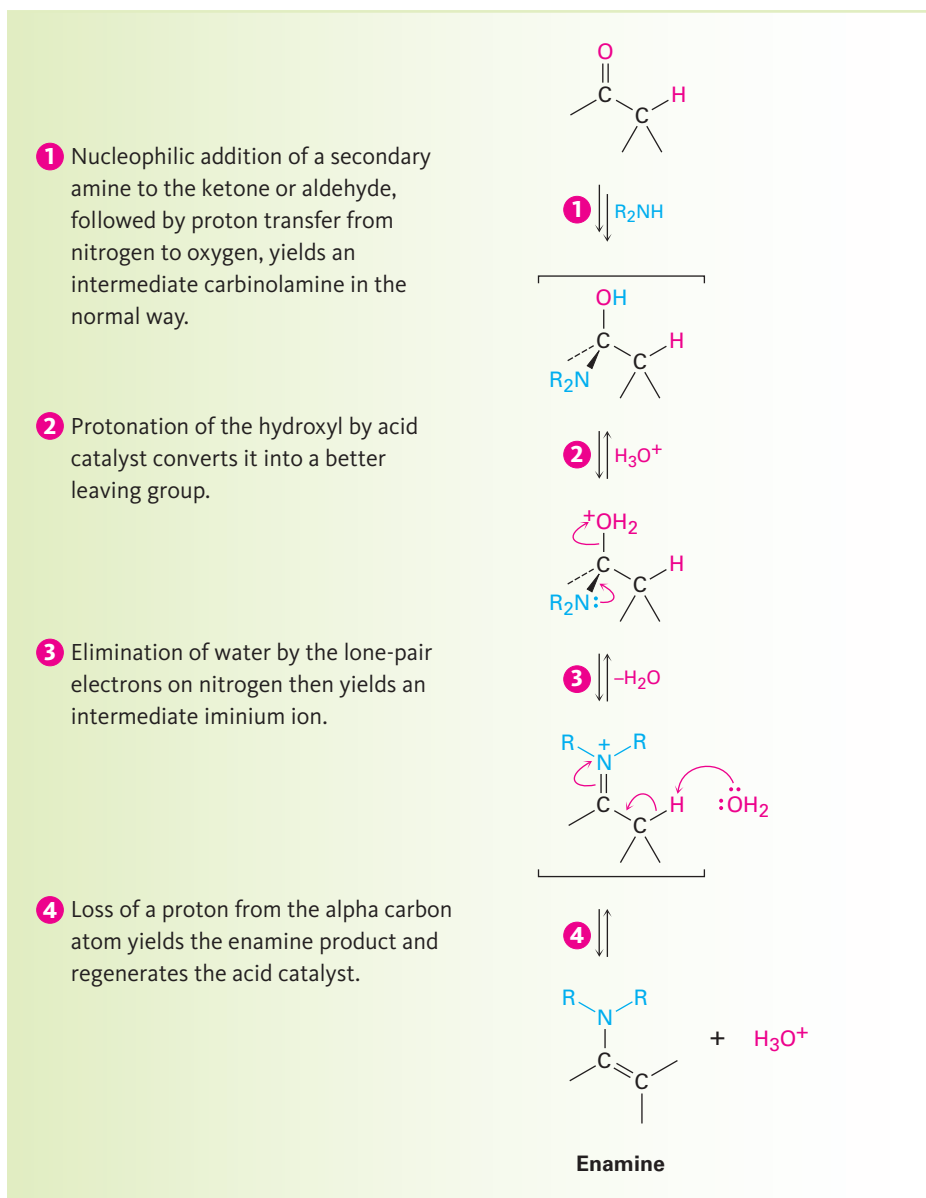


FIGURE 14.7 Mechanism of enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH .

The iminium ion intermediate produced in step 3 has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.

Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. We can explain this pH dependence by looking at the individual steps in the mechanism. As indicated for imine formation in Figure 14.6, an acid catalyst is required in step 3 to protonate the intermediate carbinolamine, thereby converting the $-OH$ into a better leaving group. Thus, reaction will be slow if not enough acid is present

(that is, at high pH). On the other hand, if too much acid is present (low pH), the basic amine nucleophile is completely protonated, so the initial nucleophilic addition step can't occur.

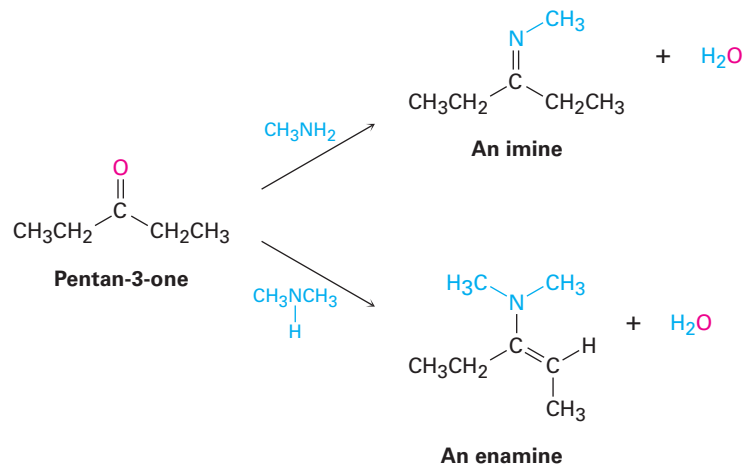
Evidently, a pH of 4.5 represents a compromise between the need for *some* acid to catalyze the rate-limiting dehydration step but *not too much* acid so as to avoid complete protonation of the amine. Each individual nucleophilic addition reaction has its own requirements, and reaction conditions must be optimized to obtain maximum reaction rates.

WORKED EXAMPLE 14.1
Predicting the Product of Reaction between a Ketone and an Amine

Show the products you would obtain by acid-catalyzed reaction of pentan-3-one with methylamine, CH_3NH_2 , and with dimethylamine, $(\text{CH}_3)_2\text{NH}$.

Strategy

An aldehyde or ketone reacts with a primary amine, RNH_2 , to yield an imine, in which the carbonyl oxygen atom has been replaced by the $=\text{N}-\text{R}$ group of the amine. Reaction of the same aldehyde or ketone with a secondary amine, R_2NH , yields an enamine, in which the oxygen atom has been replaced by the $-\text{NR}_2$ group of the amine and the double bond has moved to a position between the former carbonyl carbon and the neighboring carbon.

Solution

PROBLEM 14.9

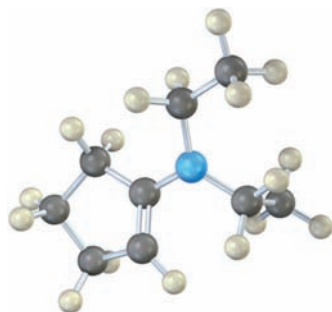
Show the products you would obtain by acid-catalyzed reaction of cyclohexanone with ethylamine, $\text{CH}_3\text{CH}_2\text{NH}_2$, and with diethylamine, $(\text{CH}_3\text{CH}_2)_2\text{NH}$.

PROBLEM 14.10

Imine formation is reversible. Show all the steps involved in the acid-catalyzed reaction of an imine with water (hydrolysis) to yield an aldehyde or ketone plus primary amine.

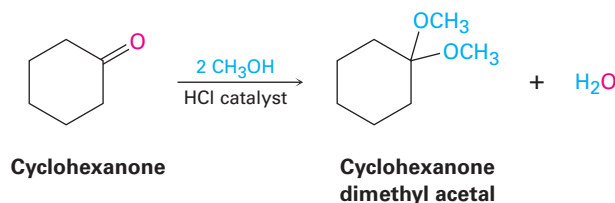
PROBLEM 14.11

Draw the following molecule as a skeletal structure, and show how it can be prepared from a ketone and an amine.

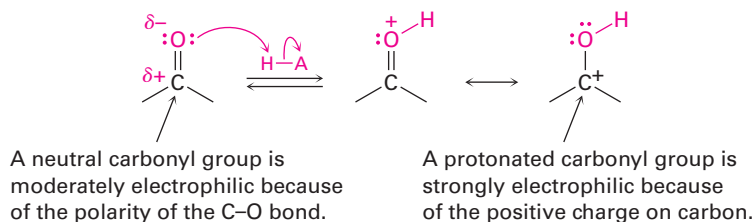


14-8 Nucleophilic Addition of Alcohols: Acetal Formation

Aldehydes and ketones react reversibly with 2 equivalents of an alcohol in the presence of an acid catalyst to yield **acetals**, $R_2C(OR')_2$, frequently called *ketals* if derived from a ketone. Cyclohexanone, for instance, reacts with methanol in the presence of HCl to give the corresponding dimethyl acetal.



Acetal formation is similar to the hydration reaction discussed in Section 14-5. Like water, alcohols are weak nucleophiles that add to aldehydes and ketones only slowly under neutral conditions. Under acidic conditions, however, the reactivity of the carbonyl group is increased by protonation, so addition of an alcohol occurs rapidly.



Nucleophilic addition of an alcohol to the carbonyl group initially yields a hydroxy ether called a **hemiacetal**, analogous to the gem diol formed by addition of water. Hemiacetals are formed reversibly, with the equilibrium normally favoring the carbonyl compound. In the presence of acid, however, a further reaction occurs. Protonation of the $-OH$ group, followed by an $E1$ -like loss of water, leads to an oxonium ion, $R_2C=OR^+$, which undergoes a second nucleophilic addition of alcohol to yield the protonated acetal. Loss of a proton completes the reaction. The mechanism is shown in **FIGURE 14.8**.

FIGURE 14.8 Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.

1 Protonation of the carbonyl oxygen strongly polarizes the carbonyl group and ...

2 ... activates the carbonyl group for nucleophilic attack by oxygen lone-pair electrons from the alcohol.

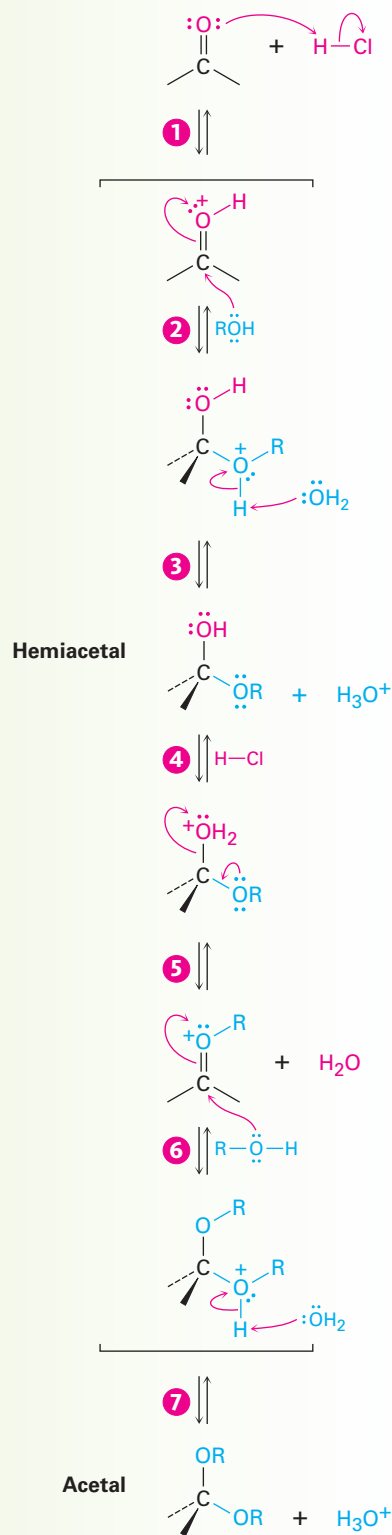
3 Loss of a proton yields a neutral hemiacetal tetrahedral intermediate.

4 Protonation of the hemiacetal hydroxyl converts it into a good leaving group.

5 Dehydration yields an intermediate oxonium ion.

6 Addition of a second equivalent of alcohol gives a protonated acetal.

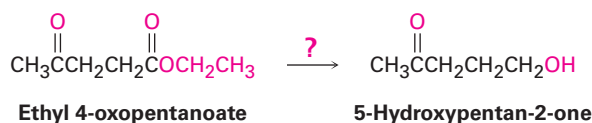
7 Loss of a proton yields the neutral acetal product.



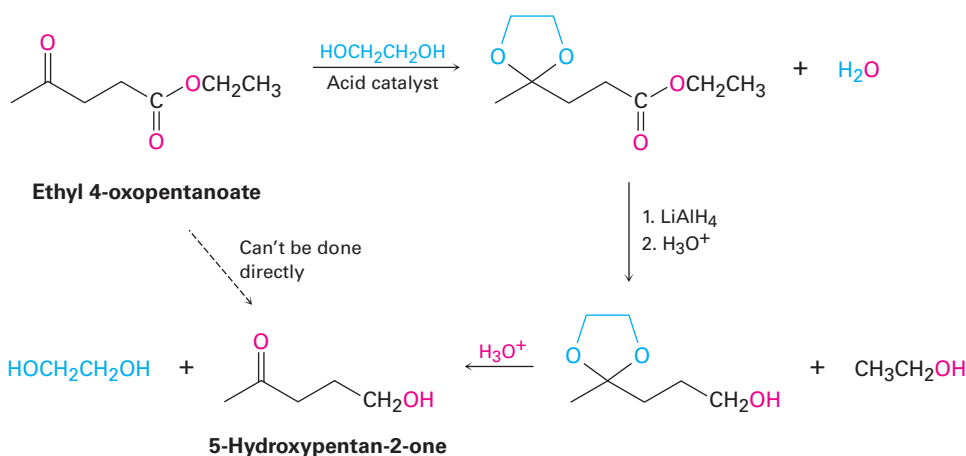
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Because all the steps in acetal formation are reversible, the reaction can be driven either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the conditions. The forward reaction is favored by conditions that remove water from the medium and thus drive the equilibrium to the right. In practice, this is often done by distilling off water as it forms. The reverse reaction is favored by treating the acetal with a large excess of aqueous acid to drive the equilibrium to the left.

Acetals are useful in the laboratory because they can act as protecting groups for aldehydes and ketones in the same way that trimethylsilyl ethers act as protecting groups for alcohols (Section 13-6). As we saw previously, it sometimes happens that one functional group interferes with intended chemistry elsewhere in a complex molecule. For example, if we wanted to reduce only the ester group of ethyl 4-oxopentanoate, the ketone would interfere. Treatment of the starting keto ester with LiAlH_4 would reduce both the keto and the ester groups to give a diol product.

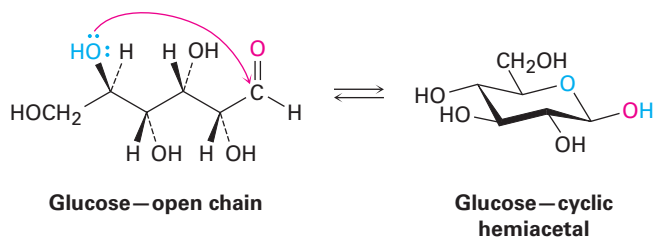


By protecting the keto group as an acetal, however, the problem can be circumvented. Like other ethers, acetals are unreactive to bases, hydride reducing agents, Grignard reagents, and catalytic hydrogenation conditions, but they are cleaved by acid. Thus, we can accomplish the selective reduction of the ester group in ethyl 4-oxopentanoate by first converting the keto group to an acetal, then reducing the ester with LiAlH_4 , and then removing the acetal by treatment with aqueous acid. (In practice, it's often convenient to use 1 equivalent of a diol such as ethylene glycol as the alcohol and to form a *cyclic* acetal. The mechanism of cyclic acetal formation using 1 equivalent of ethylene glycol is exactly the same as that using 2 equivalents of methanol or other monoalcohol.)



Acetal and hemiacetal groups are particularly common in carbohydrate chemistry. Glucose, for instance, is a polyhydroxy aldehyde that undergoes

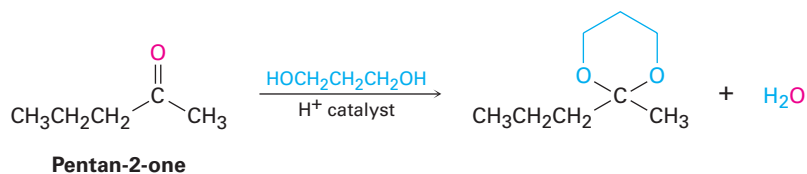
an *internal* nucleophilic addition reaction and exists primarily as a cyclic hemiacetal.

**WORKED EXAMPLE 14.2****Predicting the Product of Reaction between a Ketone and an Alcohol**

Show the structure of the acetal you would obtain by acid-catalyzed reaction of pentan-2-one with propane-1,3-diol.

Strategy

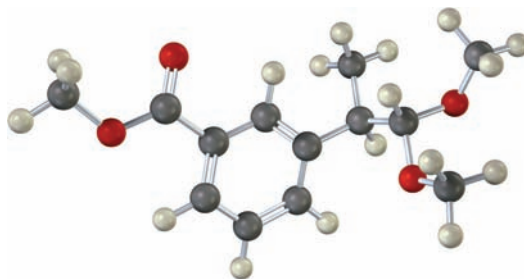
Acid-catalyzed reaction of an aldehyde or ketone with 2 equivalents of a monoalcohol or 1 equivalent of a diol yields an acetal, in which the carbonyl oxygen atom is replaced by two -OR groups from the alcohol.

Solution**PROBLEM 14.12**

Show all the steps in the acid-catalyzed formation of a cyclic acetal from ethylene glycol and an aldehyde or ketone.

PROBLEM 14.13

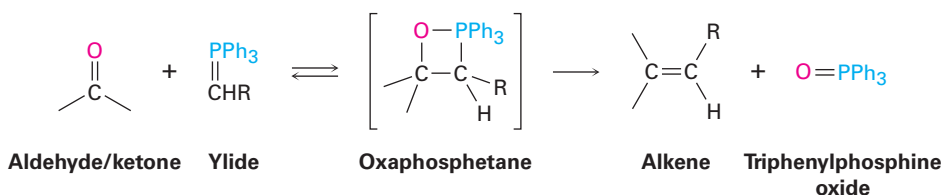
Identify the carbonyl compound and the alcohol that were used to prepare the following acetal:



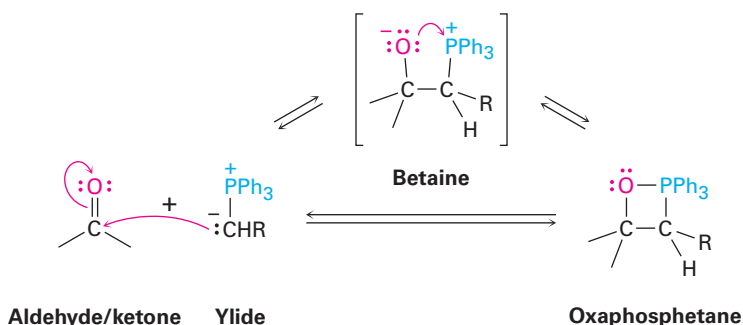
14-9 Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction

Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition called the **Wittig reaction**. The reaction has no direct biological counterpart but is worth knowing about both because of its wide use in the laboratory and drug manufacture and because of its mechanistic similarity to reactions of the coenzyme thiamin diphosphate, which we'll see in Section 22-3.

In the Wittig reaction, a triphenylphosphorus *ylide*, $R_2\bar{C}-P^+(C_6H_5)_3$, also called a *phosphorane* and sometimes written in the resonance form $R_2C=PPh_3$, adds to an aldehyde or ketone to yield a four-membered cyclic intermediate called an *oxaphosphetane*. The oxaphosphetane is not isolated, but instead spontaneously decomposes to give an alkene plus triphenylphosphine oxide, $O=PPh_3$. In effect, the oxygen atom of the aldehyde or ketone and the $R_2C=$ bonded to phosphorus exchange places. (An **ylide**—pronounced **ill-id**—is a neutral, dipolar compound with adjacent plus and minus charges.)

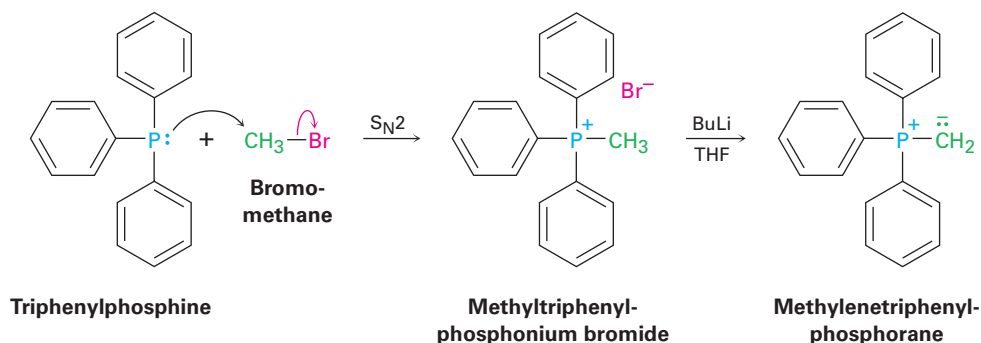


The initial addition step appears to take place by different pathways depending on the structure of the reactants and the exact experimental conditions. One pathway involves a one-step cycloaddition process analogous to the Diels–Alder cycloaddition reaction (Section 8-14). The other pathway involves a nucleophilic addition reaction to give a dipolar intermediate called a *betaine* (**bay-ta-ee-n**), which undergoes ring closure.



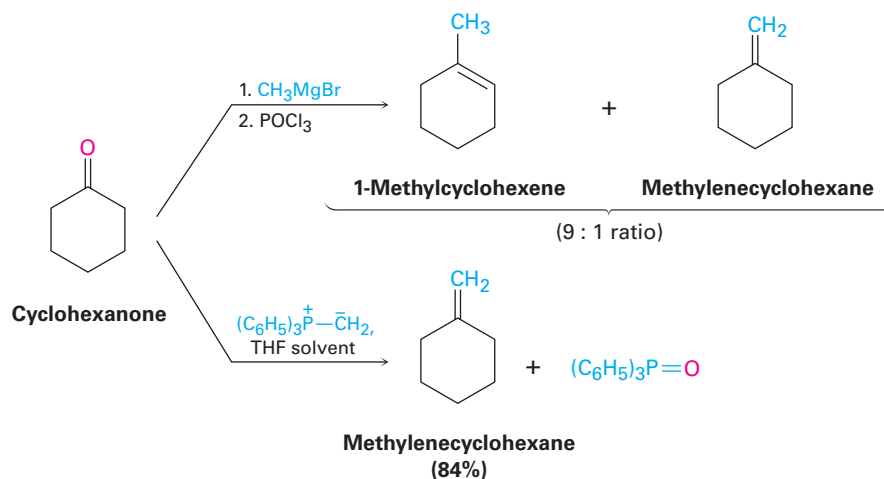
The phosphorus ylides necessary for Wittig reaction are easily prepared by S_N2 reaction of primary (and some secondary) alkyl halides with triphenylphosphine, $(Ph)_3P$, followed by treatment with base. Triphenylphosphine is a

good nucleophile in S_N2 reactions, and yields of the resultant alkyltriphenylphosphonium salts are high. Because of the positive charge on phosphorus, the hydrogen on the neighboring carbon is weakly acidic and can be removed by a strong base such as butyllithium (BuLi) to generate the neutral ylide. For example:

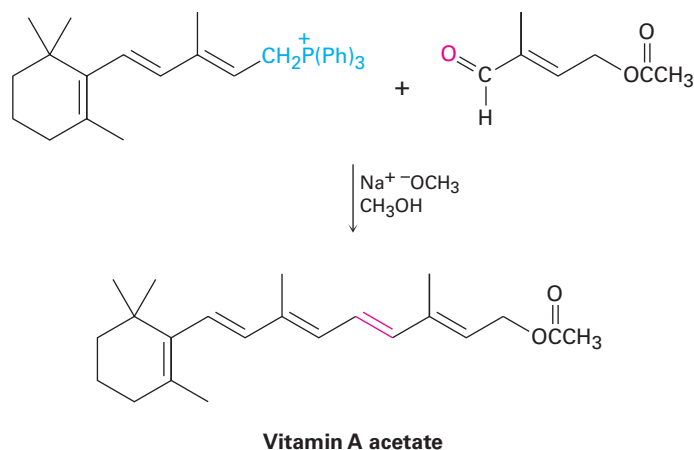


The Wittig reaction is extremely general, and a great many monosubstituted, disubstituted, and trisubstituted alkenes can be prepared from the appropriate combination of phosphorane and aldehyde or ketone. Tetrasubstituted alkenes can't be prepared, however, because of steric hindrance during the reaction.

The real value of the Wittig reaction is that it yields a pure alkene of predictable structure. The C=C bond in the product is always exactly where the C=O group was in the reactant, and no alkene isomers (except *E,Z* isomers) are formed. For example, Wittig reaction of cyclohexanone with methylenetriphenylphosphorane yields only the single alkene product methylenecyclohexane. By contrast, addition of methylmagnesium bromide to cyclohexanone, followed by dehydration with POCl_3 , yields a roughly 9:1 mixture of two alkenes.



Wittig reactions are used commercially in the synthesis of numerous pharmaceuticals. For example, the German chemical company BASF prepares vitamin A by using a Wittig reaction between a 15-carbon ylide and a 5-carbon aldehyde.



Synthesizing an Alkene Using a Wittig Reaction

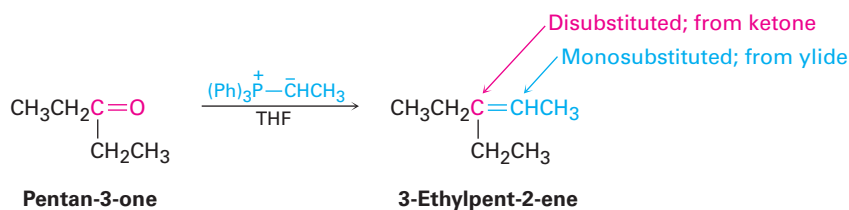
WORKED EXAMPLE 14.3

What carbonyl compound and what phosphorus ylide might you use to prepare 3-ethylpent-2-ene?

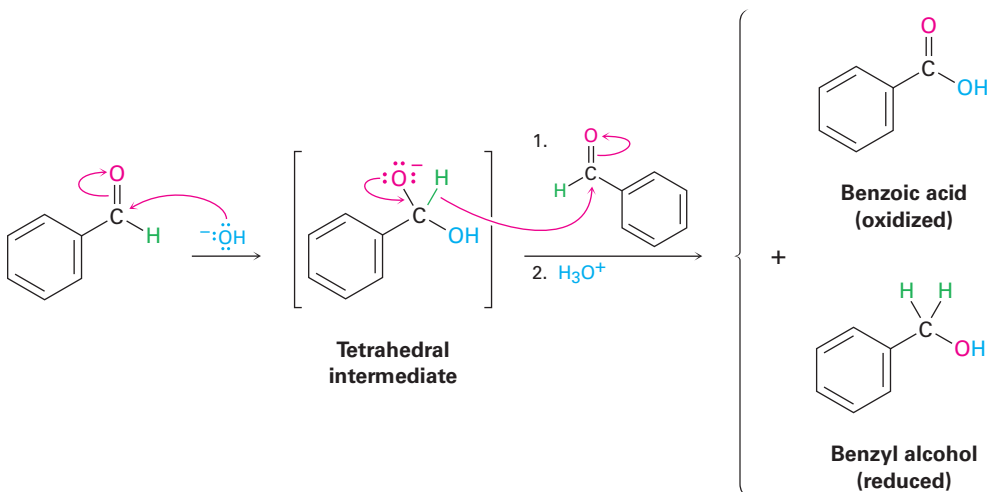
Strategy

An aldehyde or ketone reacts with a phosphorus ylide to yield an alkene in which the oxygen atom of the carbonyl reactant is replaced by the $=\text{CR}_2$ of the ylide. Preparation of the phosphorus ylide itself usually involves $\text{S}_{\text{N}}2$ reaction of a primary alkyl halide with triphenylphosphine, so the ylide is typically primary, $\text{RCH}=\text{P}(\text{Ph})_3$. This means that the disubstituted alkene carbon in the product comes from the carbonyl reactant, while the monosubstituted alkene carbon comes from the ylide.

Solution



leaving group and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced. Benzaldehyde, for instance, yields benzyl alcohol plus benzoic acid when heated with aqueous NaOH.



The Cannizzaro reaction is little used today but is interesting mechanistically because it is a simple laboratory analogy for the primary biological pathway by which carbonyl reductions occur in living organisms. In nature, as we saw in Section 13-3, one of the most important reducing agents is NADH, reduced nicotinamide adenine dinucleotide. NADH donates H^- to aldehydes and ketones, thereby reducing them, in much the same way that the tetrahedral alkoxide intermediate in a Cannizzaro reaction does. The electron lone pair on a nitrogen atom of NADH expels H^- as leaving group, which adds to a carbonyl group in another molecule (FIGURE 14.10). As an example, pyruvate is converted during intense muscle activity to (*S*)-lactate, a reaction catalyzed by lactate dehydrogenase.

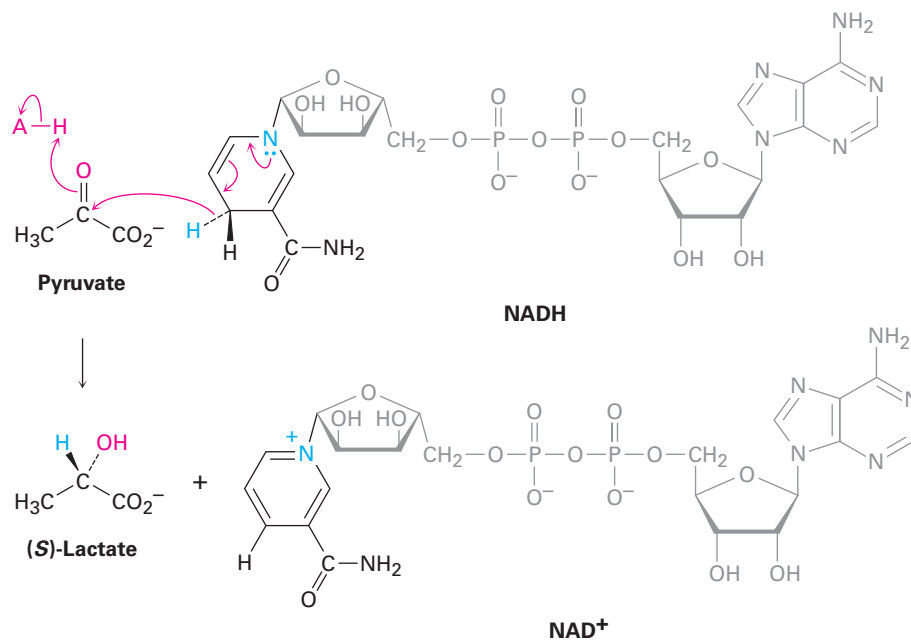
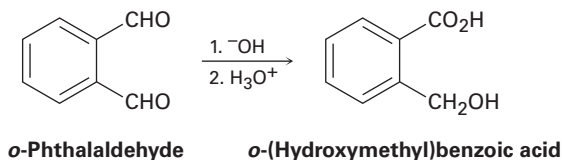


FIGURE 14.10 Mechanism of biological aldehyde and ketone reductions by the coenzyme NADH. The key step is an expulsion of hydride ion from NADH and donation to the carbonyl group.

PROBLEM 14.16

When *o*-phthalaldehyde is treated with base, *o*-(hydroxymethyl)benzoic acid is formed. Show the mechanism of this reaction.

**PROBLEM 14.17**

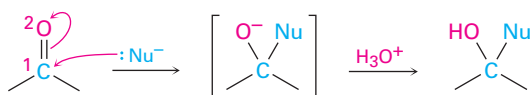
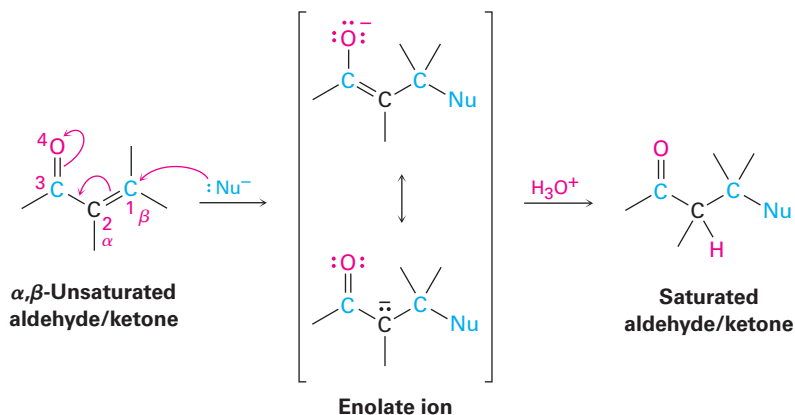
What is the stereochemistry of the pyruvate reduction shown in Figure 14.10? Does NADH lose its *pro-R* or *pro-S* hydrogen? Does addition occur to the *Si* face or *Re* face of pyruvate? (Review Section 5-11.)

14-11 Conjugate Nucleophilic Addition to α,β -Unsaturated Aldehydes and Ketones

All the reactions we've been discussing to this point have involved the addition of a nucleophile directly to the carbonyl group, a so-called **1,2-addition**. Closely related to this direct addition is the **conjugate addition**, or **1,4-addition**, of a nucleophile to the C=C bond of an α,β -unsaturated aldehyde or ketone. (The carbon atom next to a carbonyl group is often called the α carbon, the next one is the β carbon, and so on. Thus, an α,β -unsaturated aldehyde or ketone has a double bond conjugated with the carbonyl group.) The initial product of conjugate addition is a resonance-stabilized *enolate ion*, which typically undergoes protonation on the α carbon to give a saturated aldehyde or ketone product (**FIGURE 14.11**).

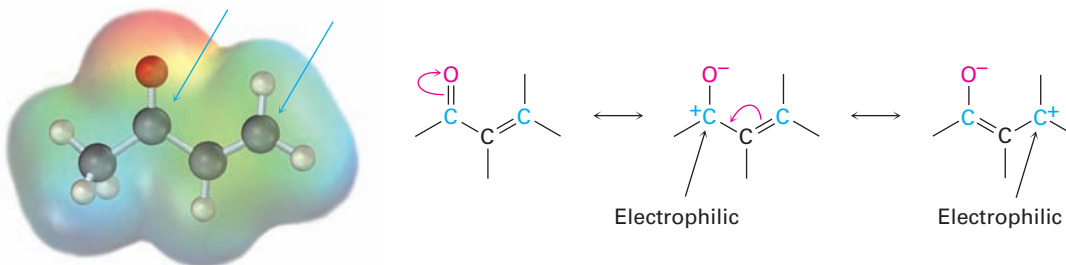
FIGURE 14.11 A comparison of direct (1,2) and conjugate (1,4) nucleophilic addition reactions.

In the conjugate addition, a nucleophile adds to the β carbon of an α,β -unsaturated aldehyde or ketone and protonation occurs on the α carbon.

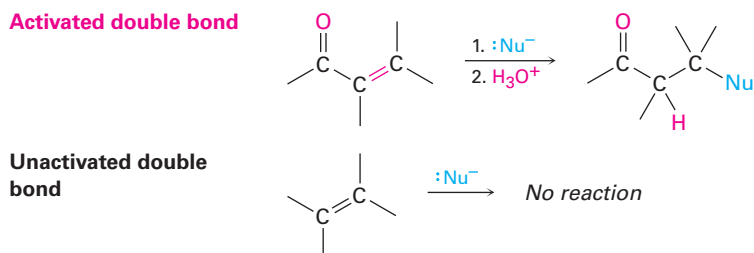
Direct (1,2) addition**Conjugate (1,4) addition**

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The conjugate addition of a nucleophile to an α,β -unsaturated aldehyde or ketone is caused by the same electronic factors that are responsible for direct addition: the electronegative oxygen atom of the α,β -unsaturated carbonyl compound withdraws electrons from the β carbon, thereby making it electron-poor and more electrophilic than a typical alkene carbon.

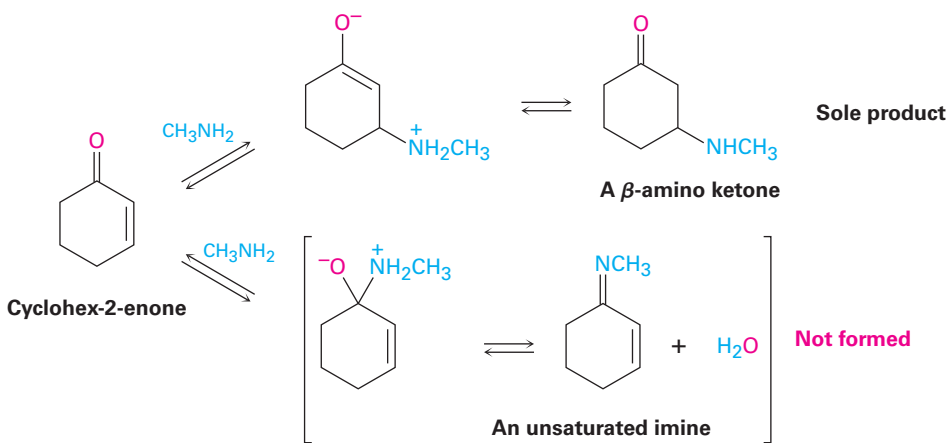


As noted above, conjugate addition of a nucleophile to the β carbon of an α,β -unsaturated aldehyde or ketone leads to an enolate ion intermediate, which is protonated on the α carbon to give the saturated product (Figure 14.11). The net effect is addition of the nucleophile to the C=C bond, with the carbonyl group itself unchanged. In fact, of course, the carbonyl group is crucial to the success of the reaction. The C=C bond would not be activated for addition and no reaction would occur without the carbonyl group.



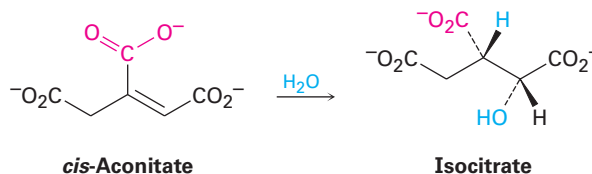
Conjugate Addition of Amines

Both primary and secondary amines add to α,β -unsaturated aldehydes and ketones to yield β -amino aldehydes and ketones rather than the alternative imines. Under typical reaction conditions, both modes of addition occur rapidly. But because the reactions are reversible, the more stable conjugate addition product accumulates and is often obtained to the complete exclusion of the less stable direct addition product.



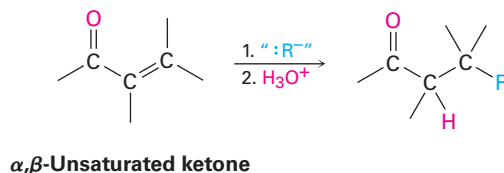
Conjugate Addition of Water

Water can add reversibly to α,β -unsaturated aldehydes and ketones to yield β -hydroxy aldehydes and ketones, although the position of the equilibrium generally favors unsaturated reactant rather than saturated adduct. Related additions to α,β -unsaturated carboxylic acids occur in numerous biological pathways, such as the citric acid cycle of food metabolism where *cis*-aconitate is converted into isocitrate by conjugate addition of water to a double bond.

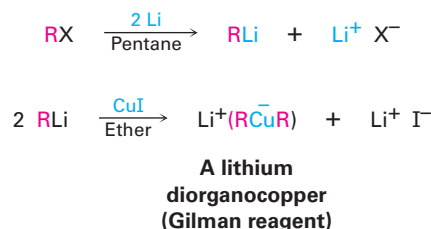


Conjugate Addition of Alkyl Groups

The conjugate addition of an alkyl or other organic group to an α,β -unsaturated ketone (but not aldehyde) is one of the more useful 1,4-addition reactions, just as direct addition of a Grignard reagent is one of the more useful 1,2-additions.

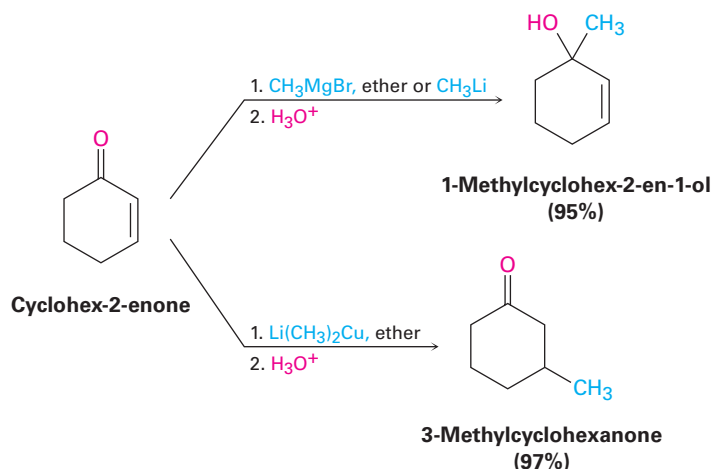


Conjugate addition of an organic group is carried out by treating the α,β -unsaturated ketone with a lithium diorganocopper (Gilman) reagent, R_2CuLi . As we saw in Section 12-5, lithium diorganocopper reagents are prepared by reaction between 1 equivalent of copper(I) iodide and 2 equivalents of an organolithium reagent, RLi . The organolithium reagent, in turn, is formed by reaction of lithium metal with an organohalide in the same way that a Grignard reagent is prepared by reaction of magnesium metal with an organohalide.

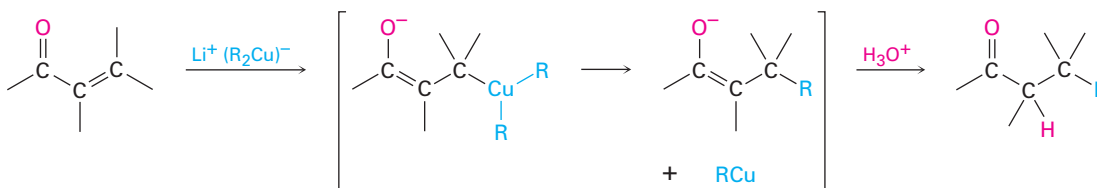


Primary, secondary, and even tertiary alkyl groups undergo the conjugate addition reaction, as do aryl and alkenyl groups. Alkynyl groups, however, react poorly in the conjugate addition process. Diorganocopper reagents are unique in their ability to give conjugate addition products. Other organometallic

compounds, such as Grignard reagents and organolithiums, normally give direct carbonyl addition on reaction with α,β -unsaturated ketones.



The mechanism of the reaction is thought to involve conjugate nucleophilic addition of the diorganocopper anion, R_2Cu^- , to the unsaturated ketone to give a copper-containing intermediate. Transfer of an R group from copper to carbon, followed by elimination of a neutral organocopper species, RCu , gives the final product.

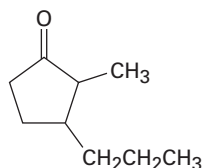


The lithium diorganocopper reaction has no direct counterpart in biological chemistry, although we'll see in Section 17-13 that conjugate addition of various other carbon-based nucleophiles to α,β -unsaturated carbonyl compounds does occur frequently in many biological pathways.

Using a Conjugate Addition Reaction

WORKED EXAMPLE 14.4

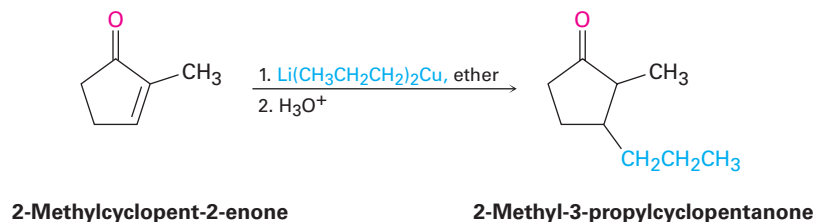
How might you use a conjugate addition reaction to prepare 2-methyl-3-propylcyclopentanone?



2-Methyl-3-propylcyclopentanone

Strategy

A ketone with a substituent group in its β position might be prepared by a conjugate addition of that group to an α,β -unsaturated ketone. In the present instance, the target molecule has a propyl substituent on the β carbon and might therefore be prepared from 2-methylcyclopenten-2-one by reaction with lithium dipropylcopper.

Solution**PROBLEM 14.18**

Assign *R* or *S* stereochemistry to the two chirality centers in isocitrate (page 520), and tell whether OH and H add to the *Si* face or the *Re* face of the double bond in *cis*-aconitate.

PROBLEM 14.19

Treatment of cyclohex-2-enone with HCN yields a saturated cyano ketone. Show the structure of the product, and propose a mechanism for the reaction.

PROBLEM 14.20

How might conjugate addition reactions of lithium diorganocopper reagents be used to synthesize the following compounds?

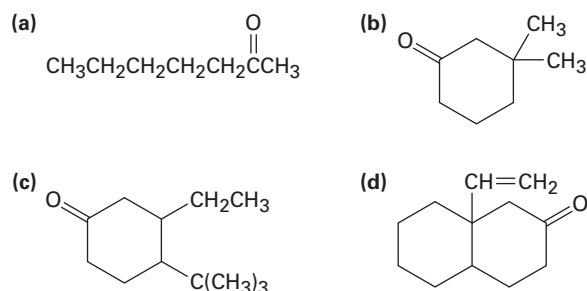


TABLE 14.2 Infrared Absorptions of Some Aldehydes and Ketones

Carbonyl type	Absorption (cm^{-1})
Saturated aldehyde	1730
Aromatic aldehyde	1705
α,β -Unsaturated aldehyde	1705
Saturated ketone	1715
Cyclohexanone	1715
Cyclopentanone	1750
Cyclobutanone	1785
Aromatic ketone	1690
α,β -Unsaturated ketone	1685

14-12 Spectroscopy of Aldehydes and Ketones

Infrared Spectroscopy

Aldehydes and ketones show a strong C=O bond absorption in the IR region from 1660 to 1770 cm^{-1} , as the spectra of benzaldehyde and cyclohexanone demonstrate (FIGURE 14.12). In addition, aldehydes show two characteristic C–H absorptions in the range 2720 to 2820 cm^{-1} .

The exact position of the C=O absorption is diagnostic of the nature of the carbonyl group. As the data in TABLE 14.2 indicate, saturated aldehydes usually show carbonyl absorptions near 1730 cm^{-1} in the IR spectrum, but conjugation of the aldehyde to an aromatic ring or a double bond lowers the absorption by 25 cm^{-1} to near 1705 cm^{-1} . Saturated aliphatic ketones and cyclohexanones

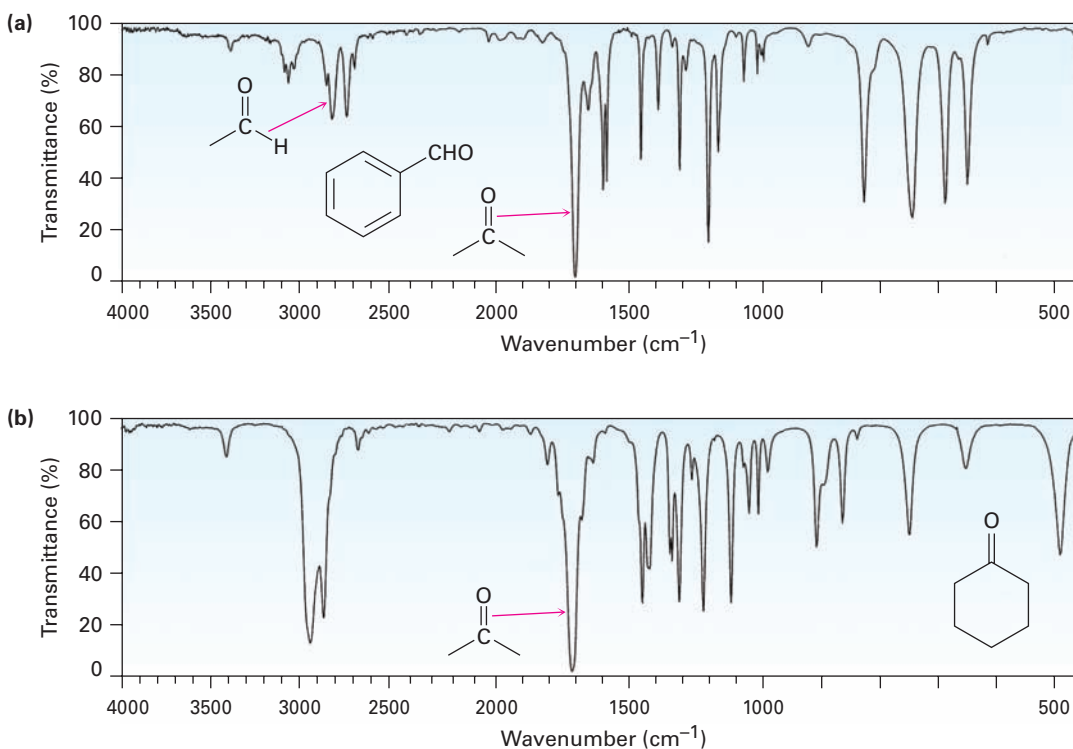


FIGURE 14.12
Infrared spectra
of (a) benz-
aldehyde and
(b) cyclohexanone.

both absorb near 1715 cm^{-1} , and conjugation with a double bond or an aromatic ring again lowers the absorption by 30 cm^{-1} to 1685 to 1690 cm^{-1} . Angle strain in the carbonyl group caused by reducing the ring size of cyclic ketones to four or five raises the absorption position.

PROBLEM 14.21

How might you use IR spectroscopy to determine whether reaction between cyclohex-2-enone and dimethylamine gives the direct addition product or the conjugate addition product?

PROBLEM 14.22

Where would you expect each of the following compounds to absorb in its IR spectrum?

- | | |
|--------------------------------|----------------------------------|
| (a) Pent-4-en-2-one | (b) Pent-3-en-2-one |
| (c) 2,2-Dimethylcyclopentanone | (d) <i>m</i> -Chlorobenzaldehyde |
| (e) Cyclohex-3-enone | (f) Hex-2-enal |

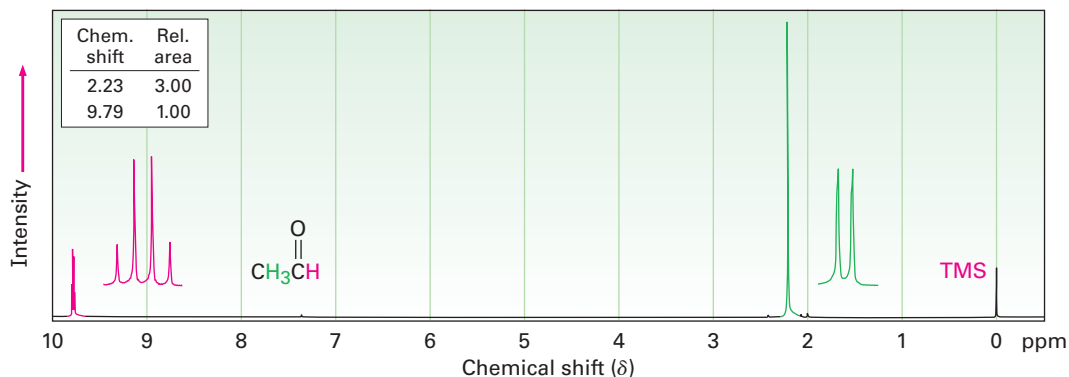
Nuclear Magnetic Resonance Spectroscopy

Aldehyde protons (RCHO) absorb near $10\ \delta$ in the ^1H NMR spectrum and are very distinctive because no other absorptions occur in this region. The aldehyde proton shows spin-spin coupling with protons on the neighboring

carbon, with coupling constant $J \approx 3$ Hz. Acetaldehyde, for example, shows a quartet at 9.8 δ for the aldehyde proton, indicating that there are three protons neighboring the $-\text{CHO}$ group (FIGURE 14.13).

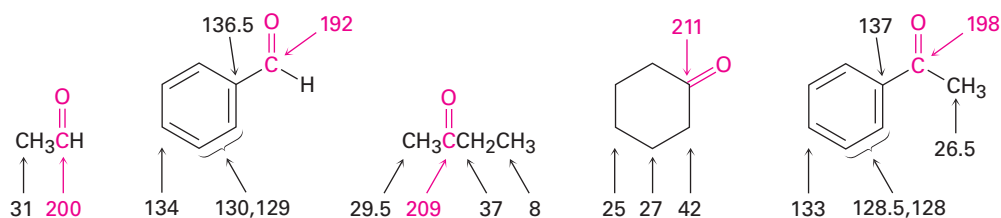
FIGURE 14.13
 ^1H NMR spectrum of acetaldehyde.

The absorption of the aldehyde proton appears at 9.8 δ and is split into a quartet.



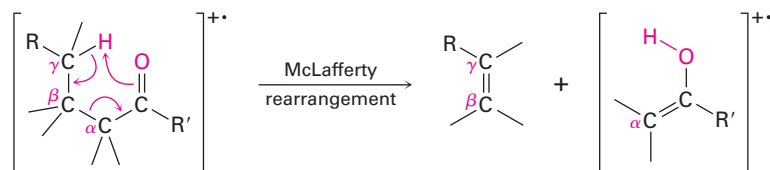
Hydrogens on the carbon next to a carbonyl group are slightly deshielded and normally absorb near 2.0 to 2.3 δ . The acetaldehyde methyl group in Figure 14.13, for instance, absorbs at 2.23 δ . Methyl ketones are particularly distinctive because they always show a sharp three-proton singlet near 2.1 δ .

The carbonyl-group carbon atoms of aldehydes and ketones have characteristic ^{13}C NMR resonances in the range 190 to 215 δ . Since no other kinds of carbons absorb in this range, the presence of an NMR absorption near 200 δ is clear evidence for a carbonyl group. Saturated aldehyde or ketone carbons usually absorb in the region from 200 to 215 δ , while aromatic and α,β -unsaturated carbonyl carbons absorb in the 190 to 200 δ region.

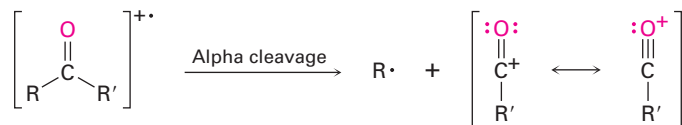


Mass Spectrometry

Aliphatic aldehydes and ketones that have hydrogens on their gamma (γ) carbon atoms undergo a characteristic mass spectral cleavage called the *McLafferty rearrangement*. A hydrogen atom is transferred from the γ carbon to the carbonyl oxygen, the bond between the α and β carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



Aldehydes and ketones also undergo fragmentation by cleavage of the bond between the carbonyl group and the α carbon, a so-called α cleavage. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.



Fragment ions from both McLafferty rearrangement and α cleavage are visible in the mass spectrum of 5-methylhexan-2-one shown in **FIGURE 14.14**. McLafferty rearrangement with loss of 2-methylpropene yields a fragment with $m/z = 58$. Alpha cleavage occurs primarily at the more substituted side of the carbonyl group, leading to a $[\text{CH}_3\text{CO}]^+$ fragment with $m/z = 43$.

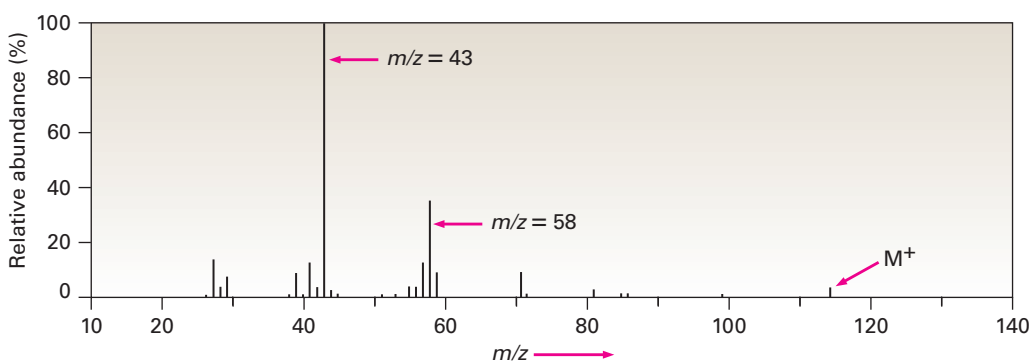
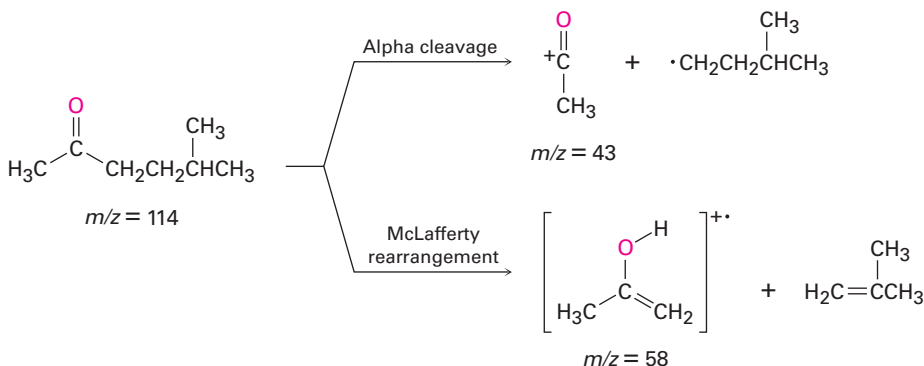


FIGURE 14.14
Mass spectrum of 5-methylhexan-2-one. The peak at $m/z = 58$ is due to McLafferty rearrangement. The abundant peak at $m/z = 43$ is due to α cleavage at the more highly substituted side of the carbonyl group. Note that the peak due to the molecular ion is very small.



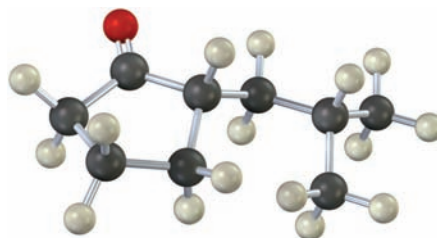
PROBLEM 14.23

How might you use mass spectrometry to distinguish between the following pairs of isomers?

- 3-Methylhexan-2-one and 4-methylhexan-2-one
- Heptan-3-one and heptan-4-one
- 2-Methylpentanal and 3-methylpentanal

PROBLEM 14.24

Tell the prominent IR absorptions and mass spectral peaks you would expect for the following compound:

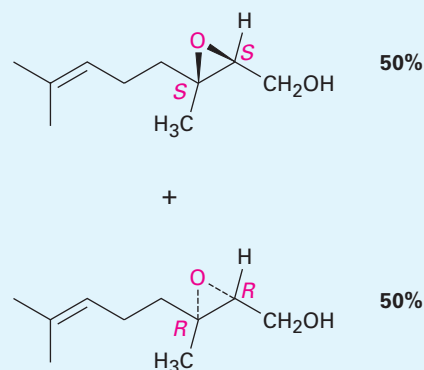
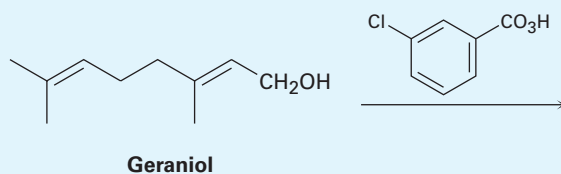


SOMETHING EXTRA

Enantioselective Synthesis

Whenever a chiral product is formed by reaction between achiral reagents, the product is racemic; that is, both enantiomers of the product are formed in equal amounts. The epoxidation reaction of geraniol with *m*-chloroperoxybenzoic acid, for instance, gives a racemic mixture of (2*S*,3*S*) and (2*R*,3*R*) epoxides.

Unfortunately, it's usually the case that only one enantiomer of a given drug or other important substance has the desired biological properties. The other enantiomer might be inactive or even dangerous. Thus, much work is currently being done on developing *enantioselective* methods of synthesis, which yield only one of two possible enantiomers. So important has enantioselective synthesis become that the 2001 Nobel Prize in Chemistry was awarded to three pioneers in the field: William S. Knowles, K. Barry Sharpless, and Ryoji Noyori.



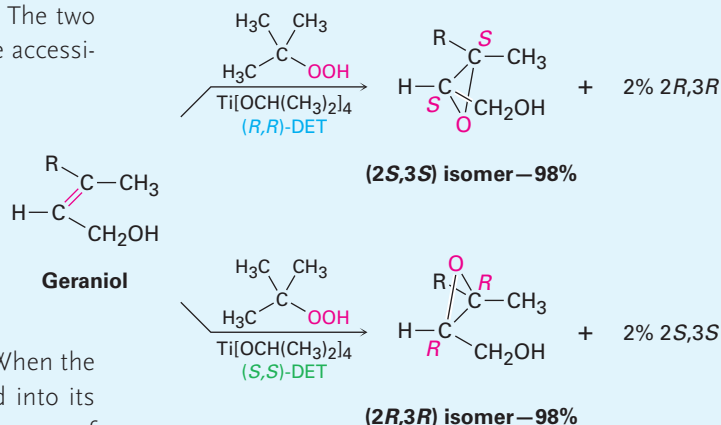
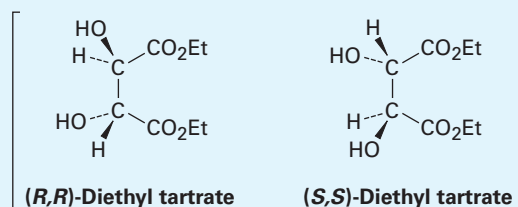
Siegfried Layda/Photographer's Choice/Getty Images

A substance made from the tartaric acid found at the bottom of this wine vat catalyzes enantioselective reactions.

Several approaches to enantioselective synthesis have been taken, but the most efficient are those that use chiral catalysts to temporarily hold a substrate molecule in an unsymmetrical environment—the same strategy that nature uses when catalyzing reactions with chiral enzymes. While in that unsymmetrical

environment, the substrate may be more open to reaction on one side than on another, leading to an excess of one enantiomeric product over another. As an analogy, think about picking up a coffee mug in your right hand to take a drink. The mug by itself is achiral, but as soon as you pick it up by the handle, it becomes chiral. One side of the mug now faces toward you so you can drink from it, but the other side faces away. The two sides are different, with one side much more accessible to you than the other.

Among the thousands of enantioselective reactions now known, one of the most useful is the so-called Sharpless epoxidation, in which an allylic alcohol, such as geraniol, is treated with *tert*-butyl hydroperoxide, $(\text{CH}_3)_3\text{C}-\text{OOH}$, in the presence of titanium tetrakisopropoxide and diethyl tartrate (DET) as a chiral auxiliary reagent. When the (*R,R*) tartrate is used, geraniol is converted into its (*2S,3S*) epoxide with 98% selectivity, whereas use of the (*S,S*) tartrate gives the (*2R,3R*) epoxide enantiomer. We say that the major product in each case is formed with an *enantiomeric excess* of 96%, meaning that 4% of the product is racemic [2% (*2S,3S*) plus 2% (*2R,3R*)] and an extra 96% of a single enantiomer is



formed. The mechanistic details by which the chiral catalyst works are a bit complex, although it appears that a chiral complex of two tartrate molecules with one titanium is involved.

SUMMARY

Aldehydes and ketones are among the most important of all compounds, both in the chemical industry and in biological pathways. In this chapter, we've looked at some of their typical reactions. Aldehydes are normally prepared in the laboratory by oxidation of primary alcohols or by partial reduction of esters. Ketones are prepared by oxidation of secondary alcohols.

The **nucleophilic addition reaction** is the most common general reaction type for aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by NaBH_4 or LiAlH_4 to yield primary and secondary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones gives secondary and tertiary alcohols, respectively. Primary amines add to carbonyl compounds yielding **imines**, or **Schiff bases**, and secondary amines yield **enamines**. Alcohols add to carbonyl groups to yield **acetals**, which are valuable as protecting groups. Phosphorus **ylides** add to aldehydes and ketones in the **Wittig reaction** to give alkenes.

α,β -Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4 addition**. Particularly useful are the conjugate addition of an amine and the conjugate addition of an organic group by reaction with a diorganocopper reagent.

KEY WORDS

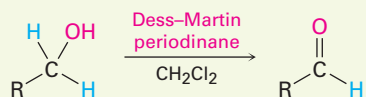
acetal $[\text{R}_2\text{C}(\text{OR}')_2]$,	509
acyl group,	494
1,2-addition,	518
1,4-addition,	518
aldehyde (RCHO),	492
conjugate addition,	518
enamine ($\text{R}_2\text{N}-\text{CR}=\text{CR}_2$),	505
hemiacetal,	509
imine ($\text{R}_2\text{C}=\text{NR}$),	505
ketone ($\text{R}_2\text{C}=\text{O}$),	492
nucleophilic addition reaction,	497
Schiff base,	505
Wittig reaction,	513
ylide,	513

IR spectroscopy is helpful for identifying aldehydes and ketones. Carbonyl groups absorb in the IR range 1660 to 1770 cm^{-1} , with the exact position highly diagnostic of the kind of carbonyl group present in the molecule. ^{13}C NMR spectroscopy is also useful for identifying aldehydes and ketones because their carbonyl carbons show resonances in the 190 to $215\ \delta$ range. Aldehydes and ketones undergo two characteristic kinds of fragmentation in the mass spectrometer: α cleavage and McLafferty rearrangement.

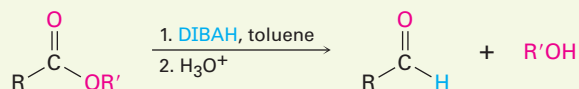
SUMMARY OF REACTIONS

1. Preparation of aldehydes

(a) Oxidation of primary alcohols (Section 13-5)

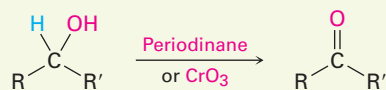


(b) Partial reduction of esters (Section 14-2)

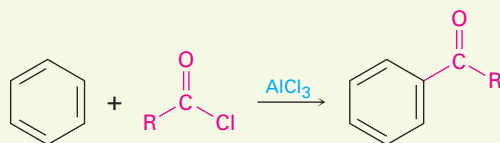


2. Preparation of ketones

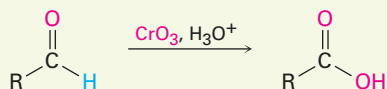
(a) Oxidation of secondary alcohols (Section 13-5)



(b) Friedel–Crafts acylation (Section 9-7)

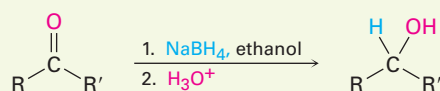


3. Oxidation of aldehydes (Section 14-3)

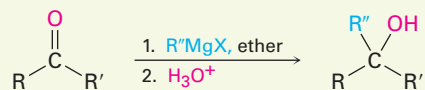


4. Nucleophilic addition reactions of aldehydes and ketones

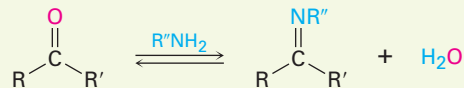
(a) Addition of hydride: reduction (Sections 13-3 and 14-6)



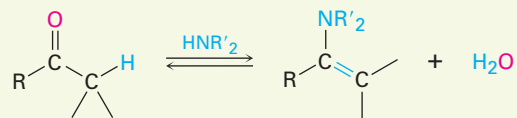
(b) Addition of Grignard reagents (Sections 13-3 and 14-6)



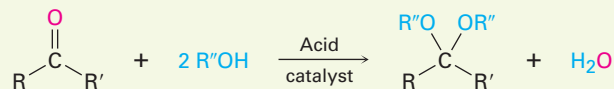
(c) Addition of primary amines to give imines (Section 14-7)



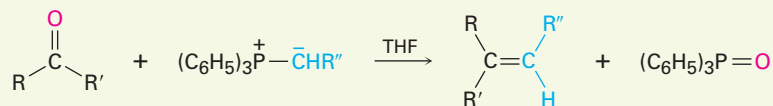
(d) Addition of secondary amines to give enamines (Section 14-7)



(e) Addition of alcohols to give acetals (Section 14-8)

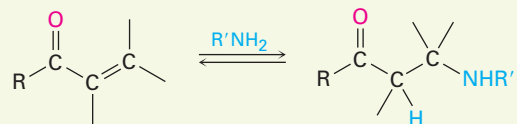


(f) Addition of phosphorus ylides to give alkenes (Wittig reaction; Section 14-9)

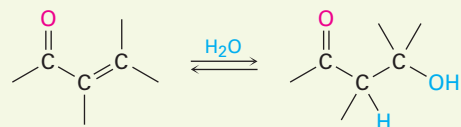


5. Conjugate additions to α,β -unsaturated aldehydes and ketones (Section 14-11)

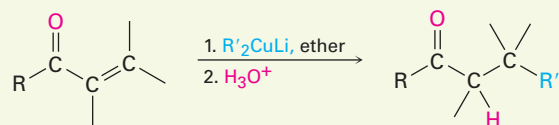
(a) Conjugate addition of amines



(b) Conjugate addition of water



(c) Conjugate addition of alkyl groups

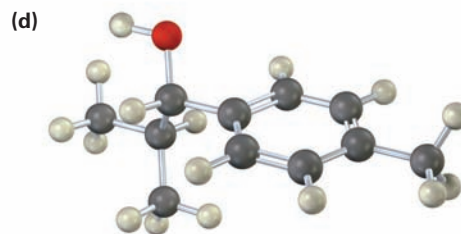
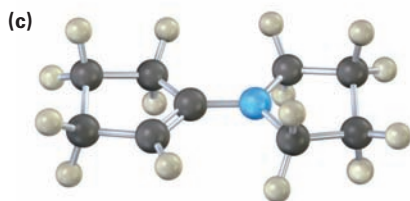
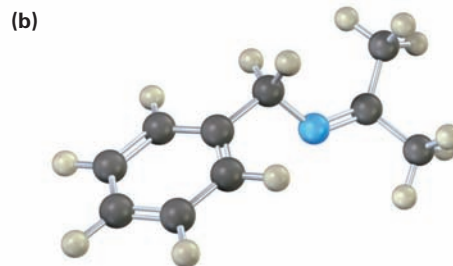
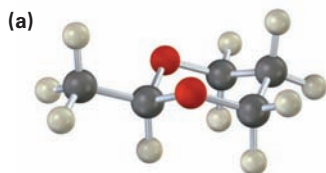


EXERCISES

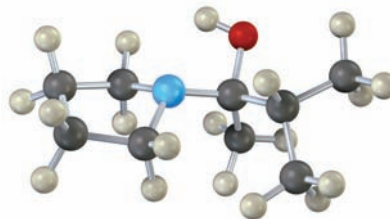
VISUALIZING CHEMISTRY

(Problems 14.1–14.24 appear within the chapter.)

14.25 Each of the following substances can be prepared by a nucleophilic addition reaction between an aldehyde or ketone and a nucleophile. Identify the reactants from which each was prepared. If the substance is an acetal, identify the carbonyl compound and the alcohol; if it is an imine, identify the carbonyl compound and the amine; and so forth.

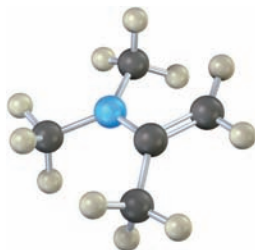


14.26 The following molecular model represents a tetrahedral intermediate resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the structure of the final product when the nucleophilic addition reaction is complete.

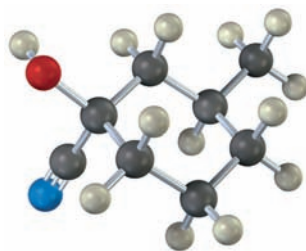


14.27 The enamine prepared from acetone and dimethylamine is shown in its lowest-energy form.

- What is the geometry and hybridization of the nitrogen atom?
- What orbital on nitrogen holds the lone pair of electrons?
- What is the geometric relationship between the p orbitals of the double bond and the nitrogen orbital that holds the lone pair? Why do you think this geometry represents the minimum energy?



14.28 Compounds called *cyanohydrins* result from the nucleophilic addition of HCN to an aldehyde or ketone. Draw and name the carbonyl compound that the following cyanohydrin was prepared from.



ADDITIONAL PROBLEMS

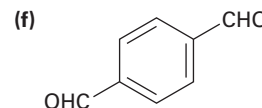
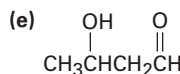
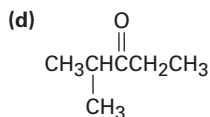
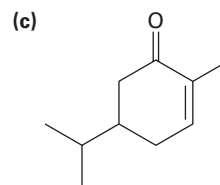
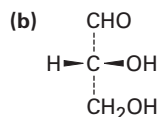
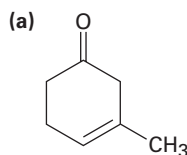
Naming Aldehydes and Ketones

14.29 Draw structures corresponding to the following names:

- | | |
|---------------------------------------|---|
| (a) Bromoacetone | (b) (<i>S</i>)-2-Hydroxypropanal |
| (c) 2-Methylheptan-3-one | (d) (2 <i>S</i> ,3 <i>R</i>)-2,3,4-Trihydroxybutanal |
| (e) 2,2,4,4-Tetramethylpentan-3-one | (f) 4-Methylpent-3-en-2-one |
| (g) Butanedial | (h) 3-Phenylprop-2-enal |
| (i) 6,6-Dimethylcyclohexa-2,4-dienone | (j) <i>p</i> -Nitroacetophenone |

14.30 Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$. Which are chiral?

14.31 Give IUPAC names for the following structures:



14.32 Draw structures of compounds that fit the following descriptions:

- (a) An α,β -unsaturated ketone, C_6H_8O (b) An α -diketone
 (c) An aromatic ketone, $C_9H_{10}O$ (d) A diene aldehyde, C_7H_8O

Reactions of Aldehydes and Ketones

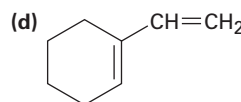
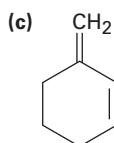
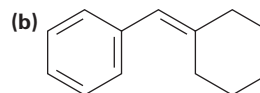
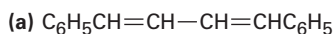
14.33 Predict the products of the reaction of (1) phenylacetaldehyde and (2) acetophenone with the following reagents:

- (a) $NaBH_4$, then H_3O^+ (b) 2 CH_3OH , HCl catalyst
 (c) $NH_2CH(CH_3)_2$, HCl catalyst (d) CH_3MgBr , then H_3O^+

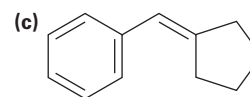
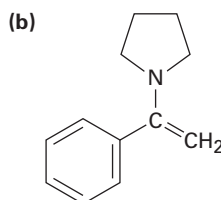
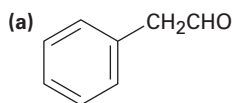
14.34 How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

- (a) Pentan-2-ol (b) Butan-1-ol
 (c) 1-Phenylcyclohexanol (d) Diphenylmethanol

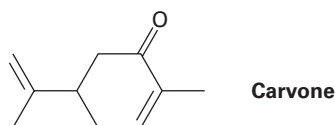
14.35 Show how the Wittig reaction might be used to prepare the following alkenes. Identify the alkyl halide and the carbonyl compound you would use in each case.



14.36 How would you synthesize the following substances from benzaldehyde and any other reagents needed?



- 14.37 Carvone is the major constituent of spearmint oil. What products would you expect from reaction of carvone with the following reagents?

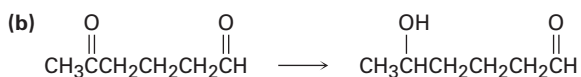


- (a) HOCH₂CH₂OH, HCl (b) LiAlH₄, then H₃O⁺ (c) CH₃NH₂
 (d) C₆H₅MgBr, then H₃O⁺ (e) 2 equiv. H₂/Pd (f) CrO₃, H₃O⁺

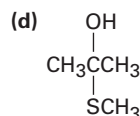
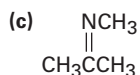
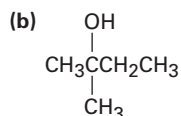
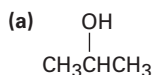
- 14.38 How would you synthesize the following compounds from cyclohexanone?

- (a) 1-Methylcyclohexene (b) 2-Phenylcyclohexanone
 (c) *cis*-Cyclohexane-1,2-diol (d) 1-Cyclohexylcyclohexanol

- 14.39 How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 14-4 that aldehydes are more reactive than ketones toward nucleophilic addition.)



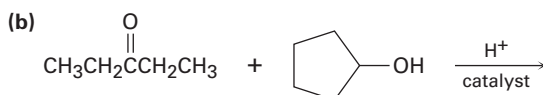
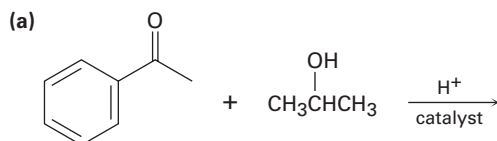
- 14.40 Identify the nucleophile that has added to acetone to give the following products:



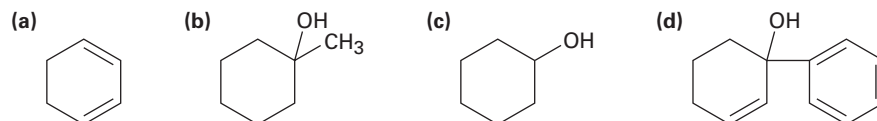
- 14.41 Show the products that result from the reaction of phenylmagnesium bromide with the following reagents:

- (a) CH₂O (b) Benzophenone (C₆H₅COC₆H₅) (c) Pentan-3-one

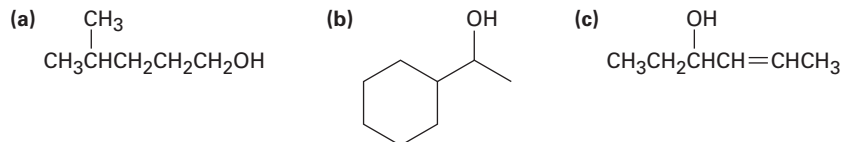
- 14.42 Show the structures of the intermediate hemiacetals and the final acetals that result from the following reactions:



14.43 Starting from cyclohex-2-enone and any other reagents needed, how would you prepare the following substances? More than one step may be required.



14.44 How could you make the following alcohols using a Grignard reaction of an aldehyde or ketone? Show all possibilities.



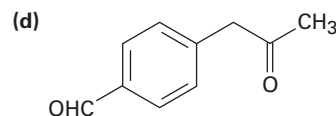
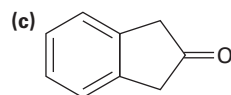
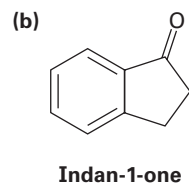
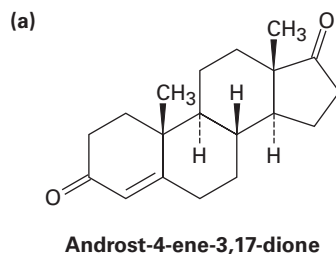
14.45 Which of the alcohols shown in Problem 14.44 could you make by reduction of a carbonyl compound? What carbonyl compound would you use in each case?

14.46 Draw the product(s) obtained by conjugate addition of the following reagents to cyclohex-2-enone:



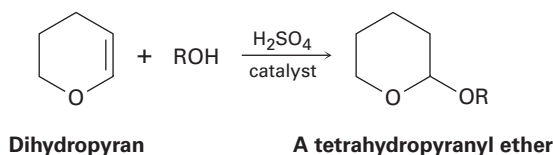
Spectroscopy of Aldehydes and Ketones

14.47 At what position would you expect to observe IR absorptions for the following molecules?

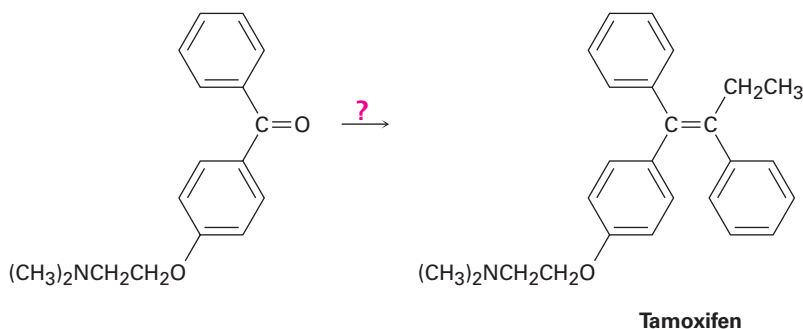


14.48 Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What are two likely structures for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{-1} , which of your structures is correct?

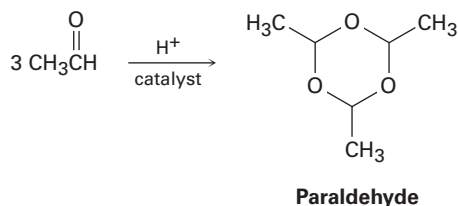
- 14.60 Treatment of an alcohol with dihydropyran yields an acetal called a tetrahydropyranyl ether. Propose a mechanism.



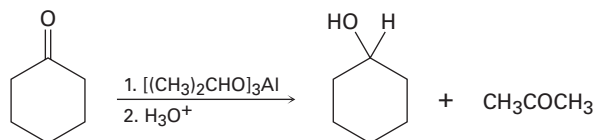
- 14.61 Tamoxifen is a drug used in the treatment of breast cancer. How would you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?



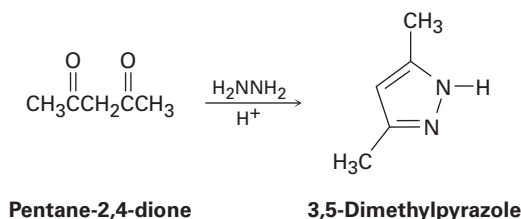
- 14.62 Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism.



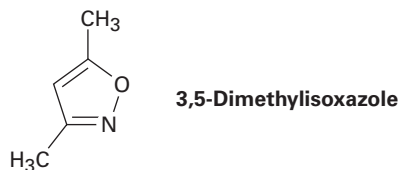
- 14.63 The Meerwein–Ponndorf–Verley reaction involves reduction of a ketone by treatment with an excess of aluminum triisopropoxide. The mechanism of the process is closely related to the Cannizzaro reaction in that a hydride ion acts as a leaving group. Propose a mechanism.



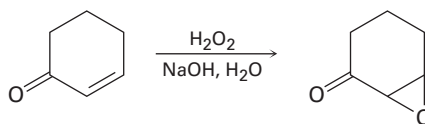
- 14.64 Propose a mechanism to account for the formation of 3,5-dimethylpyrazole from hydrazine and pentane-2,4-dione. What has happened to each carbonyl carbon in going from starting material to product?



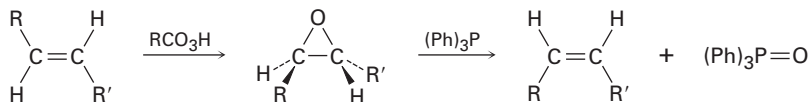
- 14.65** In light of your answer to Problem 14.64, propose a mechanism for the formation of 3,5-dimethylisoxazole from hydroxylamine (NH_2OH) and pentane-2,4-dione.



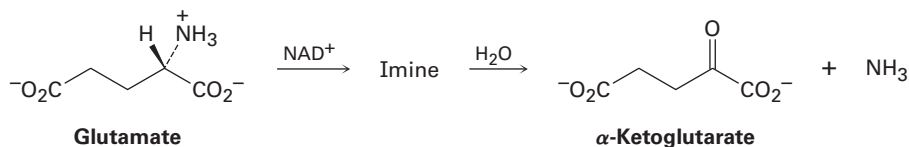
- 14.66** Treatment of an α,β -unsaturated ketone with basic aqueous hydrogen peroxide yields an epoxy ketone. The reaction is specific to unsaturated ketones and occurs by an initial conjugate addition followed by an $\text{S}_{\text{N}}2$ reaction. Propose a mechanism.



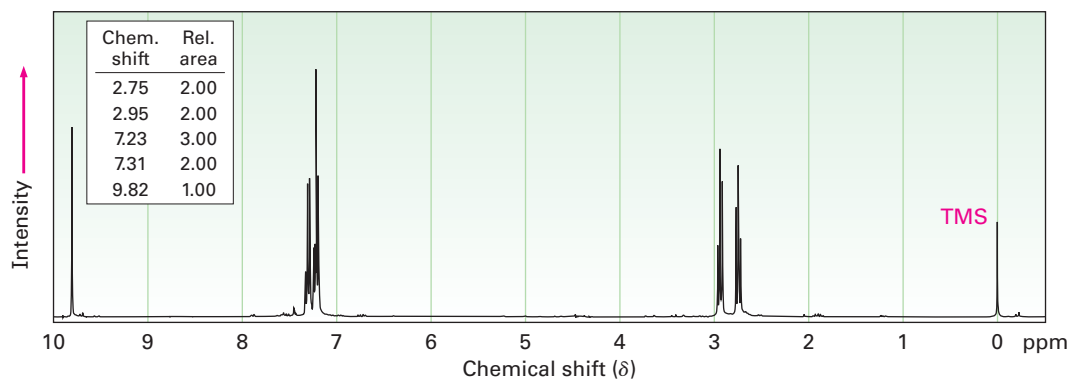
- 14.67** Trans alkenes can be converted into their cis isomers and vice versa by epoxidation followed by reaction of the epoxide with triphenylphosphine. Propose a mechanism for the epoxide \rightarrow alkene reaction.



- 14.68** One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) oxidation of the amine by NAD^+ to give an imine, and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α -ketoglutarate. Show the structure of the imine intermediate, and propose mechanisms for both steps.



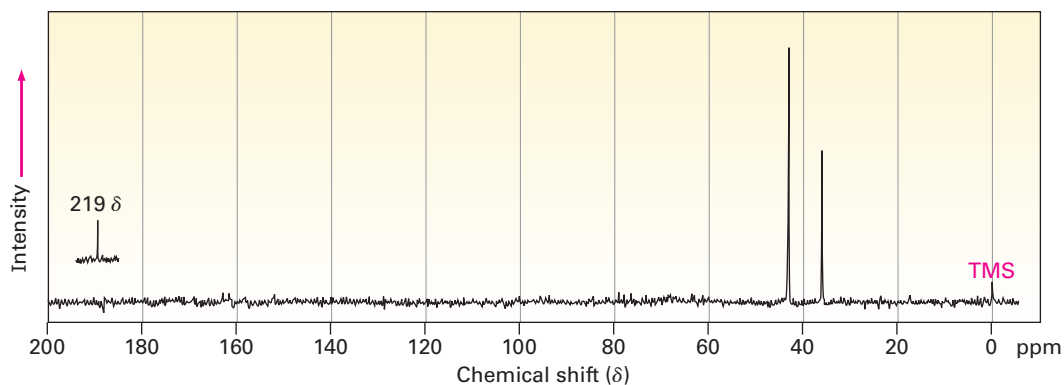
- 14.69** The ^1H NMR spectrum shown is that of a compound isomeric with the one in Problem 14.51. This isomer has an IR absorption at 1730 cm^{-1} . Propose a structure. [Note: Aldehyde protons (CHO) often show very small coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]



- 14.70** Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1° , 2° , 3° , or 4°) have been assigned by DEPT-NMR.

- (a) $\text{C}_6\text{H}_{12}\text{O}$; IR: 1715 cm^{-1} ;
 ^{13}C NMR: $8.0\ \delta$ (1°), $18.5\ \delta$ (1°), $33.5\ \delta$ (2°), $40.6\ \delta$ (3°), $214.0\ \delta$ (4°)
- (b) $\text{C}_5\text{H}_{10}\text{O}$; IR: 1730 cm^{-1} ;
 ^{13}C NMR: $22.6\ \delta$ (1°), $23.6\ \delta$ (3°), $52.8\ \delta$ (2°), $202.4\ \delta$ (3°)
- (c) $\text{C}_6\text{H}_8\text{O}$; IR: 1680 cm^{-1} ;
 ^{13}C NMR: $22.9\ \delta$ (2°), $25.8\ \delta$ (2°), $38.2\ \delta$ (2°), $129.8\ \delta$ (3°), $150.6\ \delta$ (3°), $198.7\ \delta$ (4°)

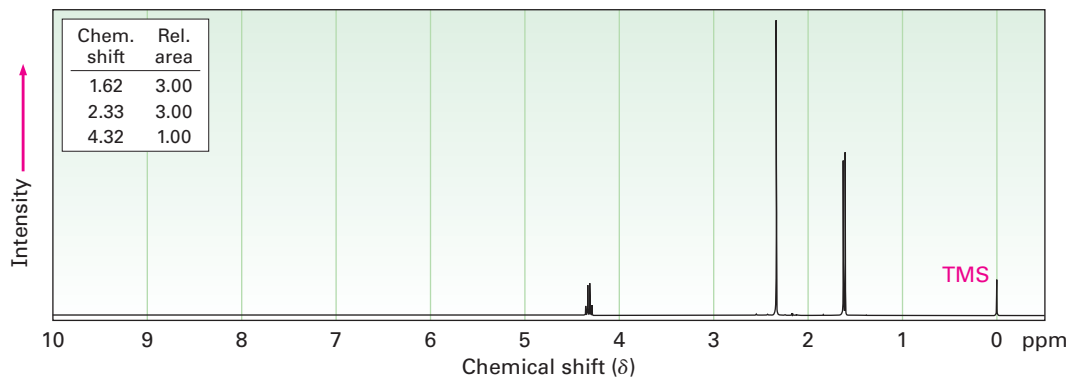
- 14.71** Compound **A**, $\text{C}_8\text{H}_{10}\text{O}_2$, has an intense IR absorption at 1750 cm^{-1} and gives the ^{13}C NMR spectrum shown. Propose a structure for **A**.



14.72 Propose structures for aldehydes or ketones that have the following ^1H NMR spectra:

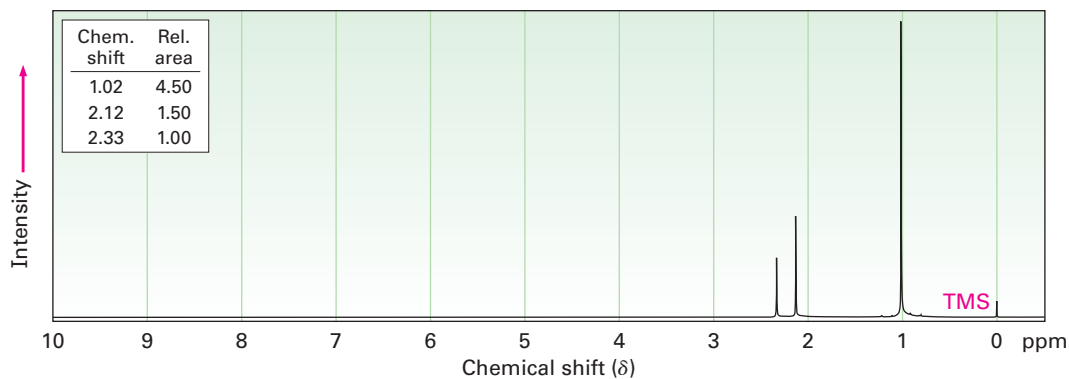
(a) $\text{C}_4\text{H}_7\text{ClO}$

IR: 1715 cm^{-1}



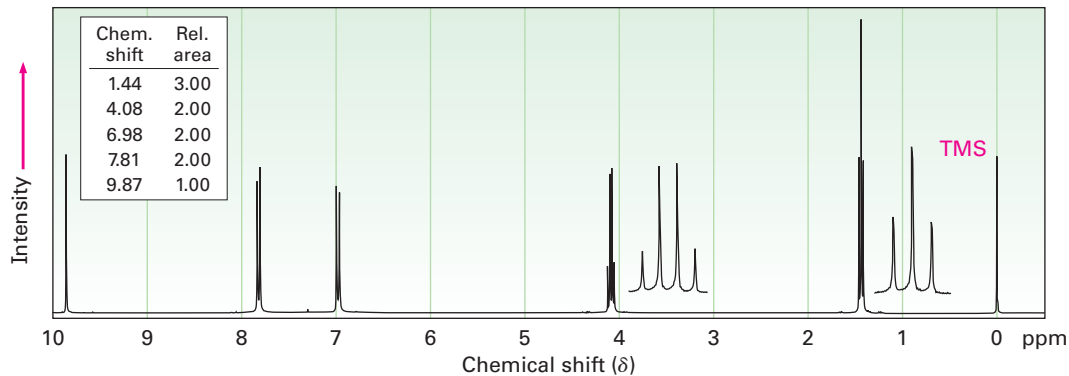
(b) $\text{C}_7\text{H}_{14}\text{O}$

IR: 1710 cm^{-1}

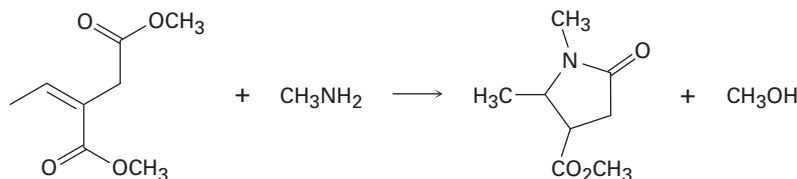


(c) $\text{C}_9\text{H}_{10}\text{O}_2$

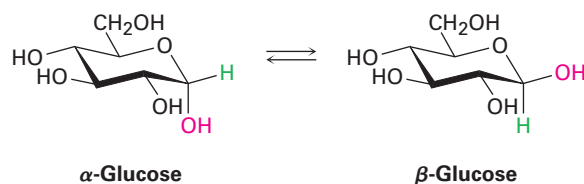
IR: 1695 cm^{-1}



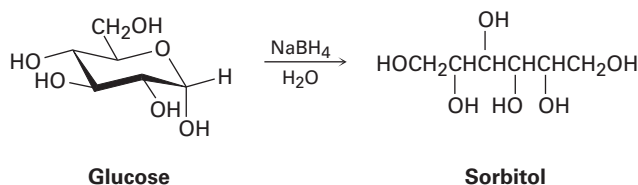
- 14.73 Primary amines react with esters to yield amides: $\text{RCO}_2\text{R}' + \text{R}''\text{NH}_2 \rightarrow \text{RCONHR}'' + \text{R}'\text{OH}$. Propose a mechanism for the following reaction of an α,β -unsaturated ester.



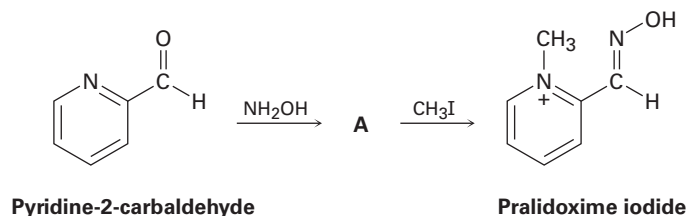
- 14.74 When crystals of pure α -glucose are dissolved in water, isomerization slowly occurs to produce β -glucose. Propose a mechanism for the isomerization.



- 14.75 When glucose (Problem 14.74) is treated with NaBH_4 , reaction occurs to yield *sorbitol*, a polyalcohol commonly used as a food additive. Show how this reduction occurs.



- 14.76 Pralidoxime iodide is a general antidote for poisoning by many insecticides. The drug is made in two steps starting with pyridine-2-carbaldehyde.



- (a) Show the mechanism of the reaction of hydroxylamine (NH_2OH) with pyridine-2-carbaldehyde, and give the structure of A.
- (b) Reaction of A with iodomethane to give pralidoxime iodide is an $\text{S}_\text{N}2$ reaction. Show the mechanism.

15

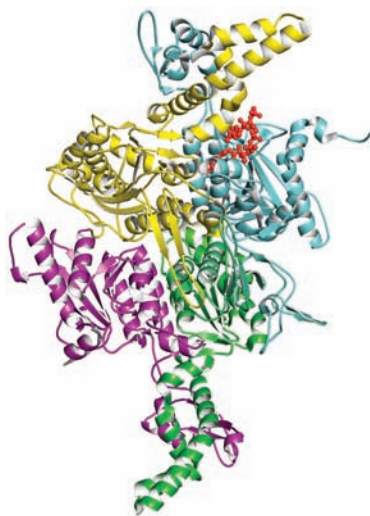
Carboxylic Acids
and Nitriles

CONTENTS

- 15-1** Naming Carboxylic Acids and Nitriles
- 15-2** Structure and Properties of Carboxylic Acids
- 15-3** Biological Acids and the Henderson–Hasselbalch Equation
- 15-4** Substituent Effects on Acidity
- 15-5** Preparing Carboxylic Acids
- 15-6** Reactions of Carboxylic Acids: An Overview
- 15-7** Chemistry of Nitriles
- 15-8** Spectroscopy of Carboxylic Acids and Nitriles

SOMETHING EXTRA

Vitamin C

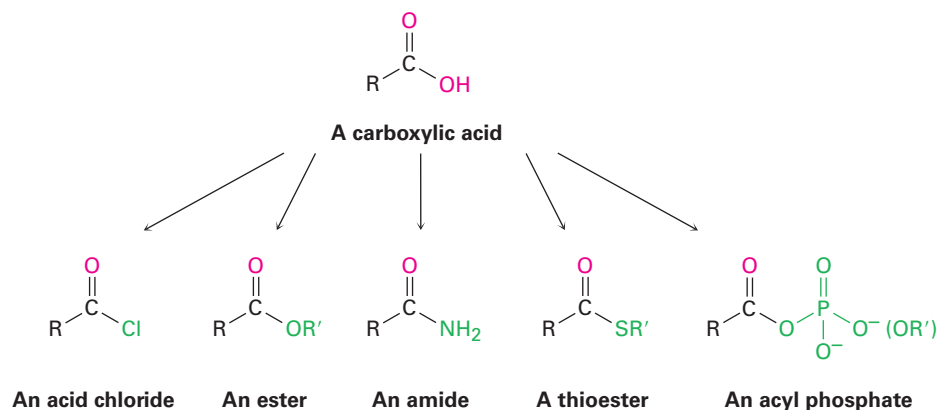


Acetyl CoA carboxylase catalyzes the carboxylation of acetyl CoA to give malonyl CoA, the first step in fatty-acid biosynthesis.

WHY THIS CHAPTER?

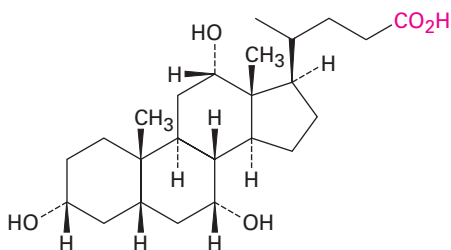
Carboxylic acids are present in many industrial processes and most biological pathways and are the starting materials from which other acyl derivatives are made. Thus, an understanding of their properties and reactions is fundamental to understanding biological chemistry. We'll look both at acids and at their close relatives, nitriles ($\text{RC}\equiv\text{N}$), in this chapter and at carboxylic acid derivatives in the next chapter.

Carboxylic acids (RCO_2H) occupy a central place among carbonyl compounds, both in living organisms and in the laboratory. Carboxylic acids are present in the majority of biological pathways and serve as starting materials for preparing numerous carboxylic acid derivatives, such as acid chlorides, esters, amides, thioesters, and acyl phosphates.

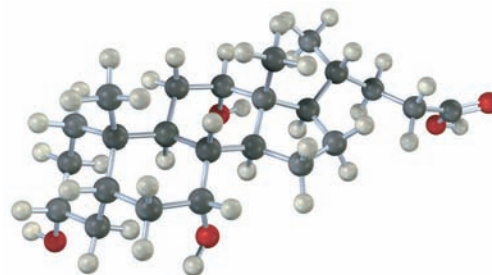


A great many carboxylic acids are found in nature: acetic acid, $\text{CH}_3\text{CO}_2\text{H}$, is the chief organic component of vinegar; butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$,

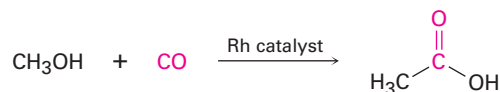
is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$, is responsible for the unmistakable aroma of goats and dirty gym socks (the name comes from the Latin *caper*, meaning “goat”). Other examples are cholic acid, a major component of human bile, and long-chain aliphatic acids such as palmitic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, a biological precursor of fats and vegetable oils.



Cholic acid



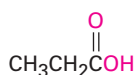
Approximately 5 million metric tons of acetic acid is produced worldwide year for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



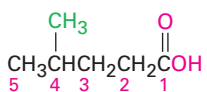
15-1 Naming Carboxylic Acids and Nitriles

Carboxylic Acids, RCO_2H

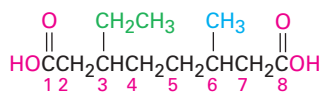
Simple carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. The $-\text{CO}_2\text{H}$ carbon atom is numbered C1.



Propanoic acid



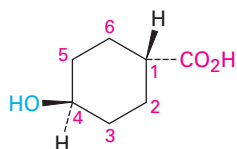
4-Methylpentanoic acid



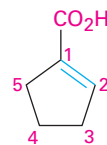
3-Ethyl-6-methyloctanedioic acid

Compounds that have a $-\text{CO}_2\text{H}$ group bonded to a ring are named using the suffix *-carboxylic acid*. The CO_2H carbon is attached to C1 in this system

and is not itself numbered. As a substituent, the CO_2H group is called a **carboxyl group**.



trans-4-Hydroxycyclohexanecarboxylic acid



Cyclopent-1-enecarboxylic acid

Because many carboxylic acids were among the first organic compounds to be isolated and purified, a large number of common names exist (TABLE 15.1). Biological chemists make frequent use of these names, so you may find yourself referring back to this list on occasion. We'll use systematic names in this book, with a few exceptions such as formic (methanoic) acid and acetic (ethanoic) acid, whose names are accepted by IUPAC.

Also listed in Table 15.1 are the common names used for acyl groups derived from the parent acids. Except for the eight entries at the top of Table 15.1, whose common names have a *-yl* ending, all others are named systematically with an *-oyl* ending.

TABLE 15.1 Common Names of Some Carboxylic Acids and Acyl Groups

Structure	Name	Acyl group	Structure	Name	Acyl group
HCO_2H	Formic	Formyl	$\text{CH}_3\text{C}(=\text{O})\text{CO}_2\text{H}$	Pyruvic	Pyruvoyl
$\text{CH}_3\text{CO}_2\text{H}$	Acetic	Acetyl	$\text{HOCH}_2\text{CH}(\text{OH})\text{CO}_2\text{H}$	Glyceric	Glyceroyl
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	Propionic	Propionyl	$\text{HO}_2\text{CCH}(\text{OH})\text{CH}_2\text{CO}_2\text{H}$	Malic	Maloyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Butyric	Butyryl	$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{CO}_2\text{H}$	Oxaloacetic	Oxaloacetyl
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{H}$	Oxalic	Oxalyl		Benzoic	Benzoyl
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{CO}_2\text{H}$	Malonic	Malonyl		Phthalic	Phthaloyl
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{H}$	Succinic	Succinyl			
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{H}$	Glutaric	Glutaryl			
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{H}$	Adipic	Adipoyl			
$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	Acrylic	Acryloyl			
$\text{HO}_2\text{C}-\text{C}(=\text{O})-\text{CH}=\text{CHCO}_2\text{H}$	Maleic (cis)	Maleoyl			
	Fumaric (trans)	Fumaroyl			
$\text{HOCH}_2\text{CO}_2\text{H}$	Glycolic	Glycoloyl			
$\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H}$	Lactic	Lactoyl			

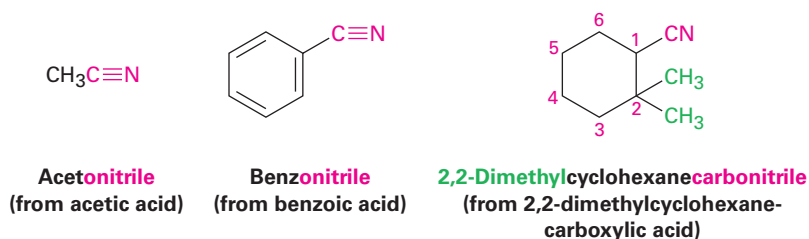
Nitriles, $\text{RC}\equiv\text{N}$

Compounds containing the $-\text{C}\equiv\text{N}$ functional group are called **nitriles** and undergo some chemistry similar to that of carboxylic acids. Simple open-chain

nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1:

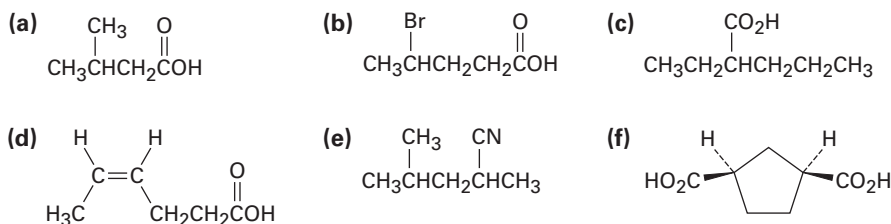


Nitriles can also be named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile* or by replacing the *-carboxylic acid* ending with *-carbonitrile*. The nitrile carbon atom is attached to C1 but is not itself numbered.



PROBLEM 15.1

Give IUPAC names for the following compounds:



PROBLEM 15.2

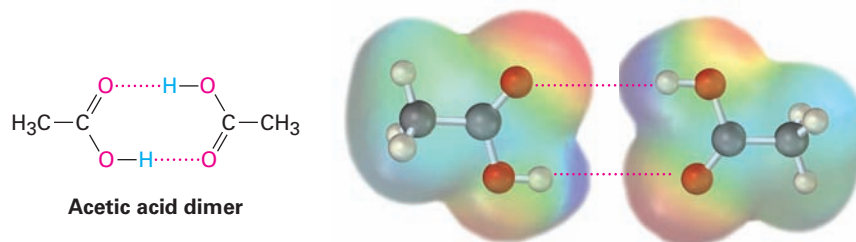
Draw structures corresponding to the following IUPAC names:

- | | |
|---|-----------------------------------|
| (a) 2,3-Dimethylhexanoic acid | (b) 4-Methylpentanoic acid |
| (c) <i>trans</i> -Cyclobutane-1,2-dicarboxylic acid | (d) <i>o</i> -Hydroxybenzoic acid |
| (e) (9 <i>Z</i> ,12 <i>Z</i>)-Octadeca-9,12-dienoic acid | (f) Pent-2-enenitrile |

15-2 Structure and Properties of Carboxylic Acids

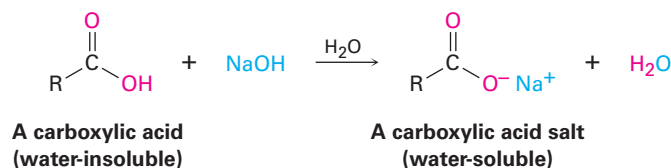
Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2 -hybridized, and carboxylic acid groups are therefore planar with $\text{C}=\text{C}=\text{O}$ and $\text{O}=\text{C}-\text{O}$ bond angles of approximately 120° . Like alcohols, carboxylic acids are strongly associated because of

hydrogen-bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds.

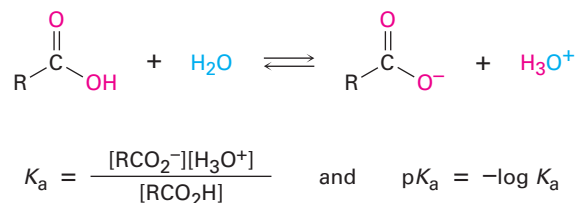


This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.

The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. They therefore react with bases such as NaOH and NaHCO₃ to give metal carboxylate salts, RCO₂⁻ M⁺. Carboxylic acids with more than six carbons are only slightly soluble in water, but the alkali metal salts of carboxylic acids are often highly water-soluble. In fact, it's often possible to purify an acid by extracting its salt into aqueous base, then reacidifying and extracting the pure acid back into an organic solvent.



Like other Brønsted–Lowry acids discussed in Section 2-7, carboxylic acids dissociate slightly in dilute aqueous solution to give H₃O⁺ and the corresponding carboxylate anion, RCO₂⁻. The extent of dissociation is given by an acidity constant, K_a:

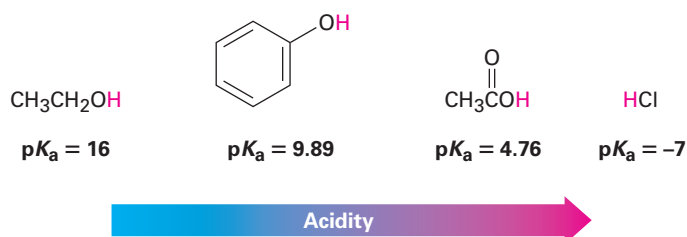


A list of K_a values for various carboxylic acids is given in **TABLE 15.2**. For most, K_a is approximately 10⁻⁴ to 10⁻⁵. Acetic acid, for instance, has K_a = 1.75 × 10⁻⁵ at 25 °C, which corresponds to a pK_a of 4.76. In practical terms, a K_a value near 10⁻⁵ means that only about 0.1% of the molecules in a 0.1 M solution are dissociated, as opposed to the 100% dissociation found with strong mineral acids like HCl.

TABLE 15.2 Acidity of Some Carboxylic Acids

Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	Stronger acid
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.83	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C=CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	
CH_3CH_2OH (ethanol)	(1.00×10^{-16})	(16.00)	

Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16} , making ethanol a weaker acid than acetic acid by a factor of 10^{11} .

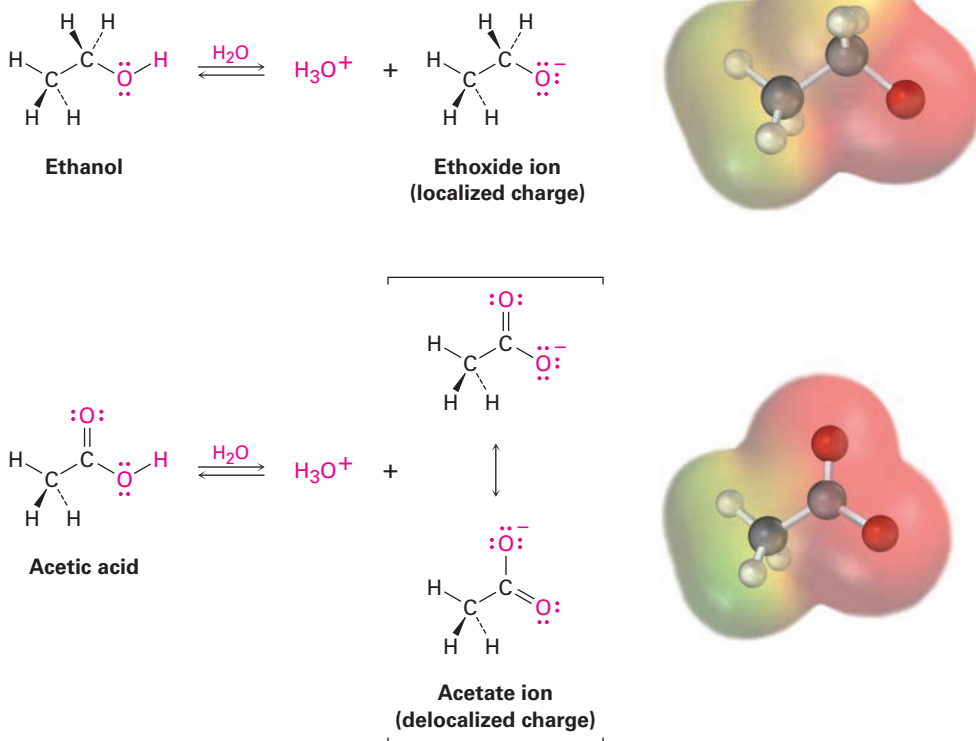


Why are carboxylic acids so much more acidic than alcohols, even though both contain $-OH$ groups? An alcohol dissociates to give an alkoxide ion, in which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge is delocalized over *two* oxygen atoms (FIGURE 15.1). In resonance terms (Section 2-4), a carboxylate ion is a stabilized resonance hybrid of two equivalent structures. Since a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and more favored in the dissociation equilibrium.

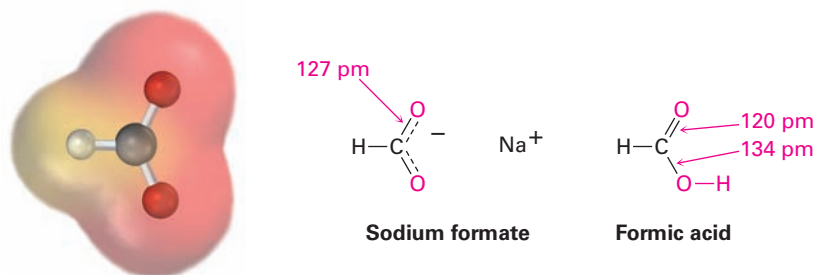
Experimental evidence for the equivalence of the two carboxylate oxygens comes from X-ray crystallographic studies on sodium formate. Both carbon–oxygen bonds are 127 pm in length, midway between the $C=O$ double bond (120 pm) and $C-O$ single bond (134 pm) of formic acid. An electrostatic

FIGURE 15.1 Comparison of alkoxide and carboxylate ions.

An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over two oxygens and is therefore more stable.



potential map of the formate ion also shows how the negative charge (red) is spread equally over both oxygens.

**PROBLEM 15.3**

Assume you have a mixture of naphthalene and benzoic acid that you want to separate. How might you take advantage of the acidity of one component in the mixture to effect a separation?

PROBLEM 15.4

The K_a for dichloroacetic acid is 3.32×10^{-2} . Approximately what percentage of the acid is dissociated in a 0.10 M aqueous solution?

15-3 Biological Acids and the Henderson–Hasselbalch Equation

In acidic solution, at low pH, a carboxylic acid is completely undissociated and exists entirely as RCO_2H . In basic solution, at high pH, a carboxylic acid is completely dissociated and exists entirely as RCO_2^- . Inside living cells, however, the pH is neither acidic nor basic but is instead buffered to nearly neutral pH—in humans, to $\text{pH} = 7.3$, a value often referred to as *physiological pH*. In what form, then, do carboxylic acids exist inside cells? The question is an important one for understanding the acid catalysts so often found in biological reactions.

If the $\text{p}K_a$ value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using the **Henderson–Hasselbalch equation**.

For any acid HA, we have

$$\begin{aligned}\text{p}K_a &= -\log \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} = -\log [\text{H}_3\text{O}^+] - \log \frac{[\text{A}^-]}{[\text{HA}]} \\ &= \text{pH} - \log \frac{[\text{A}^-]}{[\text{HA}]}\end{aligned}$$

which can be rearranged to give

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad \text{Henderson–Hasselbalch equation}$$

and
$$\log \frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_a$$

This equation says that the logarithm of the concentration of dissociated acid $[\text{A}^-]$ divided by the concentration of undissociated acid $[\text{HA}]$ is equal to the pH of the solution minus the $\text{p}K_a$ of the acid. Thus, if we know both the pH of the solution and the $\text{p}K_a$ of the acid, we can calculate the ratio of $[\text{A}^-]$ to $[\text{HA}]$. Furthermore, when $\text{pH} = \text{p}K_a$, the two forms HA and A^- are present in equal amounts because $\log 1 = 0$.

As an example of how to use the Henderson–Hasselbalch equation, let's find out what species are present in a 0.0010 M solution of acetic acid at $\text{pH} = 7.3$. According to Table 15.2, the $\text{p}K_a$ of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\log \frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_a = 7.3 - 4.76 = 2.54$$

$$\frac{[\text{A}^-]}{[\text{HA}]} = \text{antilog}(2.54) = 3.5 \times 10^2 \quad \text{so } [\text{A}^-] = (3.5 \times 10^2) [\text{HA}]$$

In addition, we know that

$$[\text{A}^-] + [\text{HA}] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives $[\text{A}^-] = 0.0010 \text{ M}$ and $[\text{HA}] = 3 \times 10^{-6} \text{ M}$. In other words, at a physiological pH of 7.3, essentially 100% of acetic acid molecules in a 0.0010 M solution are dissociated to the acetate ion.

What's true for acetic acid is also true for other carboxylic acids: at the physiological pH that exists inside cells, carboxylic acids are almost entirely dissociated. To reflect this fact, we always refer to cellular carboxylic acids by the name of their anion: acetate, lactate, citrate, and so forth rather than acetic acid, lactic acid, and citric acid.

PROBLEM 15.5

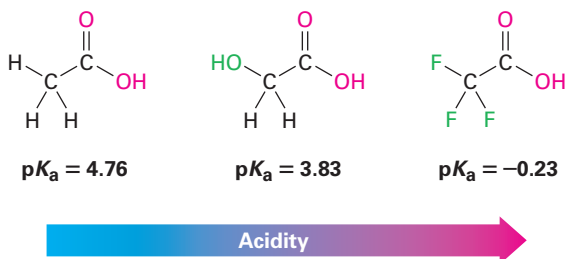
Calculate the percentages of dissociated and undissociated forms present in the following solutions:

- (a) 0.0010 M glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$; $\text{p}K_a = 3.83$) at $\text{pH} = 4.50$
 (b) 0.0020 M propanoic acid ($\text{p}K_a = 4.87$) at $\text{pH} = 5.30$

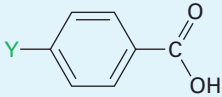
15-4 Substituent Effects on Acidity

The listing of K_a values shown previously in Table 15.2 indicates that there are substantial differences in acidity from one carboxylic acid to another. For example, trifluoroacetic acid ($K_a = 0.59$) is 33,000 times as strong as acetic acid ($K_a = 1.75 \times 10^{-5}$). How can we account for such differences?

Because the dissociation of a carboxylic acid is an equilibrium process, any factor that stabilizes the carboxylate anion relative to undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. For instance, the electron-withdrawing inductive effect of three fluorine atoms delocalizes the negative charge in the trifluoroacetate anion, thereby stabilizing the ion and increasing the acidity of $\text{CF}_3\text{CO}_2\text{H}$. In the same way, glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$; $\text{p}K_a = 3.83$) is stronger than acetic acid because of the electron-withdrawing inductive effect of the electronegative oxygen atom.

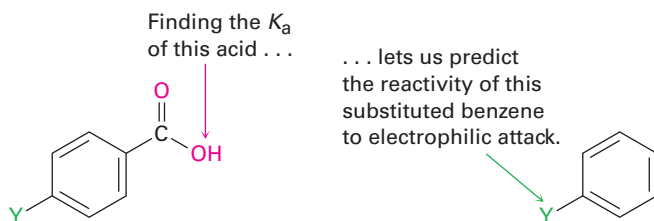


Substituent effects on acidity are also found in substituted benzoic acids. We said during the discussion of electrophilic aromatic substitution in Section 9-8 that substituents on the aromatic ring strongly affect reactivity. Aromatic rings with electron-donating groups are activated toward further electrophilic substitution, and aromatic rings with electron-withdrawing groups are deactivated. Exactly the same effects are noted on the acidity of substituted benzoic acids (TABLE 15.3). Thus, an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion, and an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion.

TABLE 15.3 Substituent Effects on the Acidity of *p*-Substituted Benzoic Acids


	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid ↑	-NO ₂	39	3.41	Deactivating groups
	-CN	28	3.55	
	-CHO	18	3.75	
	-Br	11	3.96	
	-Cl	10	4.0	
Weaker acid ↓	-H	6.46	4.19	Activating groups
	-CH ₃	4.3	4.34	
	-OCH ₃	3.5	4.46	
	-OH	3.3	4.48	

Because it's much easier to measure the acidity of a substituted benzoic acid than it is to determine the relative reactivity of an aromatic ring toward electrophilic substitution, the correlation between the two effects is useful for predicting reactivity. If we want to know the effect of a certain substituent on electrophilic reactivity, we can simply find the acidity of the corresponding benzoic acid. Worked Example 15.1 gives an illustration.



Predicting the Effect of a Substituent on the Reactivity of an Aromatic Ring toward Electrophilic Substitution

WORKED EXAMPLE 15.1

The pK_a of *p*-(trifluoromethyl)benzoic acid is 3.6. Is the trifluoromethyl substituent an activating or deactivating group in electrophilic aromatic substitution?

Strategy

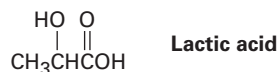
Decide whether *p*-(trifluoromethyl)benzoic acid is stronger or weaker than benzoic acid. A substituent that strengthens the acid is a deactivating group because it withdraws electrons, and a substituent that weakens the acid is an activating group because it donates electrons.

Solution

A pK_a of 3.6 means that *p*-(trifluoromethyl)benzoic acid is stronger than benzoic acid, whose pK_a is 4.19. Thus, the trifluoromethyl substituent favors dissociation by helping stabilize the negative charge. Trifluoromethyl must therefore be an electron-withdrawing, deactivating group.

PROBLEM 15.6

Which would you expect to be a stronger acid, the lactic acid found in tired muscles or acetic acid? Explain.

**PROBLEM 15.7**

Dicarboxylic acids have two dissociation constants, one for the initial dissociation into a monoanion and one for the second dissociation into a dianion. For oxalic acid, $\text{HO}_2\text{C}-\text{CO}_2\text{H}$, the first ionization constant is $pK_{a1} = 1.2$ and the second ionization constant is $pK_{a2} = 4.2$. Why is the second carboxyl group so much less acidic than the first?

PROBLEM 15.8

The pK_a of *p*-cyclopropylbenzoic acid is 4.45. Is cyclopropylbenzene likely to be more reactive or less reactive than benzene toward electrophilic bromination? Explain.

PROBLEM 15.9

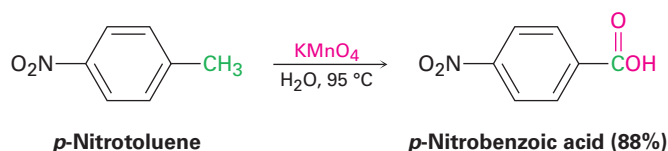
Rank the following compounds in order of increasing acidity. Don't look at a table of pK_a data to help with your answer.

- (a) Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid
 (b) *p*-Nitrobenzoic acid, acetic acid, benzoic acid

15-5 Preparing Carboxylic Acids

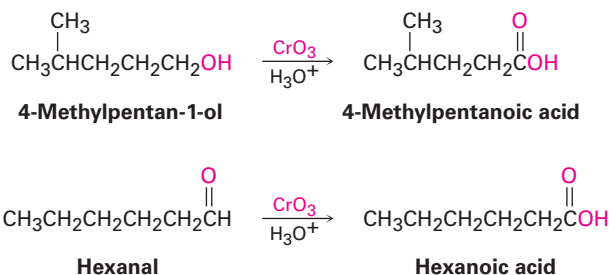
Let's review briefly the methods for preparing carboxylic acids that we've seen in past chapters:

- Oxidation of a substituted alkylbenzene with KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ gives a substituted benzoic acid (Section 9-10). Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



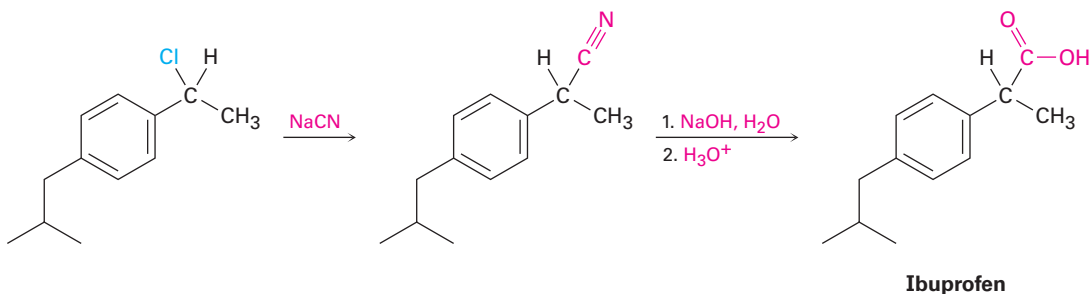
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- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid (Sections 13-5 and 14-3). Both oxidations are often carried out with CrO_3 in aqueous acid.



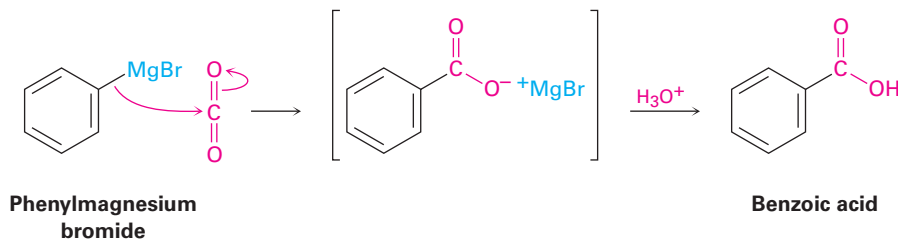
Hydrolysis of Nitriles

Carboxylic acids can be prepared from nitriles on heating with aqueous acid or base by a mechanism that we'll see in Section 15-7. Since nitriles themselves are usually made by $\text{S}_{\text{N}}2$ reaction of a primary or secondary alkyl halide with CN^- , the two-step sequence of cyanide displacement followed by nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($\text{RBr} \rightarrow \text{RC}\equiv\text{N} \rightarrow \text{RCO}_2\text{H}$). Note that the product acid has one more carbon than the starting alkyl halide. An example occurs in one commercial route for the synthesis of the nonsteroidal anti-inflammatory drug ibuprofen.

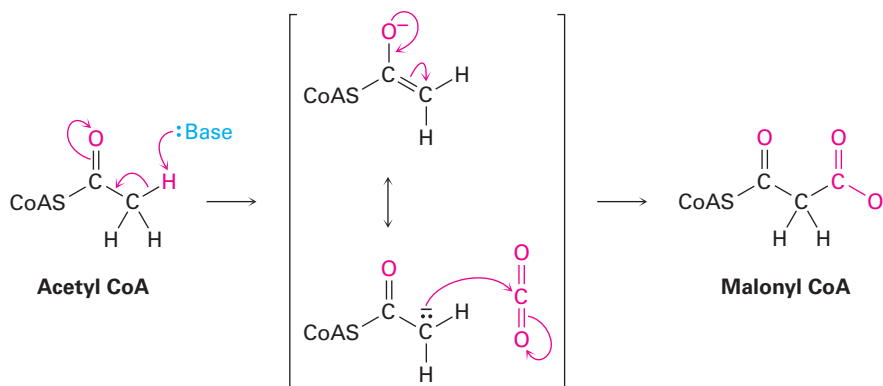


Carboxylation of Grignard Reagents

Another method for preparing carboxylic acids is by reaction of a Grignard reagent with CO_2 to yield a metal carboxylate, followed by protonation to give the carboxylic acid. This **carboxylation** reaction is usually carried out by bubbling a stream of dry CO_2 gas through a solution of the Grignard reagent. The organomagnesium halide adds to a $\text{C}=\text{O}$ bond of carbon dioxide in a typical nucleophilic carbonyl addition reaction, and protonation of the carboxylate by addition of aqueous HCl in a separate step then gives the free carboxylic acid. For example



As noted previously, there are no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated. One of the initial steps in fatty-acid biosynthesis, for instance, involves formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.



WORKED EXAMPLE 15.2

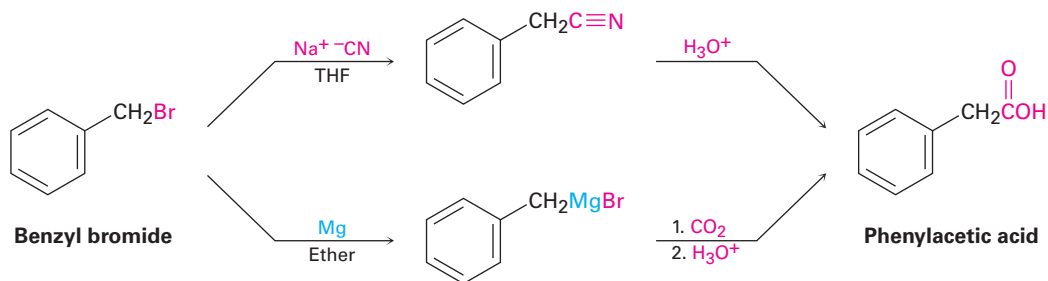
Devising a Synthesis Route for a Carboxylic Acid

How would you prepare phenylacetic acid (PhCH₂CO₂H) from benzyl bromide (PhCH₂Br)?

Strategy

We've seen two methods for preparing carboxylic acids from alkyl halides: (1) cyanide ion displacement followed by hydrolysis and (2) formation of a Grignard reagent followed by carboxylation. The first method involves an S_N2 reaction and is therefore limited to use with primary and some secondary alkyl halides. The second method involves formation of a Grignard reagent and is therefore limited to use with organic halides that have no acidic hydrogens or reactive functional groups elsewhere in the molecule. In the present instance, either method would work well.

Solution



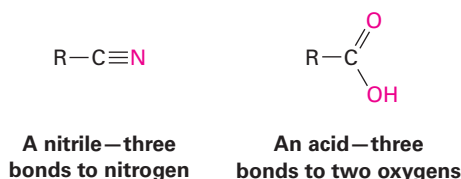
PROBLEM 15.10

How would you prepare the following carboxylic acids?

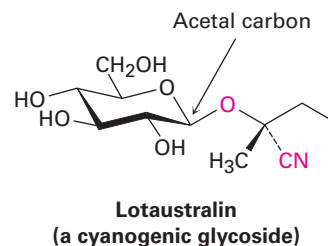
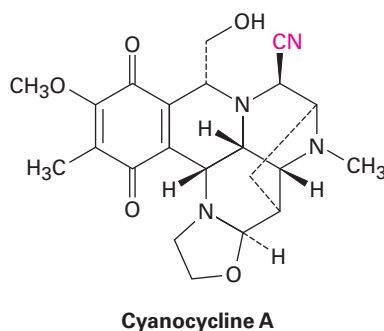
(a) (CH₃)₃CCO₂H from (CH₃)₃CCl

(b) CH₃CH₂CH₂CO₂H from CH₃CH₂CH₂Br

of compounds are electrophiles, for instance, and both undergo nucleophilic addition reactions.

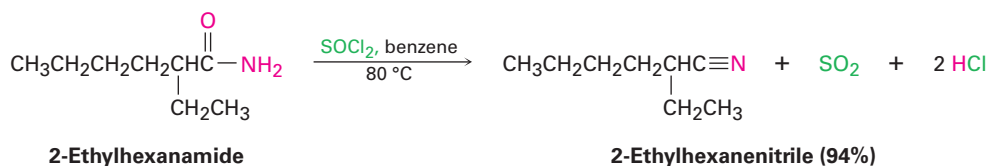


Nitriles occur infrequently in living organisms, although several hundred examples are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and found to have both antimicrobial and antitumor activity. In addition, more than 1000 compounds called *cyanogenic glycosides* are known. Derived primarily from plants, cyanogenic glycosides contain a sugar with an acetal carbon, one oxygen of which is bonded to a nitrile-bearing carbon (Sugar–O–C–CN). On hydrolysis with aqueous acid, the acetal is cleaved (Section 14-8), generating a cyanohydrin (HO–C–CN), which releases hydrogen cyanide. It's thought that the primary function of cyanogenic glycosides is to protect the plant by poisoning any animal foolish enough to eat it. Lotaustralin from the cassava plant is an example.

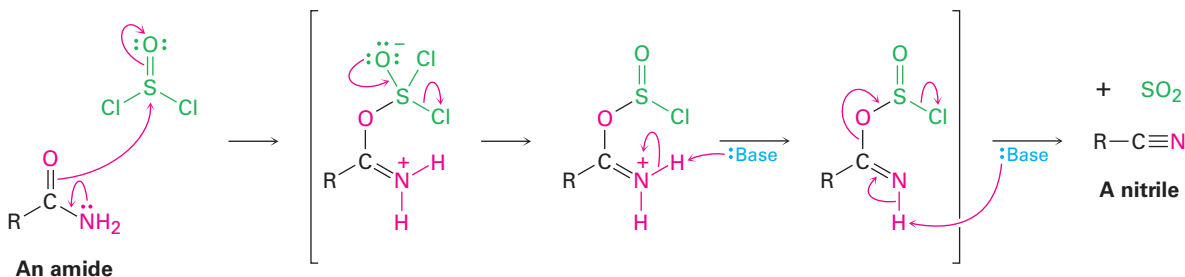


Preparation of Nitriles

The simplest method of nitrile preparation in the laboratory is the S_N2 reaction of CN^- with a primary or secondary alkyl halide, as mentioned in Section 15-5. Another method for preparing nitriles is by dehydration of a primary amide, RCONH_2 . Thionyl chloride (SOCl_2) is often used for the reaction.



The dehydration occurs by initial reaction of SOCl_2 on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.



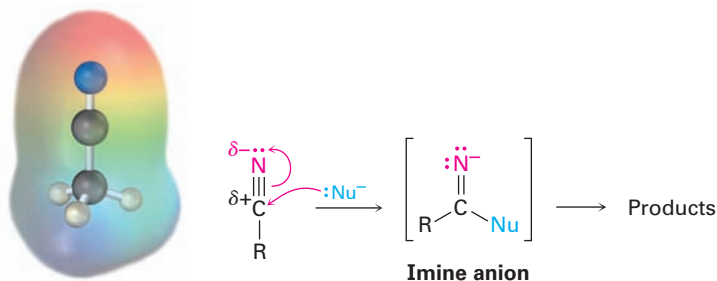
Both methods of nitrile synthesis— $\text{S}_{\text{N}}2$ displacement by CN^- on an alkyl halide and amide dehydration—are useful, but the synthesis from amides is more general because it is not limited by steric hindrance.

Reactions of Nitriles

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2 -hybridized imine anions in a reaction analogous to the formation of an sp^3 -hybridized alkoxide ion by nucleophilic addition to a carbonyl group.

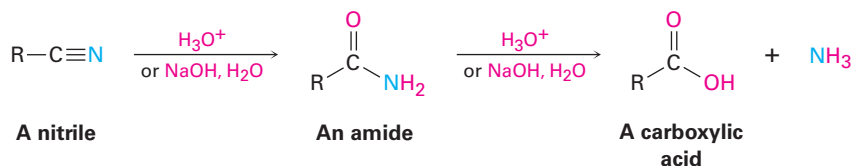


Nitrile



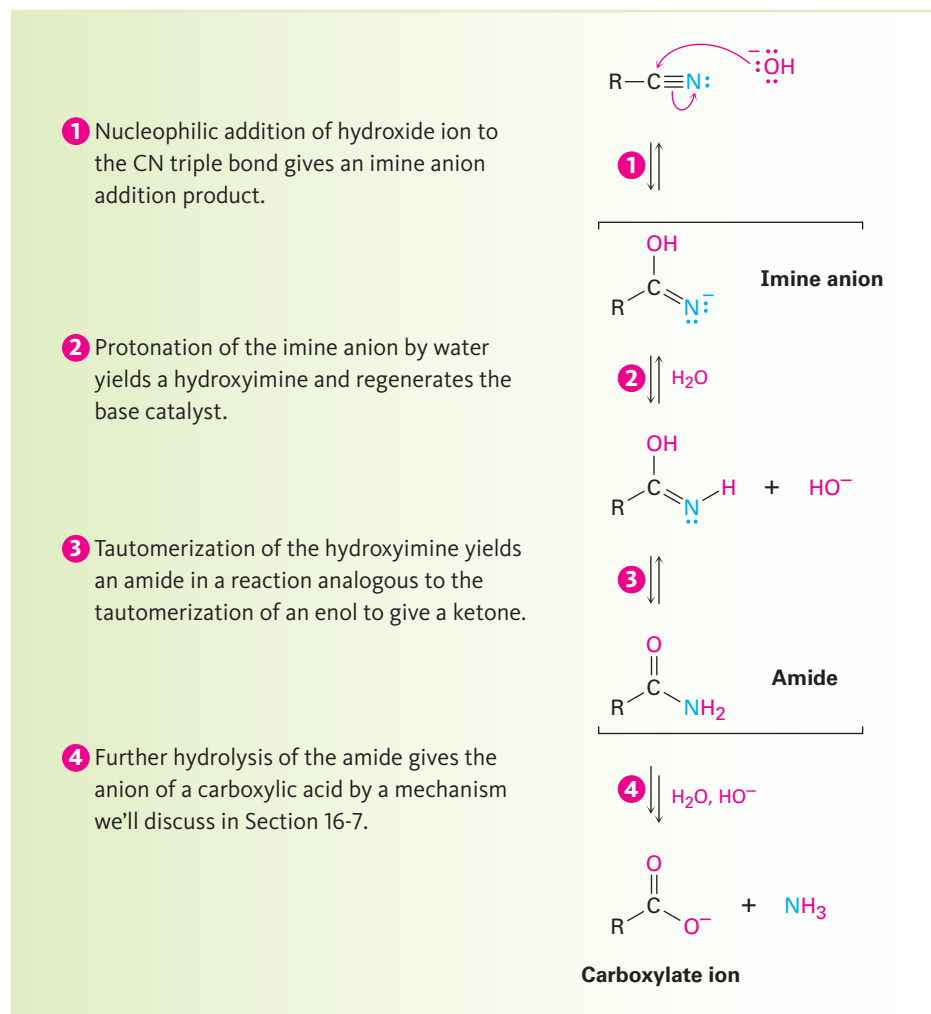
HYDROLYSIS: CONVERSION OF NITRILES TO CARBOXYLIC ACIDS

Among the most useful reactions of nitriles is their hydrolysis to yield first an amide and then a carboxylic acid plus ammonia or an amine. The reaction occurs in either basic or acidic aqueous solution:

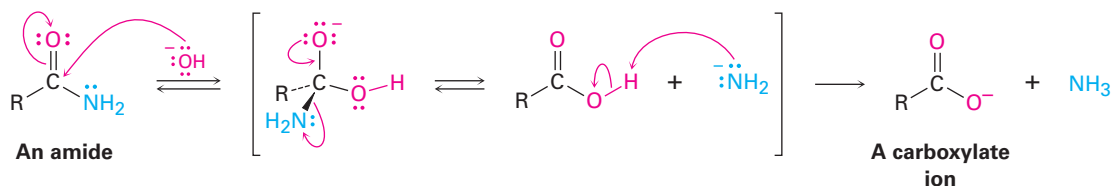


Base-catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion. Protonation then gives a hydroxy imine, which isomerizes to an amide. Further hydrolysis gives a carboxylate ion. The mechanism is shown in **FIGURE 15.3**.

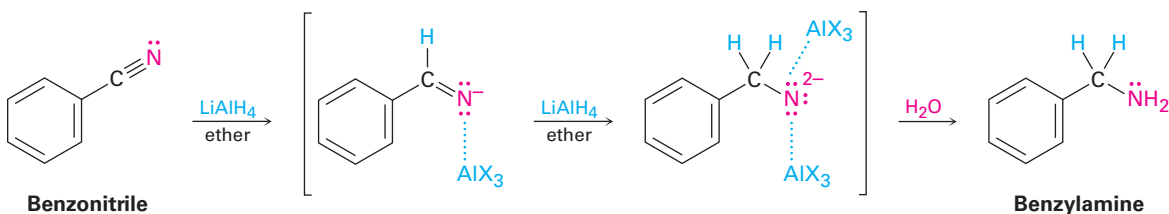
FIGURE 15.3 Mechanism of the basic hydrolysis of a nitrile to yield an amide. The amide is subsequently hydrolyzed further to a carboxylic acid anion.



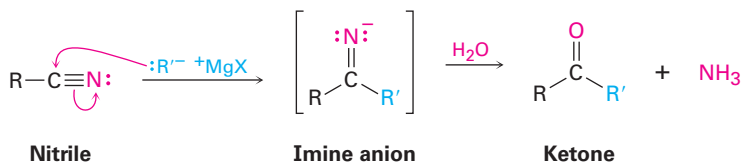
The further hydrolysis of the amide intermediate to give a carboxylate ion occurs by a nucleophilic acyl substitution mechanism that is the subject of the next chapter. Nucleophilic addition of hydroxide ion to the amide carbonyl group yields a tetrahedral alkoxide ion, which expels amide ion, NH_2^- , as leaving group and gives the carboxylate ion, thereby driving the reaction toward products. Subsequent acidification in a separate step yields the carboxylic acid.



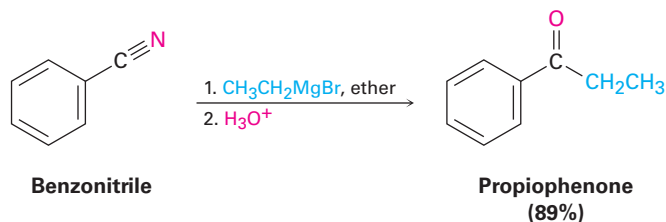
REDUCTION: CONVERSION OF NITRILES TO AMINES Reduction of a nitrile with LiAlH_4 gives a primary amine, RNH_2 . The reaction occurs by nucleophilic addition of hydride ion to the polar $\text{C}\equiv\text{N}$ bond, yielding an imine anion, which still contains a $\text{C}=\text{N}$ bond and therefore undergoes a second nucleophilic addition of hydride to give a *dianion*. Both monoanion and dianion intermediates are undoubtedly stabilized by Lewis acid–base complexation to an aluminum species, facilitating the second addition that would otherwise be difficult. Protonation of the dianion by addition of water in a subsequent step gives the amine.



REACTION OF NITRILES WITH GRIGNARD REAGENTS Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone. The mechanism of the hydrolysis is the exact reverse of imine formation (Figure 14.6 on page 506).



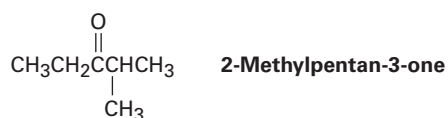
The reaction is similar to the reduction of a nitrile to an amine, except that only one nucleophilic addition occurs rather than two, and the attacking nucleophile is a carbanion (R'^-) rather than a hydride ion. For example:



Synthesizing a Ketone from a Nitrile

WORKED EXAMPLE 15.3

How would you prepare 2-methylpentan-3-one from a nitrile?

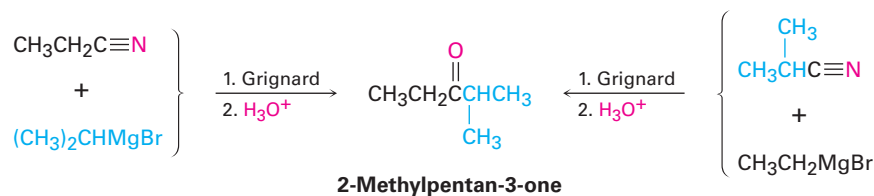


Strategy

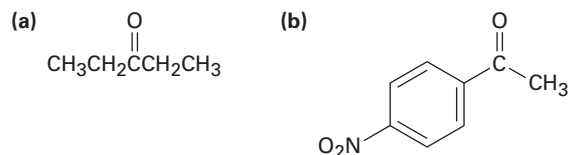
A ketone results from the reaction between a Grignard reagent and a nitrile, with the C≡N carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent, and the other will come from the nitrile.

Solution

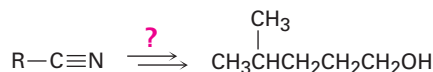
There are two possibilities.

**PROBLEM 15.12**

How would you prepare the following carbonyl compounds from a nitrile?

**PROBLEM 15.13**

How would you prepare 4-methylpentan-1-ol starting with a nitrile? More than one step is needed.

**15-8 Spectroscopy of Carboxylic Acids and Nitriles****Infrared Spectroscopy**

Carboxylic acids have two characteristic IR absorptions that make the $-\text{CO}_2\text{H}$ group easily identifiable. The O–H bond of the carboxyl group gives rise to a very broad absorption over the range 2500 to 3300 cm^{-1} , and the C=O bond shows an absorption between 1710 and 1760 cm^{-1} . The exact position of C=O absorption depends both on the structure of the molecule and on whether the acid is free (monomeric) or hydrogen-bonded (dimeric). Free carboxyl groups absorb at 1760 cm^{-1} , but the more commonly encountered dimeric carboxyl groups absorb in a broad band centered around 1710 cm^{-1} .

Both the broad O–H absorption and the C=O absorption at 1710 cm^{-1} (dimeric) are visible in the IR spectrum of butanoic acid shown in **FIGURE 15.4**.

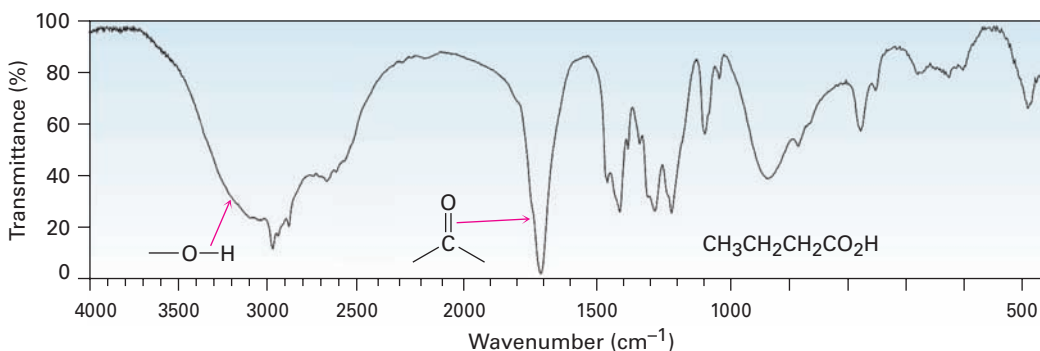


FIGURE 15.4
IR spectrum of
butanoic acid,
 $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$.

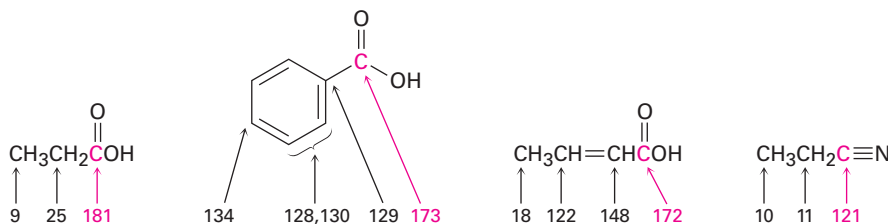
Nitriles show an intense and easily recognizable $\text{C}\equiv\text{N}$ bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules. Few other functional groups absorb in this region, so IR spectroscopy is highly diagnostic for nitriles.

PROBLEM 15.14

Cyclopentanecarboxylic acid and 4-hydroxycyclohexanone have the same formula ($\text{C}_6\text{H}_{10}\text{O}_2$), and both contain an –OH and a C=O group. How could you distinguish between them by IR spectroscopy?

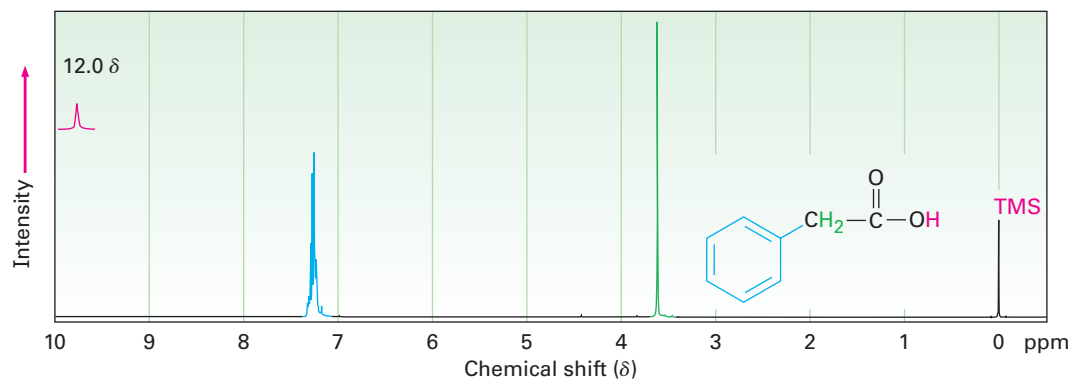
Nuclear Magnetic Resonance Spectroscopy

Carboxyl carbon atoms absorb in the range 165 to $185\ \delta$ in the ^{13}C NMR spectrum, with aromatic and α,β -unsaturated acids near the upfield end of the range ($\sim 165\ \delta$) and saturated aliphatic acids near the downfield end ($\sim 185\ \delta$). Nitrile carbons absorb in the range 115 to $130\ \delta$.



In the ^1H NMR spectrum, the acidic $-\text{CO}_2\text{H}$ proton normally absorbs as a singlet near $12\ \delta$. As with alcohols (Section 13-13), the $-\text{CO}_2\text{H}$ proton can be replaced by deuterium when D_2O is added to the sample tube, causing the absorption to disappear from the NMR spectrum. **FIGURE 15.5** shows the ^1H NMR spectrum of phenylacetic acid. Note that the carboxyl proton absorption occurs at $12.0\ \delta$.

FIGURE 15.5
 ^1H NMR spectrum
 of phenylacetic acid,
 $\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{H}$.



PROBLEM 15.15

How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by ^1H and ^{13}C NMR spectroscopy? (See Problem 15.14.)

SOMETHING EXTRA

Vitamin C

The word *vitamin*, despite its common usage, is actually an imprecise term. Generally speaking, a vitamin is an organic substance that a given organism requires in small amounts to live and grow but is unable to synthesize and must obtain in its diet. Thus, to be considered a vitamin, only a *small* amount of the substance is needed—anywhere from a few micrograms to 100 mg or so per day. Dietary substances needed in larger amounts, such as some amino acids and unsaturated fats, are not considered vitamins.

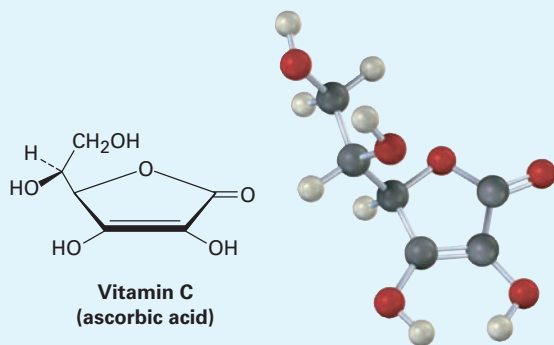
Furthermore, different organisms need different vitamins. More than 4000 species of mammals can synthesize ascorbic acid in their bodies, for instance, but humans are not among them. Ascorbic acid is therefore a human vitamin—what we all know as vitamin C—and must be obtained in our diet. Small amounts of more than a dozen other substances are similarly required by humans: retinol (vitamin A), thiamine (vitamin B₁), and tocopherol (vitamin E), for instance.

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In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency.

Vitamin C is surely the best known of all human vitamins. It was the first to be discovered (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 110,000 metric tons of vitamin C is synthesized worldwide each year, more than the total amount of all other vitamins combined. In addition to its use as a vitamin supplement, vitamin C is used as a food preservative, a “flour improver” in bakeries, and an animal food additive.

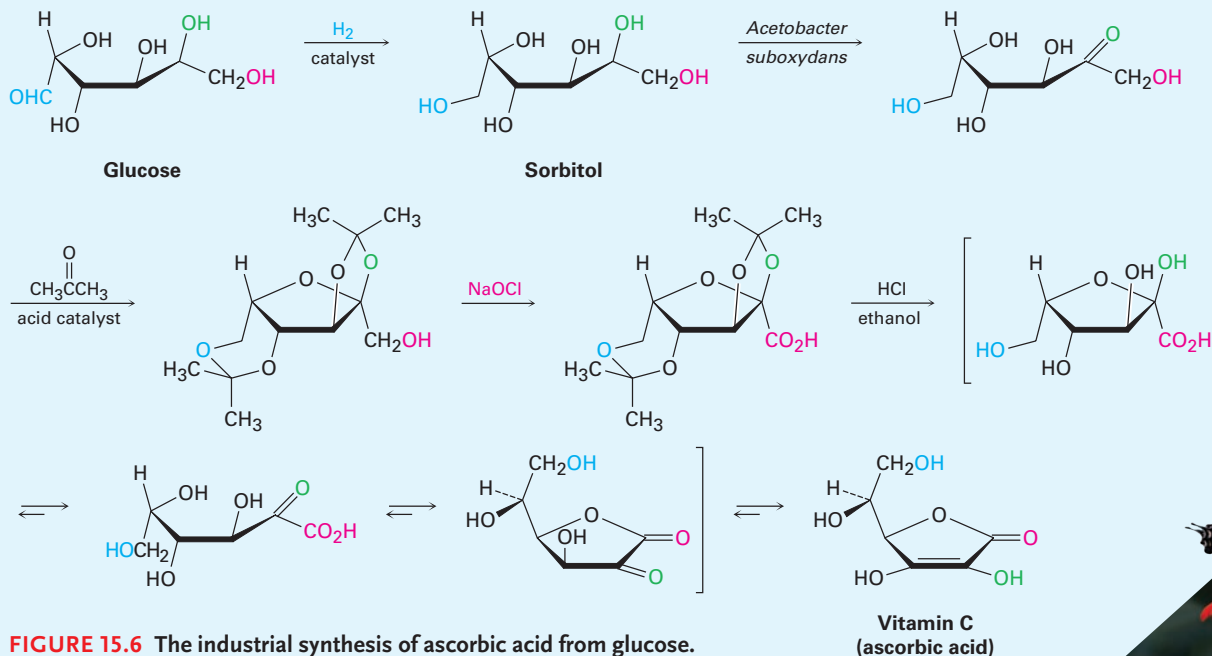


Vitamin C is perhaps most well known for its anti-scorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high. The Portuguese explorer Vasco da Gama lost more than half his crew to scurvy during his 2 year voyage around the Cape of Good Hope in 1497–1499.

In more recent times, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in AIDS, and inhibit the development of gastric and cervical cancers. None of these claims have been backed by medical evidence, however. In the largest study yet done of the effect of

vitamin C on the common cold, a meta-analysis of more than 100 separate trials covering 40,000 people found no difference in the incidence of colds between those who took supplemental vitamin C regularly and those who did not. When taken *during* a cold, however, vitamin C does appear to decrease the cold's duration by perhaps a day.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry, beginning with glucose and following the five-step route shown in **FIGURE 15.6**. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which is then oxidized by the microorganism *Acetobacter suboxydans*. No chemical reagent is known that is selective enough to oxidize only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used. Treatment with acetone and an acid catalyst then converts four of the other hydroxyl groups into acetal linkages, and the remaining hydroxyl group is chemically oxidized to a carboxylic acid by reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetal groups and causes an internal ester-forming reaction to take place to give ascorbic acid. Each of the five steps takes place in better than 90% yield.



KEY WORDS

carboxyl group (CO₂H), 532
carboxylation, 541
carboxylic acid (RCO₂H),
530
Henderson–Hasselbalch
equation, 537
nitrile (RC≡N), 532

SUMMARY

Carboxylic acids are among the most useful building blocks for synthesizing other molecules, both in nature and in the chemical laboratory. Thus, an understanding of their properties and reactions is fundamental to understanding biological chemistry. In this chapter, we've looked both at acids and at their close relatives, **nitriles (RC≡N)**.

Carboxylic acids are named systematically by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. Like aldehydes and ketones, the carbonyl carbon atom is *sp*²-hybridized; like alcohols, carboxylic acids are associated through hydrogen-bonding and therefore have high boiling points.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids such as HCl, carboxylic acids dissociate much more readily than alcohols because the resultant carboxylate ions are stabilized by resonance between two equivalent forms.

Most carboxylic acids have *pK*_a values near 5, but the exact *pK*_a of a given acid depends on structure. Carboxylic acids substituted by electron-withdrawing groups are more acidic (have a lower *pK*_a) because their carboxylate ions are stabilized. Carboxylic acids substituted by electron-donating groups are less acidic (have a higher *pK*_a) because their carboxylate ions are destabilized. The extent of dissociation of a carboxylic acid in a buffered solution of a given pH can be calculated with the **Henderson–Hasselbalch equation**. Inside living cells, where the physiological pH = 7.3, carboxylic acids are entirely dissociated and exist as their carboxylate anions.

Methods of synthesis for carboxylic acids include (1) oxidation of alkylbenzenes, (2) oxidation of primary alcohols or aldehydes, (3) reaction of Grignard reagents with CO₂ (**carboxylation**), and (4) hydrolysis of nitriles. General reactions of carboxylic acids include (1) loss of the acidic proton, (2) nucleophilic acyl substitution at the carbonyl group, (3) substitution on the α carbon, and (4) reduction.

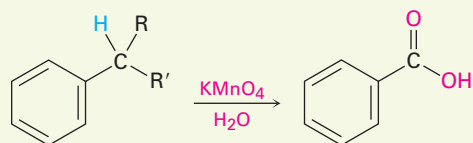
Nitriles are similar in some respects to carboxylic acids and are prepared either by S_N2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar C≡N bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with Grignard reagents to yield ketones.

Carboxylic acids and nitriles are easily distinguished spectroscopically. Acids show a characteristic IR absorption at 2500 to 3300 cm⁻¹ due to the O–H bond and another at 1710 to 1760 cm⁻¹ due to the C=O bond; nitriles have an absorption at 2250 cm⁻¹. Acids also show ¹³C NMR absorptions at 165 to 185 δ and ¹H NMR absorptions near 12 δ ; nitriles have a ¹³C NMR absorption in the range 115 to 130 δ .

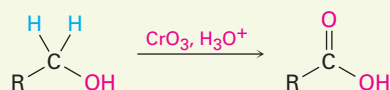
SUMMARY OF REACTIONS

1. Preparation of carboxylic acids

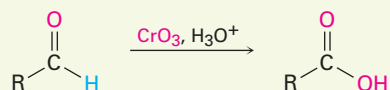
(a) Oxidation of alkylbenzenes (Section 9-10)



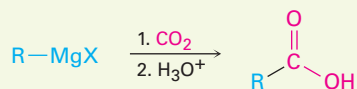
(b) Oxidation of primary alcohols (Section 13-5)



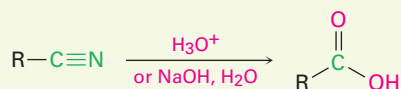
(c) Oxidation of aldehydes (Section 14-3)



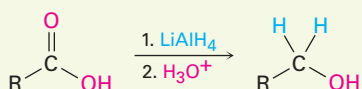
(d) Carboxylation of Grignard reagents (Section 15-5)



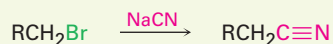
(e) Hydrolysis of nitriles (Section 15-7)



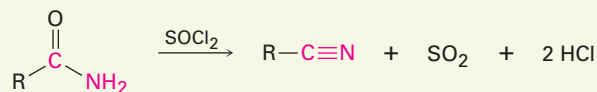
2. Reactions of carboxylic acids (Section 15-6)

Reduction with LiAlH_4 to give alcohols

3. Preparation of nitriles (Section 15-7)

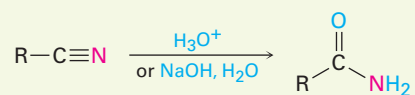
(a) $\text{S}_{\text{N}}2$ reaction of alkyl halides

(b) Dehydration of amides

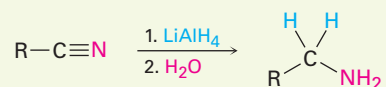


4. Reactions of nitriles (Section 15-7)

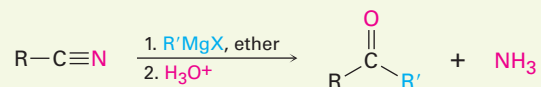
(a) Hydrolysis to give amides



(b) Reduction to give amines



(c) Reaction with Grignard reagents to yield ketones

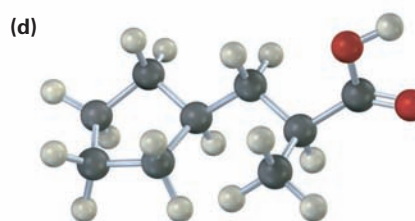
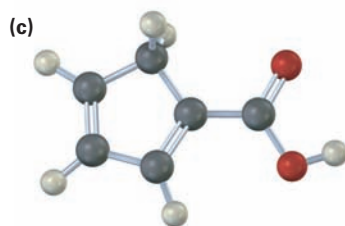
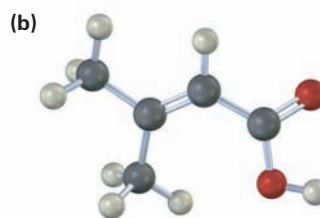
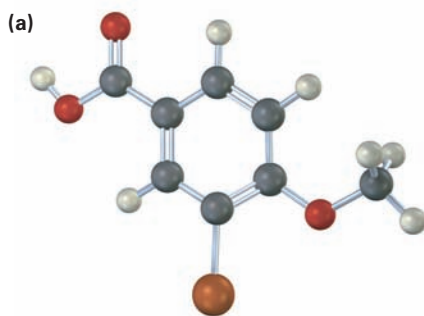


EXERCISES

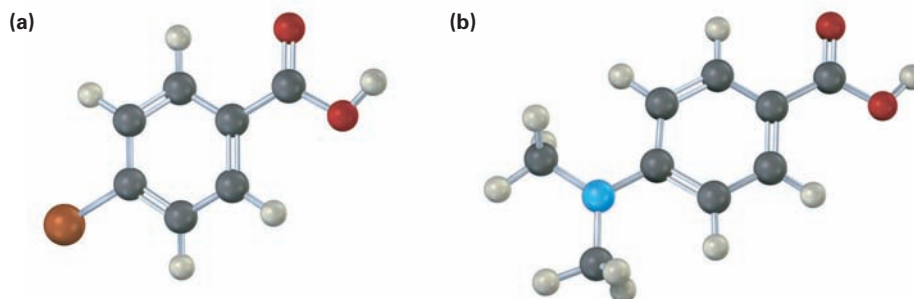
VISUALIZING CHEMISTRY

(Problems 15.1–15.15 appear within the chapter.)

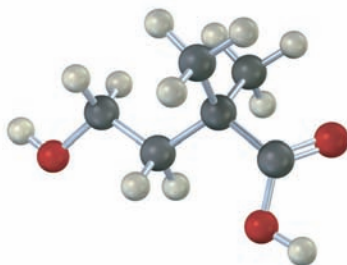
15.16 Give IUPAC names for the following carboxylic acids (red-brown = Br):



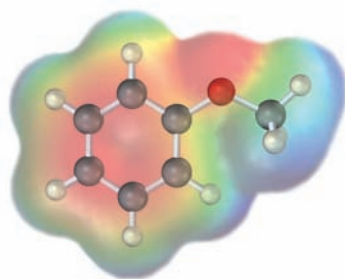
15.17 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Red-brown = Br.)



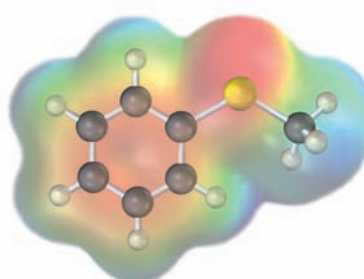
15.18 The following carboxylic acid can't be prepared from an alkyl halide by either the nitrile hydrolysis route or the Grignard carboxylation route. Explain.



15.19 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.



Anisole ($C_6H_5OCH_3$)

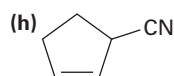
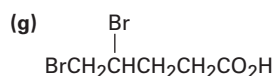
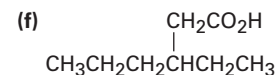
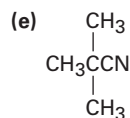
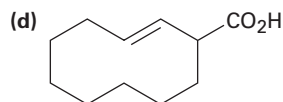
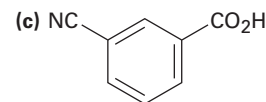
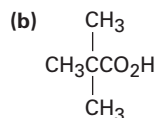
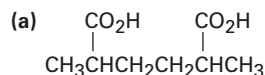


Thioanisole ($C_6H_5SCH_3$)

ADDITIONAL PROBLEMS

Naming Carboxylic Acids and Nitriles

15.20 Give IUPAC names for the following compounds:



15.21 Draw structures corresponding to the following IUPAC names:

(a) *cis*-Cyclohexane-1,2-dicarboxylic acid

(b) Heptanedioic acid

(c) Hex-2-en-4-ynoic acid

(d) 4-Ethyl-2-propyloctanoic acid

(e) 3-Chlorophthalic acid

(f) Triphenylacetic acid

(g) Cyclobut-2-enecarbonitrile

(h) *m*-Benzoylbenzonitrile

15.22 Draw and name the following:

(a) The eight carboxylic acids with the formula $\text{C}_6\text{H}_{12}\text{O}_2$

(b) Three nitriles with the formula $\text{C}_5\text{H}_7\text{N}$

15.23 Pregabalin, marketed as Lyrica, is an anticonvulsant drug that is also effective in treating chronic pain. The IUPAC name of pregabalin is (*S*)-3-(aminomethyl)-5-methylhexanoic acid. (An aminomethyl group is $-\text{CH}_2\text{NH}_2$.) Draw the structure of pregabalin.

15.24 Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentane-dioic acid. Draw the structure.

Acidity of Carboxylic Acids

15.25 Order the compounds in each set in order of increasing acidity:

- (a) Acetic acid, oxalic acid, formic acid
 (b) *p*-Bromobenzoic acid, *p*-nitrobenzoic acid, 2,4-dinitrobenzoic acid
 (c) Fluoroacetic acid, 3-fluoropropanoic acid, 4-fluorobutanoic acid

15.26 Arrange the compounds in each set in order of increasing basicity:

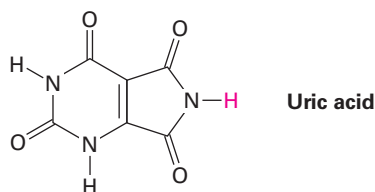
- (a) Magnesium acetate, magnesium hydroxide, methylmagnesium bromide
 (b) Sodium benzoate, sodium *p*-nitrobenzoate, sodium acetylide
 (c) Lithium hydroxide, lithium ethoxide, lithium formate

15.27 Calculate K_a 's for the following acids:

- (a) Citric acid, $pK_a = 3.14$ (b) Tartaric acid, $pK_a = 2.98$

15.28 Thioglycolic acid, $\text{HSCH}_2\text{CO}_2\text{H}$, a substance used in depilatory agents (hair removers) has $pK_a = 3.42$. What is the percent dissociation of thioglycolic acid in a buffer solution at $\text{pH} = 3.00$?

15.29 In humans, the final product of purine degradation from DNA is uric acid, $pK_a = 5.61$, which is excreted in the urine. What is the percent dissociation of uric acid in urine at a typical $\text{pH} = 6.0$? Why do you think uric acid is acidic even though it does not have a CO_2H group?



15.30 Following are some pK_a data for simple dibasic acids. How can you account for the fact that the difference between the first and second ionization constants decreases with increasing distance between the carboxyl groups?

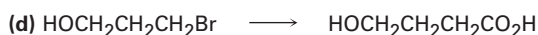
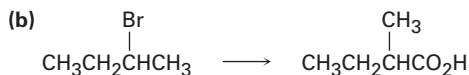
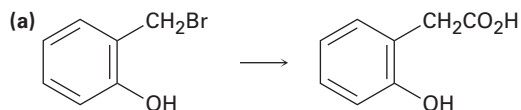
Name	Structure	pK_{a1}	pK_{a2}
Oxalic	$\text{HO}_2\text{CCO}_2\text{H}$	1.2	4.2
Succinic	$\text{HO}_2\text{C}(\text{CH}_2)_2\text{CO}_2\text{H}$	4.2	5.6
Adipic	$\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$	4.4	5.4

15.31 Order the compounds in each of the following sets according to increasing acidity:

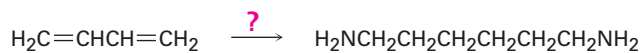
- (a) Acetic acid, phenol, benzoic acid
 (b) Benzoic acid, phenol, *p*-bromobenzoic acid
 (c) Chloroacetic acid, propanoic acid, difluoroacetic acid

Reactions of Carboxylic Acids and Nitriles

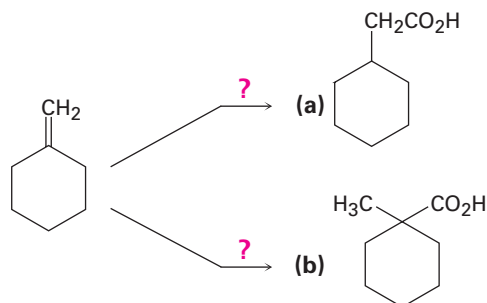
- 15.32** How could you convert butanoic acid into the following compounds? More than one step may be required.
(a) Butan-1-ol **(b)** 1-Bromobutane
(c) Pentanoic acid **(d)** But-1-ene
- 15.33** How could you convert each of the following compounds into butanoic acid? More than one step may be required.
(a) Butan-1-ol **(b)** 1-Bromobutane
(c) But-1-ene **(d)** 1-Bromopropane
- 15.34** How could you convert butanenitrile into the following compounds? More than one step may be required.
(a) Butan-1-ol **(b)** Butanal **(c)** Pentanoic acid
- 15.35** How would you prepare the following compounds from benzene? More than one step is required in each case.
(a) *m*-Chlorobenzoic acid **(b)** *p*-Bromobenzoic acid
(c) Phenylacetic acid, $C_6H_5CH_2CO_2H$
- 15.36** Predict the product of the reaction of *p*-methylbenzoic acid with each of the following:
(a) CH_3MgBr in ether, then H_3O^+ **(b)** $KMnO_4$, H_3O^+
(c) $LiAlH_4$, then H_3O^+
- 15.37** Using $^{13}CO_2$ as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?
(a) $CH_3CH_2^{13}CO_2H$ **(b)** $CH_3^{13}CH_2CO_2H$
- 15.38** Which method—Grignard carboxylation or nitrile hydrolysis—would you use for each of the following reactions? Explain.



- 15.39 Hexane-1,6-diamine, a starting material needed for making nylon, can be made from buta-1,3-diene. How would you accomplish this synthesis?

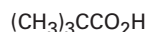
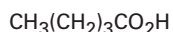


- 15.40 How would you carry out the following transformations?



Spectroscopy of Carboxylic Acids and Nitriles

- 15.41 Propose a structure for a compound $\text{C}_6\text{H}_{12}\text{O}_2$ that dissolves in dilute NaOH and shows the following ^1H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).
- 15.42 What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.

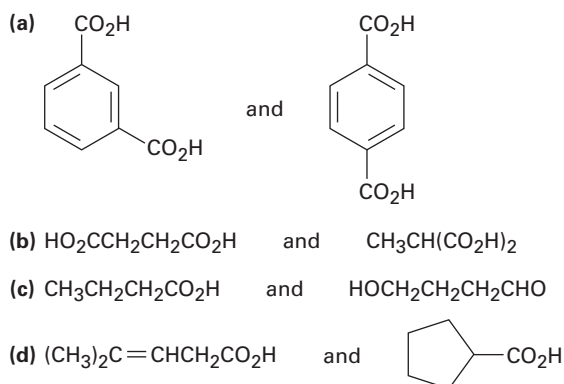


Pentanoic acid

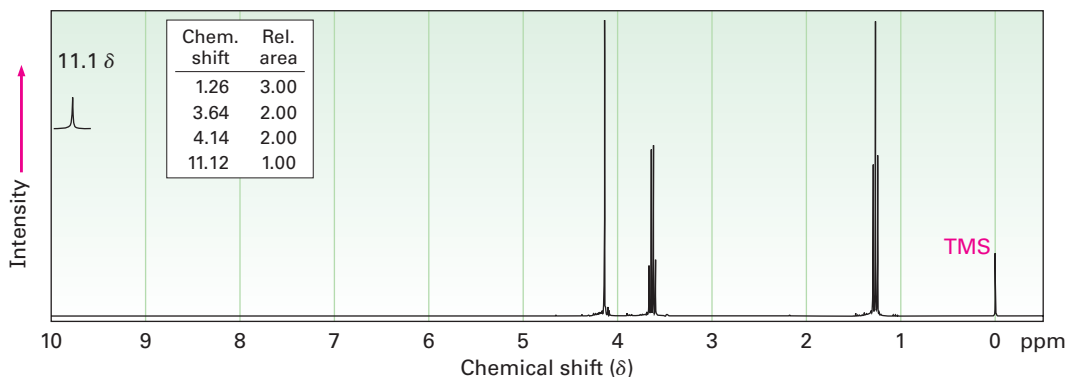
3-Methylbutanoic acid

2,2-Dimethylpropanoic acid

- 15.43 How could you use NMR (either ^{13}C or ^1H) to distinguish between the following isomeric pairs?



- 15.44 Compound **A**, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for **A**.

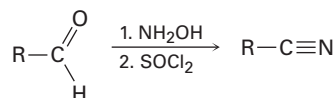


General Problems

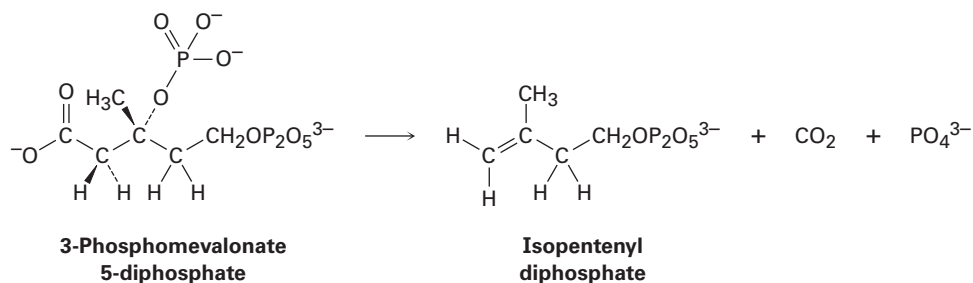
- 15.45 Calculate $\text{p}K_a$'s for the following acids:

(a) Lactic acid, $K_a = 8.4 \times 10^{-4}$ (b) Acrylic acid, $K_a = 5.6 \times 10^{-6}$

- 15.46 Nitriles can be prepared from aldehydes by a two-step procedure that involves formation of an imine with NH_2OH , followed by dehydration with SOCl_2 . Show the mechanism of the reaction.

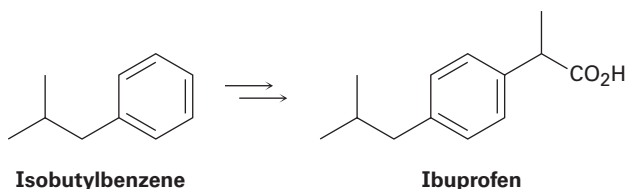


- 15.47 In plants, terpenes (see *Something Extra* in Chapter 7) are biosynthesized by a pathway that involves loss of CO_2 from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.



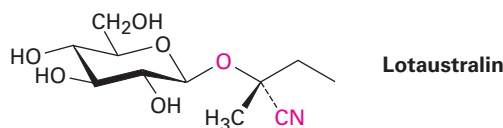
- 15.48 A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN , followed by hydrolysis of the product. After the reaction sequence was carried out, however, none of the desired product could be found. What do you suppose went wrong?

- 15.49 Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.

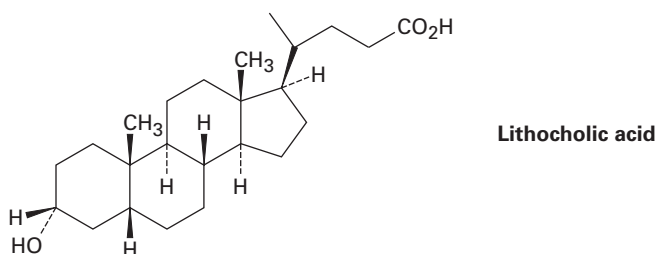


- 15.50 Cyanogenic glycosides, such as lotaustralin (Section 15-7), release hydrogen cyanide, HCN, when treated with aqueous acid. The reaction occurs by hydrolysis of the acetal linkage to form a cyanohydrin—a compound with a hydroxyl group and a cyano group bonded to the same carbon. The cyanohydrin then expels HCN and gives a carbonyl compound.

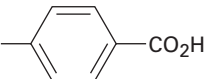
- (a) Show the mechanism of the acetal hydrolysis (see Section 14-8) and the structure of the cyanohydrin that results.
- (b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.



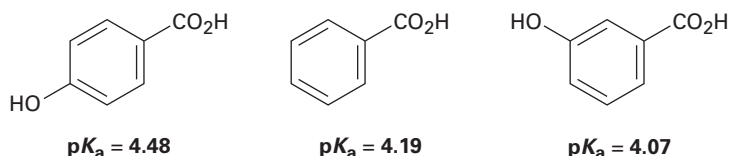
- 15.51 Acid-catalyzed hydrolysis of a nitrile to give a carboxylic acid occurs by initial protonation of the nitrogen atom, followed by nucleophilic addition of water. Review the mechanism of base-catalyzed nitrile hydrolysis in Section 15-7, and then write all the steps involved in the acid-catalyzed reaction, using curved arrows to represent electron flow in each step.
- 15.52 Predict the product of reaction of lithocholic acid, a steroid found in human bile, with each of the following reagents. Don't worry about the size of the molecule; concentrate on the functional groups.
- (a) $\text{CrO}_3, \text{H}_3\text{O}^+$ (b) CH_3MgBr , then H_3O^+ (c) LiAlH_4 , then H_3O^+



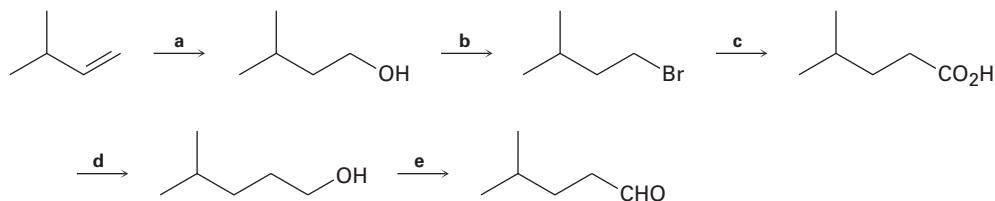
- 15.53 The pK_a 's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) follow. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has $pK_a = 4.19$, which of the substituents are activators and which are deactivators?

Substituent Y	pK_a of Y- 
$-\text{Si}(\text{CH}_3)_3$	4.27
$-\text{CH}=\text{CHC}\equiv\text{N}$	4.03
$-\text{HgCH}_3$	4.10
$-\text{OSO}_2\text{CH}_3$	3.84
$-\text{PCl}_2$	3.59

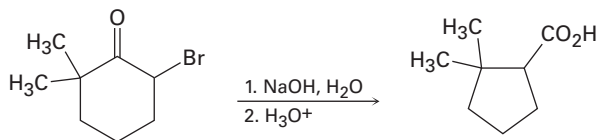
- 15.54 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.



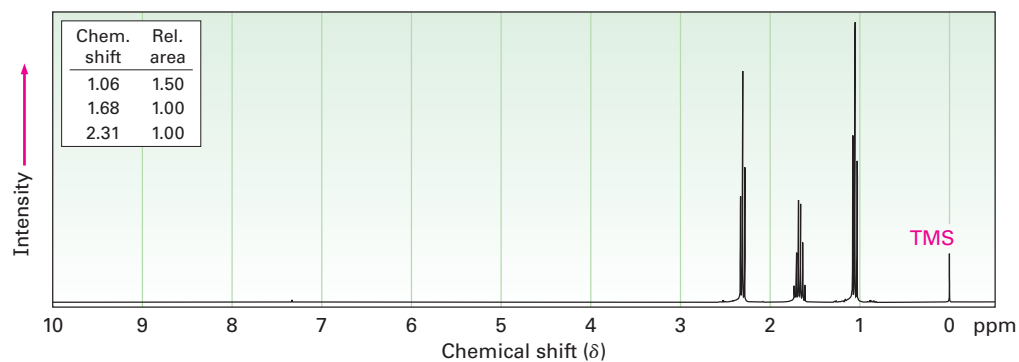
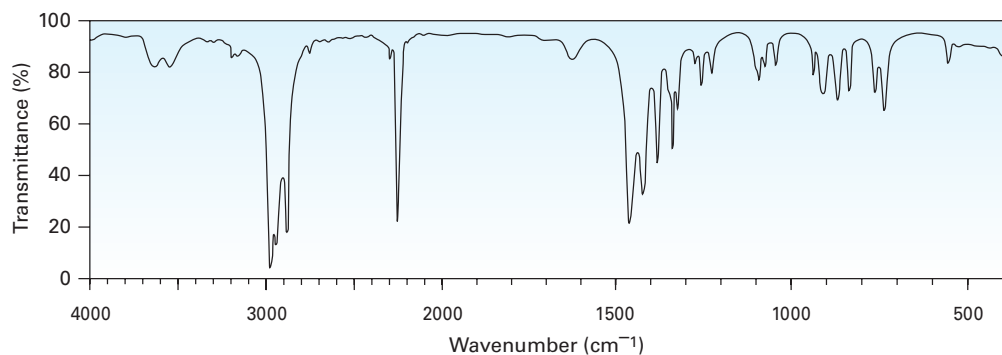
- 15.55 Identify the missing reagents **a–e** in the following scheme:



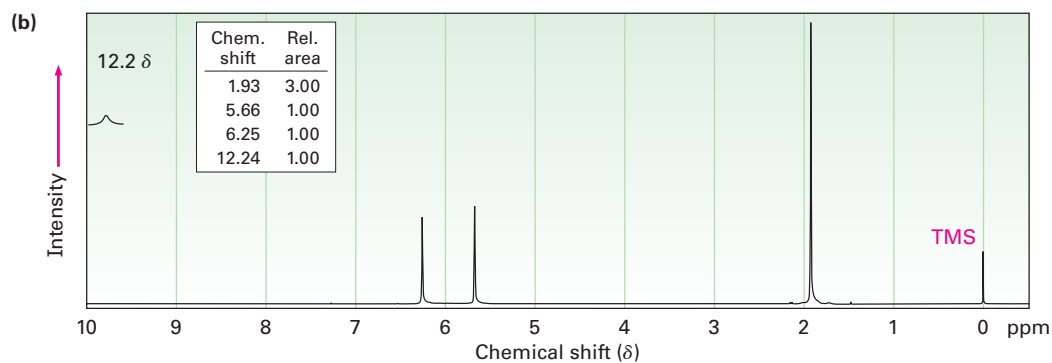
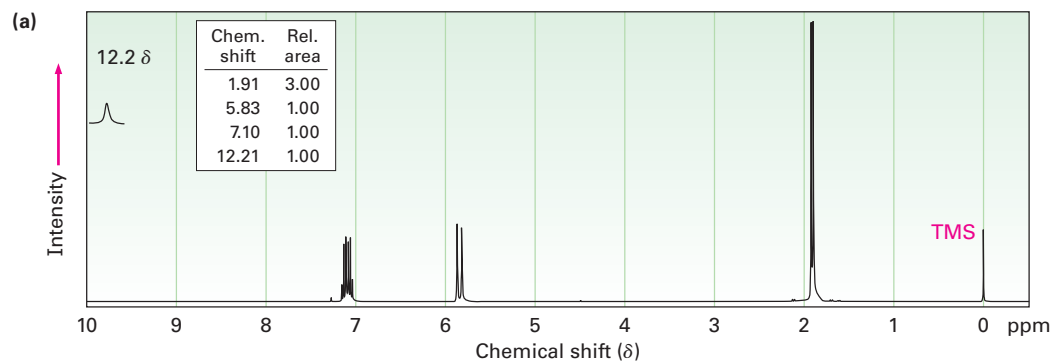
- 15.56 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentanecarboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the *Favorskii reaction*. The reaction takes place by initial nucleophilic addition to the carbonyl group, followed by a rearrangement with loss of bromide ion. Propose a mechanism.



- 15.57 Propose a structure for a compound, C_4H_7N , that has the following IR and 1H NMR spectra:



- 15.58 The two 1H NMR spectra shown here belong to crotonic acid (*trans*- $CH_3CH=CHCO_2H$) and methacrylic acid [$H_2C=C(CH_3)CO_2H$]. Which spectrum corresponds to which acid? Explain.

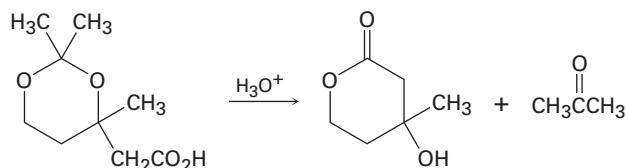


15.59 Propose structures for carboxylic acids that show the following peaks in their ^{13}C NMR spectra. Assume that the kinds of carbons (1° , 2° , 3° , or 4°) have been assigned by DEPT-NMR.

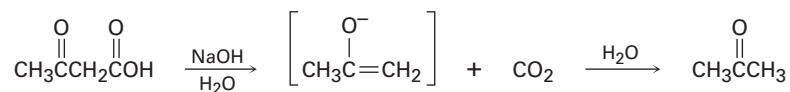
(a) $\text{C}_7\text{H}_{12}\text{O}_2$: 25.5 δ (2°), 25.9 δ (2°), 29.0 δ (2°), 43.1 δ (3°), 183.0 δ (4°)

(b) $\text{C}_8\text{H}_8\text{O}_2$: 21.4 δ (1°), 128.3 δ (4°), 129.0 δ (3°), 129.7 δ (3°), 143.1 δ (4°), 168.2 δ (4°)

15.60 We'll see in the next chapter that carboxylic acids react with alcohols to yield esters: $\text{RCO}_2\text{H} + \text{R}'\text{OH} \rightarrow \text{RCO}_2\text{R}'$. Propose a mechanism for the following reaction.



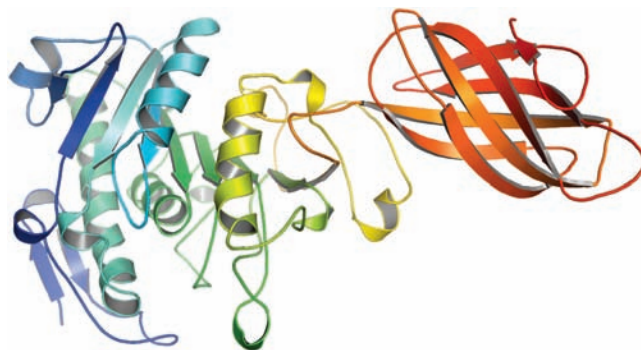
15.61 Carboxylic acids having a second carbonyl group two atoms away lose CO_2 (*decarboxylate*) through an intermediate enolate ion when treated with base. Write the mechanism of this decarboxylation reaction using curved arrows to show the electron flow in each step.



An enolate ion

Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

16



Pancreatic lipase catalyzes the hydrolysis of ester bonds in dietary fats, the initial step in fat metabolism.

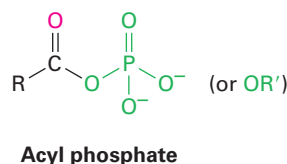
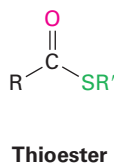
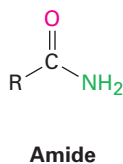
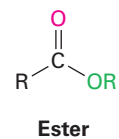
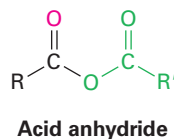
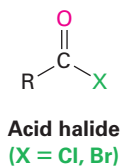
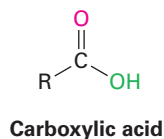
WHY THIS CHAPTER?

Carboxylic acid derivatives are among the most widely occurring of all molecules, and their primary reaction—nucleophilic acyl substitution—is one of the four fundamental carbonyl-group processes. Nucleophilic acyl substitutions are found in one variation or another in almost all biological pathways, so a detailed understanding of them is necessary to understand the chemistry of living organisms.

Closely related to the carboxylic acids and nitriles discussed in the previous chapter are the **carboxylic acid derivatives**, compounds in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in the nucleophilic acyl substitution reaction that we saw briefly in the *Preview of Carbonyl Chemistry*:



Many kinds of acid derivatives are known, but we'll be concerned primarily with four of the more common ones: **acid halides**, **acid anhydrides**, **esters**, and **amides**. Acid halides and acid anhydrides are used only in the laboratory, while esters and amides are common in both laboratory and biological chemistry. In addition, carboxylic acid derivatives called **thioesters** and **acyl phosphates** are encountered primarily in biological chemistry. Note the structural similarity between acid anhydrides and acyl phosphates.



CONTENTS

- 16-1 Naming Carboxylic Acid Derivatives
- 16-2 Nucleophilic Acyl Substitution Reactions
- 16-3 Reactions of Carboxylic Acids
- 16-4 Reactions of Acid Halides
- 16-5 Reactions of Acid Anhydrides
- 16-6 Reactions of Esters
- 16-7 Reactions of Amides
- 16-8 Reactions of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives
- 16-9 Polyamides and Polyesters: Step-Growth Polymers
- 16-10 Spectroscopy of Carboxylic Acid Derivatives

SOMETHING EXTRA

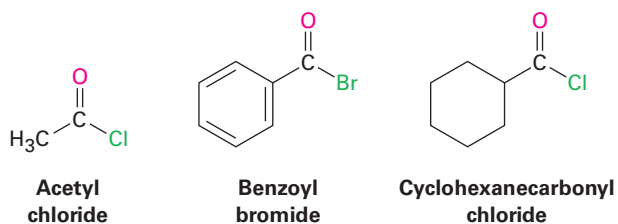
β -Lactam Antibiotics



16-1 Naming Carboxylic Acid Derivatives

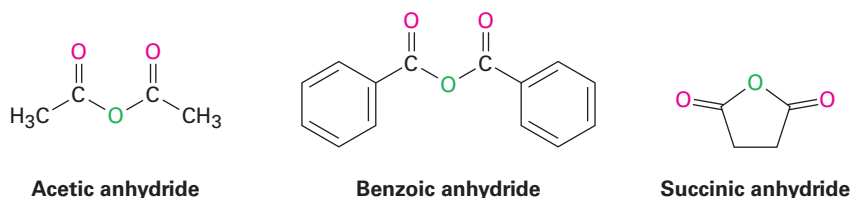
Acid Halides, RCOX

Acid halides are named by identifying first the acyl group and then the halide. As described previously in Section 15-1 and shown in Table 15.1 on page 532, the acyl group name is derived from the carboxylic acid name by replacing the *-ic acid* or *-oic acid* ending with *-oyl*, or the *-carboxylic acid* ending with *-carbonyl*. To keep things interesting, however, IUPAC recognizes eight exceptions for which a *-yl* rather than an *-oyl* ending is used: formic (formyl), acetic (acetyl), propionic (propionyl), butyric (butyryl), oxalic (oxalyl), malonic (malonyl), succinic (succinyl), and glutaric (glutaryl).

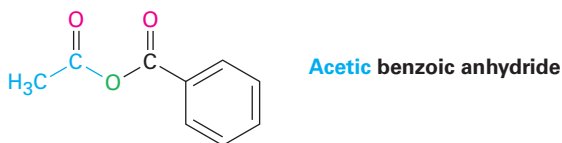


Acid Anhydrides, RCO₂COR'

Symmetrical anhydrides of unsubstituted monocarboxylic acids and cyclic anhydrides of dicarboxylic acids are named by replacing the word *acid* with *anhydride*:

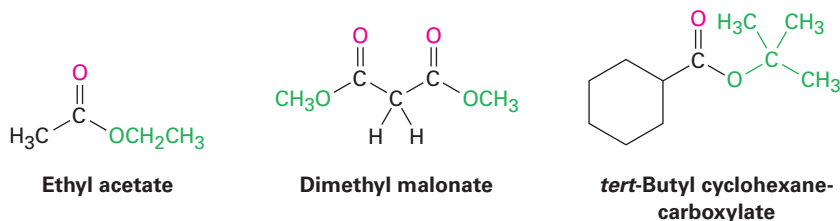


Unsymmetrical anhydrides—those prepared from two different carboxylic acids—are named by citing the two acids alphabetically and then adding *anhydride*:



Esters, RCO₂R'

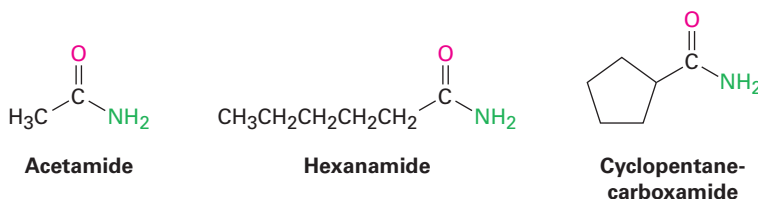
Esters are named by first identifying the alkyl group attached to oxygen and then the carboxylic acid, with the *-ic acid* ending replaced by *-ate*:



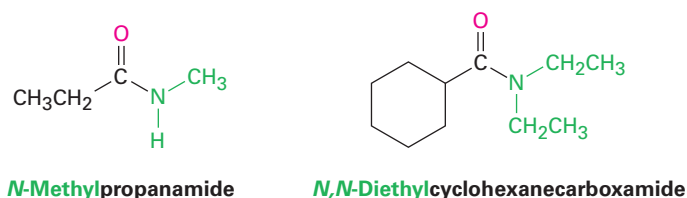
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Amides, RCONH₂

Amides with an unsubstituted -NH_2 group are named by replacing the *-oic acid* or *-ic acid* ending with *-amide*, or by replacing the *-carboxylic acid* ending with *-carboxamide*.

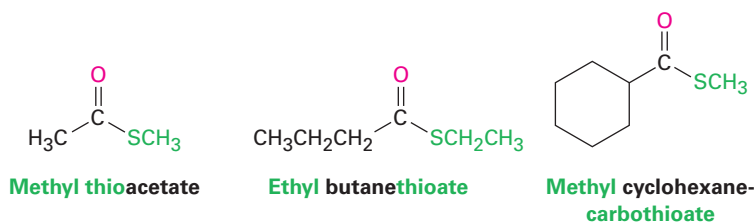


If the nitrogen atom is further substituted, the compound is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter *N* to identify them as being directly attached to nitrogen.



Thioesters, RCO₂S[']

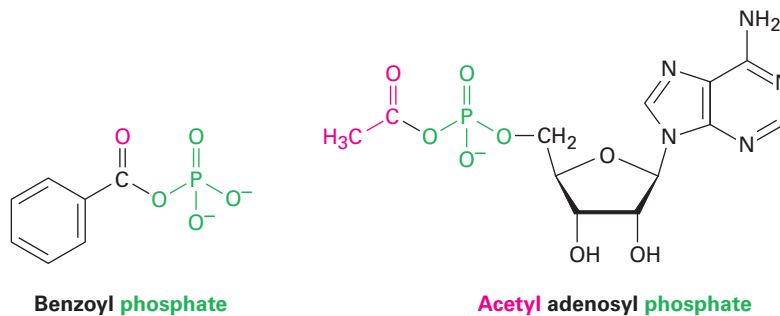
Thioesters are named like the corresponding esters. If the related ester has a common name, the prefix *thio-* is added to the name of the carboxylate: acetate becomes thioacetate, for instance. If the related ester has a systematic name, the *-oate* or *-carboxylate* ending is replaced by *-thioate* or *-carbothioate*: butanoate becomes butanethioate and cyclohexanecarboxylate becomes cyclohexanecarbothioate, for instance.



Acyl Phosphates, RCO₂PO₃²⁻ and RCO₂PO₃R^{'-}

Acyl phosphates are named by citing the acyl group and adding the word *phosphate*. If an alkyl group is attached to one of the phosphate oxygens,

it is identified after the name of the acyl group. In biological chemistry, acyl adenosyl phosphates are particularly common.

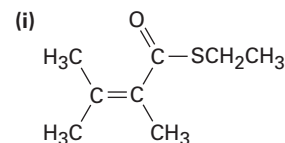
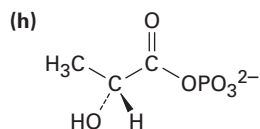
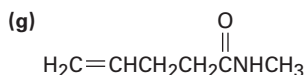
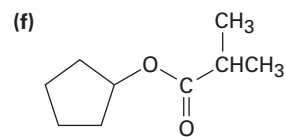
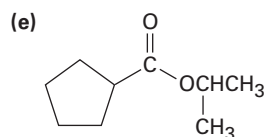
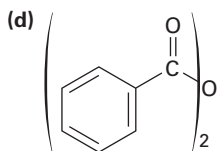
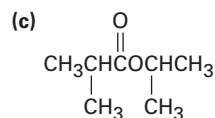
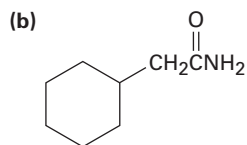
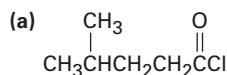


A summary of nomenclature rules for carboxylic acid derivatives is given in **TABLE 16.1**.

TABLE 16.1 Nomenclature of Carboxylic Acid Derivatives		
Functional group	Structure	Name ending
Carboxylic acid		<i>-ic acid</i> (<i>-carboxylic acid</i>)
Acid halide		<i>-oyl halide</i> (<i>-carbonyl halide</i>)
Acid anhydride		<i>anhydride</i>
Ester		<i>-ate</i> (<i>-carboxylate</i>)
Amide		<i>-amide</i> (<i>-carboxamide</i>)
Thioester		<i>-thioate</i> (<i>-carbothioate</i>)
Acyl phosphate		<i>-yl phosphate</i>

PROBLEM 16.1

Give IUPAC names for the following substances:

**PROBLEM 16.2**

Draw structures corresponding to the following names:

- Phenyl benzoate
- N*-Ethyl-*N*-methylbutanamide
- 2,4-Dimethylpentanoyl chloride
- Methyl 1-methylcyclohexanecarboxylate
- Ethyl 3-oxopentanoate
- Methyl *p*-bromothiobenzoate
- Formic propanoic anhydride
- cis*-2-Methylcyclopentanecarbonyl bromide

16-2 Nucleophilic Acyl Substitution Reactions

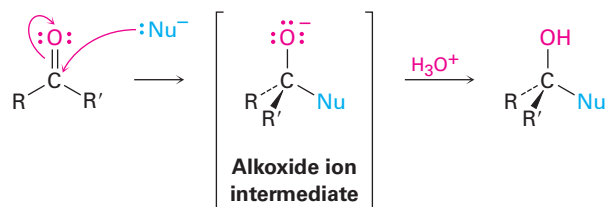
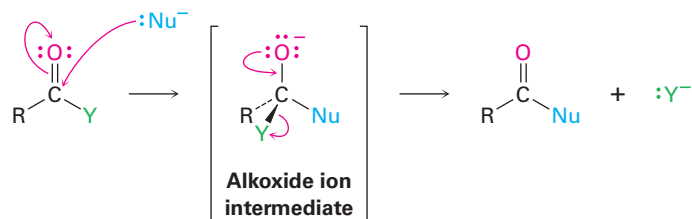
The addition of a nucleophile to a polar C=O bond is the key step in three of the four major carbonyl-group reactions. We saw in Chapter 14 that when a nucleophile adds to an aldehyde or ketone, the initially formed tetrahedral intermediate can be protonated to yield an alcohol. When a nucleophile adds to a carboxylic acid derivative, however, a different reaction course is followed. The initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net **nucleophilic acyl substitution reaction** (FIGURE 16.1).

The difference in behavior between aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group -Y that can act as a leaving group. As

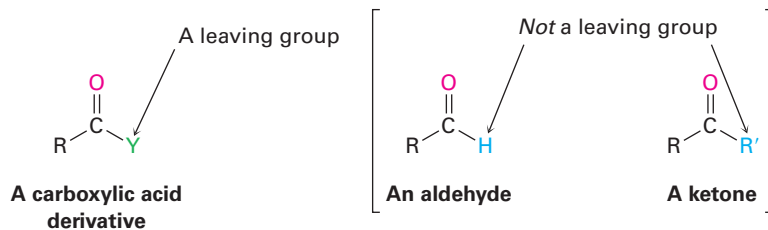
FIGURE 16.1 General mechanisms of nucleophilic addition and nucleophilic acyl substitution reactions.

Both reactions begin with addition of a nucleophile to a polar C=O bond to give a tetrahedral, alkoxide ion intermediate.

(a) The intermediate formed from an aldehyde or ketone is protonated to give an alcohol, but (b) the intermediate formed from a carboxylic acid derivative expels a leaving group to give a new carbonyl compound. (© John McMurry)

(a) Aldehyde or ketone: nucleophilic addition**(b) Carboxylic acid derivative: nucleophilic acyl substitution**

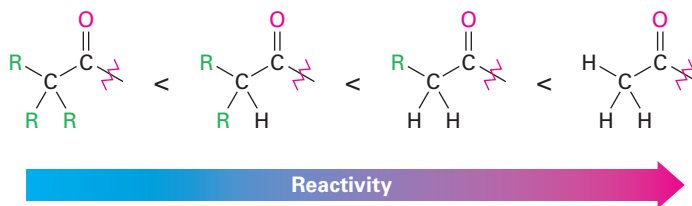
soon as the tetrahedral intermediate is formed, the leaving group is expelled to generate a new carbonyl compound. Aldehydes and ketones have no such leaving group, however, and therefore don't undergo substitution.



The net effect of the addition–elimination sequence is a substitution of the nucleophile for the –Y group originally bonded to the acyl carbon. Thus, the overall reaction is superficially similar to the kind of nucleophilic substitution that occurs during an S_N2 reaction (Section 12-7), but the mechanisms of the two processes are completely different. An S_N2 reaction occurs in a single step by backside displacement of the leaving group, while a nucleophilic acyl substitution takes place in two steps and involves a tetrahedral intermediate.

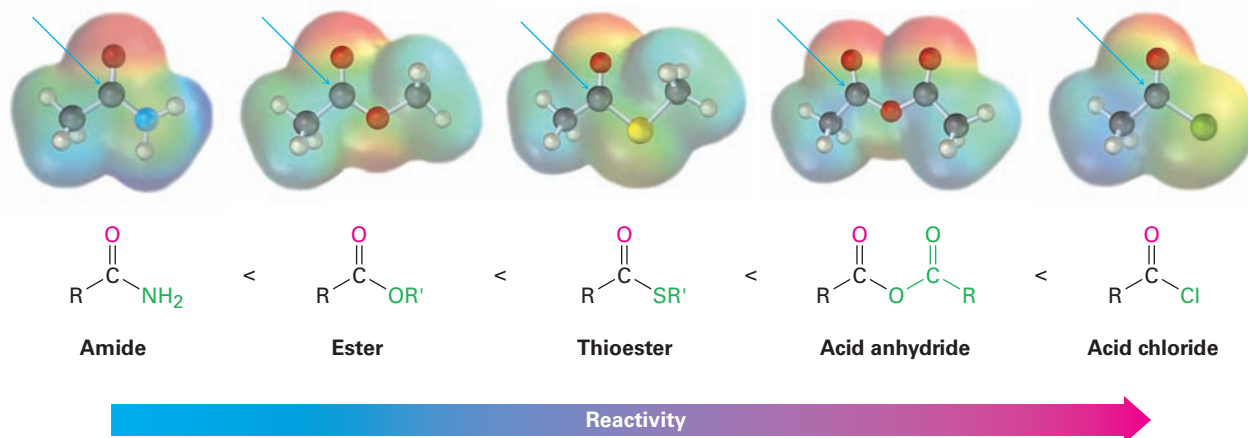
Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition step is generally the rate-limiting one. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

Steric and electronic factors are both important in determining reactivity. Sterically, we find within a series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups. The reactivity order is:



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Electronically, we find that strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate the differences by the relative blueness on the C=O carbons. Acyl phosphates are hard to place on this scale because they are not often used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.



The way in which various substituents affect the polarization of a carbonyl group is similar to the way they affect the reactivity of an aromatic ring toward electrophilic substitution (Section 9-8). A chlorine substituent, for example, inductively withdraws electrons from an acyl group in the same way that it withdraws electrons from and thus deactivates an aromatic ring. Similarly, amino, methoxy, and methylthio substituents donate electrons to acyl groups by resonance in the same way that they donate electrons to and thus activate aromatic rings.

As a consequence of these reactivity differences, it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides, but amides can't be directly converted into esters, thioesters, anhydrides, or acid chlorides. Remembering the reactivity order is therefore a way to keep track of a large number of reactions (FIGURE 16.2). Another consequence, as noted previously, is that only acyl phosphates, thioesters, esters, and amides are commonly found in nature. Acid halides and acid anhydrides react with water so rapidly that they can't exist for long in living organisms.

In studying the chemistry of carboxylic acid derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions keep occurring (FIGURE 16.3).

- **Hydrolysis:** Reaction with water to yield a carboxylic acid
- **Alcoholysis:** Reaction with an alcohol to yield an ester
- **Aminolysis:** Reaction with ammonia or an amine to yield an amide
- **Reduction:** Reaction with a hydride reducing agent to yield an aldehyde or an alcohol
- **Grignard reaction:** Reaction with an organomagnesium reagent to yield an alcohol

FIGURE 16.2 Interconversions of carboxylic acid derivatives. A more reactive acid derivative can be converted into a less reactive one, but not vice versa.

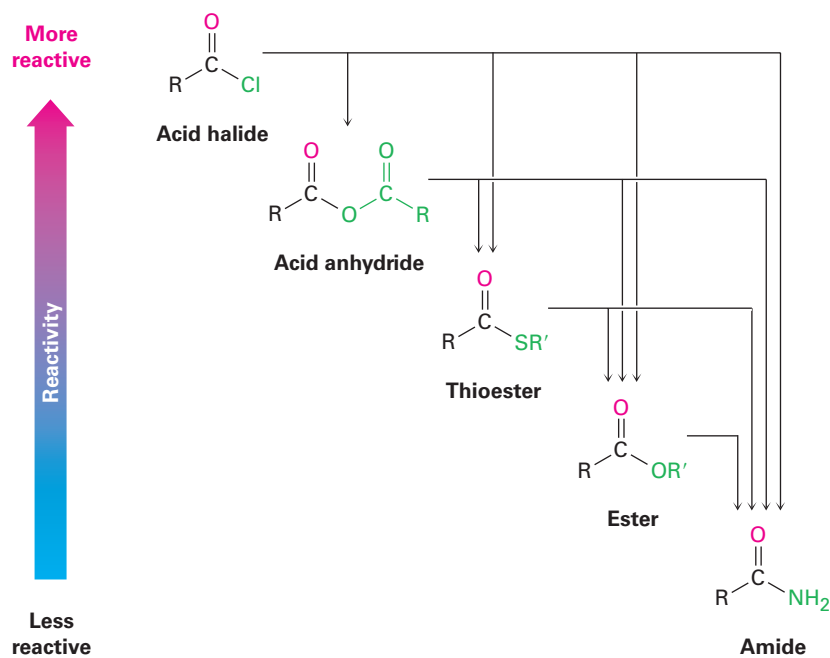
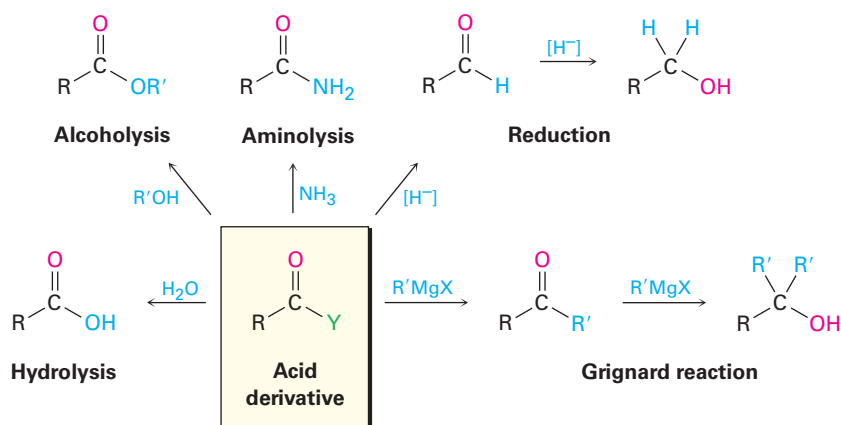
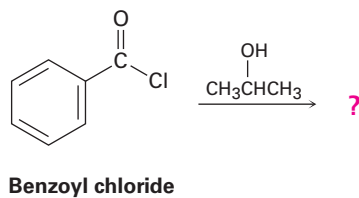


FIGURE 16.3 Some general reactions of carboxylic acid derivatives.



WORKED EXAMPLE 16.1 Predicting the Product of a Nucleophilic Acyl Substitution Reaction

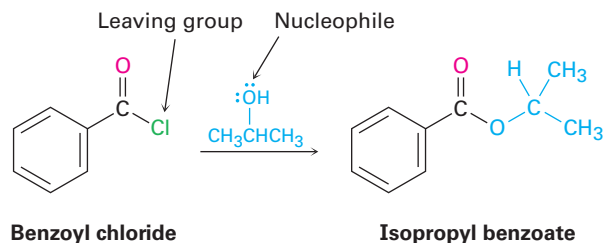
Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with propan-2-ol:



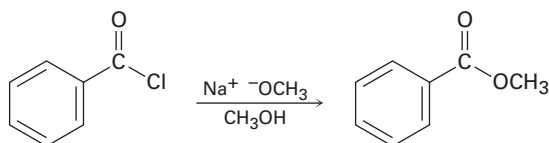
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Strategy

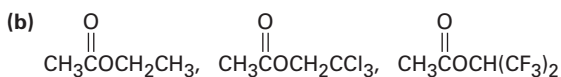
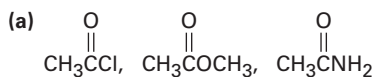
A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is isopropyl benzoate.

Solution**PROBLEM 16.3**

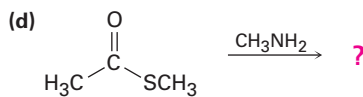
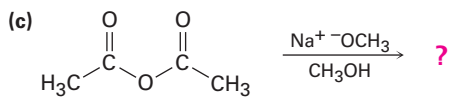
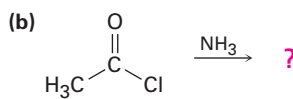
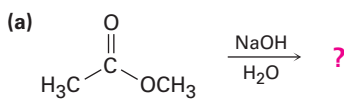
Show the mechanism of the following nucleophilic acyl substitution reaction, using curved arrows to indicate the electron flow in each step:

**PROBLEM 16.4**

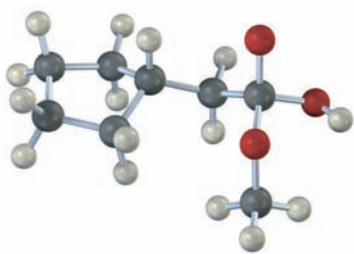
Rank the compounds in each of the following sets in order of their expected reactivity toward nucleophilic acyl substitution:

**PROBLEM 16.5**

Predict the products of the following nucleophilic acyl substitution reactions:



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**PROBLEM 16.6**

The adjacent structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product.

16-3 Reactions of Carboxylic Acids

The direct nucleophilic acyl substitution of a carboxylic acid is difficult because $-\text{OH}$ is a poor leaving group (Section 12-8). Thus, it's usually necessary to enhance the reactivity of the acid, either by using a strong acid catalyst to protonate the carboxyl and make it a better acceptor or by converting the $-\text{OH}$ into a better leaving group. Under the right circumstances, however, acid chlorides, anhydrides, esters, and amides can all be prepared from carboxylic acids by nucleophilic acyl substitution reactions.

Conversion of Carboxylic Acids into Acid Halides ($\text{RCO}_2\text{H} \rightarrow \text{RCOX}$)

In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, SOCl_2 , and into acid bromides by treatment with PBr_3 .



The SOCl_2 reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the $-\text{OH}$ of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. You might recall from Section 13-4 that an analogous chlorosulfite is involved in reaction of an alcohol with SOCl_2 to yield an alkyl chloride.

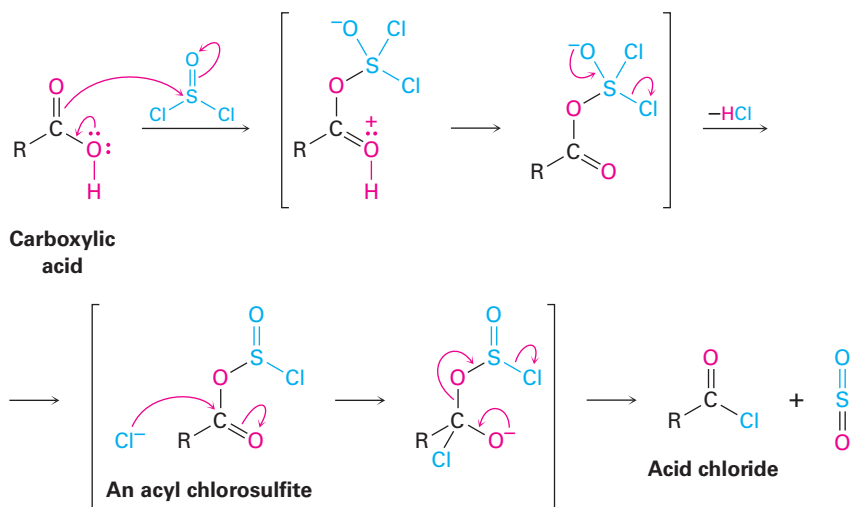
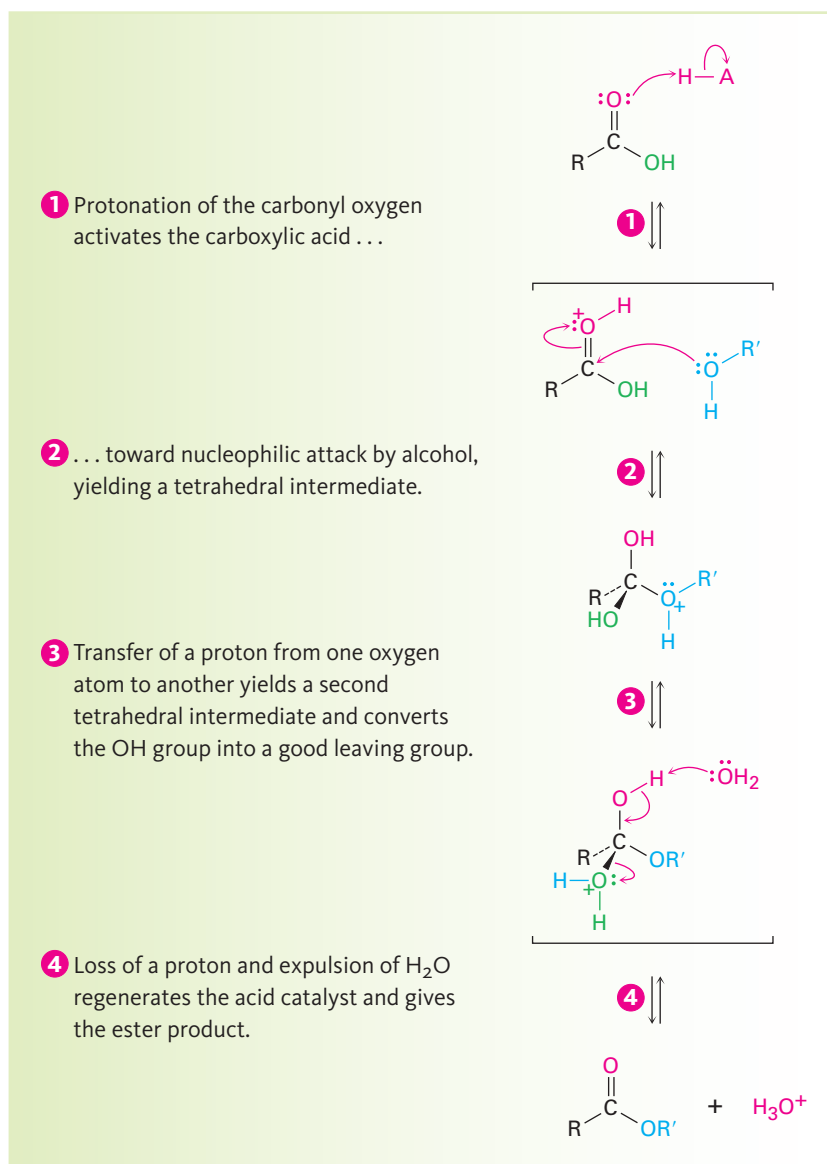


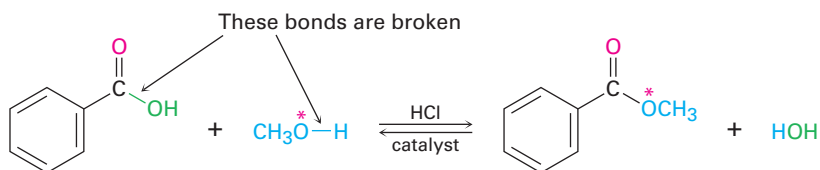
FIGURE 16.4 Mechanism of Fischer esterification. The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.



The net effect of Fischer esterification is substitution of an $-\text{OH}$ group by $-\text{OR}'$. All steps are reversible, and the reaction typically has an equilibrium constant close to 1. Thus, the reaction can be driven in either direction by choice of reaction conditions. Ester formation is favored when a large excess of alcohol is used as solvent, but carboxylic acid formation is favored when a large excess of water is present.

Evidence in support of the mechanism shown in Figure 16.4 comes from isotope-labeling experiments. When ^{18}O -labeled methanol reacts with benzoic acid, the methyl benzoate produced is found to be ^{18}O -labeled but the water produced is unlabeled. Thus, it is the $\text{C}-\text{OH}$ bond of the carboxylic

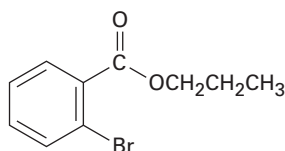
acid that is broken during the reaction rather than the CO–H bond and the RO–H bond of the alcohol that is broken rather than the R–OH bond.



Synthesizing an Ester from an Acid

WORKED EXAMPLE 16.2

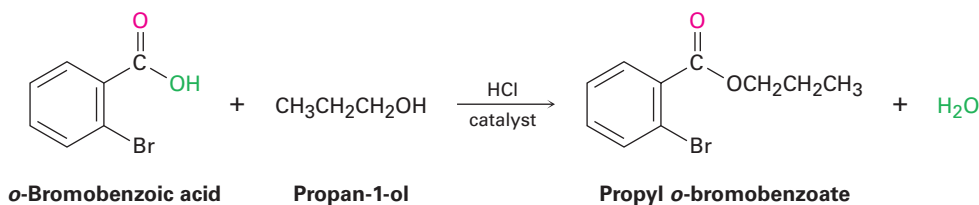
How might you prepare the following ester using a Fischer esterification reaction?



Strategy

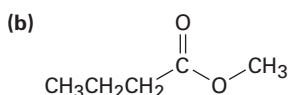
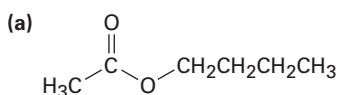
Begin by identifying the two parts of the ester. The acyl part comes from the carboxylic acid, and the –OR part comes from the alcohol. In this case, the target molecule is propyl *o*-bromobenzoate, so it can be prepared by treating *o*-bromobenzoic acid with propan-1-ol.

Solution



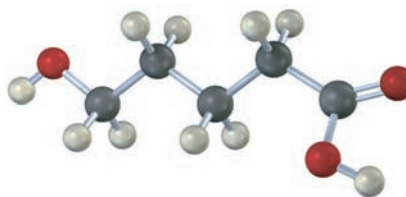
PROBLEM 16.7

How might you prepare the following esters from the corresponding acids?



PROBLEM 16.8

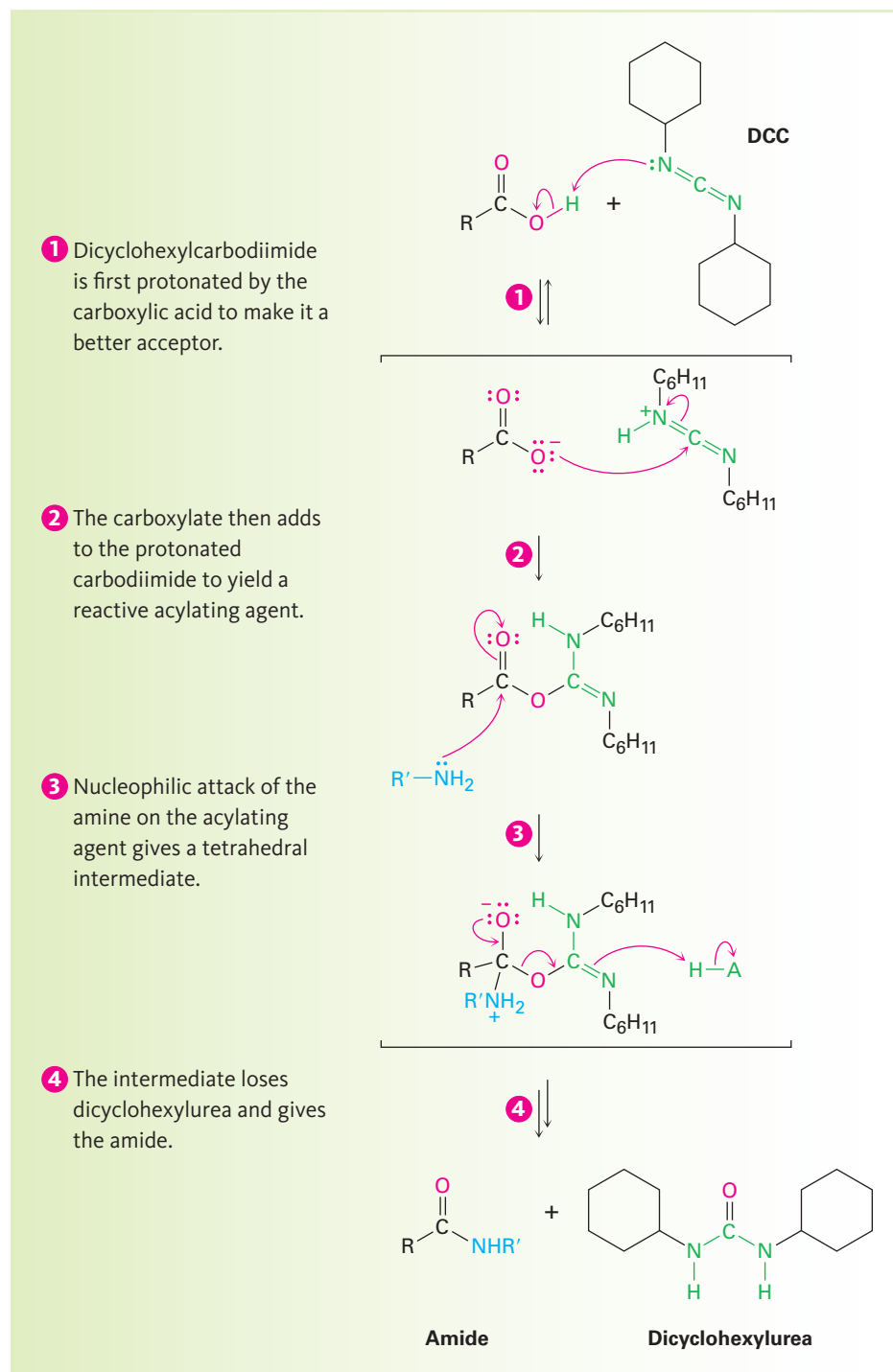
If the following molecule is treated with acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)



Conversion of Carboxylic Acids into Amides ($\text{RCO}_2\text{H} \rightarrow \text{RCONH}_2$)

Amides are difficult to prepare by direct reaction of carboxylic acids with amines because amines are bases that convert acidic carboxyl groups into their unreactive carboxylate anions. Thus, the $-\text{OH}$ must be replaced by a

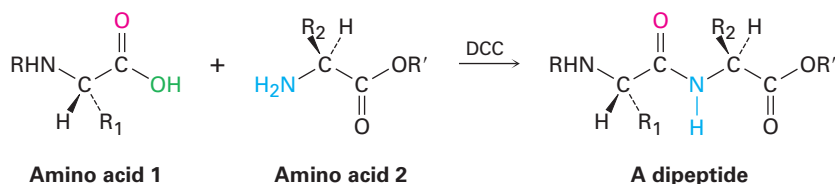
FIGURE 16.5 Mechanism of amide formation by reaction of a carboxylic acid and an amine with dicyclohexylcarbodiimide (DCC).



© John McMurry

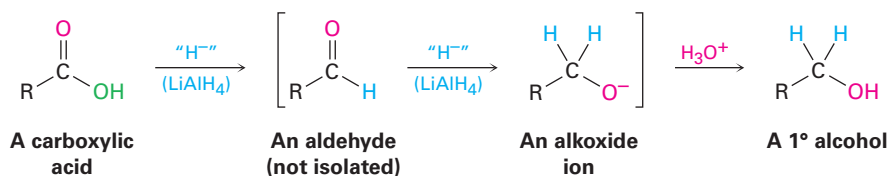
better, nonacidic leaving group. In practice, amides are usually prepared by treating the carboxylic acid with dicyclohexylcarbodiimide (DCC) to activate it, followed by addition of the amine. The acid first adds to a C=N bond of DCC, and nucleophilic acyl substitution by amine then ensues, as shown in **FIGURE 16.5**. Alternatively, and depending on the reaction solvent, the reactive acyl intermediate might also react with a second equivalent of carboxylate ion to generate an acid anhydride that then reacts with the amine. The product from either pathway is the same.

We'll see in Section 19-7 that this DCC-induced method of amide formation is the key step in the laboratory synthesis of small proteins, or *peptides*. For instance, when one amino acid with its NH_2 rendered unreactive and a second amino acid with its $-\text{CO}_2\text{H}$ rendered unreactive are treated with DCC, a dipeptide is formed:

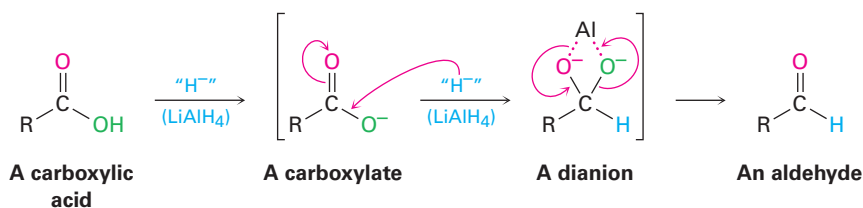


Conversion of Carboxylic Acids into Alcohols ($\text{RCO}_2\text{H} \rightarrow \text{RCH}_2\text{OH}$)

We saw in Section 13-3 that carboxylic acids are reduced by LiAlH_4 to give primary alcohols, but we deferred a discussion of the reaction mechanism at that time. In fact, the reduction is a nucleophilic acyl substitution reaction in which $-\text{H}$ replaces $-\text{OH}$ to give an aldehyde, which is further reduced to a primary alcohol by nucleophilic addition. The aldehyde intermediate is much more reactive than the starting acid, so it reacts immediately and is not isolated.



Because hydride ion is a base as well as a nucleophile, the actual nucleophilic acyl substitution step takes place on the carboxylate ion rather than on the free carboxylic acid and gives a high-energy *dianion* intermediate. In this intermediate, the two oxygens are complexed to a Lewis acidic aluminum species. Thus, the reaction is relatively difficult, and acid reductions require higher temperatures and extended reaction times.



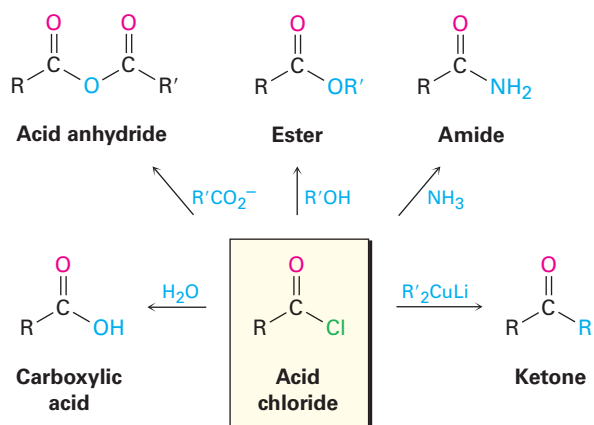
Biological Conversions of Carboxylic Acids

The direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur in biological chemistry. As in the laboratory, the acid must first be activated by converting the $-OH$ into a better leaving group. This activation is often accomplished in living organisms by reaction of the acid with adenosine triphosphate (ATP) to give an acyl adenosyl phosphate, or *acyl adenylate*, a mixed anhydride between a carboxylic acid and adenosine monophosphate (AMP, also known as adenylic acid). In the biosynthesis of fats, for example, a long-chain carboxylic acid reacts with ATP to give an acyl adenylate, followed by subsequent nucleophilic acyl substitution of a thiol group in coenzyme A to give the corresponding acyl CoA (FIGURE 16.6).

The first step in Figure 16.6—reaction of the carboxylate with ATP to give an acyl adenylate—is itself a nucleophilic acyl substitution on *phosphorus*. The carboxylate first adds to a $P=O$ double bond, giving a five-coordinate phosphorus intermediate that expels diphosphate ion as leaving group.

16-4 Reactions of Acid Halides

Acid halides are among the most reactive carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by $-OH$ to yield an acid, by $-OCOR$ to yield an anhydride, by $-OR$ to yield an ester, by $-NH_2$ to yield an amide, or by R' to yield a ketone. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with acid bromides.



Conversion of Acid Halides into Acids: Hydrolysis ($RCOCl \rightarrow RCO_2H$)

Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate

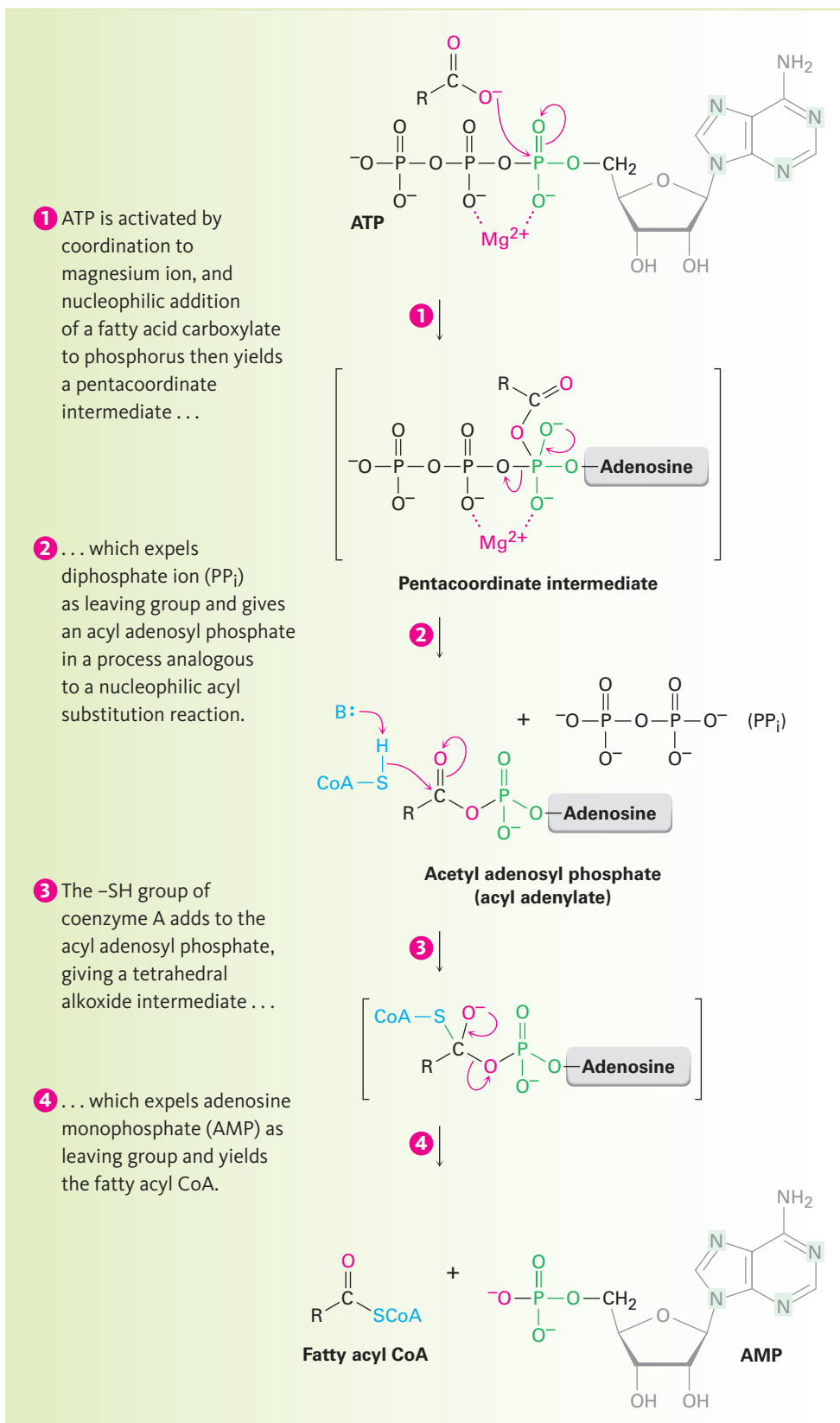
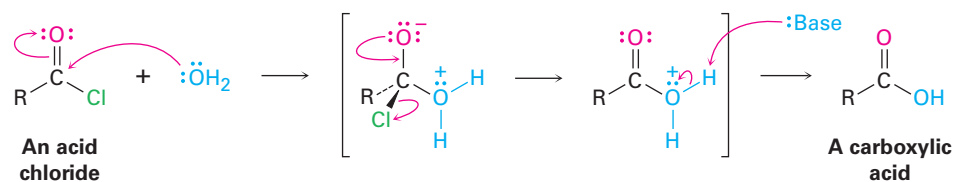


FIGURE 16.6 Mechanism of a nucleophilic acyl substitution reaction in fatty-acid biosynthesis. A carboxylic acid is activated by reaction with ATP to give an acyl adenylate, which undergoes nucleophilic acyl substitution with the $-\text{SH}$ group on coenzyme A. (ATP = adenosine triphosphate; AMP = adenosine monophosphate.)

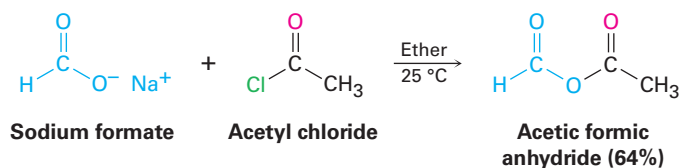
undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl .



Because HCl is formed during the hydrolysis, the reaction is often carried out in the presence of a base such as pyridine or NaOH to remove the HCl and prevent it from causing side reactions.

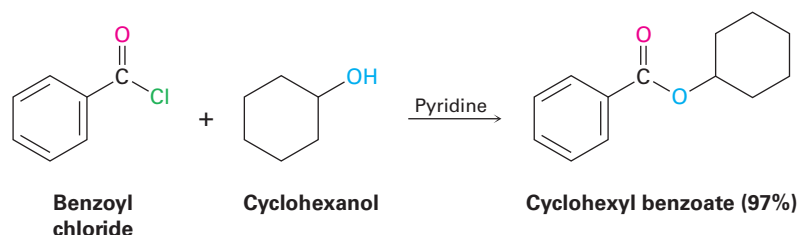
Conversion of Acid Halides into Anhydrides ($\text{RCOCl} \rightarrow \text{RCO}_2\text{COR}'$)

Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared.



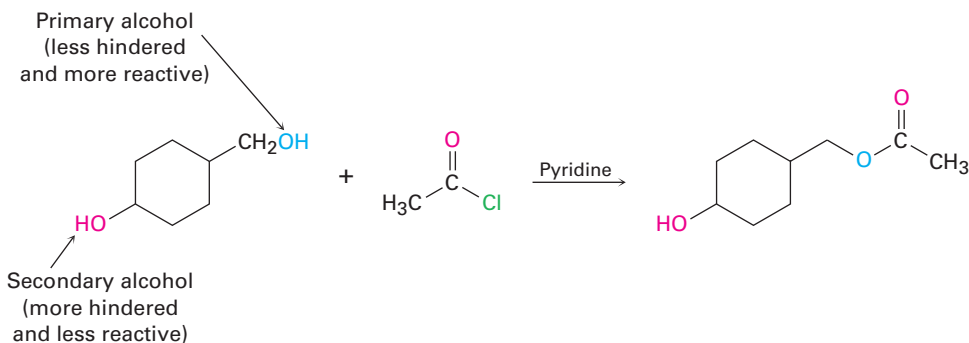
Conversion of Acid Halides into Esters: Alcoholysis ($\text{RCOCl} \rightarrow \text{RCO}_2\text{R}'$)

Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed.



The reaction of an alcohol with an acid chloride is strongly affected by steric hindrance. Bulky groups on either partner slow down the reaction considerably, resulting in a reactivity order among alcohols of primary $>$ secondary $>$ tertiary. As a result, it's often possible to esterify an unhindered alcohol selectively in the presence of a more hindered one. This can be important in

complex syntheses in which it's sometimes necessary to distinguish between similar functional groups. For example,



PROBLEM 16.9

How might you prepare the following esters using a nucleophilic acyl substitution reaction of an acid chloride?

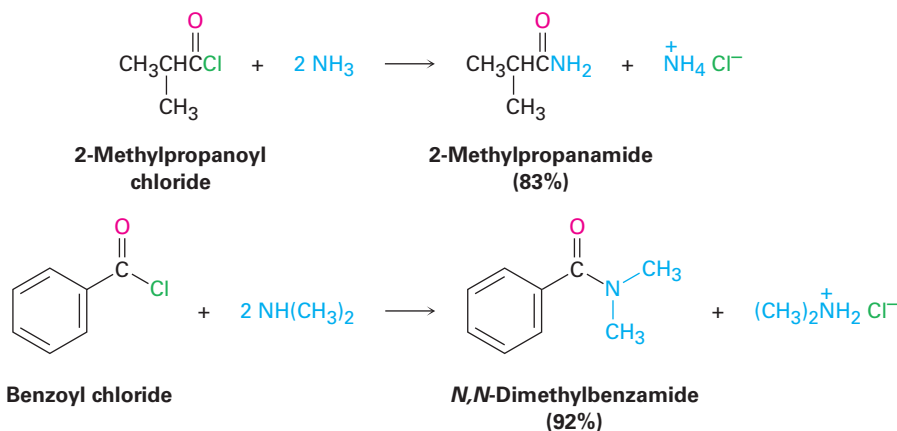
- (a) $\text{CH}_3\text{CH}_2\text{CO}_2\text{CH}_3$ (b) $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ (c) Ethyl benzoate

PROBLEM 16.10

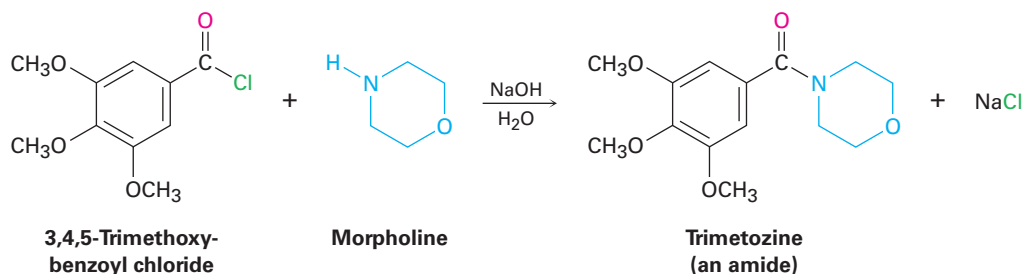
Which method would you choose if you wanted to prepare cyclohexyl benzoate—Fischer esterification of the carboxylic acid or reaction of the acid chloride with an alcohol? Explain.

Conversion of Acid Halides into Amides: Aminolysis ($\text{RCOCl} \rightarrow \text{RCONH}_2$)

Acid chlorides react rapidly with ammonia and amines to give amides. As with the acid chloride-plus-alcohol method for preparing esters, this reaction of acid chlorides with amines is the most commonly used laboratory method for preparing amides. Both monosubstituted and disubstituted amines can be used, but not trisubstituted amines (R_3N).



Because HCl is formed during the reaction, 2 equivalents of the amine must be used. One equivalent reacts with the acid chloride, and 1 equivalent reacts with the HCl by-product to form an ammonium chloride salt. If, however, the amine component is valuable, amide synthesis is often carried out using 1 equivalent of the amine plus 1 equivalent of an inexpensive base such as NaOH. For example, the sedative trimetozine is prepared commercially by reaction of 3,4,5-trimethoxybenzoyl chloride with the amine morpholine in the presence of 1 equivalent of NaOH.



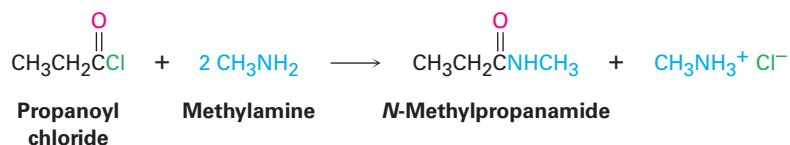
WORKED EXAMPLE 16.3 Synthesizing an Amide from an Acid Chloride

How might you prepare *N*-methylpropanamide by reaction of an acid chloride with an amine?

Strategy

As its name implies, *N*-methylpropanamide can be made by reaction of *methylamine* with the acid chloride of *propanoic acid*.

Solution



PROBLEM 16.11

How could you prepare the following amides using an acid chloride and an amine or ammonia?

- (a) $\text{CH}_3\text{CH}_2\text{CONHCH}_3$ (b) *N,N*-Diethylbenzamide (c) Propanamide

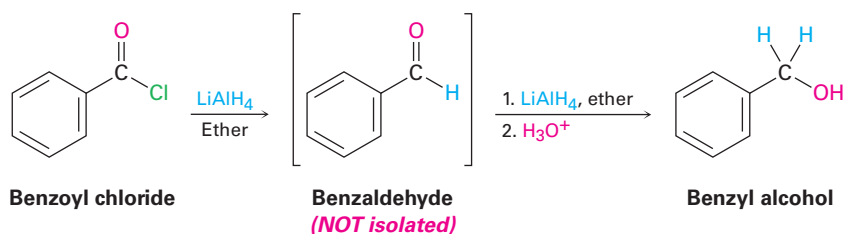
PROBLEM 16.12

Write the mechanism of the reaction between 3,4,5-trimethoxybenzoyl chloride and morpholine to form trimetozine. Use curved arrows to show the electron flow in each step.

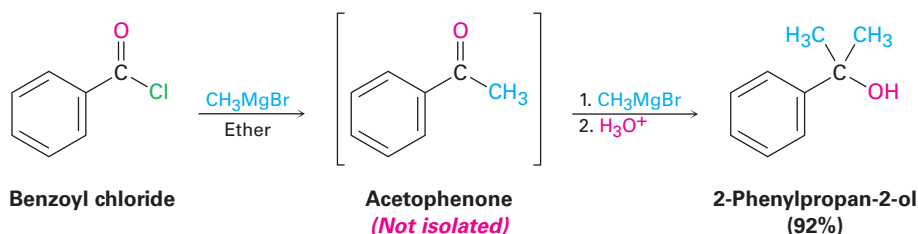
Conversion of Acid Chlorides into Alcohols: Reduction and Grignard Reaction

Acid chlorides are reduced by LiAlH_4 to yield primary alcohols. The reaction is of little practical value, however, because the parent carboxylic acids are generally more readily available and can themselves be reduced by LiAlH_4 to yield alcohols.

Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion (H^-) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^- . The net effect is a substitution of $-\text{Cl}$ by $-\text{H}$ to yield an aldehyde, which is then further reduced by LiAlH_4 in a second step to yield the primary alcohol.



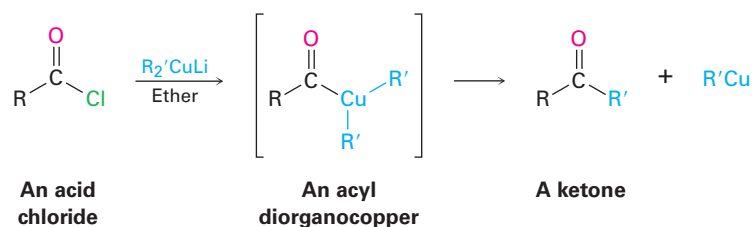
Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same. The mechanism of the reaction is similar to that of LiAlH_4 reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.



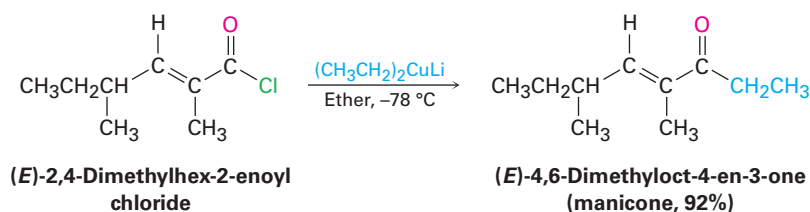
Conversion of Acid Chlorides into Ketones ($\text{RCOCl} \rightarrow \text{RCOR}'$)

The ketone intermediate formed during the reaction of an acid chloride with a Grignard reagent can't usually be isolated because addition of the second equivalent of organomagnesium reagent occurs too rapidly. A ketone *can*, however, be isolated from the reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $\text{Li}^+ \text{R}_2\text{Cu}^-$, which is itself formed by reaction of CuI with 2 equivalents of an organolithium (Section 12-5). The reaction occurs by initial nucleophilic acyl substitution on the acid chloride by the

diorganocopper anion to yield an acyl diorganocopper intermediate, followed by loss of $R'Cu$ and formation of the ketone.



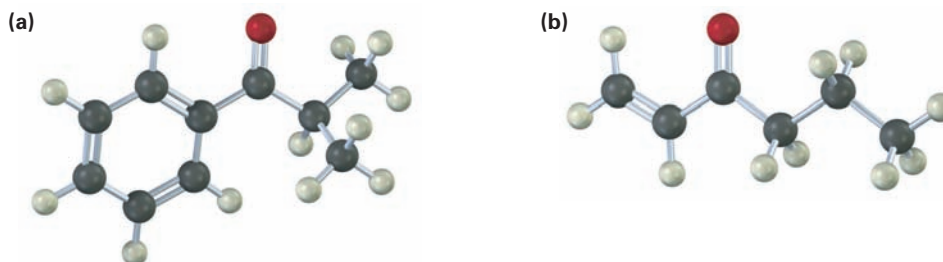
As an example of the process, manicone, a substance secreted by male ants to coordinate ant pairing and mating, has been synthesized by reaction of lithium diethylcopper with (*E*)-2,4-dimethylhex-2-enoyl chloride. The synthetic material is used as bait in some commercial ant traps.



Note that the diorganocopper reaction occurs only with acid chlorides. Carboxylic acids, esters, acid anhydrides, and amides do not react with lithium diorganocopper reagents.

PROBLEM 16.13

How could you prepare the following ketones by reaction of an acid chloride with a lithium diorganocopper reagent?



16-5 Reactions of Acid Anhydrides

The chemistry of acid anhydrides is similar to that of acid chlorides, although anhydrides react more slowly. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with

LiAlH_4 to form primary alcohols (FIGURE 16.7). Only the ester and amide forming reactions are commonly used, however.

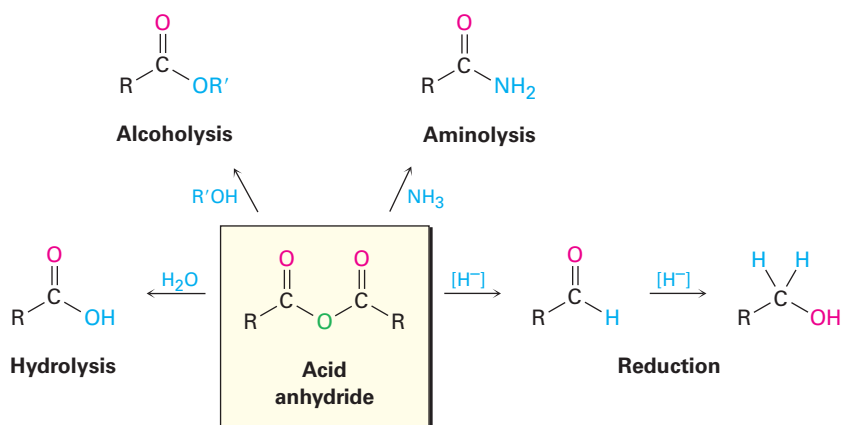
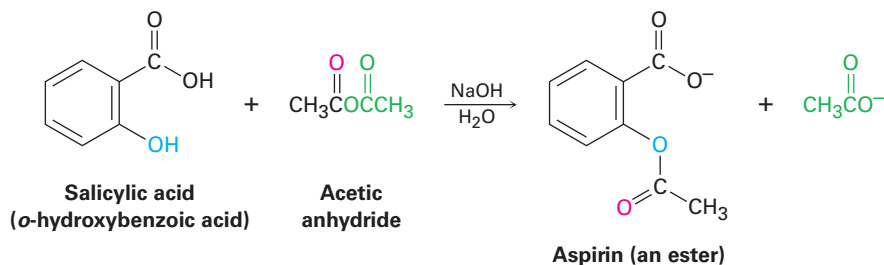


FIGURE 16.7 Some reactions of acid anhydrides.

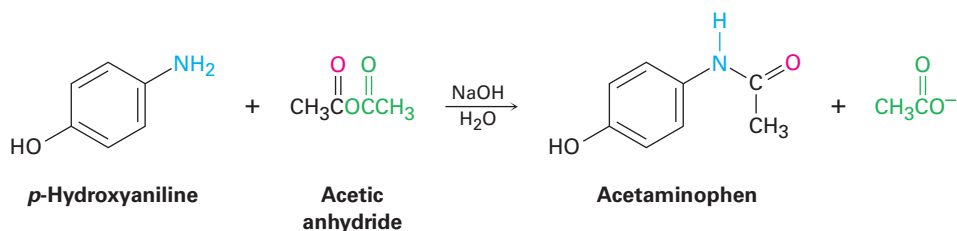
Conversion of Acid Anhydrides into Esters ($\text{RCO}_2\text{COR}' \rightarrow \text{RCO}_2\text{R}'_2$)

Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of *o*-hydroxybenzoic acid (salicylic acid) with acetic anhydride.



Conversion of Acid Anhydrides into Amides ($\text{RCO}_2\text{COR}' \rightarrow \text{RCONH}_2$)

Acetic anhydride is also commonly used to prepare *N*-substituted acetamides from amines. For example, acetaminophen, a drug used in over-the-counter analgesics such as Tylenol, is prepared by reaction of *p*-hydroxyaniline with acetic anhydride. Only the more nucleophilic $-\text{NH}_2$ group reacts rather than the less nucleophilic $-\text{OH}$ group.



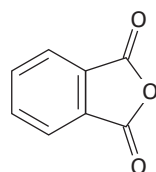
Notice in both of the previous reactions that only “half” of the anhydride molecule is used, while the other half acts as the leaving group during the nucleophilic acyl substitution step and produces acetate ion as a by-product. Thus, anhydrides are inefficient to use, and acid chlorides are normally preferred for introducing acyl substituents other than acetyl groups.

PROBLEM 16.14

Write the mechanism of the reaction between *p*-hydroxyaniline and acetic anhydride to prepare acetaminophen.

PROBLEM 16.15

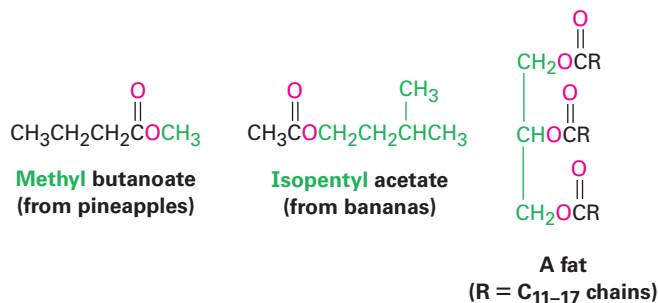
What product would you expect from reaction of 1 equivalent of methanol with a cyclic anhydride, such as phthalic anhydride (benzene-1,2-dicarboxylic anhydride)? What is the fate of the second “half” of the anhydride?



Phthalic anhydride

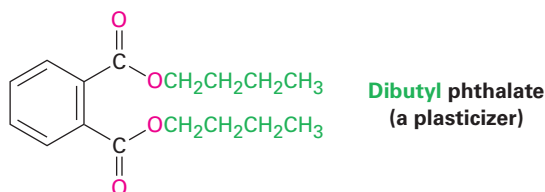
16-6 Reactions of Esters

Esters are among the most widespread of all naturally occurring compounds. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many biologically important molecules.

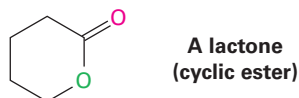


The chemical industry uses esters for a variety of purposes. Ethyl acetate, for instance, is a commonly used solvent, and dialkyl phthalates are used as

plasticizers to keep polymers from becoming brittle. You may be aware that there is current concern about possible toxicity of phthalates at high concentrations. Although an assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, voluntary withdrawals by many manufacturers have taken place.

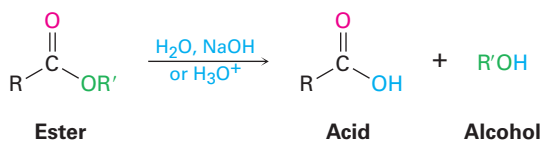


Esters undergo the same kinds of reactions that we've seen for other carboxylic acid derivatives, but they are less reactive toward nucleophiles than either acid chlorides or anhydrides. All their reactions are applicable to both acyclic and cyclic esters, called **lactones**.



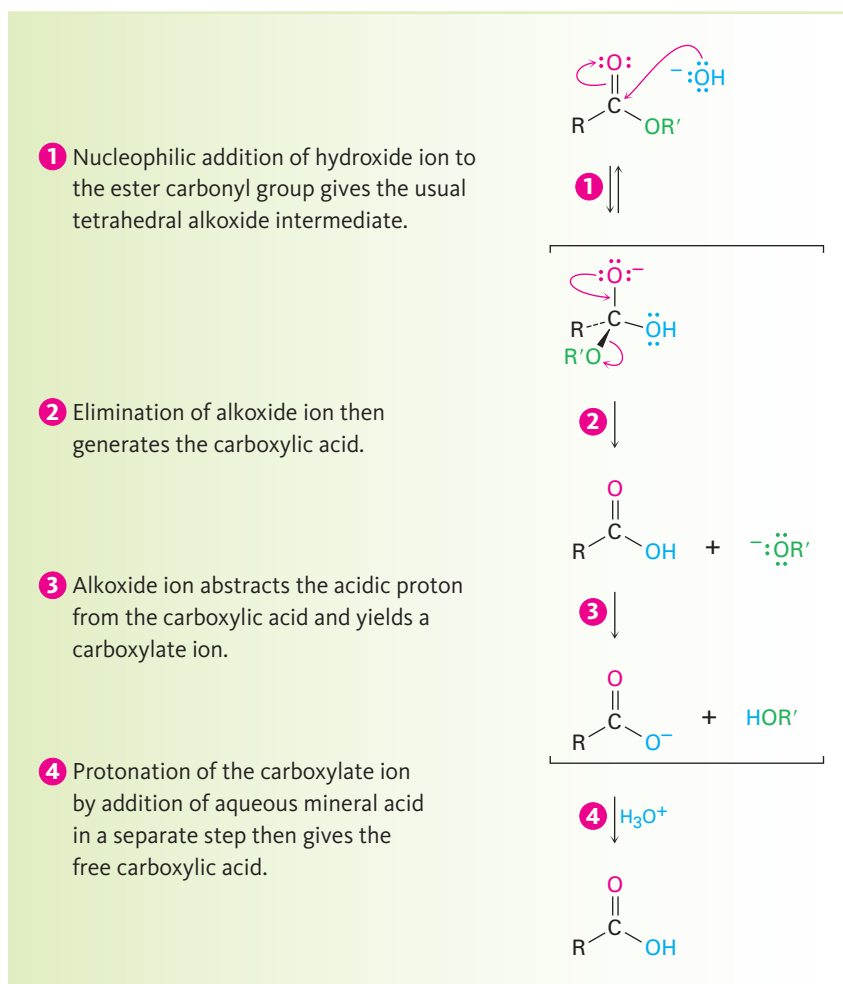
Conversion of Esters into Carboxylic Acids: Hydrolysis ($\text{RCO}_2\text{R}' \rightarrow \text{RCO}_2\text{H}$)

Esters are hydrolyzed, either by aqueous base or by aqueous acid, to yield a carboxylic acid plus an alcohol:

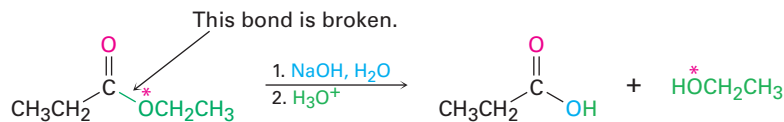


Ester hydrolysis in basic solution is called **saponification**, after the Latin word *sapo*, meaning “soap.” We’ll see in Section 23-2 that soap is in fact made by boiling animal fat with aqueous base to hydrolyze the ester linkages.

Ester hydrolysis occurs through a typical nucleophilic acyl substitution pathway in which hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of alkoxide ion then gives a carboxylic acid, which is deprotonated to give the carboxylate ion. Addition of aqueous HCl in a separate step after the saponification is complete protonates the carboxylate ion and gives the carboxylic acid (**FIGURE 16.8**).

FIGURE 16.8 Mechanism of base-induced ester hydrolysis (saponification).

The mechanism shown in Figure 16.8 is supported by isotope-labeling studies. When ethyl propanoate labeled with ^{18}O in the ether-like oxygen is hydrolyzed in aqueous NaOH , the ^{18}O label shows up exclusively in the ethanol product. None of the label remains with the propanoic acid, indicating that saponification occurs by cleavage of the $\text{C}-\text{OR}'$ bond rather than the $\text{CO}-\text{R}'$ bond.



Acid-catalyzed ester hydrolysis can occur by more than one mechanism, depending on the structure of the ester. The usual pathway, however, is just the reverse of a Fischer esterification reaction (Section 16-3). As shown in **FIGURE 16.9**, the ester is first activated toward nucleophilic attack by protonation of the carboxyl oxygen atom, and nucleophilic addition of water then

occurs. Transfer of a proton and elimination of alcohol yields the carboxylic acid. Because this hydrolysis reaction is the reverse of a Fischer esterification reaction, Figure 16.9 is the reverse of Figure 16.4.

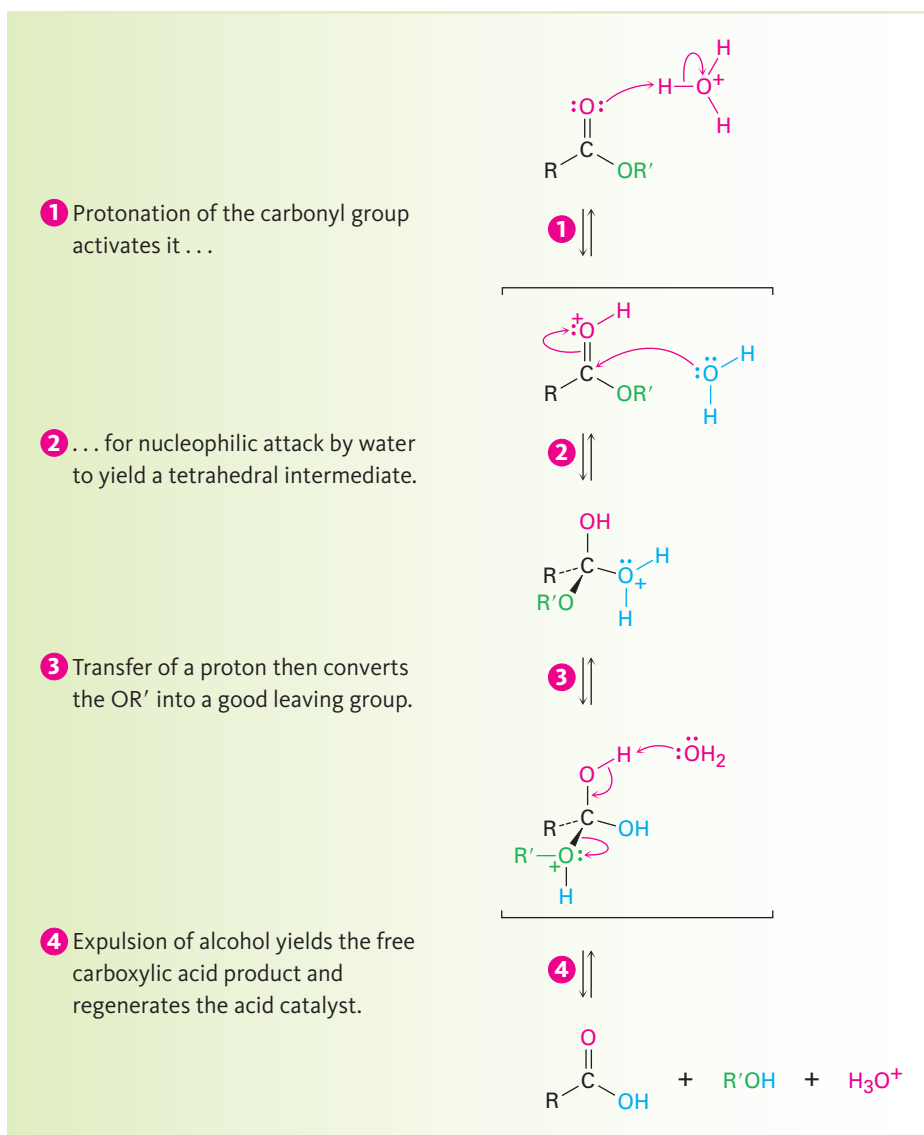
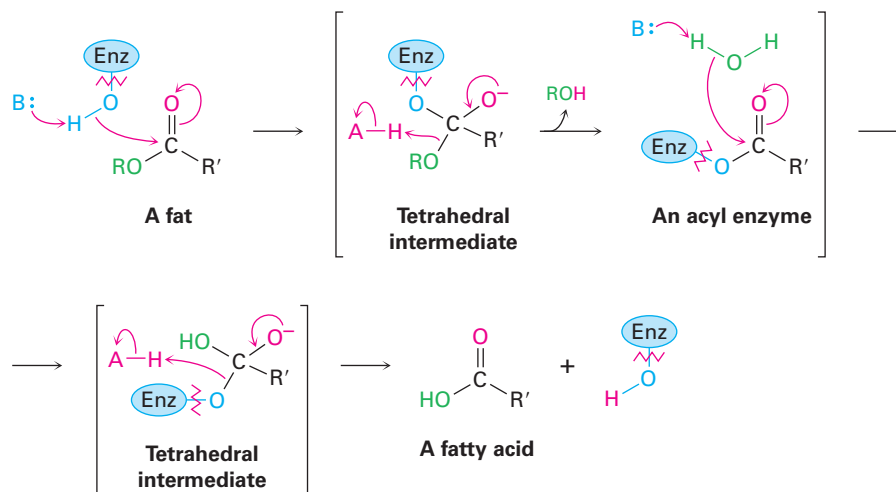


FIGURE 16.9 Mechanism of acid-catalyzed ester hydrolysis.

The forward reaction is a hydrolysis; the back-reaction is a Fischer esterification and is thus the reverse of Figure 16.4.

Ester hydrolysis is common in biological chemistry, particularly in the digestion of dietary fats and oils. We'll save a complete discussion of the mechanistic details of fat hydrolysis until Section 23-4 but will note for now that the reaction is catalyzed by various lipase enzymes and involves two sequential nucleophilic acyl substitution reactions. The first is a *transesterification* reaction in which an alcohol group on the lipase adds to an ester linkage in the fat molecule to give a tetrahedral intermediate that expels alcohol and forms an acyl enzyme intermediate. The second is an

addition of water to the acyl enzyme, followed by expulsion of the enzyme to give a hydrolyzed acid plus regenerated enzyme.

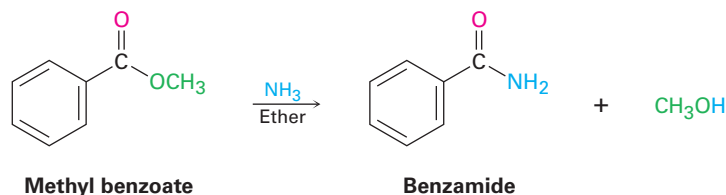


PROBLEM 16.16

Why is the saponification of an ester irreversible? In other words, why doesn't treatment of a carboxylic acid with an alkoxide ion yield an ester?

Conversion of Esters into Amides: Aminolysis ($\text{RCO}_2\text{R}' \rightarrow \text{RCONH}_2$)

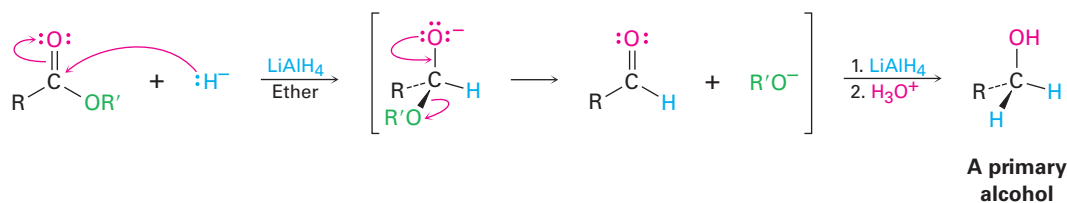
Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to prepare an amide by starting with an acid chloride (Section 16-4).



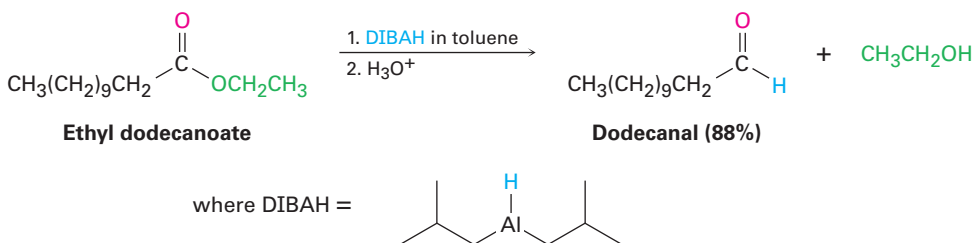
Conversion of Esters into Alcohols: Reduction and Grignard Reaction

Esters are reduced by treatment with LiAlH_4 to yield primary alcohols, as we saw in Section 13-3. The mechanism is similar to that of acid chloride reduction in that a hydride ion first adds to the carbonyl group, followed by elimination

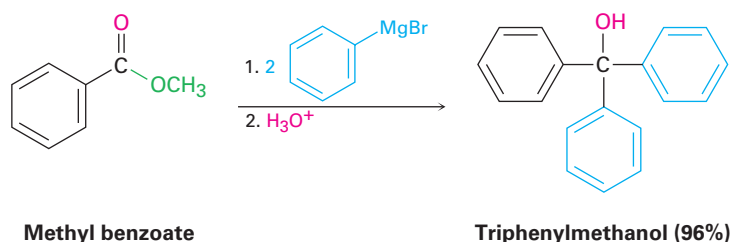
of alkoxide ion to yield an aldehyde. Further reduction of the aldehyde gives the primary alcohol.



The aldehyde intermediate can be isolated if 1 equivalent of the less reactive reducing agent diisobutylaluminum hydride (DIBAH) is used instead of LiAlH_4 . The reaction is carried out at -78°C to avoid further reduction to the alcohol. Such partial reductions of carboxylic acid derivatives to aldehydes also occur in numerous biological pathways, although the substrate is either a thioester or an acyl phosphate rather than an ester. We'll see an example in Section 16-8.

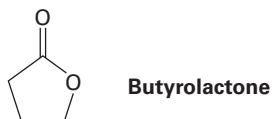


As noted in Section 13-3, esters (and lactones) react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical. The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.



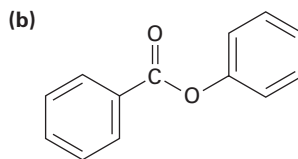
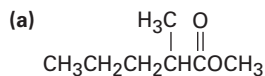
PROBLEM 16.17

What product would you expect from the reaction of butyrolactone with LiAlH_4 ? With DIBAH?

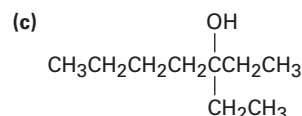
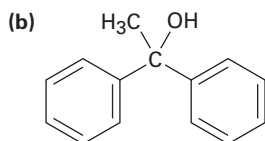
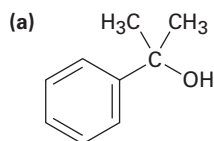


PROBLEM 16.18

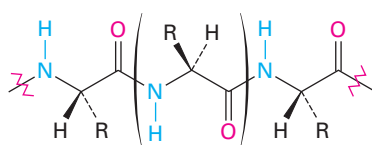
Show the products you would obtain by reduction of the following esters with LiAlH_4 :

**PROBLEM 16.19**

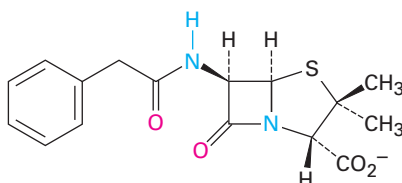
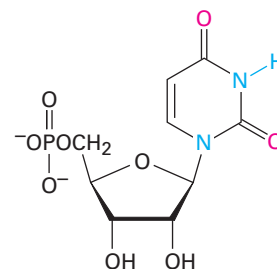
What ester and what Grignard reagent might you start with to prepare the following alcohols?

**16-7 Reactions of Amides**

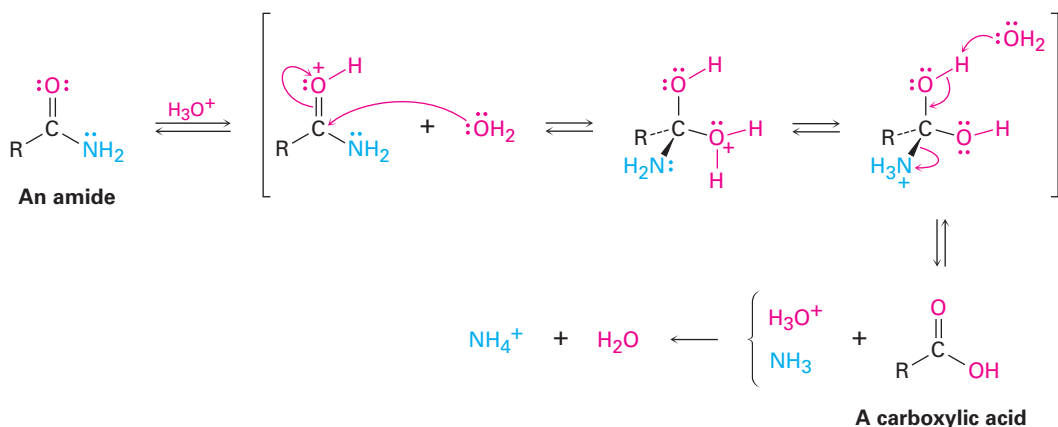
Amides, like esters, are abundant in all living organisms. Proteins, nucleic acids, and many pharmaceutical agents have amide functional groups. The reason for this abundance of amides is that they are stable to the aqueous conditions found in living organisms. Amides are the least reactive of the common acid derivatives and undergo relatively few nucleophilic acyl substitution reactions.



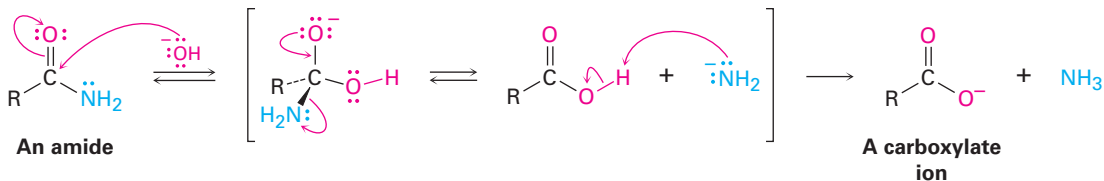
A protein segment

Benzylpenicillin
(penicillin G)Uridine 5'-phosphate
(a ribonucleotide)**Conversion of Amides into Carboxylic Acids:
Hydrolysis ($\text{RCONH}_2 \rightarrow \text{RCO}_2\text{H}$)**

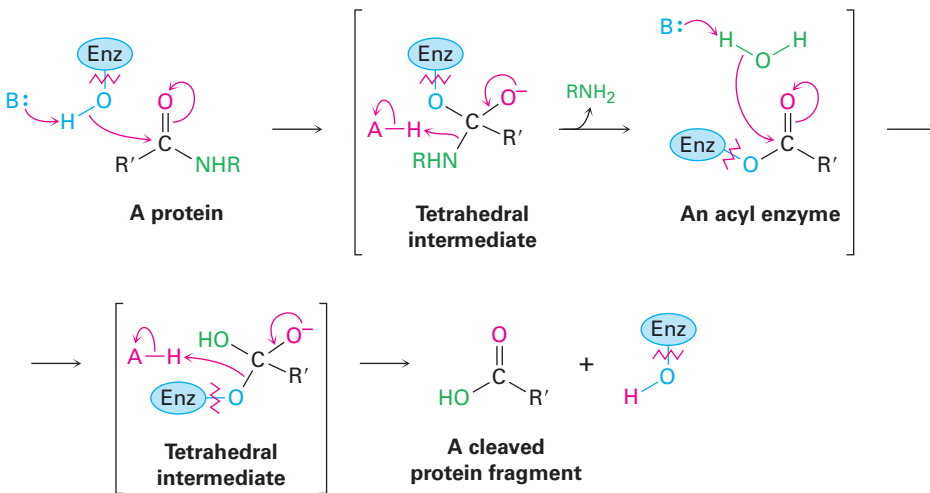
Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine on heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more severe than those required for the hydrolysis of acid chlorides or esters, but the mechanisms are similar. Acidic hydrolysis occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group and subsequent elimination. The steps are reversible, with the equilibrium shifted toward product by protonation of NH_3 in the final step.



Basic hydrolysis occurs by nucleophilic addition of OH^- to the amide carbonyl group, followed by elimination of amide ion ($^-\text{NH}_2$) and subsequent deprotonation of the initially formed carboxylic acid by ammonia. The steps are reversible, with the equilibrium shifted toward product by the final deprotonation of the carboxylic acid. Basic hydrolysis is substantially more difficult than the analogous acid-catalyzed reaction because amide ion is a very poor leaving group, making the elimination step difficult.

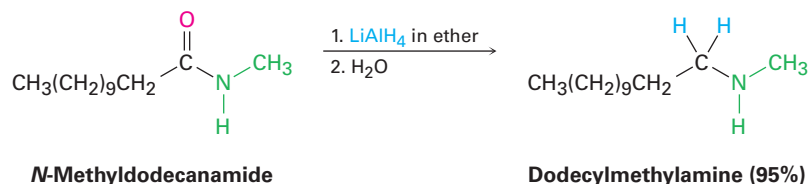


Amide hydrolysis is common in biological chemistry. Just as the hydrolysis of esters is the initial step in the digestion of dietary fats, the hydrolysis of amides is the initial step in the digestion of dietary proteins. The reaction is catalyzed by protease enzymes and occurs by a mechanism almost identical to that we just saw for fat hydrolysis. That is, an initial nucleophilic acyl substitution of an alcohol group in the enzyme on an amide linkage in the protein gives an acyl enzyme intermediate that then undergoes hydrolysis.

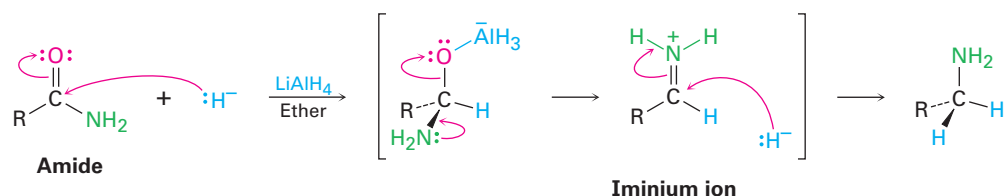


Conversion of Amides into Amines: Reduction ($\text{RCONH}_2 \rightarrow \text{RCH}_2\text{NH}_2$)

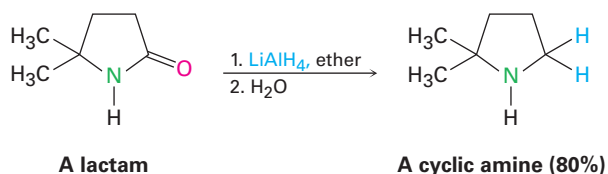
Like other carboxylic acid derivatives, amides can be reduced by LiAlH_4 . The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction reaction is thus the conversion of the amide carbonyl group into a methylene group ($\text{C}=\text{O} \rightarrow \text{CH}_2$). This kind of reaction is specific for amides and does not occur with other carboxylic acid derivatives.



Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the oxygen atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is then further reduced by LiAlH_4 to yield the amine.



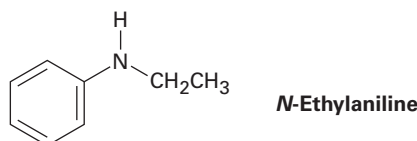
The reaction is effective with both acyclic and cyclic amides, or **lactams**, and is a good method for preparing cyclic amines.



WORKED EXAMPLE 16.4

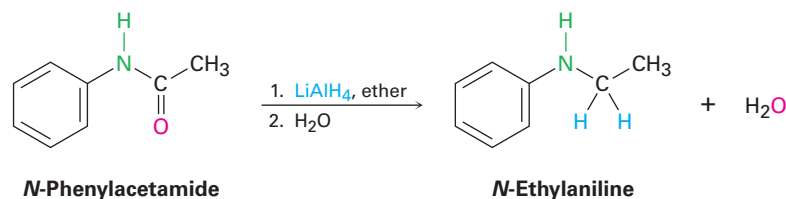
Synthesizing an Amine from an Amide

How could you prepare *N*-ethylaniline by reduction of an amide with LiAlH_4 ?



Strategy

Reduction of an amide with LiAlH_4 yields an amine. To find the starting material for synthesis of *N*-ethylaniline, look for a CH_2 position next to the nitrogen atom and replace that CH_2 by $\text{C}=\text{O}$. In this case, the amide is *N*-phenylacetamide.

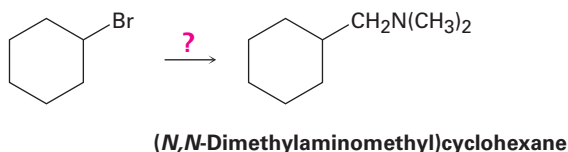
Solution**PROBLEM 16.20**

How would you convert *N*-ethylbenzamide to each of the following products?

(a) Benzoic acid (b) Benzyl alcohol (c) C₆H₅CH₂NHCH₂CH₃

PROBLEM 16.21

How would you use the reaction of an amide with LiAlH₄ as the key step in going from bromocyclohexane to (*N,N*-dimethylaminomethyl)cyclohexane? Write all the steps in the reaction sequence.

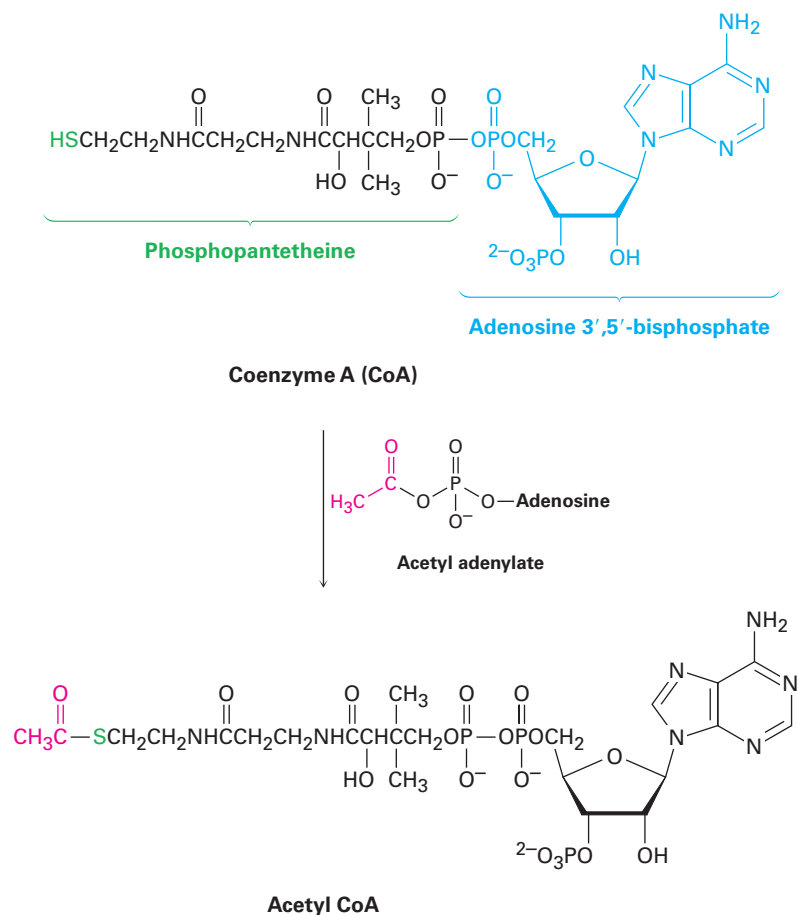


16-8 Reactions of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives

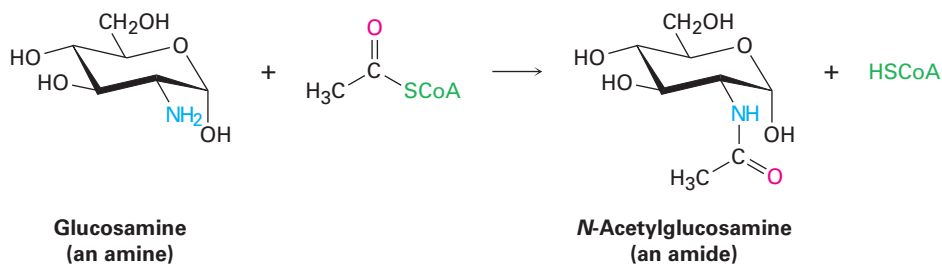
As mentioned in the chapter introduction, the substrate for a nucleophilic acyl substitution reaction in living organisms is generally either a thioester (RCOSR') or an acyl phosphate [RCO₂PO₃²⁻ or RCO₂PO₃R'⁻]. Neither is as reactive as an acid chloride or acid anhydride, yet both are stable enough to exist in living organisms while still reactive enough to undergo acyl substitution.

Acyl CoA's, such as acetyl CoA, are the most common thioesters in nature. Coenzyme A, abbreviated CoA, is a thiol formed by a phosphoric anhydride linkage (O=P-O-P=O) between phosphopantetheine and adenosine 3',5'-bisphosphate. (The prefix "bis-" means "two" and indicates that adenosine 3',5'-bisphosphate has two phosphate groups, one on C3' and one on C5'.) Reaction of coenzyme A with an acyl phosphate or acyl adenylate gives the acyl CoA (FIGURE 16.10). As we saw in Section 16-5 (Figure 16.6), formation of the acyl adenylate occurs by reaction of a carboxylic acid with ATP and is itself a nucleophilic acyl substitution reaction that takes place on phosphorus.

FIGURE 16.10 Formation of the thioester acetyl CoA by nucleophilic acyl substitution reaction of coenzyme A (CoA) with acetyl adenylate.

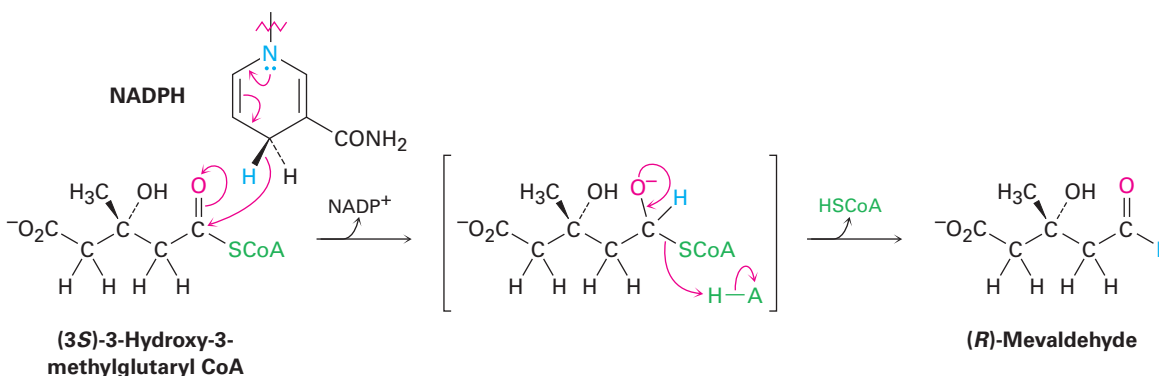


Once formed, an acyl CoA is a substrate for further nucleophilic acyl substitution reactions. For example, *N*-acetylglucosamine, a component of cartilage and other connective tissues, is synthesized by an aminolysis reaction between glucosamine and acetyl CoA.



Another example of a nucleophilic acyl substitution reaction on a thioester, this one a substitution by hydride ion to effect partial reduction of a thioester to an aldehyde, occurs in the biosynthesis of mevaldehyde, an intermediate in terpenoid synthesis (Chapter 7 *Something Extra* and Section 23-8).

In this reaction, (3*S*)-3-hydroxy-3-methylglutaryl CoA is reduced by hydride donation from NADPH.

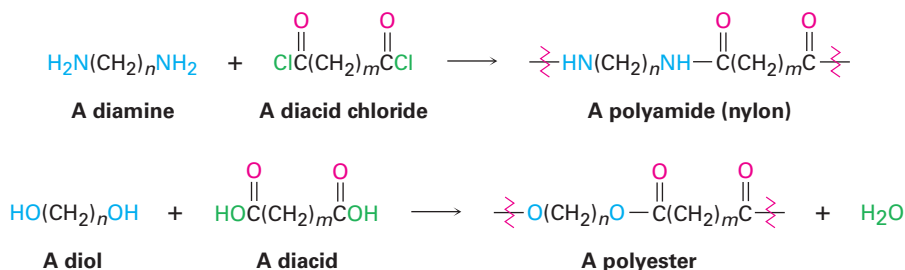


PROBLEM 16.22

Write the mechanism of the reaction shown in Figure 16.10 between coenzyme A and acetyl adenylate to give acetyl CoA.

16-9 Polyamides and Polyesters: Step-Growth Polymers

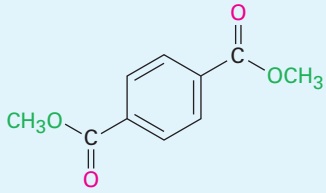
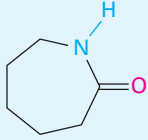
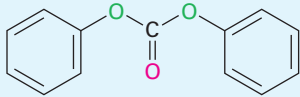
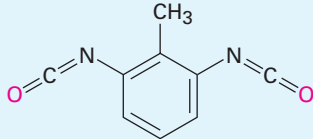
When an amine reacts with an acid chloride, an amide is formed. What would happen, though, if a *diamine* and a *diacid chloride* were allowed to react? Each partner could form two amide bonds, linking more and more molecules together until a giant polyamide resulted. In the same way, reaction of a diol with a diacid would lead to a polyester.



There are two main classes of synthetic polymers: *chain-growth polymers* and *step-growth polymers*. Polyethylene and other alkene polymers like those we saw in Section 8-10 are chain-growth polymers because they are produced in chain reaction processes. An initiator adds to a C=C bond to give a reactive intermediate, which adds to a second alkene molecule to produce a new intermediate, which adds to a third molecule, and so on. By contrast, polyamides

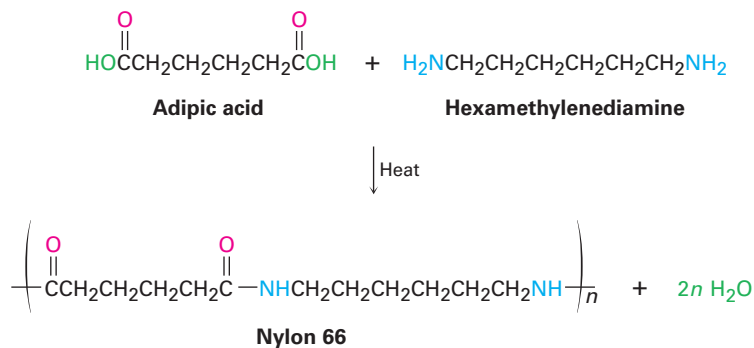
and polyesters are **step-growth polymers** because each bond in the polymer is formed independently of the others. The key bond-forming step is often a nucleophilic acyl substitution of a carboxylic acid derivative. Some commercially important step-growth polymers are shown in **TABLE 16.2**.

TABLE 16.2 Some Common Step-Growth Polymers and Their Uses

Monomers	Structure	Polymer	Uses
Adipic acid + Hexamethylenediamine	$\text{HO}\overset{\text{O}}{\parallel}\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\overset{\text{O}}{\parallel}\text{COH}$ $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$	Nylon 66	Fibers, clothing, tire cord
Dimethyl terephthalate + Ethylene glycol	 $\text{HOCH}_2\text{CH}_2\text{OH}$		
Caprolactam		Nylon 6, Perlon	Fibers, castings
Diphenyl carbonate + Bisphenol A	 $\text{H}_3\text{C}-\text{C}(\text{CH}_3)_2-\text{C}_6\text{H}_4-\text{OH}$		
Toluene-2,6-diisocyanate + Hydroxyl-terminated polybutadiene	 $\text{HO}-(\text{CH}_2\text{CH}=\text{CHCH}_2)_n\text{OH}$	Polyurethane, Spandex	Fibers, coatings, foams

Polyamides (Nylons)

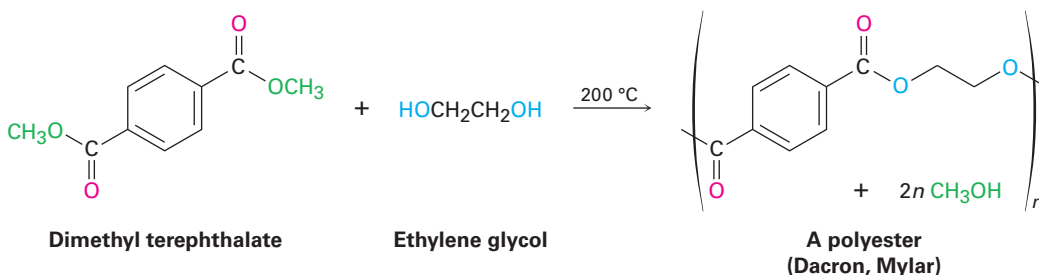
The best known step-growth polymers are the polyamides, or *nylons*, first prepared by heating a diamine with a diacid. For example, nylon 66 is prepared by reaction of adipic acid (hexanedioic acid) with hexamethylenediamine (hexane-1,6-diamine) at 280 °C. The designation “66” tells the number of carbon atoms in the diamine (the first 6) and the diacid (the second 6).



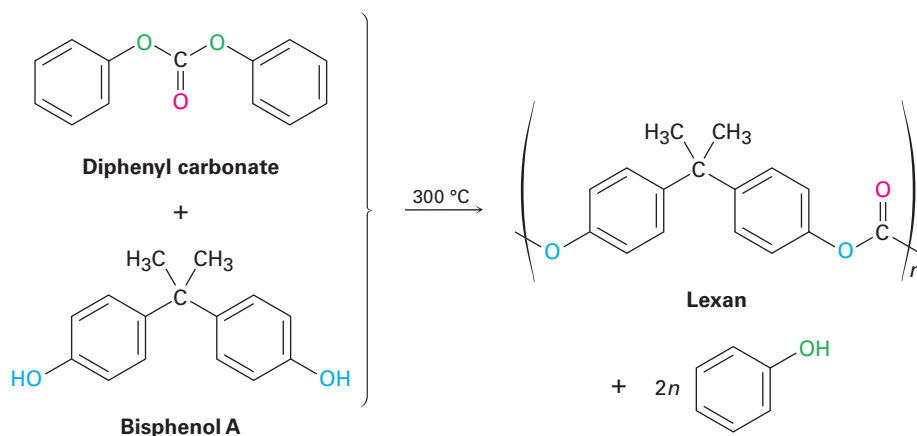
Nylons are used both in engineering applications and in making fibers. A combination of high impact strength and abrasion resistance makes nylon an excellent metal substitute for bearings and gears. As fiber, nylon is used in a variety of applications, from clothing to tire cord to mountaineering ropes.

Polyesters

The most generally useful polyester is that made by reaction between dimethyl terephthalate (dimethyl benzene-1,4-dicarboxylate) and ethylene glycol (ethane-1,2-diol). The product is used under the trade name Dacron to make clothing fiber and tire cord, and under the name Mylar to make recording tape. The tensile strength of poly(ethylene terephthalate) film is nearly equal to that of steel.

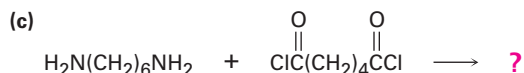
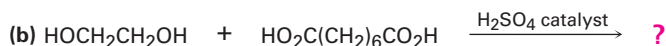


Lexan, a polycarbonate prepared from diphenyl carbonate and bisphenol A, is another commercially valuable polyester. Lexan has an unusually high impact strength, making it valuable for use in telephones, bicycle safety helmets, and laptop computer cases.



PROBLEM 16.23

Draw structures of the step-growth polymers you would expect to obtain from the following reactions:

**PROBLEM 16.24**

Kevlar, a nylon polymer prepared by reaction of benzene-1,4-dicarboxylic acid (terephthalic acid) with benzene-1,4-diamine (*p*-phenylenediamine), is so strong that it's used to make body armor. Draw the structure of a segment of Kevlar.

16-10 Spectroscopy of Carboxylic Acid Derivatives

Infrared Spectroscopy

All carbonyl-containing compounds have intense IR absorptions in the range 1650 to 1850 cm^{-1} . As shown in **TABLE 16.3**, the exact position of the absorption provides information about the specific kind of carbonyl group. For comparison, the IR absorptions of aldehydes, ketones, and carboxylic acids are included in the table, along with values for carboxylic acid derivatives.

TABLE 16.3 Infrared Absorptions of Some Carbonyl Compounds

Carbonyl type	Example	Absorption (cm^{-1})
Saturated acid chloride	Acetyl chloride	1810
Aromatic acid chloride	Benzoyl chloride	1770
Saturated acid anhydride	Acetic anhydride	1820, 1760
Saturated ester	Ethyl acetate	1735
Aromatic ester	Ethyl benzoate	1720
Saturated amide	Acetamide	1690
Aromatic amide	Benzamide	1675
<i>N</i> -Substituted amide	<i>N</i> -Methylacetamide	1680
<i>N,N</i> -Disubstituted amide	<i>N,N</i> -Dimethylacetamide	1650
Saturated aldehyde	Acetaldehyde	1730
Saturated ketone	Acetone	1715
Saturated carboxylic acid	Acetic acid	1710

Acid chlorides are easily detected by their characteristic absorption near 1800 cm^{-1} . Acid anhydrides can be identified because they show two absorptions in the carbonyl region, one at 1820 cm^{-1} and another at 1760 cm^{-1} . Esters are detected by their absorption at 1735 cm^{-1} , a position somewhat higher than that for either aldehydes or ketones. Amides, by contrast, absorb near the low wavenumber end of the carbonyl region, with the degree of substitution on nitrogen affecting the exact position of the IR band.

PROBLEM 16.25

What kinds of functional groups might compounds have if they show the following IR absorptions?

- (a) Absorption at 1735 cm^{-1}
- (b) Absorption at 1810 cm^{-1}
- (c) Absorptions at $2500\text{--}3300\text{ cm}^{-1}$ and 1710 cm^{-1}
- (d) Absorption at 1715 cm^{-1}

PROBLEM 16.26

Propose structures for compounds that have the following formulas and IR absorptions:

- (a) $\text{C}_6\text{H}_{12}\text{O}_2$, 1735 cm^{-1}
- (b) $\text{C}_4\text{H}_9\text{NO}$, 1650 cm^{-1}
- (c) $\text{C}_4\text{H}_5\text{ClO}$, 1780 cm^{-1}

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the carbon next to a carbonyl group are slightly deshielded and absorb near 2δ in the ^1H NMR spectrum. The identity of the carbonyl group can't be determined by ^1H NMR, however, because the α hydrogens of all acid derivatives absorb in the same range. FIGURE 16.11 shows the ^1H NMR spectrum of ethyl acetate.

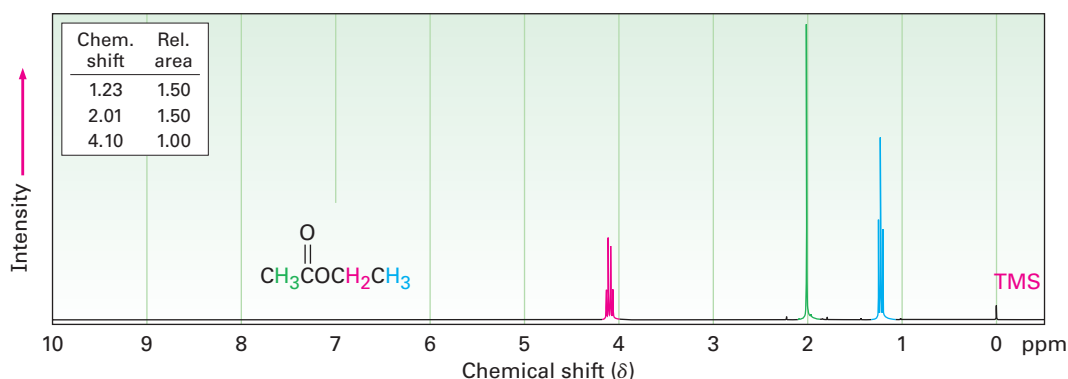


FIGURE 16.11
 ^1H NMR spectrum of ethyl acetate.

Although ^{13}C NMR is useful for determining the presence or absence of a carbonyl group in a molecule, the identity of the carbonyl group is difficult to determine. Aldehydes and ketones absorb near 200δ , while the carbonyl carbon atoms of various acid derivatives absorb in the range 160 to 180δ (TABLE 16.4).

TABLE 16.4 ^{13}C NMR Absorptions in Some Carbonyl Compounds

Compound	Absorption (δ)	Compound	Absorption (δ)
Acetic acid	177.3	Acetic anhydride	166.9
Ethyl acetate	170.7	Acetone	205.6
Acetyl chloride	170.3	Acetaldehyde	201.0
Acetamide	172.6		

SOMETHING EXTRA

 β -Lactam Antibiotics

You should never underestimate the value of hard work and logical thinking, but it's also true that blind luck plays a role in most real scientific breakthroughs. What has been called "the supreme example of luck in all scientific history" occurred in the late summer of 1928, when the Scottish bacteriologist Alexander Fleming went on vacation, leaving in his lab a culture plate recently inoculated with the bacterium *Staphylococcus aureus*.

While Fleming was away, an extraordinary chain of events occurred. First, a 9-day cold spell lowered the laboratory temperature to a point where the *Staphylococcus* on the plate could not grow. During this time, spores from a colony of the mold *Penicillium notatum* being grown on the floor below wafted up into Fleming's lab and landed in the culture plate. The temperature then rose, and both *Staphylococcus* and *Penicillium* began to grow. On returning from vacation, Fleming discarded the plate into a tray of antiseptic, intending to sterilize it. Evidently, though, the plate did not sink deeply enough into the antiseptic, because when Fleming happened to glance at it a few days later, what he saw changed the course of human history. He noticed that the growing *Penicillium* mold appeared to dissolve the colonies of staphylococci.

Fleming realized that the *Penicillium* mold must be producing a chemical that killed the *Staphylococcus*



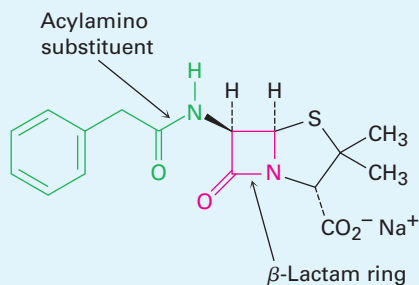
Leonard Lessin / Science Source

Penicillium mold growing in a petri dish.

bacteria, and he spent several years trying to isolate the substance. Finally, in 1939, the Australian pathologist Howard Florey and the German refugee Ernst Chain managed to isolate the active substance, called *penicillin*. The dramatic ability of penicillin to cure infections in mice was soon demonstrated, and successful tests in humans followed shortly thereafter. By 1943, penicillin was being produced on a large scale for military use in World War II, and by 1944 it was being used on civilians. Fleming, Florey, and Chain shared the 1945 Nobel Prize in Medicine.

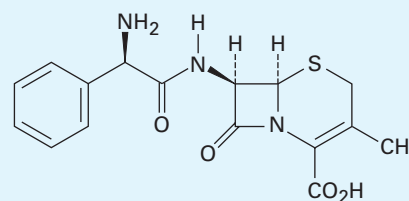
Now called benzylpenicillin, or penicillin G, the substance first discovered by Fleming is but one member of a large class of so-called β -lactam antibiotics, compounds with a four-membered lactam (cyclic amide) ring. The four-membered lactam ring is fused to a five-membered, sulfur-containing ring, and the carbon atom next to the lactam carbonyl group is

bonded to an acylamino substituent, RCONH- . This acylamino side chain can be varied in the laboratory to provide many hundreds of penicillin analogs with different biological activity profiles. Ampicillin, for instance, has an α -aminophenylacetamido substituent [$\text{PhCH}(\text{NH}_2)\text{CONH-}$].



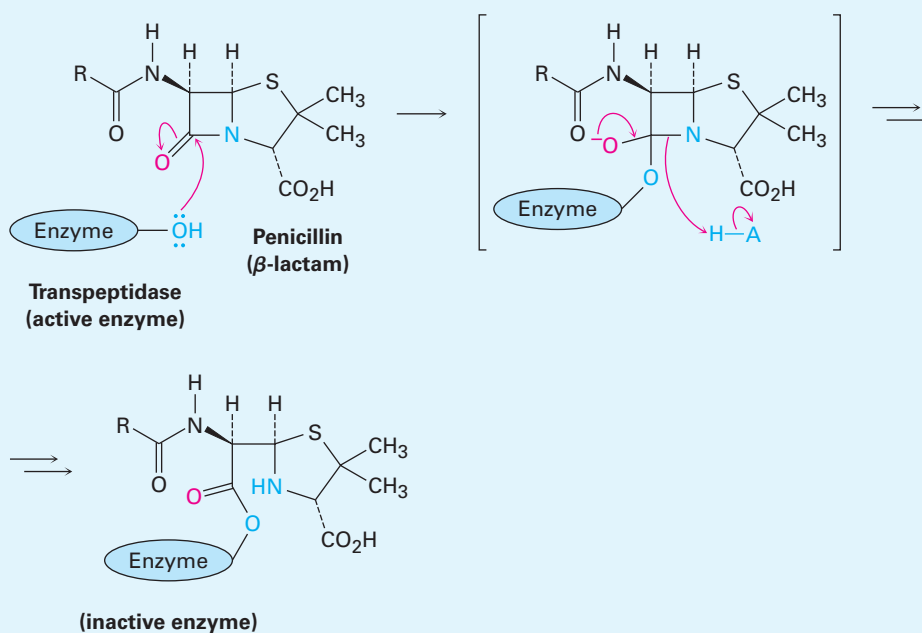
**Benzylpenicillin
(penicillin G)**

Closely related to the penicillins are the *cephalosporins*, a group of β -lactam antibiotics that contain an



**Cephalixin
(a cephalosporin)**

The biological activity of penicillins and cephalosporins is due to the presence of the strained β -lactam ring, which reacts with and deactivates the transpeptidase enzyme needed to synthesize and repair bacterial cell walls. With the wall either incomplete or weakened, the bacterial cell ruptures and dies.



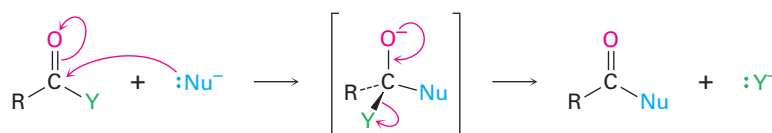
KEY WORDS

acid anhydride (RCO ₂ COR'),	555
acid halide (RCOX),	555
acyl phosphate (RCOPO ₃ ²⁻),	555
amide (RCONH ₂),	555
carboxylic acid derivative,	555
ester (RCO ₂ R'),	555
lactam,	586
lactone,	579
nucleophilic acyl substitution reaction,	559
saponification,	579
step-growth polymer,	590
thioester (RCOSR'),	555

SUMMARY

Carboxylic acid derivatives—compounds in which the –OH group of a carboxylic acid has been replaced by another substituent—are among the most widely occurring of all molecules and are involved in almost all biological pathways. In this chapter, we covered the chemistry necessary for understanding them and thus also necessary for understanding the chemistry of living organisms. **Acid halides, acid anhydrides, esters, and amides** are the most common such derivatives in the laboratory; **thioesters** and **acyl phosphates** are common in biological molecules.

The chemistry of carboxylic acid derivatives is dominated by the **nucleophilic acyl substitution reaction**. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group.



The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the substituent, Y. The reactivity order is acid halide > acid anhydride > thioester > ester > amide.

The most common reactions of carboxylic acid derivatives are substitution by water to yield an acid (hydrolysis), by an alcohol to yield an ester (alcoholysis), by an amine to yield an amide (aminolysis), by hydride ion to yield an alcohol (reduction), and by an organomagnesium halide to yield an alcohol (Grignard reaction).

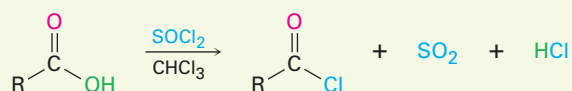
Step-growth polymers, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

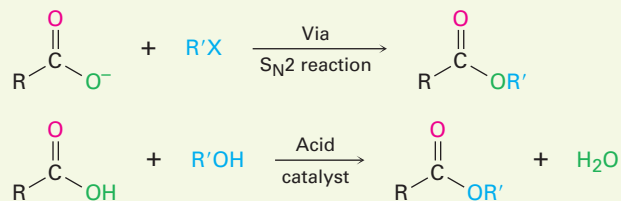
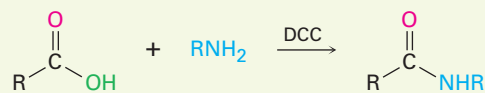
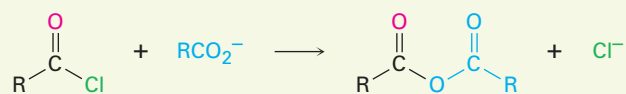
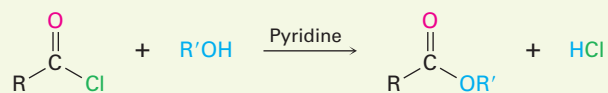
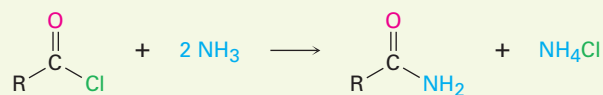
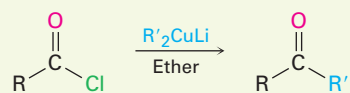
IR spectroscopy is a valuable tool for the structural analysis of acid derivatives. Acid chlorides, anhydrides, esters, and amides all show characteristic IR absorptions that can be used to identify these functional groups.

SUMMARY OF REACTIONS

1. Reactions of carboxylic acids (Section 16-3)

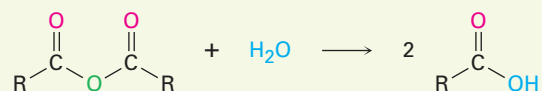
(a) Conversion into acid chlorides



(b) Conversion into esters**(c) Conversion into amides****(d) Reduction to yield primary alcohols****2. Reactions of acid chlorides (Section 16-4)****(a) Hydrolysis to yield acids****(b) Reaction with carboxylates to yield anhydrides****(c) Alcoholysis to yield esters****(d) Aminolysis to yield amides****(e) Lithium diorganocopper reaction to yield ketones**

3. Reactions of acid anhydrides (Section 16-5)

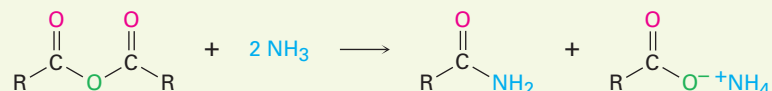
(a) Hydrolysis to yield acids



(b) Alcoholysis to yield esters

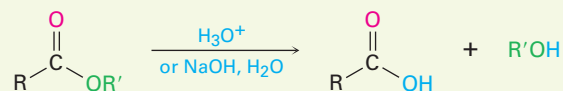


(c) Aminolysis to yield amides

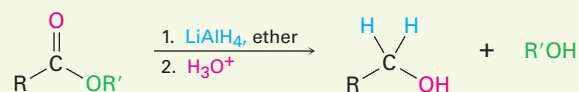


4. Reactions of esters and lactones (Section 16-6)

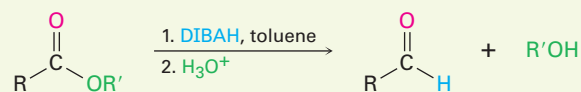
(a) Hydrolysis to yield acids



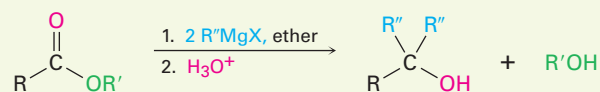
(b) Reduction to yield primary alcohols



(c) Partial reduction to yield aldehydes

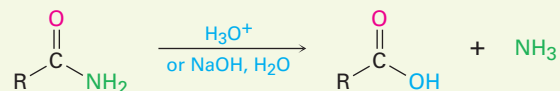


(d) Grignard reaction to yield tertiary alcohols

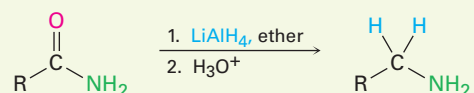


5. Reactions of amides (Section 16-7)

(a) Hydrolysis to yield acids



(b) Reduction to yield amines



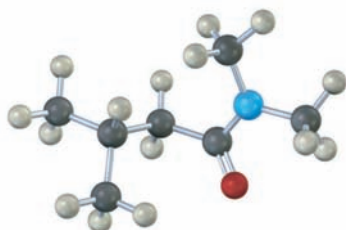
EXERCISES

VISUALIZING CHEMISTRY

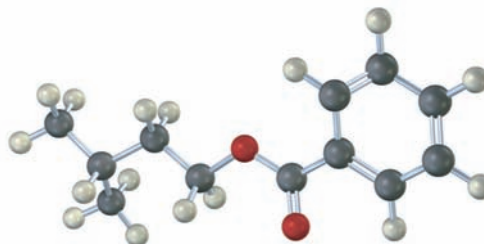
(Problems 16.1–16.26 appear within the chapter.)

16.27 Name the following compounds:

(a)

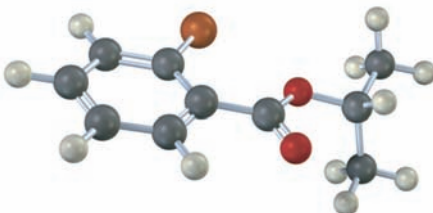


(b)

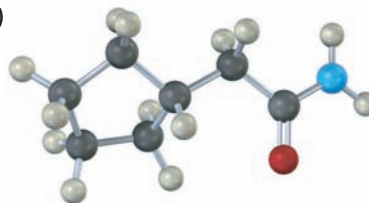


16.28 How would you prepare the following compounds starting with an appropriate carboxylic acid and any other reagents needed? (Red-brown = Br.)

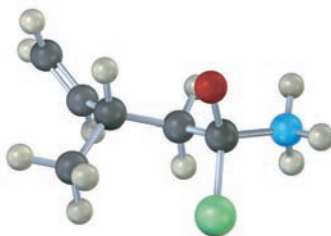
(a)



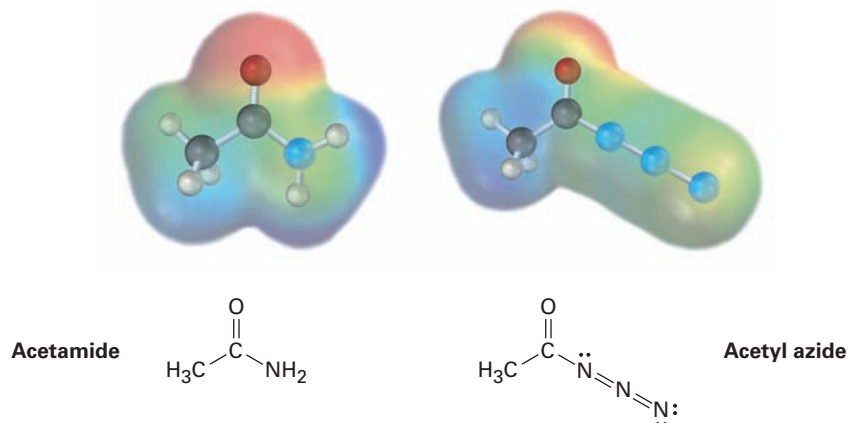
(b)



16.29 The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (green = Cl).



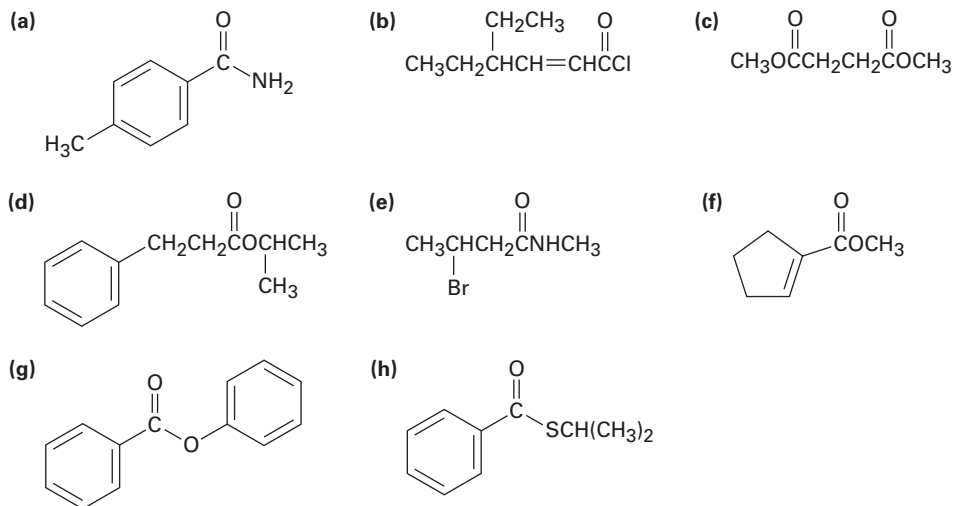
- 16.30** Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.



ADDITIONAL PROBLEMS

Naming Carboxylic Acid Derivatives

- 16.31** Give IUPAC names for the following compounds:



- 16.32** Draw structures corresponding to the following names:

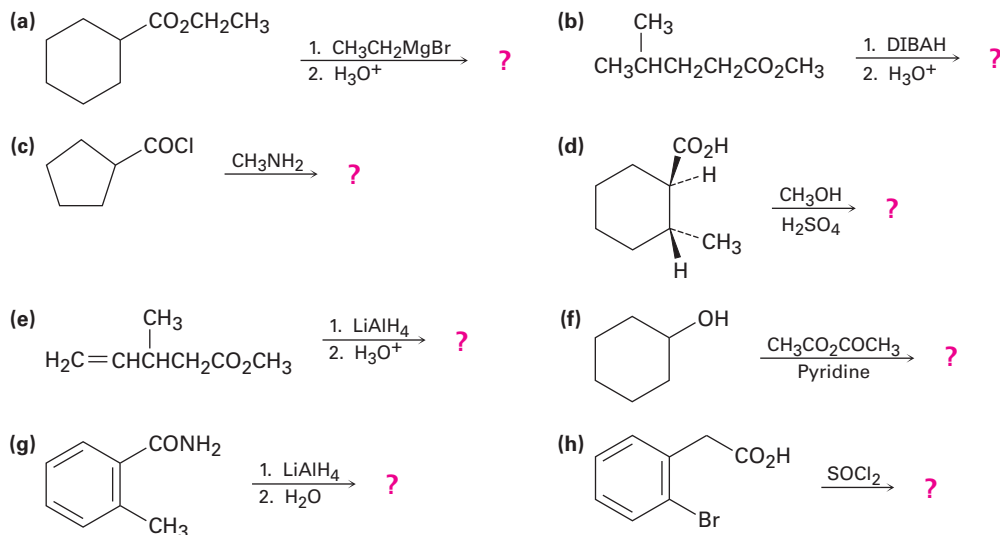
- (a) *p*-Bromophenylacetamide
 (b) *m*-Benzoylbenzamide
 (c) 2,2-Dimethylhexanamide
 (d) Cyclohexyl cyclohexanecarboxylate
 (e) Ethyl cyclobut-2-enecarboxylate
 (f) Succinic anhydride

16.33 Draw and name compounds that meet the following descriptions:

- (a) Three thioesters having the formula $C_6H_{10}OS$
 (b) Three amides having the formula $C_7H_{11}NO$

Nucleophilic Acyl Substitution Reactions

16.34 Predict the product(s) of the following reactions:



16.35 Predict the product, if any, of reaction between methyl acetate and the following reagents:

- (a) $LiAlH_4$, then H_3O^+ (b) CH_3MgBr , then H_3O^+
 (c) $NaOH$, H_2O (d) Aniline

16.36 Answer Problem 16.35 for reaction of the listed reagents with propanamide.

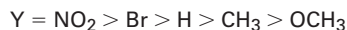
16.37 How might you prepare the following compounds from butanoic acid?

- (a) Butan-1-ol (b) Butanal (c) 1-Bromobutane
 (d) Butyl acetate (e) Pentanenitrile (f) *N*-Methylpentanamide

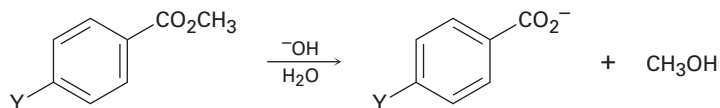
16.38 Predict the product, if any, of reaction between propanoyl chloride and the following reagents:

- (a) $Li(Ph)_2Cu$ in ether (b) $LiAlH_4$, then H_3O^+
 (c) CH_3MgBr , then H_3O^+ (d) H_3O^+
 (e) Cyclohexanol (f) Aniline
 (g) $CH_3CO_2^- + Na$

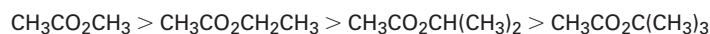
- 16.39** What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, $\text{CH}_3\text{OCO}_2\text{CH}_3$?
- 16.40** The following reactivity order has been found for the saponification of *p*-substituted methyl benzoates:



How can you explain this reactivity order? Where would you expect $Y = \text{CHO}$ and $Y = \text{NH}_2$ to be in the reactivity list?



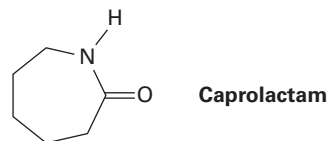
- 16.41** The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH. Explain.



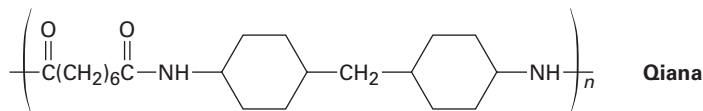
- 16.42** We said in Section 16-6 that mechanistic studies on ester hydrolysis have been carried out using ethyl propanoate labeled with ^{18}O in the ether-like oxygen. Assuming that ^{18}O -labeled acetic acid is your only source of isotopic oxygen, propose a synthesis of the labeled ethyl propanoate.
- 16.43** Methyl trifluoroacetate, $\text{CF}_3\text{CO}_2\text{CH}_3$, is more reactive than methyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_3$, in nucleophilic acyl substitution reactions. Explain.

Step-Growth Polymers

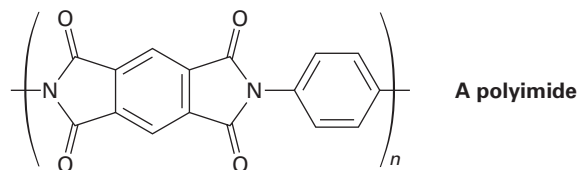
- 16.44** The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



- 16.45** *Qiana*, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of *Qiana*?

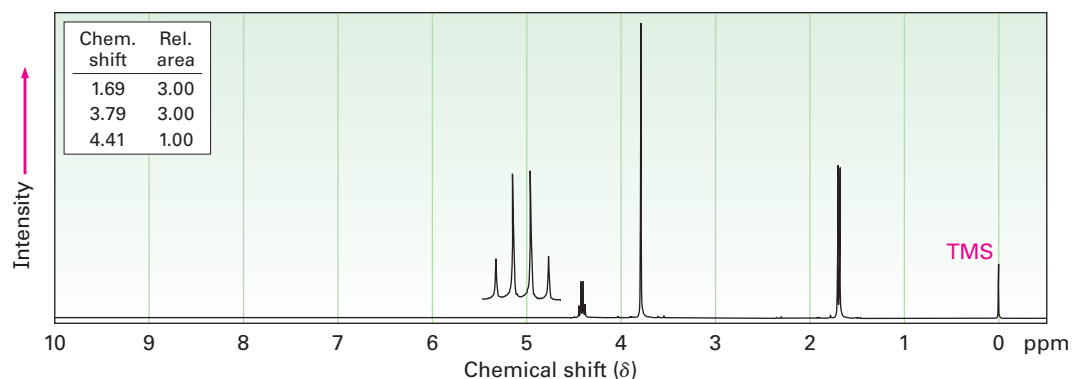
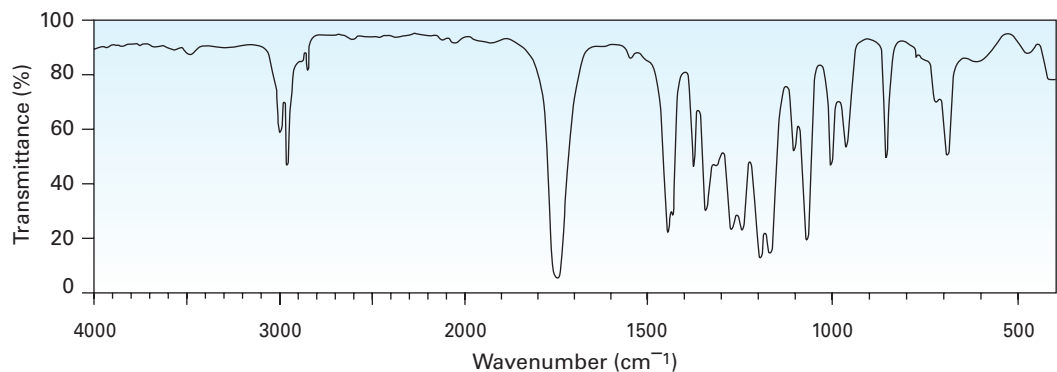


- 16.46** Polyimides having the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 16.45.)



Spectroscopy of Carboxylic Acid Derivatives

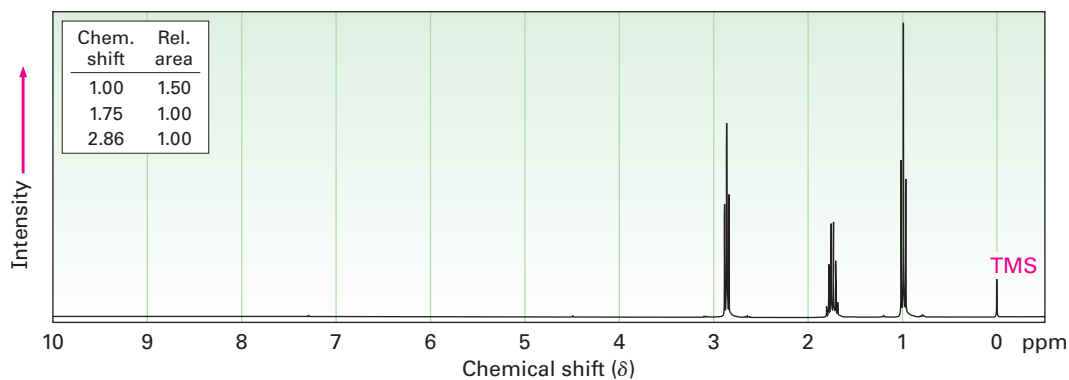
- 16.47** How would you distinguish spectroscopically between the following isomer pairs? Tell what differences you would expect to see.
- N*-Methylpropanamide and *N,N*-dimethylacetamide
 - 5-Hydroxypentanenitrile and cyclobutanecarboxamide
 - 4-Chlorobutanoic acid and 3-methoxypropanoyl chloride
 - Ethyl propanoate and propyl acetate
- 16.48** Propose a structure for a compound, $C_4H_7ClO_2$, that has the following IR and 1H NMR spectra:



16.49 Assign structures to compounds with the following ^1H NMR spectra:

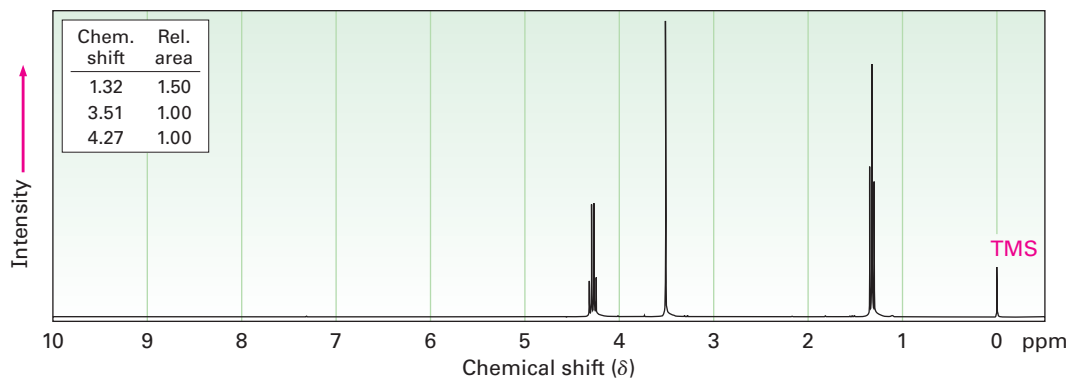
(a) $\text{C}_4\text{H}_7\text{ClO}$

IR: 1810 cm^{-1}



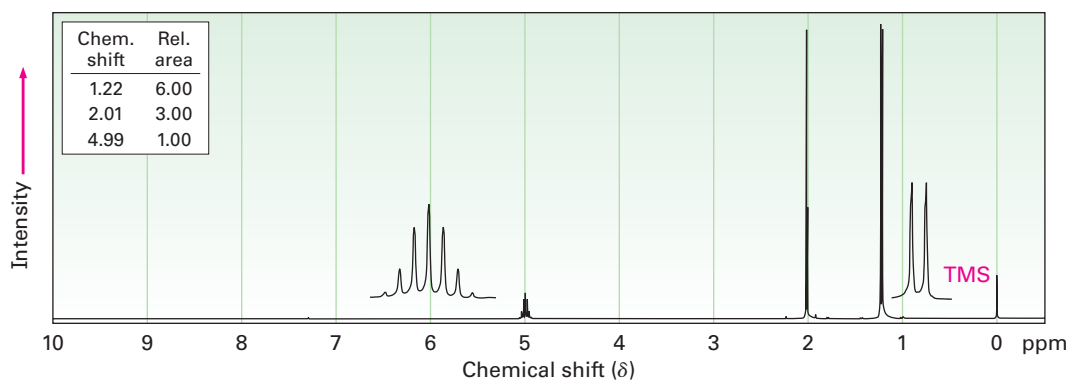
(b) $\text{C}_5\text{H}_7\text{NO}_2$

IR: $2250, 1735\text{ cm}^{-1}$



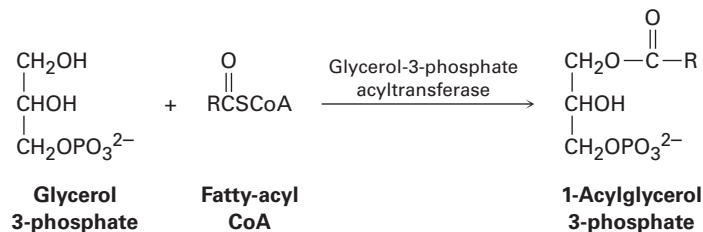
(c) $\text{C}_5\text{H}_{10}\text{O}_2$

IR: 1735 cm^{-1}

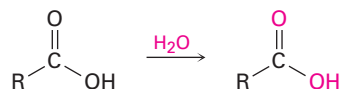


General Problems

- 16.50** Treatment of 5-aminopentanoic acid with DCC (dicyclohexylcarbodiimide) yields a lactam. Show the structure of the product and the mechanism of the reaction.
- 16.51** Explain the observation that attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol and HCl is unsuccessful. No ester is obtained, and the acid is recovered unchanged. What alternative method of esterification might be successful?
- 16.52** Draw the structure of the polymer you would expect to obtain from reaction of dimethyl terephthalate with a triol such as glycerol. What structural feature would this new polymer have that was not present in Dacron? How do you think this new feature might affect the properties of the polymer?
- 16.53** Fats are biosynthesized from glycerol 3-phosphate and fatty-acyl CoA by a reaction sequence that begins with the following step. Show the mechanism of the reaction.



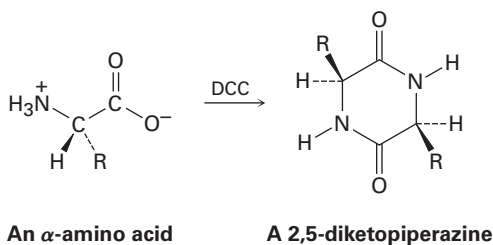
- 16.54** When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into *both* oxygen atoms of the carboxylic acid. Explain.



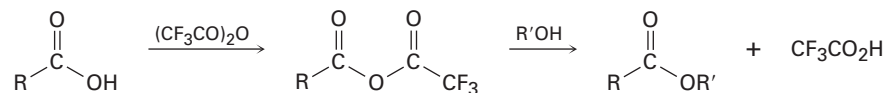
- 16.55** When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.
- 16.56** *tert*-Butoxycarbonyl azide, a reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.



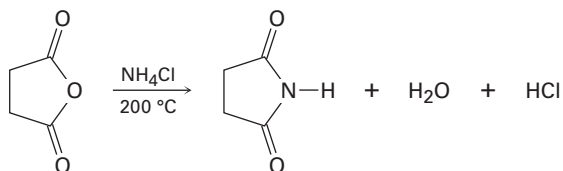
- 16.57** Treatment of an α -amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.



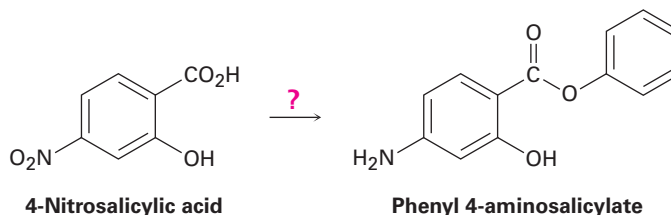
- 16.58** Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester:



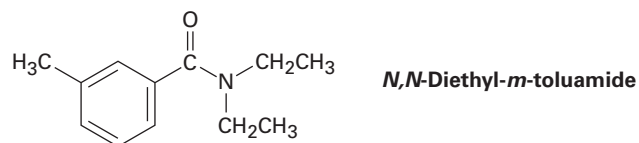
- (a) Propose a mechanism for formation of the unsymmetrical anhydride.
 (b) Why is the unsymmetrical anhydride unusually reactive?
 (c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?
- 16.59** Succinic anhydride yields succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?



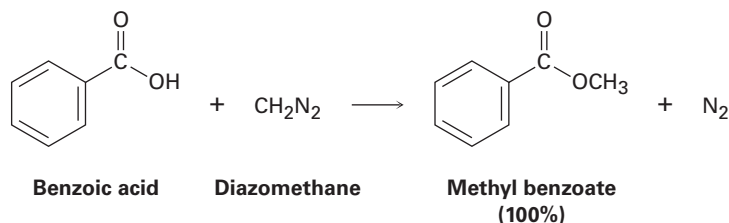
- 16.60** Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



- 16.61** *N,N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize DEET from *m*-bromotoluene?



- 16.62** One frequently used method for preparing methyl esters is by reaction of carboxylic acids with diazomethane, CH_2N_2 :

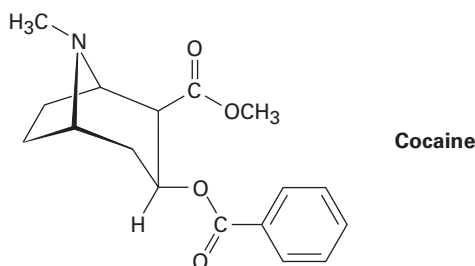


The reaction occurs in two steps: (1) protonation of diazomethane by the carboxylic acid to yield methyl diazonium ion, CH_3N_2^+ , plus a carboxylate ion, and (2) reaction of the carboxylate ion with CH_3N_2^+ .

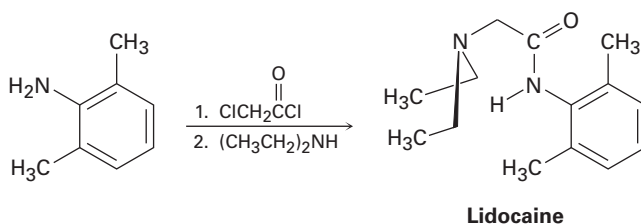
(a) Draw two resonance structures of diazomethane, and account for step 1.

(b) What kind of reaction occurs in step 2?

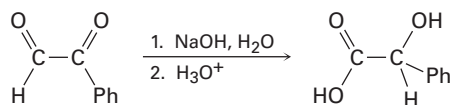
- 16.63** Yesterday's drug can be today's poison. Cocaine enjoyed a much better reputation 100 years ago, when it was used as a stimulant in many products (including Coca-Cola) as well as in drops to treat toothaches and depression. What three molecules are produced by hydrolysis of cocaine?



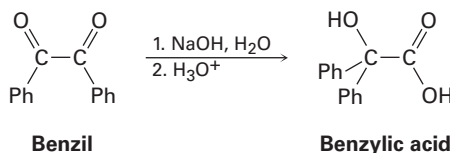
- 16.64** Cocaine's addictive properties led researchers to look for less addictive alternatives to relieve pain. Lidocaine, for instance, has many of the structural features of cocaine (Problem 16.63) but doesn't have the same risk. Lidocaine is prepared by the reaction sequence shown. Indicate the type of reaction in each step, and draw a mechanism.



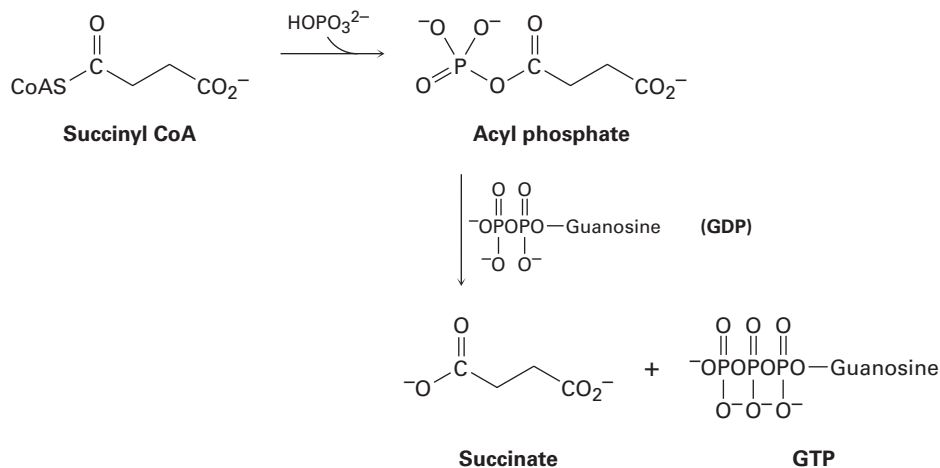
- 16.65** The following conversion takes place by typical carbonyl-group reactions (Ph = phenyl). Propose a mechanism.



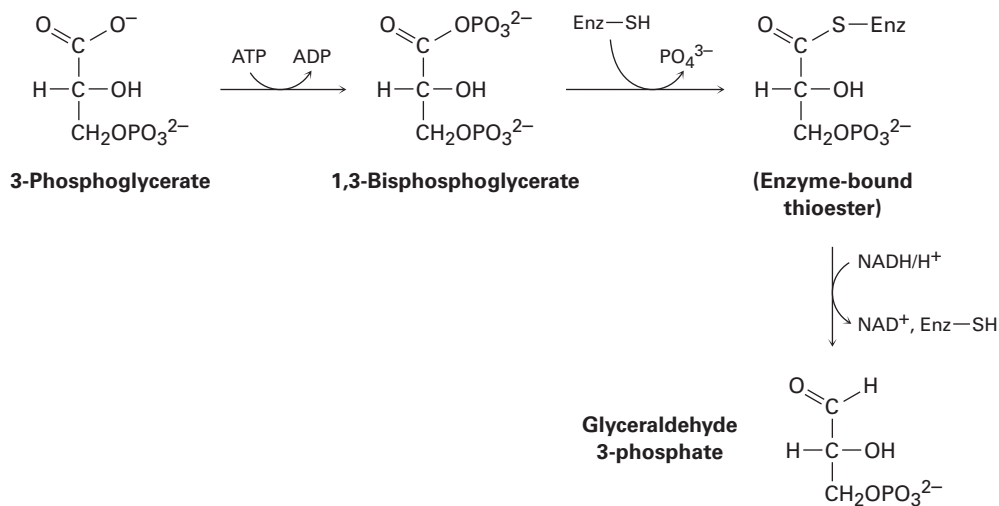
- 16.66** The following reaction, called the *benzylic acid rearrangement*, takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).



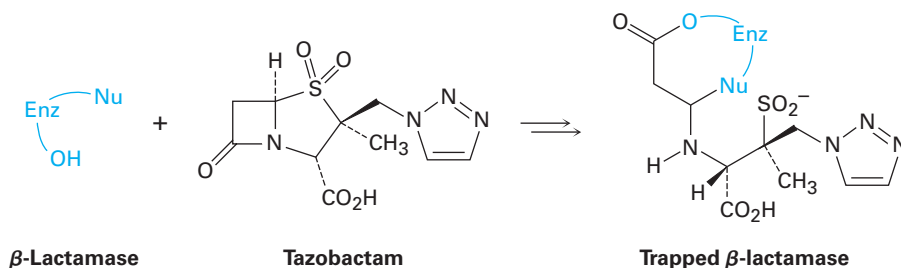
16.67 The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine diphosphate (GDP, a relative of ADP) to give succinate and guanosine triphosphate (GTP, a relative of ATP). Suggest mechanisms for both steps.



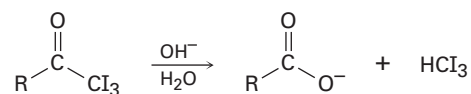
16.68 One step in the *gluconeogenesis* pathway for the biosynthesis of glucose is the partial reduction of 3-phosphoglycerate to give glyceraldehyde 3-phosphate. The process occurs by phosphorylation with ATP to give 1,3-bisphosphoglycerate, reaction with a thiol group on the enzyme to give an enzyme-bound thioester, and reduction with NADH. Suggest mechanisms for all three reactions.



- 16.69** Penicillins and other β -lactam antibiotics (see the *Something Extra* in this chapter) typically develop a resistance to bacteria due to bacterial synthesis of β -lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the β -lactamase by trapping it, thereby preventing resistance from developing.

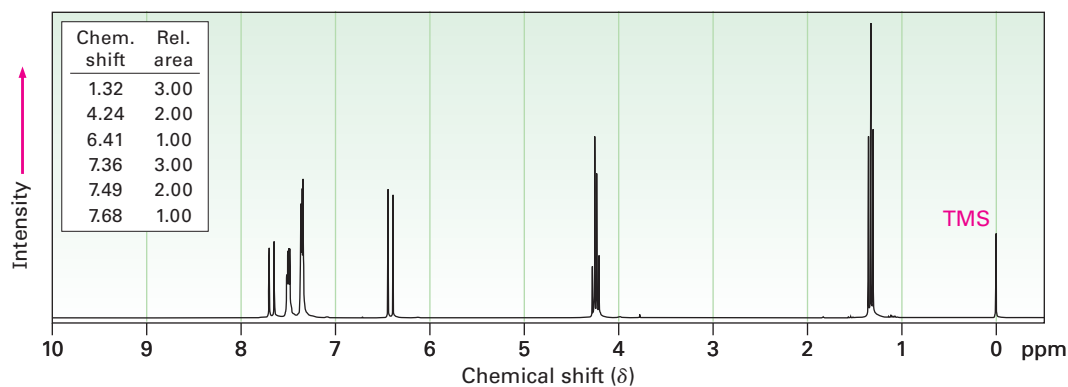


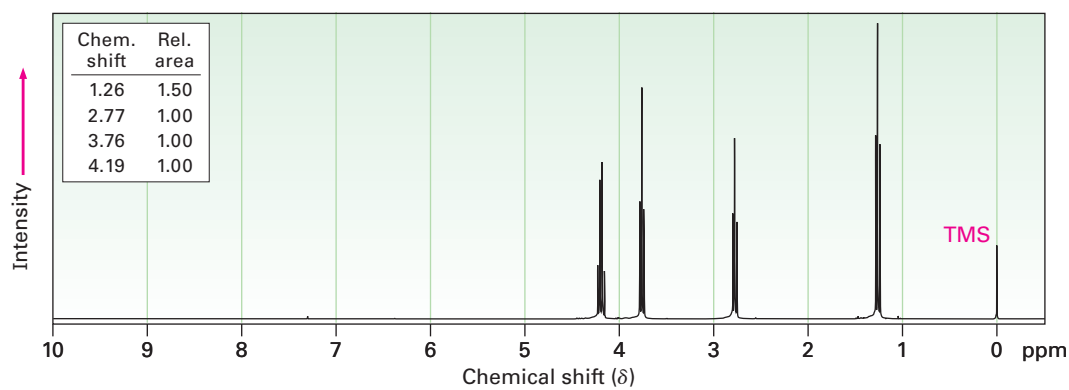
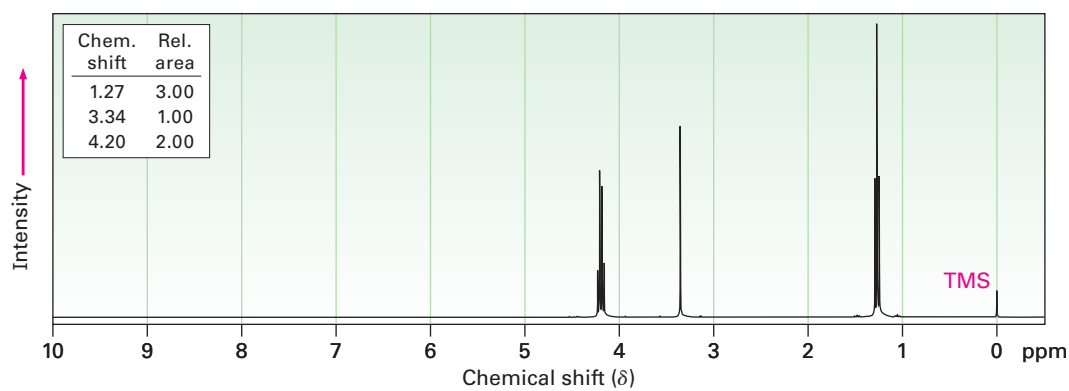
- (a) The first step in trapping is reaction of a hydroxyl group on the β -lactamase to open the β -lactam ring of tazobactam. Show the mechanism.
- (b) The second step is opening of the sulfur-containing ring in tazobactam to give an acyclic iminium ion intermediate. Show the mechanism.
- (c) Cyclization of the iminium ion intermediate gives the trapped β -lactamase product. Show the mechanism.
- 16.70** In the *iodoform reaction*, a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism.



- 16.71** Assign structures to compounds with the following ^1H NMR spectra:

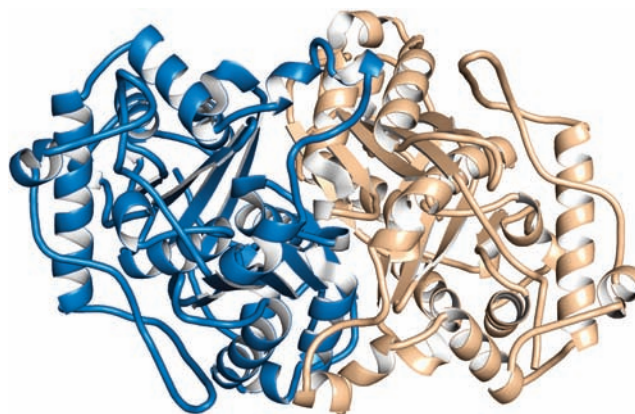
- (a) $\text{C}_{11}\text{H}_{12}\text{O}_2$
IR: 1710 cm^{-1}



(b) $C_5H_9ClO_2$ IR: 1735 cm^{-1} **(c)** $C_7H_{12}O_4$ IR: 1735 cm^{-1} 

Carbonyl Alpha-Substitution and Condensation Reactions

17



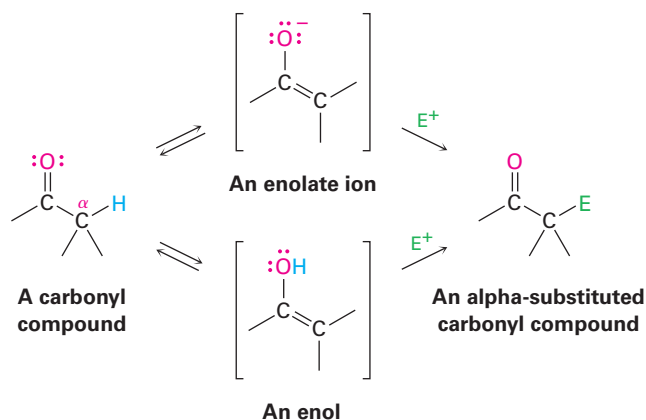
β -Ketoacyl-CoA thiolase catalyzes the cleavage of a β -ketoacyl CoA to give acetyl CoA, the final step in the β -oxidation cycle of fatty-acid metabolism.

WHY THIS CHAPTER?

As with nucleophilic additions and nucleophilic acyl substitutions, many laboratory schemes, pharmaceutical syntheses, and biochemical pathways make frequent use of carbonyl α -substitution reactions. In fact, practically every biosynthetic pathway for building up larger molecules from smaller precursors uses carbonyl condensation reactions for the purpose. We'll see how and why these reactions occur in this chapter.

We said in the *Preview of Carbonyl Chemistry* that much of the chemistry of carbonyl compounds can be explained by just four fundamental reaction types: nucleophilic additions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Having now studied the first two of these reactions, we'll look in this chapter at the remaining two major carbonyl-group processes—the **α -substitution reaction** and the **carbonyl condensation reaction**.

Alpha-substitution reactions occur at the position next to the carbonyl group—the α position—and involve the substitution of an α hydrogen atom by an electrophile, E or E^+ , through either an enol or enolate ion intermediate.



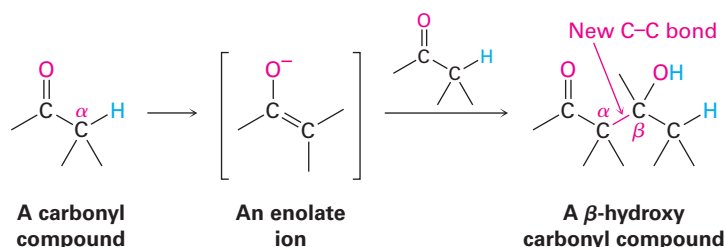
CONTENTS

- 17-1 Keto-Enol Tautomerism
- 17-2 Reactivity of Enols: α -Substitution Reactions
- 17-3 Alpha Bromination of Carboxylic Acids
- 17-4 Acidity of α Hydrogen Atoms: Enolate Ion Formation
- 17-5 Alkylation of Enolate Ions
- 17-6 Carbonyl Condensations: The Aldol Reaction
- 17-7 Dehydration of Aldol Products
- 17-8 Intramolecular Aldol Reactions
- 17-9 The Claisen Condensation Reaction
- 17-10 Intramolecular Claisen Condensations: The Dieckmann Cyclization
- 17-11 Conjugate Carbonyl Additions: The Michael Reaction
- 17-12 Carbonyl Condensations with Enamines: The Stork Reaction
- 17-13 Biological Carbonyl Condensation Reactions

SOMETHING EXTRA
Barbiturates

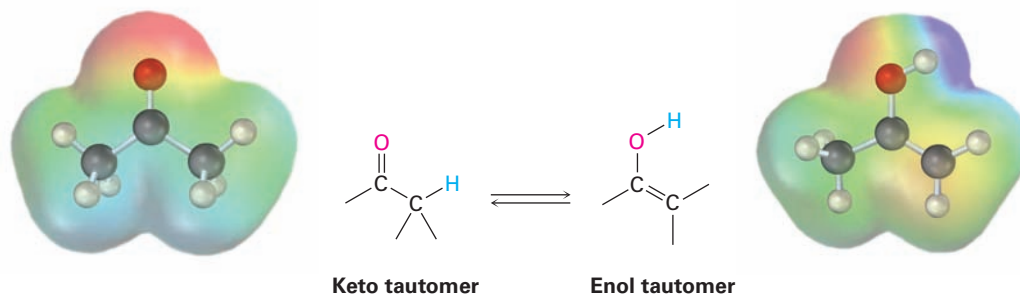


Carbonyl condensation reactions take place between two carbonyl partners and involve a *combination* of α -substitution and nucleophilic addition steps. One partner is converted into its enolate ion and undergoes an α -substitution reaction when it carries out a nucleophilic addition to the second partner, giving a β -hydroxy carbonyl compound as product.



17-1 Keto–Enol Tautomerism

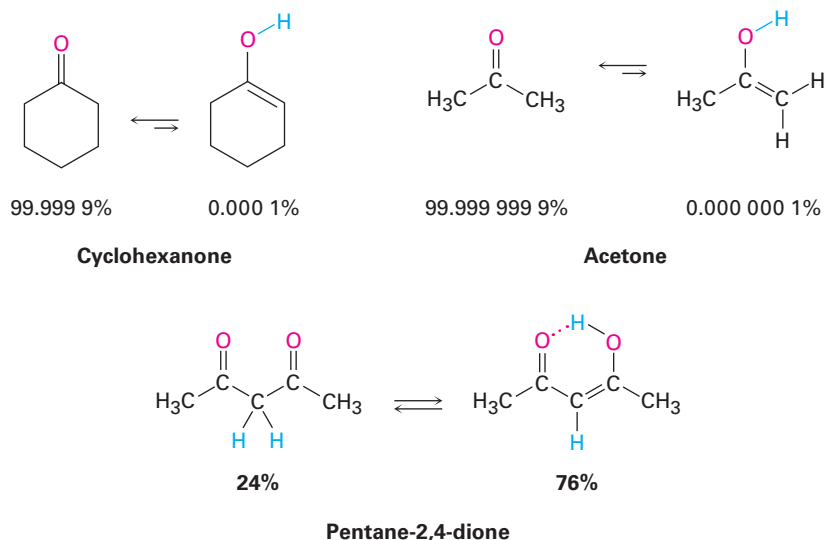
A carbonyl compound with a hydrogen atom on its α carbon is in an equilibrium with its corresponding **enol** isomer (Section 8-15). This spontaneous interconversion between two isomers, usually with the change in position of a hydrogen, is called *tautomerism*, from the Greek *tauto*, meaning “the same,” and *meros*, meaning “part.” The individual keto and enol isomers are called **tautomers**.



Note the difference between tautomers and resonance forms, which were discussed in Section 2-5: tautomers are constitutional isomers—different compounds with different structures—while resonance forms are different representations of a single compound. Tautomers have their *atoms* arranged differently, while resonance forms differ only in the position of their π and nonbonding *electrons*.

Most monocarbonyl compounds exist almost entirely in their keto form at equilibrium, and it's usually difficult to isolate the pure enol. Cyclohexanone, for example, contains only about 0.0001% of its enol tautomer at room temperature. The percentage of enol tautomer is even less for carboxylic acids, esters, and amides. Only when the enol can be stabilized by conjugation or by

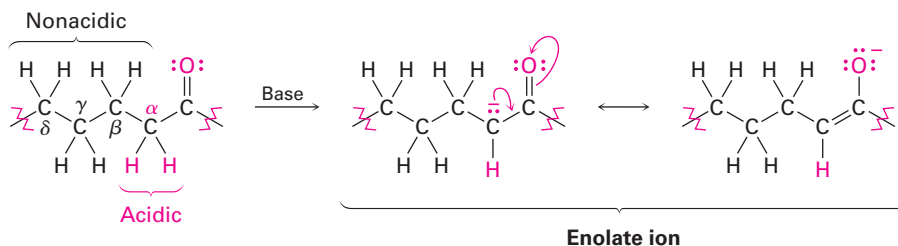
intramolecular hydrogen bond formation does the enol sometimes predominate. Thus, pentane-2,4-dione is about 76% enol tautomer. Even though enols are present only to a small extent at equilibrium, they are nevertheless responsible for much of the chemistry of carbonyl compounds because they are so reactive.



Keto-enol tautomerism of carbonyl compounds is catalyzed by both acids and bases. Acid-catalyzed enol formation (FIGURE 17.1a) occurs by protonation of the carbonyl oxygen atom to give an intermediate cation that loses H^+ from its α carbon to yield a neutral enol. This proton loss from the cation intermediate is similar to what occurs during an E1 reaction when a carbocation loses H^+ to form an alkene (Section 12-14).

Base-catalyzed enol formation (FIGURE 17.1b) occurs because the presence of a carbonyl group makes the hydrogens on the α carbon weakly acidic. Thus, a carbonyl compound can act as an acid and donate one of its α hydrogens to a sufficiently strong base. The resultant resonance-stabilized anion, an **enolate ion**, is then protonated to yield a neutral compound. If protonation of the enolate ion takes place on the α carbon, the keto tautomer is regenerated and no net change occurs. If, however, protonation takes place on the oxygen atom, then an enol tautomer is formed.

Note that only the hydrogens on the α position of carbonyl compounds are acidic. Hydrogens at β , γ , δ , and so on, aren't acidic and can't be removed by base because the resulting anions can't be resonance-stabilized by the carbonyl group.



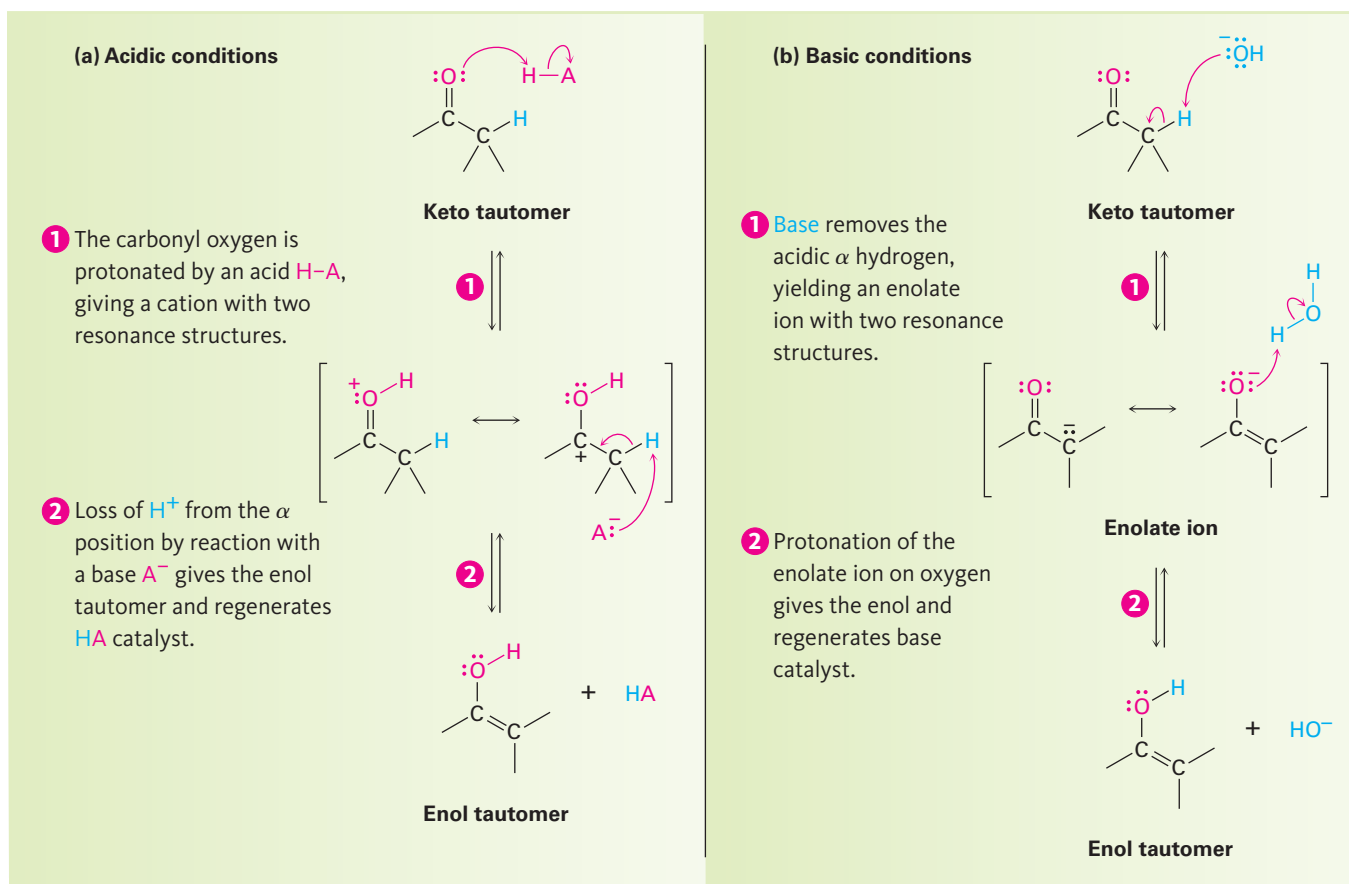


FIGURE 17.1 Mechanism of enol formation under both acid-catalyzed and base-catalyzed conditions. **(a)** Acid catalysis involves **1** initial protonation of the carbonyl oxygen followed by **2** removal of H^+ from the α position. **(b)** Base catalysis involves **1** initial deprotonation of the α position to give an enolate ion, followed by **2** reprotonation on oxygen.

PROBLEM 17.1

Draw structures for the enol tautomers of the following compounds:

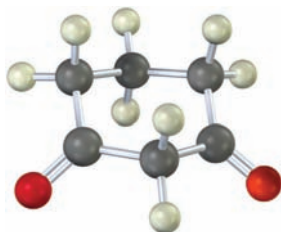
- (a)** Cyclopentanone **(b)** Methyl thioacetate **(c)** Ethyl acetate
(d) Propanal **(e)** Acetic acid **(f)** Phenylacetone

PROBLEM 17.2

How many acidic hydrogens does each of the molecules listed in Problem 17.1 have? Identify them.

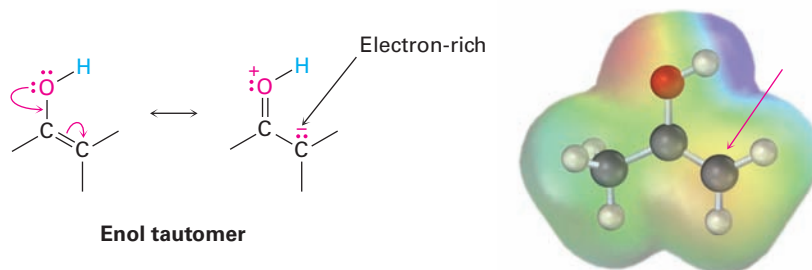
PROBLEM 17.3

Draw structures for all mono-enol forms of the adjacent molecule. Which would you expect to be most stable? Explain.



17-2 Reactivity of Enols: α -Substitution Reactions

What kind of chemistry do enols have? Because their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in much the same way that alkenes do. But because of resonance electron donation of a lone-pair of electrons on the neighboring oxygen, enols are more electron-rich and correspondingly more reactive than alkenes. Notice in the following electrostatic potential map of propenol [$\text{CH}_3\text{C}(\text{OH})=\text{CH}_2$] how there is a substantial amount of electron density (yellow/red) on the α carbon.



When an *alkene* reacts with an electrophile, E^+ , initial addition gives an intermediate cation and subsequent reaction with a nucleophile such as a halide ion yields an addition product (Section 7-6). When an *enol* reacts with an electrophile, however, only the initial addition step is the same (FIGURE 17.2). Instead of reacting with a nucleophile to give an addition product, the intermediate cation loses the $-\text{OH}$ proton to give an α -substituted carbonyl compound.

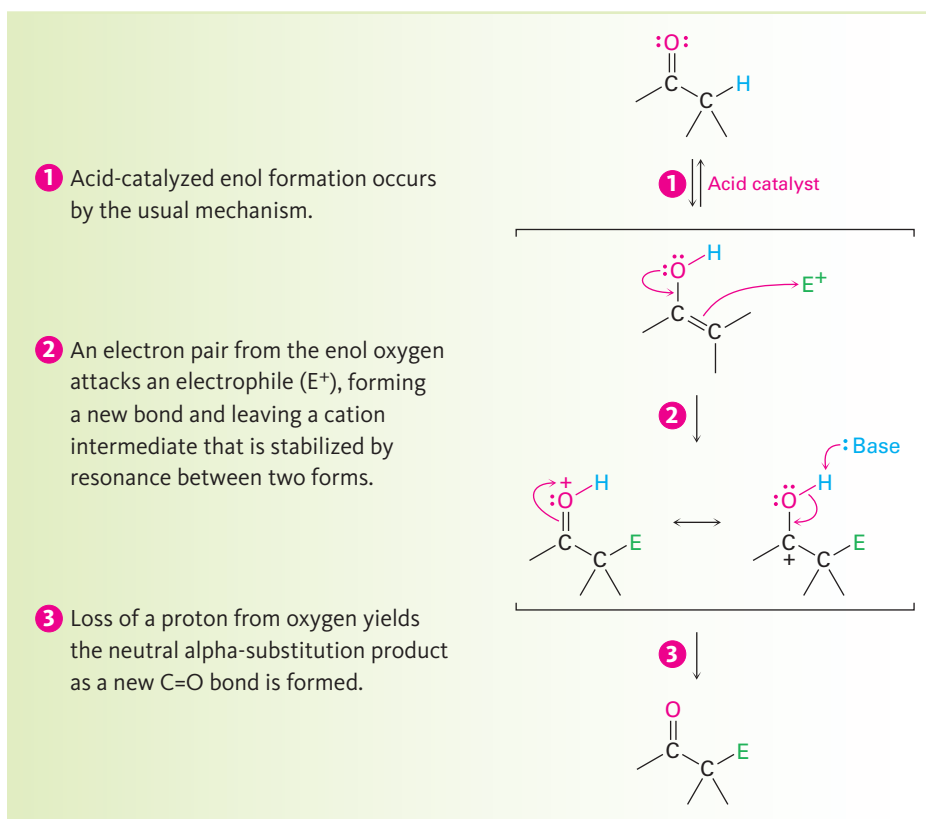


FIGURE 17.2 General mechanism of a carbonyl α -substitution reaction. In step 1 the initially formed cation loses H^+ to regenerate a carbonyl compound.

© John McMurry

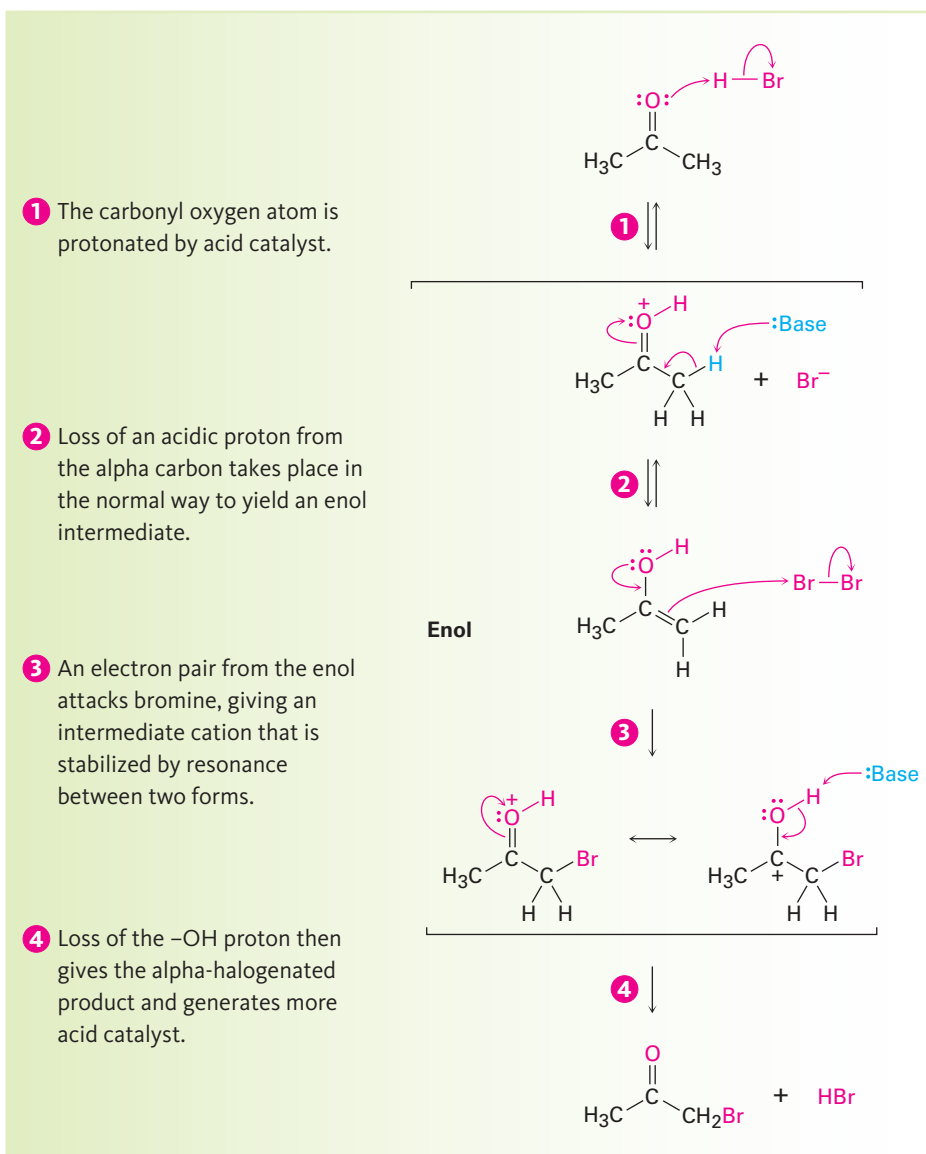
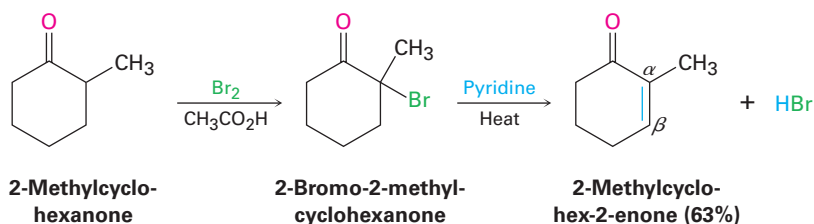


FIGURE 17.3 Mechanism of the acid-catalyzed bromination of acetone.

the more highly substituted α position because the more highly substituted enol is favored over the less highly substituted one (Section 7-5).

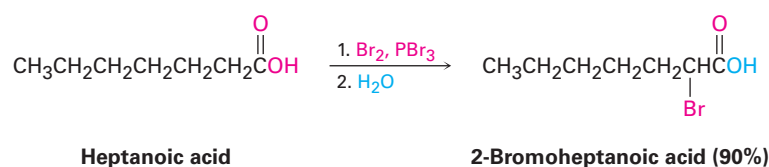


PROBLEM 17.4

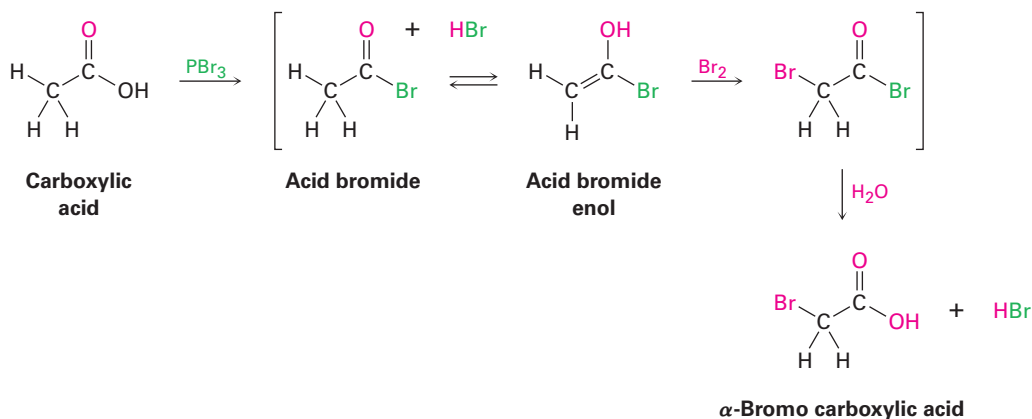
Show how you might prepare pent-1-en-3-one from pentan-3-one.

17-3 Alpha Bromination of Carboxylic Acids

The α bromination of carbonyl compounds by Br_2 in acetic acid is limited to aldehydes and ketones because acids, esters, and amides don't enolize to a sufficient extent. Carboxylic acids, however, can be α brominated by a mixture of Br_2 and PBr_3 in the *Hell-Volhard-Zelinskii (HVZ) reaction*.

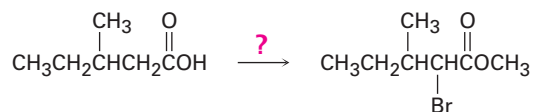


The Hell-Volhard-Zelinskii reaction is a bit more complex than it looks and actually involves α substitution of an acid bromide enol rather than a carboxylic acid enol. The process begins with reaction of the carboxylic acid with PBr_3 to form an acid bromide plus HBr (Section 16-3). The HBr then catalyzes enolization of the acid bromide, and the resultant enol reacts with Br_2 in an α -substitution reaction to give an α -bromo acid bromide. Addition of water hydrolyzes the acid bromide in a nucleophilic acyl substitution reaction and yields the α -bromo carboxylic acid product.

**PROBLEM 17.5**

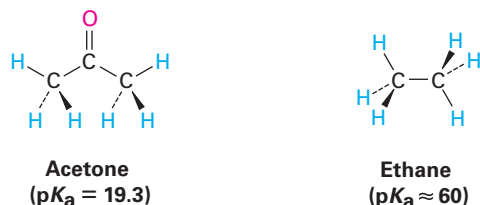
If methanol rather than water is added at the end of a Hell-Volhard-Zelinskii reaction, an ester rather than an acid is produced. Show how you could carry

out the following transformation, and propose a mechanism for the ester-forming step.



17-4 Acidity of α Hydrogen Atoms: Enolate Ion Formation

As noted in Section 17-1, a hydrogen on the α position of a carbonyl compound is weakly acidic and can be removed by a strong base to yield an enolate ion. In comparing acetone ($\text{p}K_{\text{a}} = 19.3$) with ethane ($\text{p}K_{\text{a}} \approx 60$), for instance, the presence of a neighboring carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40} .



Proton abstraction from a carbonyl compound occurs when the α C–H bond is oriented roughly parallel to the p orbitals of the carbonyl group. The α carbon atom of the enolate ion is sp^2 -hybridized and has a p orbital that overlaps the neighboring carbonyl p orbitals. Thus, the negative charge is shared by the electronegative oxygen atom, and the enolate ion is stabilized by resonance (FIGURE 17.4).

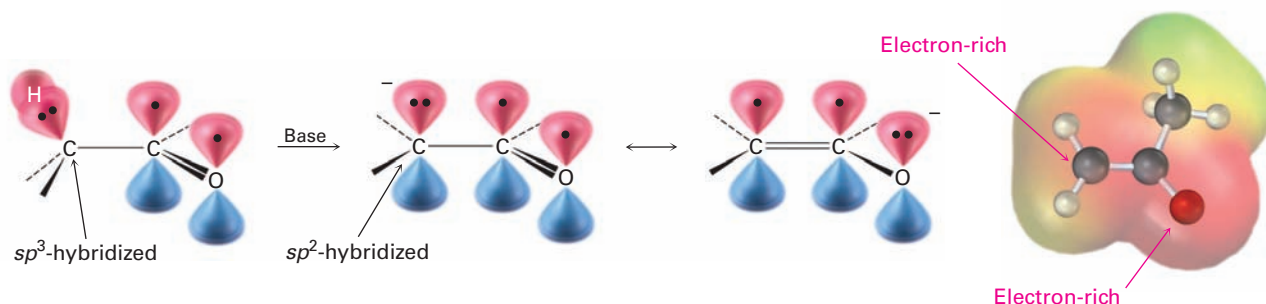
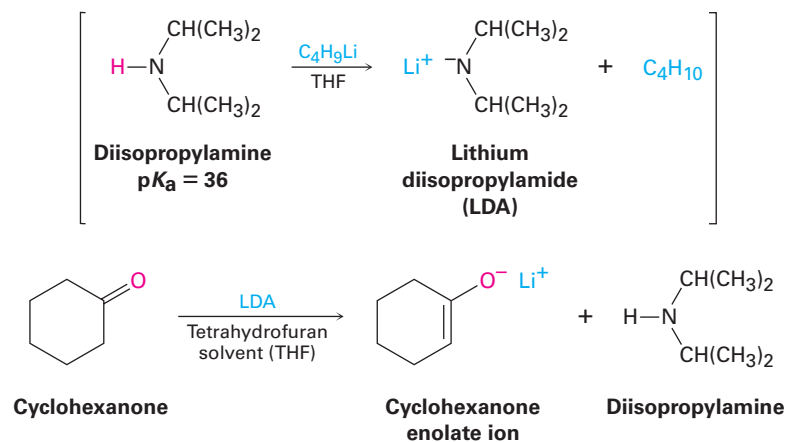


FIGURE 17.4 Mechanism of enolate ion formation by abstraction of an α proton from a carbonyl compound. The enolate ion is stabilized by resonance, and the **negative charge** is shared by the oxygen and the α carbon atom, as indicated by the electrostatic potential map.

Because carbonyl compounds are only weakly acidic, a strong base is needed for enolate ion formation. If an alkoxide ion, such as sodium ethoxide,

is used as base, deprotonation takes place only to the extent of about 0.1% because acetone is a weaker acid than ethanol ($pK_a = 16$). If, however, a more powerful base is used, then a carbonyl compound is completely converted into its enolate ion.

In practice, the strong base lithium diisopropylamide [$\text{LiN}(i\text{-C}_3\text{H}_7)_2$, abbreviated LDA] is commonly used for making enolate ions. As the lithium salt of the weak acid diisopropylamine, $pK_a = 36$, LDA can readily deprotonate most carbonyl compounds. It is easily prepared by reaction of butyllithium with diisopropylamine and is soluble in organic solvents because of its two alkyl groups.

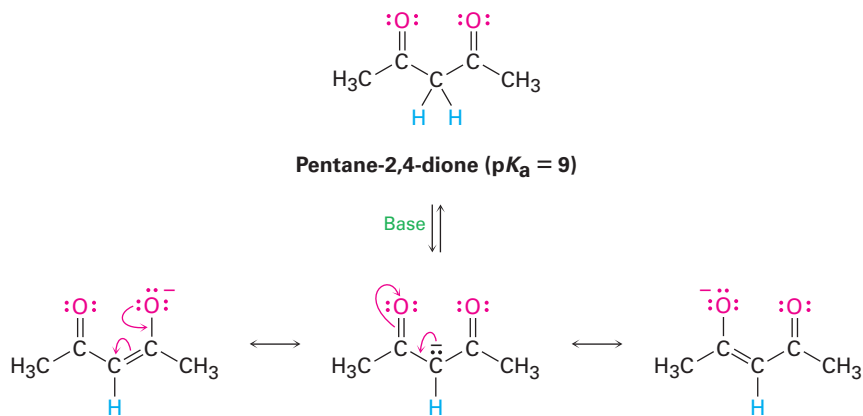


Many types of carbonyl compounds, including aldehydes, ketones, esters, thioesters, acids, and amides, can be converted into enolate ions by reaction with LDA. TABLE 17.1 lists the approximate pK_a values of different types of carbonyl compounds and shows how these values compare to other acidic substances we've seen. Note that nitriles are also acidic and can be converted into enolate-like anions.

TABLE 17.1 Acidity Constants for Some Organic Compounds

Functional group	Example	pK_a	Functional group	Example	pK_a
Carboxylic acid	CH_3COH	5	Aldehyde	CH_3CH	17
1,3-Diketone	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{CH}_3$	9	Ketone	$\text{CH}_3\text{C}(\text{O})\text{CH}_3$	19
3-Keto ester	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{COCH}_3$	11	Thioester	CH_3CSCH_3	21
1,3-Diester	$\text{CH}_3\text{OC}(\text{O})\text{CH}_2\text{C}(\text{O})\text{CH}_3$	13	Ester	CH_3COCH_3	25
Alcohol	CH_3OH	16	Nitrile	$\text{CH}_3\text{C}\equiv\text{N}$	25
Acid chloride	CH_3COCl	16	<i>N,N</i> -Dialkylamide	$\text{CH}_3\text{CN}(\text{CH}_3)_2$	30
			Dialkylamine	$\text{HN}(i\text{-C}_3\text{H}_7)_2$	36

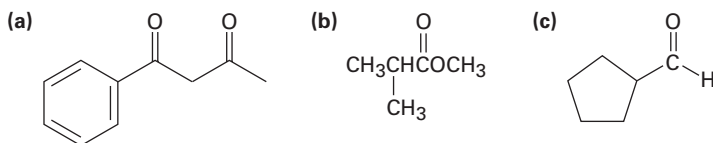
When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced even more. Table 17.1 thus shows that 1,3-diketones (β -diketones), 3-keto esters (β -keto esters), and 1,3-diester (malonic esters) are even more acidic than water. The enolate ions derived from these β -dicarbonyl compounds are stabilized by sharing of the negative charge by both neighboring carbonyl oxygens. The enolate ion of pentane-2,4-dione, for instance, has three resonance forms. Similar resonance forms can be drawn for other doubly stabilized enolate ions.



Identifying Acidic Hydrogens in a Compound

WORKED EXAMPLE 17.1

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

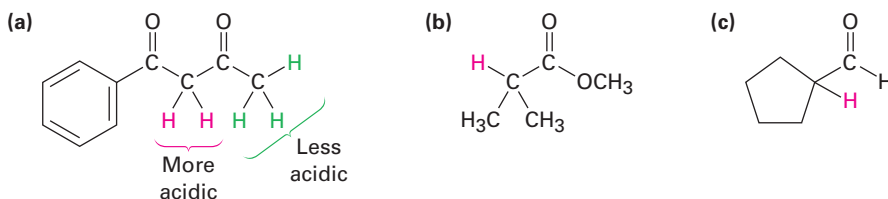


Strategy

Hydrogens on carbon next to a carbonyl group are acidic. In general, a β -dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their $-\text{OH}$ hydrogens.

Solution

The acidity order is (a) > (c) > (b). Acidic hydrogens are shown in red:



PROBLEM 17.6

Identify the most acidic hydrogens in each of the following molecules:

- (a) $\text{CH}_3\text{CH}_2\text{CHO}$ (b) $(\text{CH}_3)_3\text{CCOCH}_3$ (c) $\text{CH}_3\text{CO}_2\text{H}$
 (d) Benzamide (e) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$ (f) $\text{CH}_3\text{CON}(\text{CH}_3)_2$

PROBLEM 17.7

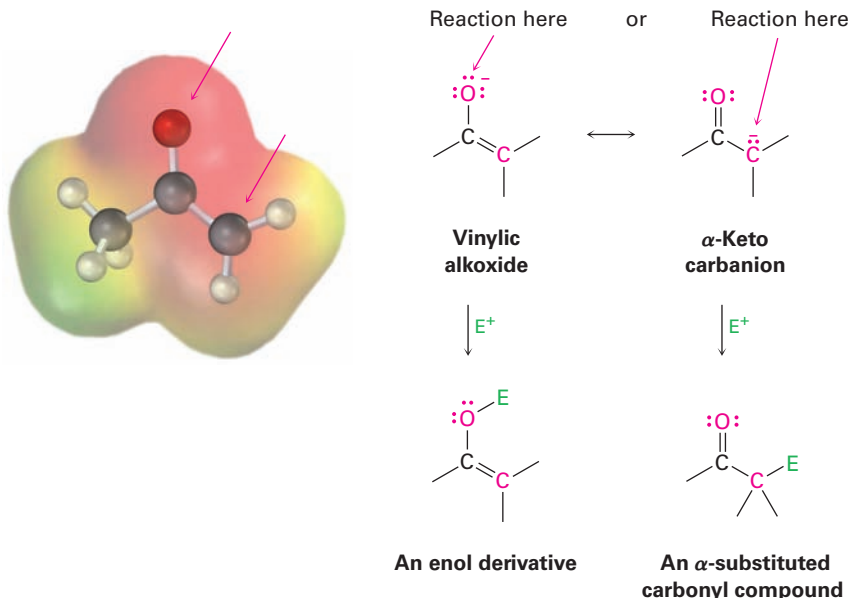
Draw a resonance structure of the acetonitrile anion, $^-\text{CH}_2\text{C}\equiv\text{N}$, and account for the acidity of nitriles.

17-5 Alkylation of Enolate Ions

Enolate ions are more useful than enols for two reasons. First, pure enols can't normally be isolated but are instead generated only as short-lived intermediates in low concentration. By contrast, stable solutions of pure enolate ions are easily prepared from most carbonyl compounds by reaction with a strong base. Second, enolate ions are more reactive than enols and undergo many reactions that enols don't. Whereas enols are neutral, enolate ions are negatively charged, making them much better nucleophiles.

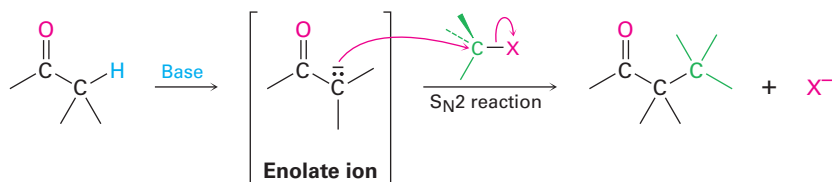
Because they are resonance hybrids of two nonequivalent forms, enolate ions can be looked at either as vinylic alkoxides ($\text{C}=\text{C}-\text{O}^-$) or as α -keto carbanions ($^-\text{C}-\text{C}=\text{O}$). Thus, enolate ions can react with electrophiles either on oxygen or on carbon. Reaction on oxygen yields an enol derivative, while reaction on carbon yields an α -substituted carbonyl compound (FIGURE 17.5). Both kinds of reactivity are known, but reaction on carbon is more common.

FIGURE 17.5 Enolate-ion reactivity. An electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E^+ are possible. Reaction on carbon to yield an α -substituted carbonyl product is more common.

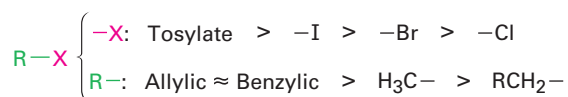


Perhaps the most useful reaction of enolate ions is their alkylation by treatment with an alkyl halide or tosylate (Section 12-7), thereby forming a

new C–C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by backside attack.

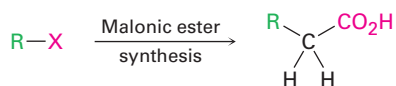


Alkylation reactions are subject to the same constraints that affect all S_N2 reactions (Section 12-8). Thus, the leaving group X in the alkylating agent R–X can be chloride, bromide, iodide, or tosylate. The alkyl group R should be primary or methyl and preferably should be allylic or benzylic. Secondary halides react poorly, and tertiary halides don't react at all because a competing E2 elimination of HX occurs instead. Vinylic and aryl halides are also unreactive because backside approach is sterically prevented.

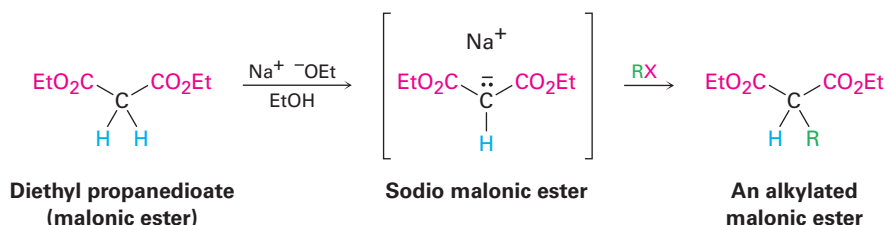


The Malonic Ester Synthesis

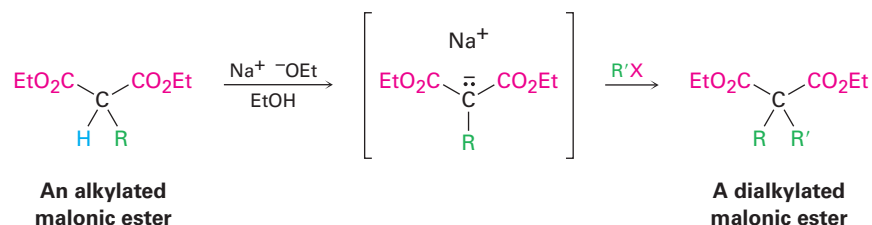
One of the oldest and best known carbonyl alkylation reactions in the laboratory is the **malonic ester synthesis**, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.



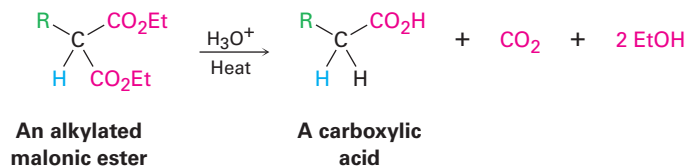
Diethyl propanedioate, commonly called diethyl malonate, or *malonic ester*, is relatively acidic ($pK_a = 13$) because its α hydrogens are flanked by two carbonyl groups. Thus, malonic ester is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol. The enolate ion, in turn, is a good nucleophile that reacts rapidly with an alkyl halide to give an α -substituted malonic ester. Note in the following examples that the abbreviation “Et” is used for an ethyl group, $-\text{CH}_2\text{CH}_3$:



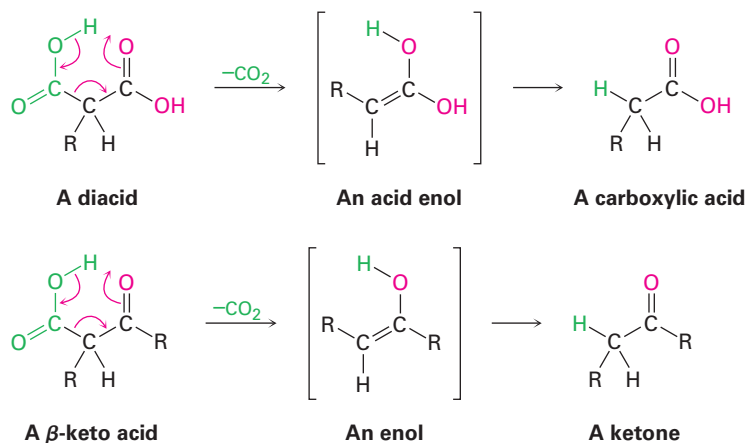
The product of a malonic ester alkylation has one acidic α hydrogen remaining, so the alkylation process can be repeated to yield a dialkylated malonic ester:



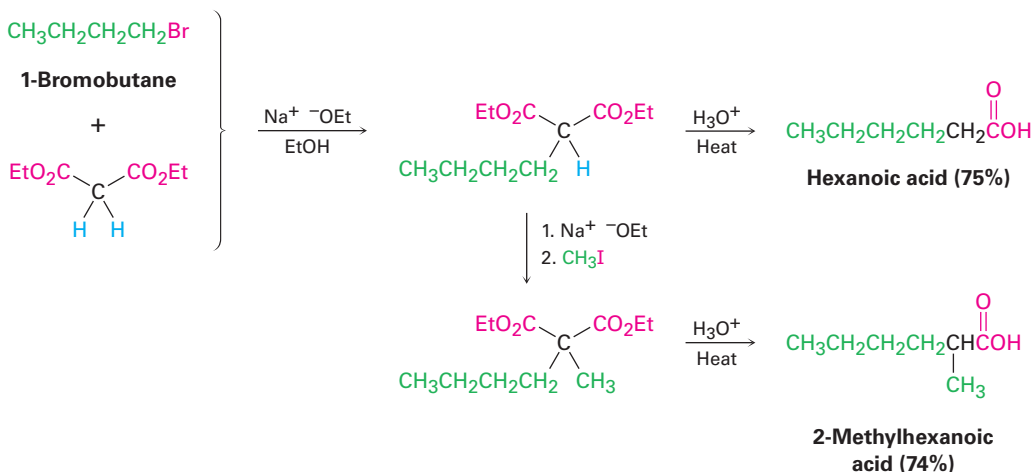
On heating with aqueous hydrochloric acid, the alkylated (or dialkylated) malonic ester undergoes hydrolysis of its two ester groups followed by *decarboxylation* (loss of CO_2) to yield a substituted monocarboxylic acid.



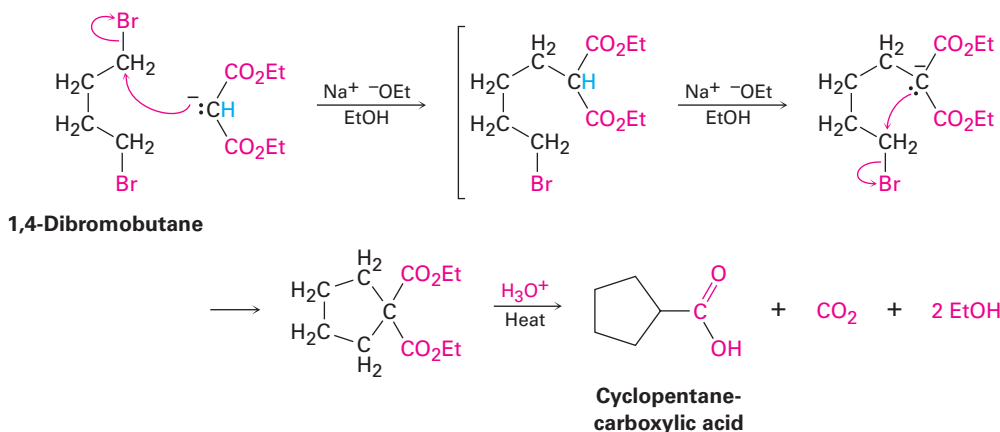
Decarboxylation is not a general reaction of carboxylic acids. Rather, it is unique to compounds that have a second carbonyl group two atoms away from the $-\text{CO}_2\text{H}$. That is, only substituted malonic acids and β -keto acids undergo loss of CO_2 on heating. The decarboxylation reaction occurs by a cyclic mechanism and involves initial formation of an enol, thereby accounting for the need to have a second carbonyl group appropriately positioned.



As noted previously, the overall effect of the malonic ester synthesis is to convert an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms ($\text{RX} \rightarrow \text{RCH}_2\text{CO}_2\text{H}$).



The malonic ester synthesis can also be used to prepare *cycloalkane*-carboxylic acids. For example, when 1,4-dibromobutane is treated with diethyl malonate in the presence of 2 equivalents of sodium ethoxide base, the second alkylation step occurs intramolecularly to yield a cyclic product. Hydrolysis and decarboxylation then give cyclopentanecarboxylic acid. Three-, four-, five-, and six-membered rings can all be prepared in this way.



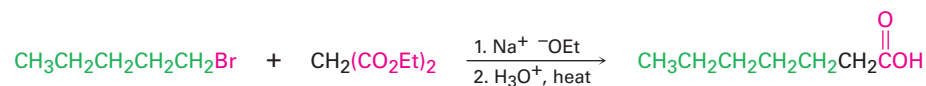
Using the Malonic Ester Synthesis to Prepare a Carboxylic Acid

WORKED EXAMPLE 17.2

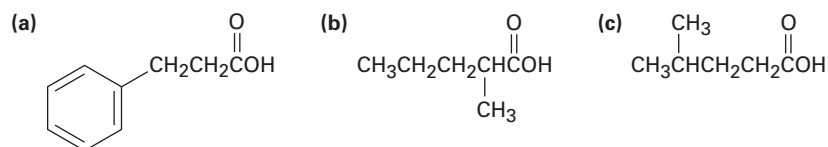
How would you prepare heptanoic acid using a malonic ester synthesis?

Strategy

The malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbons. Thus, a seven-carbon acid chain must be derived from the five-carbon alkyl halide 1-bromopentane.

Solution**PROBLEM 17.8**

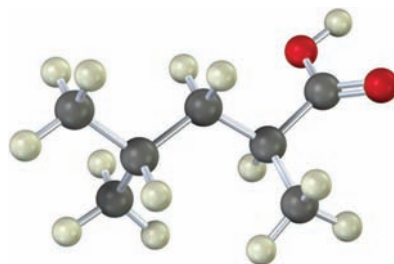
How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.

**PROBLEM 17.9**

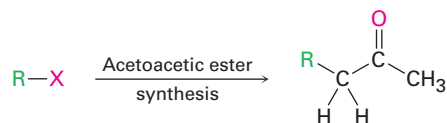
Monoalkylated and dialkylated acetic acids can be prepared by the malonic ester synthesis, but trialkylated acetic acids ($\text{R}_3\text{CCO}_2\text{H}$) can't be prepared. Explain.

PROBLEM 17.10

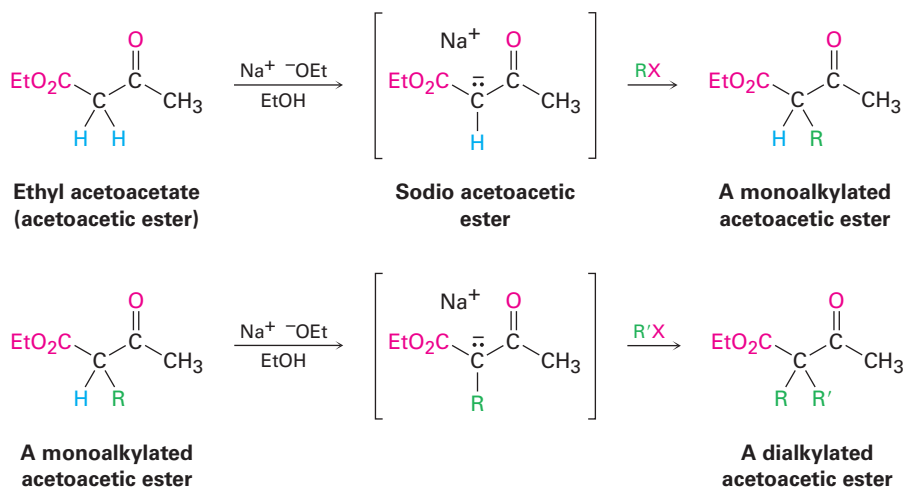
How could you use a malonic ester synthesis to prepare the following compound?

**The Acetoacetic Ester Synthesis**

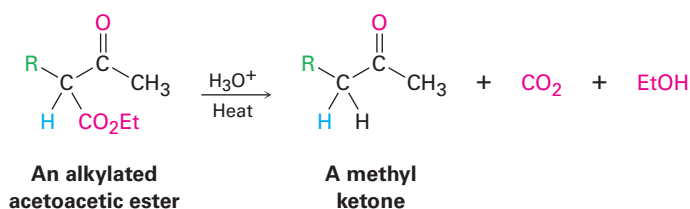
Just as the malonic ester synthesis converts an alkyl halide into a carboxylic acid, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone having three more carbons.



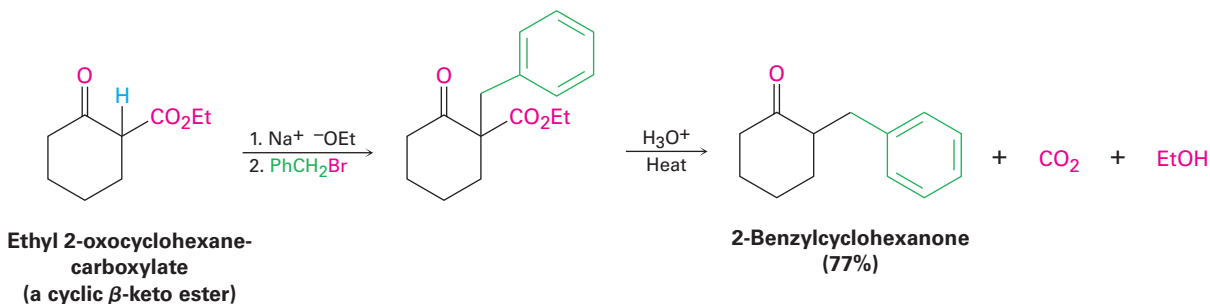
Ethyl 3-oxobutanoate, commonly called ethyl acetoacetate, or *acetoacetic ester*, is much like malonic ester in that its α hydrogens are flanked by two carbonyl groups. It is therefore readily converted into its enolate ion, which can be alkylated by reaction with an alkyl halide. A second alkylation can also be carried out if desired, since acetoacetic ester has two acidic α hydrogens.



On heating with aqueous HCl, the alkylated (or dialkylated) acetoacetic ester is hydrolyzed to a β -keto acid, which then undergoes decarboxylation to yield a ketone product. The decarboxylation occurs in the same way as in the malonic ester synthesis and involves a ketone enol as the initial product.



The three-step sequence of (1) enolate ion formation, (2) alkylation, and (3) hydrolysis/decarboxylation is applicable to all β -keto esters with acidic α hydrogens, not just to acetoacetic ester itself. For example, cyclic β -keto esters, such as ethyl 2-oxocyclohexanecarboxylate, can be alkylated and decarboxylated to give 2-substituted cyclohexanones.



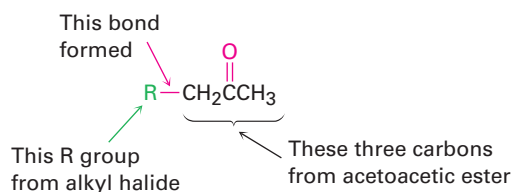
WORKED EXAMPLE 17.3

Using the Acetoacetic Ester Synthesis to Prepare a Ketone

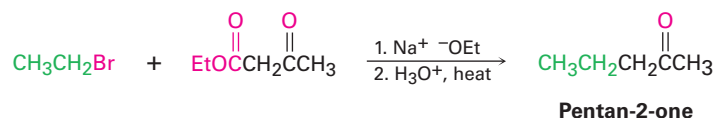
How would you prepare pentan-2-one by an acetoacetic ester synthesis?

Strategy

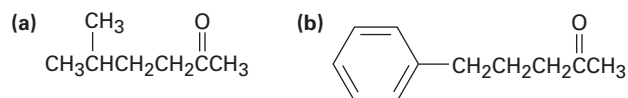
The acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide:



Thus, the acetoacetic ester synthesis of pentan-2-one must involve reaction of bromoethane.

Solution**PROBLEM 17.11**

What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?

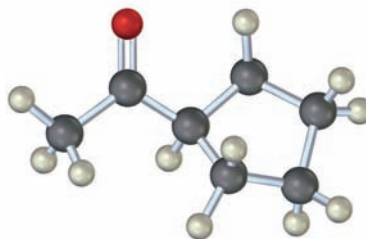
**PROBLEM 17.12**

Which of the following compounds *cannot* be prepared by an acetoacetic ester synthesis? Explain.

- (a) Phenylacetone (b) Acetophenone (c) 3,3-Dimethylbutan-2-one

PROBLEM 17.13

How would you prepare the following compound using an acetoacetic ester synthesis?

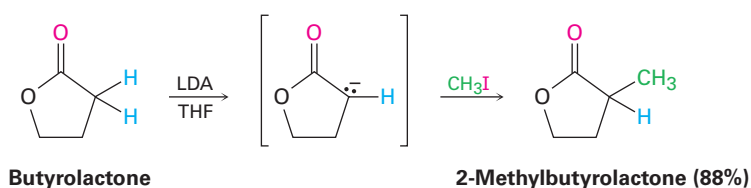


Direct Alkylation of Ketones, Esters, and Nitriles

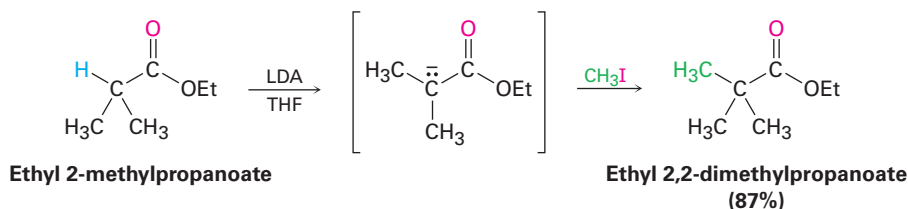
Both the malonic ester synthesis and the acetoacetic ester synthesis are easy to carry out because they involve relatively acidic dicarbonyl compounds. As a result, sodium ethoxide in ethanol as solvent can be used to prepare the necessary enolate ions. Alternatively, however, it's also possible in many cases to directly alkylate the α position of *monocarbonyl* compounds. A strong, sterically hindered base such as LDA is needed so that complete conversion to the enolate ion takes place rather than a nucleophilic addition, and a nonprotic solvent must be used.

Ketones, esters, and nitriles can all be alkylated using LDA or related dialkylamide bases in THF. Aldehydes, however, rarely give high yields of pure products because their enolate ions undergo carbonyl condensation reactions instead of alkylation. Some specific examples of alkylation reactions are shown:

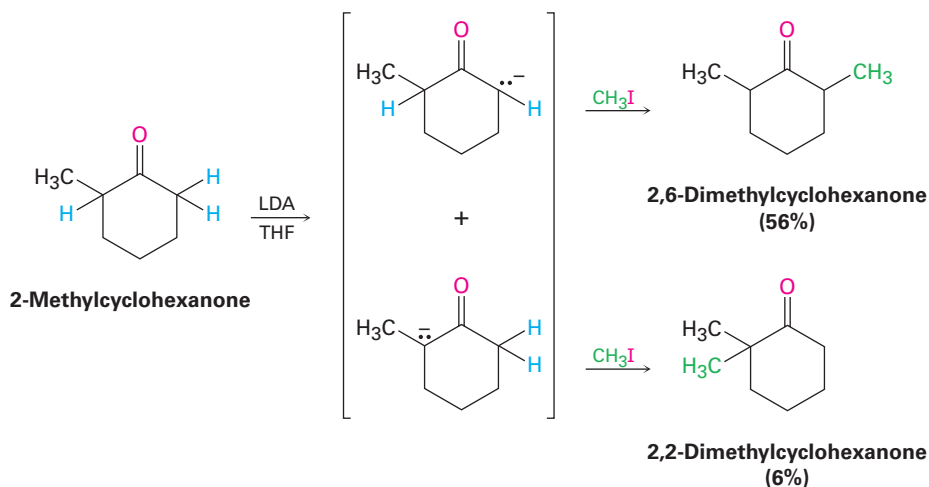
Lactone



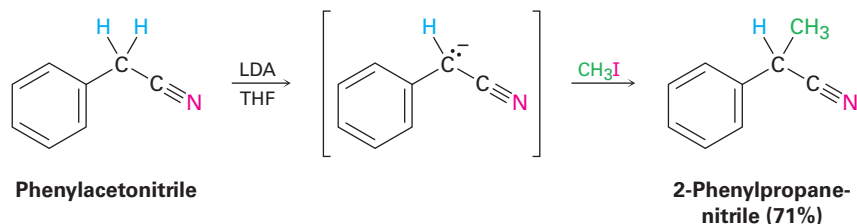
Ester



Ketone



Nitrile

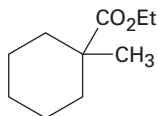


Note in the ketone example that alkylation of 2-methylcyclohexanone leads to a mixture of products because both possible enolate ions are formed. In general, the major product in such cases occurs by alkylation at the less hindered, more accessible position. Thus, alkylation of 2-methylcyclohexanone occurs primarily at C6 (secondary) rather than at C2 (tertiary).

WORKED EXAMPLE 17.4

Using an Alkylation Reaction to Prepare a Substituted Ester

How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?

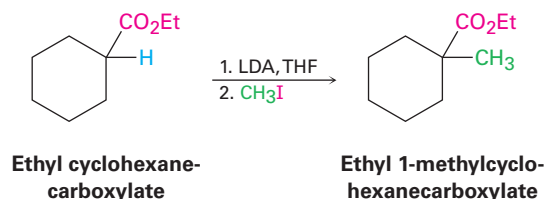


Ethyl 1-methylcyclohexanecarboxylate

Strategy

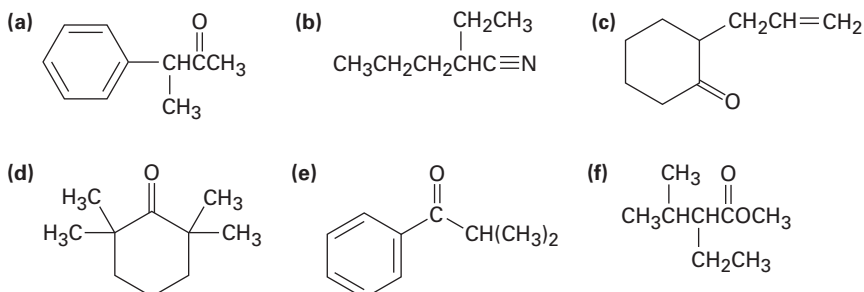
An alkylation reaction is used to introduce a methyl or primary alkyl group onto the α position of a ketone, ester, or nitrile by S_N2 reaction of an enolate ion with an alkyl halide. Thus, we need to look at the target molecule and identify any methyl or primary alkyl groups attached to an α carbon. In the present instance, the target has an α methyl group, which might be introduced by alkylation of an ester enolate ion with iodomethane.

Solution



PROBLEM 17.14

Show how you might prepare the following compounds using an alkylation reaction as the key step:

**Biological Alkylations**

Alkylations are rare but not unknown in biological chemistry. One example occurs during biosynthesis of the antibiotic indolmycin from indolylpyruvate when a base abstracts an acidic hydrogen from an α position and the resultant enolate ion carries out an S_N2 alkylation reaction on the methyl group of *S*-adenosylmethionine (SAM; Section 12-11). Although it's convenient to speak of "enolate ion" intermediates in biological pathways, it's unlikely that they exist for long in an aqueous cellular environment. Rather, proton removal and alkylation probably occur at essentially the same time (FIGURE 17.6).

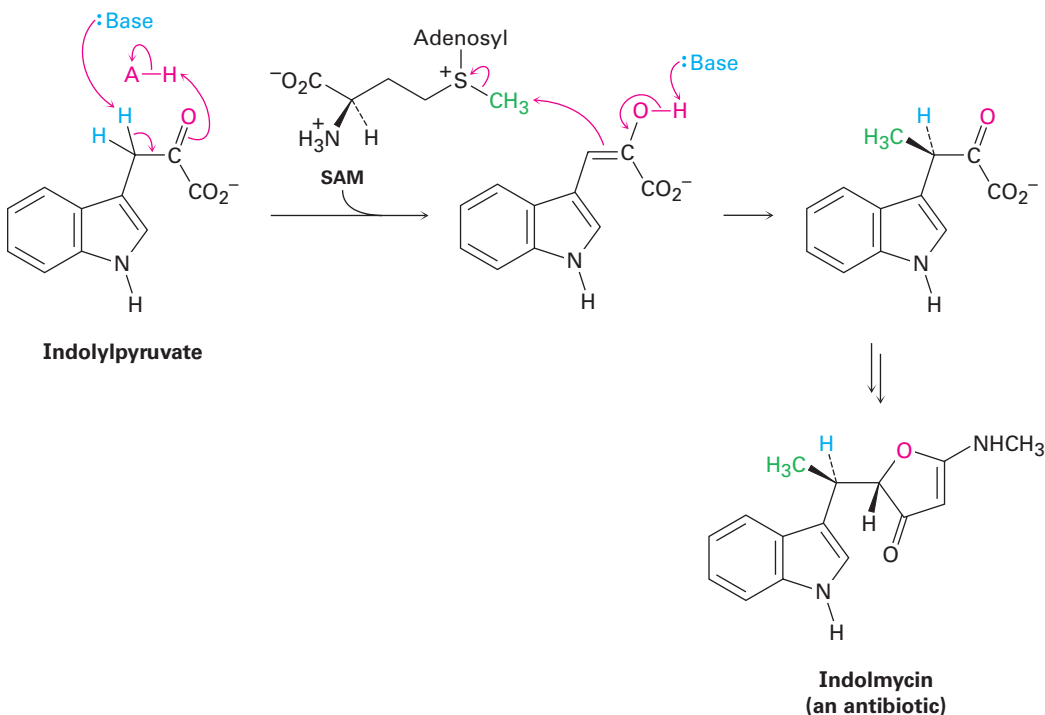


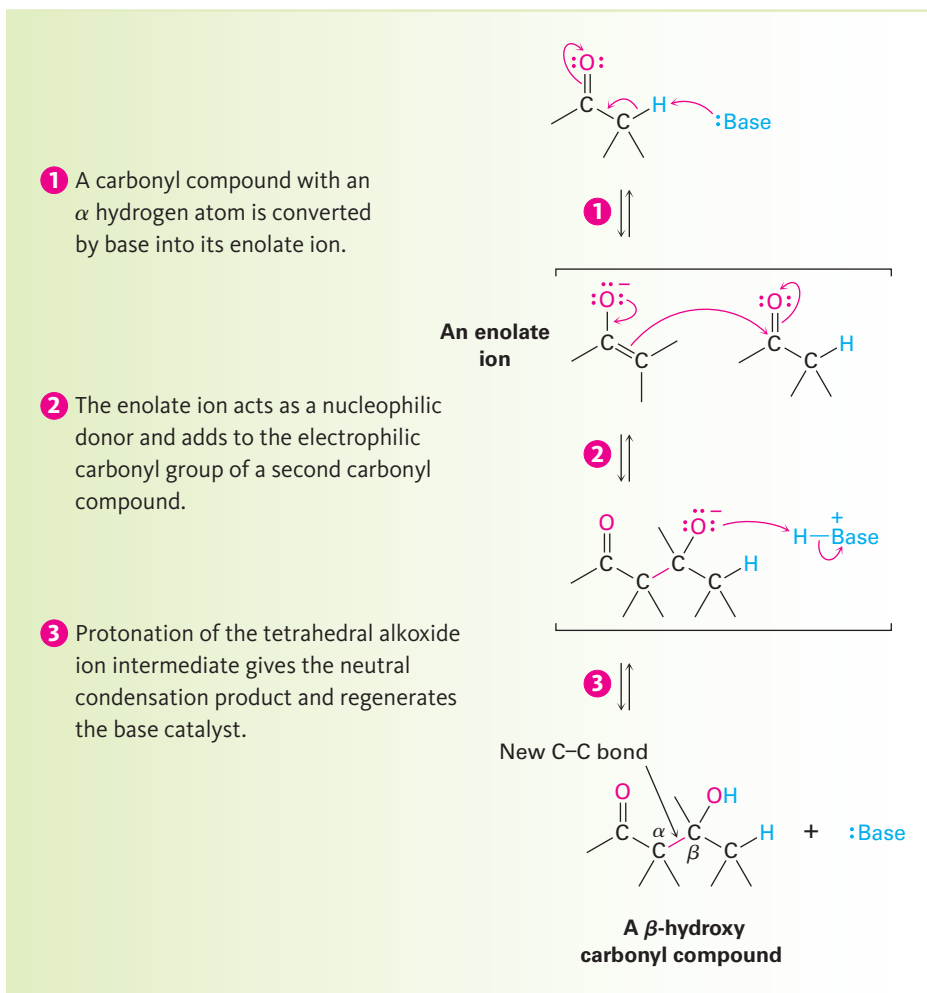
FIGURE 17.6 Biosynthesis of indolmycin from indolylpyruvate. The process occurs through a pathway that includes an alkylation reaction of a short-lived enolate ion intermediate.

17-6 Carbonyl Condensations: The Aldol Reaction

As noted in the chapter introduction, carbonyl condensation reactions take place between two carbonyl partners and involve a combination of α -substitution and nucleophilic addition steps. One partner is converted into an enolate ion, which acts as a nucleophile and adds to the electrophilic carbonyl group of the second partner. In so doing, the nucleophilic partner undergoes an α -substitution reaction and the electrophilic partner undergoes a nucleophilic addition. The general mechanism of the process is shown in **FIGURE 17.7**.

FIGURE 17.7 General mechanism of a carbonyl condensation reaction.

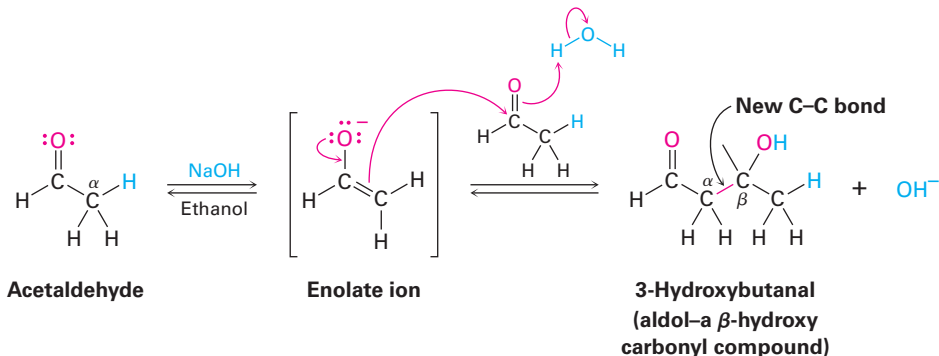
One partner becomes a nucleophilic donor and adds to the second partner as an electrophilic acceptor. The product is a β -hydroxy carbonyl compound.



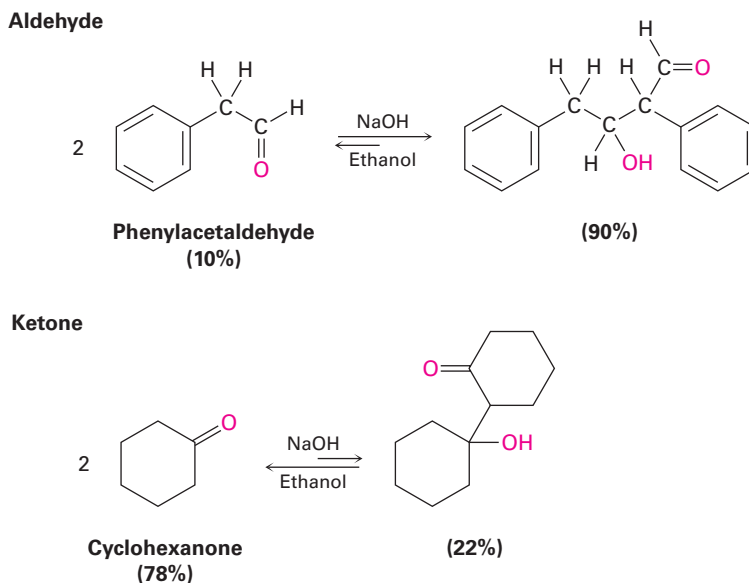
© John McMurry

Aldehydes and ketones with an α hydrogen atom undergo a reversible base-catalyzed carbonyl condensation reaction called the **aldol reaction**. For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation

of 3-hydroxybutanal, known commonly as *aldol* (*aldehyde* + *alcohol*), hence the general name of the reaction.



The position of the aldol equilibrium depends both on reaction conditions and on substrate structure. The equilibrium generally favors condensation product in the case of aldehydes with no α substituent (RCH₂CHO) but favors reactant for disubstituted aldehydes (R₂CHCHO) and for most ketones. Steric factors are probably responsible for these trends, since increased substitution near the reaction site increases steric congestion in the aldol product.



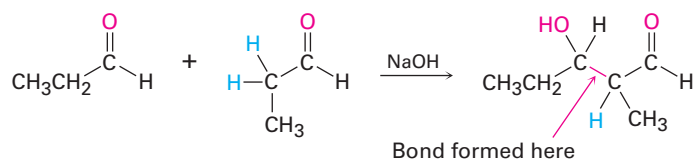
Predicting the Product of an Aldol Reaction

WORKED EXAMPLE 17.5

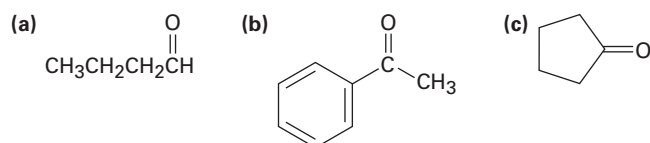
What is the structure of the aldol product from propanal?

Strategy

An aldol reaction combines two molecules of reactant, forming a bond between the α carbon of one partner and the carbonyl carbon of the second partner.

Solution**PROBLEM 17.15**

Predict the aldol reaction product of the following compounds:

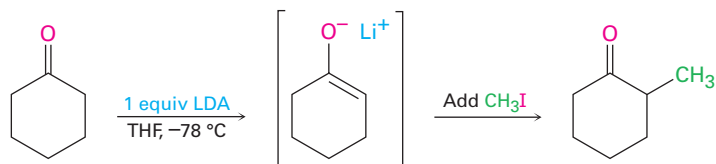
**PROBLEM 17.16**

Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed retro-aldol reaction of 4-hydroxy-4-methylpentan-2-one takes place to yield 2 equivalents of acetone.

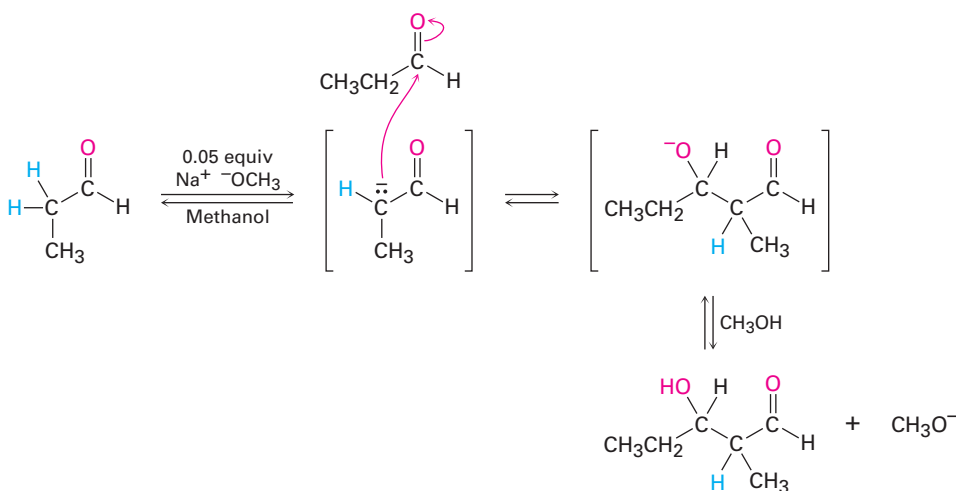
Carbonyl Condensations versus Alpha Substitutions

Two of the four general carbonyl-group reactions—carbonyl condensations and α substitutions—take place under basic conditions and involve enolate-ion intermediates. Because the experimental conditions for the two reactions are similar, how can we predict which will occur in a given case? When we generate an enolate ion with the intention of carrying out an α alkylation, how can we be sure that a carbonyl condensation reaction won't occur instead?

There is no simple answer to this question, but the experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of a strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at -78°C . Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would be left, so no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.

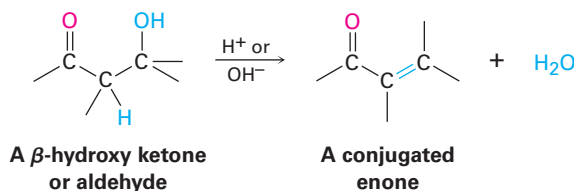


On the other hand, carbonyl condensation reactions require only a small, catalytic amount of a relatively weak base rather than a full equivalent so that only a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation has occurred, the basic catalyst is regenerated, so the process continues. To carry out an aldol reaction on propanal, for instance, we might dissolve the aldehyde in methanol, add 0.05 equivalent of sodium methoxide, and then warm the mixture to give the aldol product.



17-7 Dehydration of Aldol Products

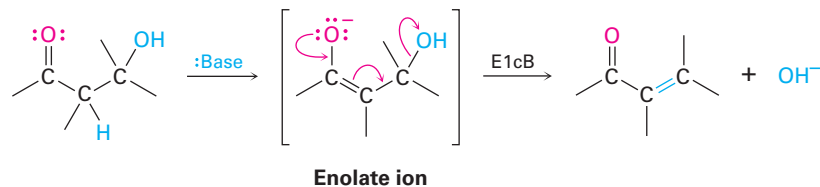
The β -hydroxy aldehydes or ketones formed in aldol reactions can be easily dehydrated to yield α,β -unsaturated products, or *conjugated enones*. In fact, it's this loss of water that gives the carbonyl *condensation* reaction its name, because water condenses out of the reaction when the enone product forms.



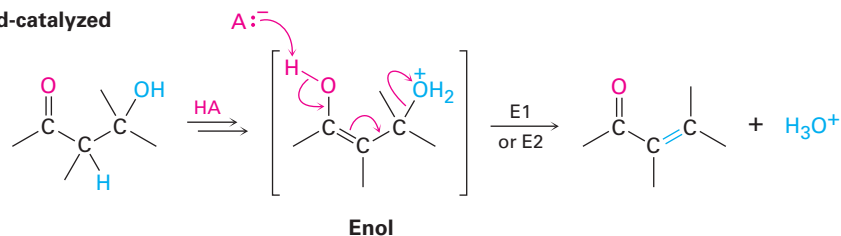
Most alcohols are resistant to dehydration by base (Section 13-4) because hydroxide ion is a poor leaving group, but aldol products dehydrate easily because of the carbonyl group. Under basic conditions, an acidic α hydrogen is removed, yielding an enolate ion that expels the $^- \text{OH}$ leaving group in an

E1cB reaction (Section 12-14). Under acidic conditions, an enol is formed, the $-OH$ group is protonated, and water is expelled in an E1 or E2 reaction.

Base-catalyzed



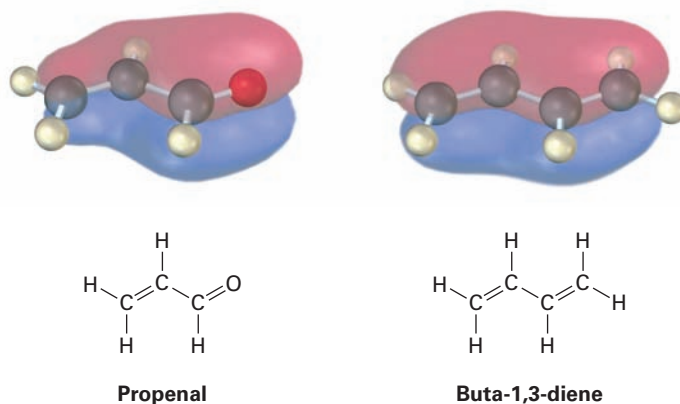
Acid-catalyzed



The reaction conditions needed for aldol dehydration are often only a bit more vigorous (slightly higher temperature, for instance) than the conditions needed for the aldol formation itself. As a result, conjugated enones are usually obtained directly from aldol reactions without isolating the intermediate β -hydroxy carbonyl compounds.

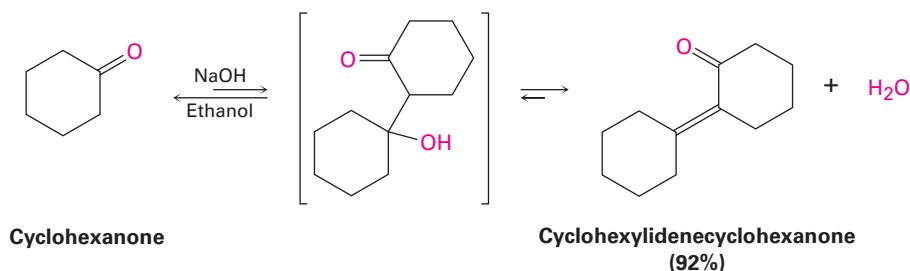
Conjugated enones are more stable than nonconjugated enones for the same reason that conjugated dienes are more stable than nonconjugated dienes (Section 8-12). Interaction between the π electrons of the $C=C$ bond and the π electrons of the $C=O$ group leads to a molecular orbital description for a conjugated enone that shows how the electrons are distributed over all four atomic centers (**FIGURE 17.8**).

FIGURE 17.8 Comparison of a conjugated enone with a conjugated diene. The π bonding molecular orbitals of a conjugated enone (propenal) and a conjugated diene (buta-1,3-diene) are similar in shape and are spread over the entire π system.



The real value of aldol dehydration is that removal of water from the reaction mixture can be used to drive the aldol equilibrium toward product. Even though the initial aldol step itself may be unfavorable, as it usually is for ketones, the subsequent dehydration step is so strongly favorable that it allows many aldol condensations to be carried out in good yield. Cyclohexanone, for

example, gives cyclohexylidenecyclohexanone in 92% yield even though the initial equilibrium is unfavorable.



Predicting the Product of an Aldol Reaction

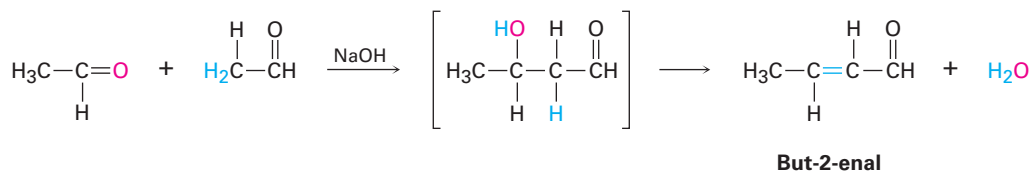
WORKED EXAMPLE 17.6

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

Strategy

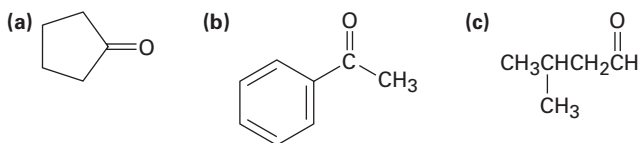
In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the carbonyl oxygen from the second partner.

Solution



PROBLEM 17.17

What enone product would you expect from aldol condensation of each of the following compounds?



PROBLEM 17.18

Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

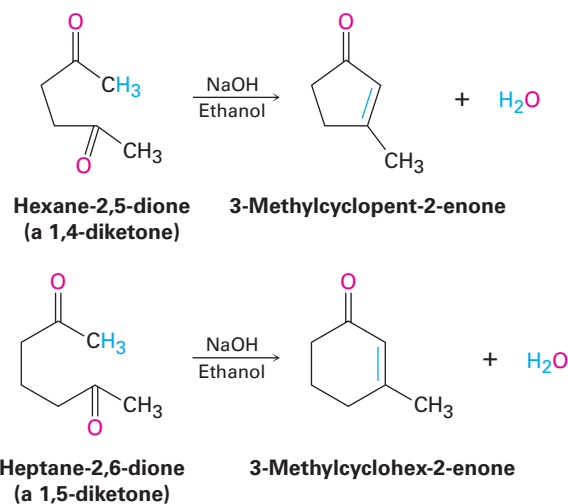
PROBLEM 17.19

Which of the following compounds are aldol condensation products? What is the aldehyde or ketone precursor of each?

- (a) 2-Hydroxy-2-methylpentanal (b) 5-Ethyl-4-methylhept-4-en-3-one

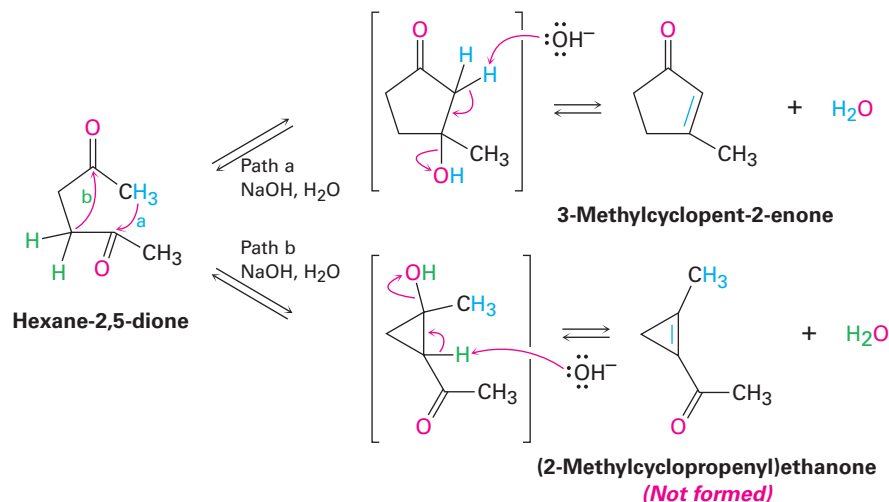
17-8 Intramolecular Aldol Reactions

The aldol reactions we've seen thus far have been *intermolecular*, meaning that they have taken place between two different molecules. When certain *dicarbonyl* compounds are treated with base, however, an *intramolecular* aldol reaction can occur, leading to the formation of a cyclic product. For example, base treatment of a 1,4-diketone such as hexane-2,5-dione yields a cyclopentenone product, and base treatment of a 1,5-diketone such as heptane-2,6-dione yields a cyclohexenone.



The mechanism of intramolecular aldol reactions is similar to that of intermolecular reactions. The only difference is that both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule. One complication, however, is that intramolecular aldol reactions might lead to a mixture of products, depending on which enolate ion is formed. For example, hexane-2,5-dione might yield either the five-membered-ring product 3-methylcyclopent-2-enone or the three-membered-ring product (2-methylcyclopropenyl)ethanone (FIGURE 17.9). In practice, though, only the cyclopentenone is formed.

FIGURE 17.9 Intramolecular aldol reaction of hexane-2,5-dione. 3-Methylcyclopent-2-enone is formed rather than the alternative cyclopropene.



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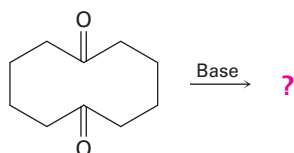
The selectivity observed in the intramolecular aldol reaction of hexane-2,5-dione is due to the fact that all steps in the mechanism are readily reversible, so an equilibrium is reached and the most stable product is formed. That is, the relatively strain-free cyclopentenone product results rather than the highly strained cyclopropene alternative. For similar reasons, intramolecular aldol reactions of 1,5-diketones lead only to cyclohexenone products rather than to acyl cyclobutenes.

PROBLEM 17.20

Treatment of a 1,3-diketone such as pentane-2,4-dione with base does not give an aldol condensation product. Explain.

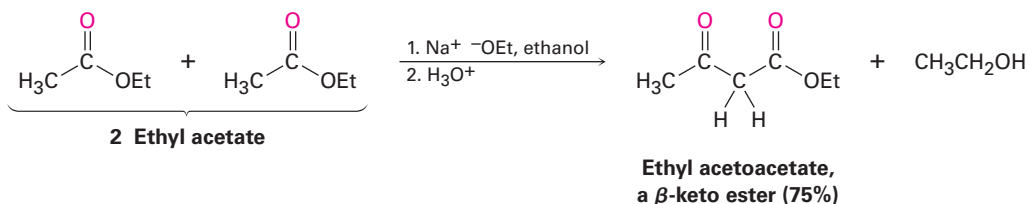
PROBLEM 17.21

What product would you expect to obtain from base treatment of cyclodecane-1,6-dione?



17-9 The Claisen Condensation Reaction

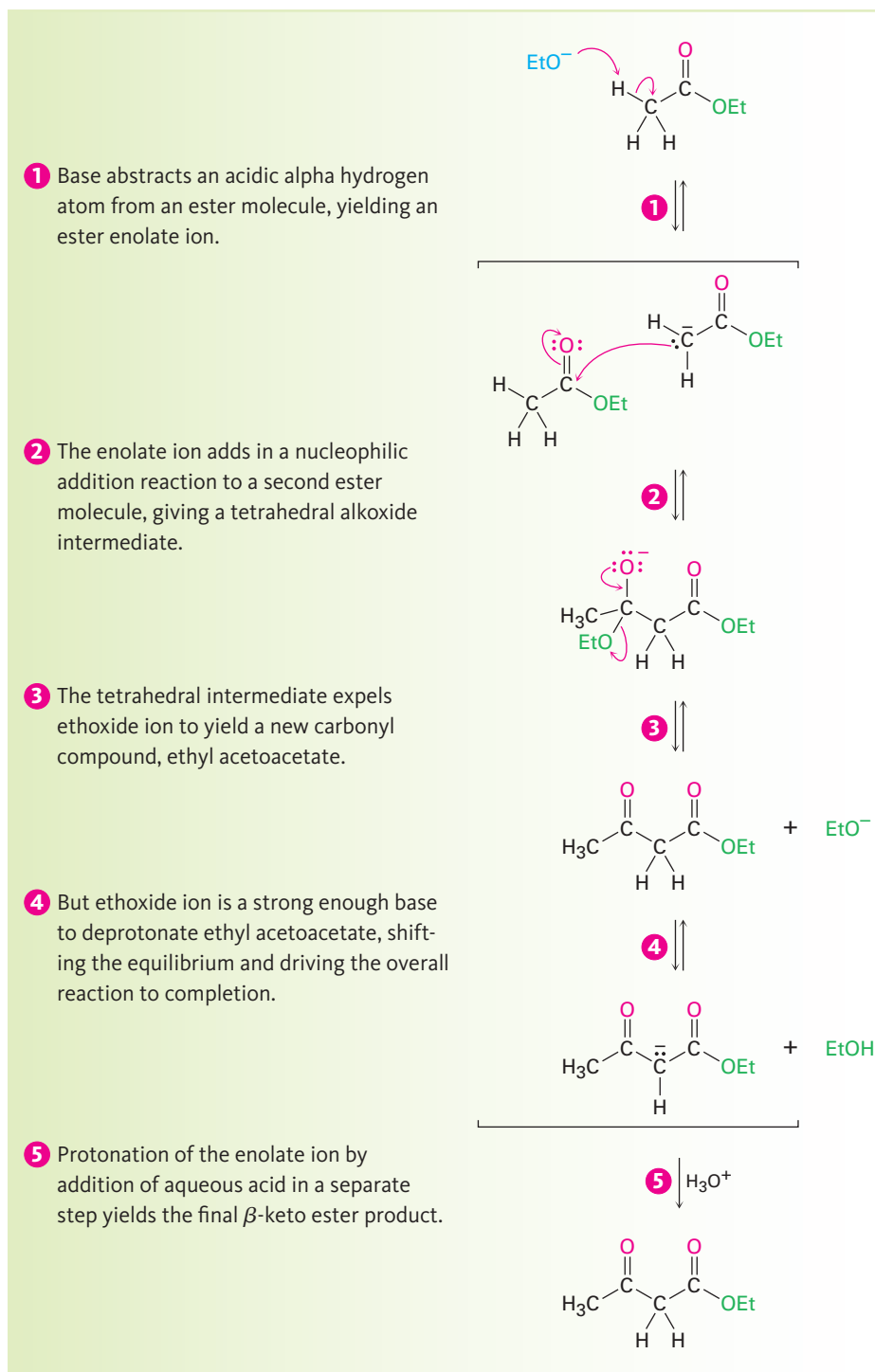
Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with 1 equivalent of a base such as sodium ethoxide, a reversible carbonyl condensation reaction occurs to yield a β -keto ester. For example, ethyl acetate yields ethyl acetoacetate on base treatment. This reaction between two ester molecules is known as the **Claisen condensation reaction**. (We'll use ethyl esters, abbreviated "Et," for consistency, but other esters will also work.)



The mechanism of the Claisen condensation is similar to that of the aldol condensation and involves the nucleophilic addition of an ester enolate ion to the carbonyl group of a second ester molecule. The only difference between the aldol condensation of an aldehyde or ketone and the Claisen condensation of an ester involves the fate of the initially formed tetrahedral intermediate. The tetrahedral intermediate in the aldol reaction is protonated to give an alcohol product—exactly the behavior previously seen for aldehydes

and ketones (Section 14-4). The tetrahedral intermediate in the Claisen reaction, however, expels an alkoxide leaving group to yield an acyl substitution product—exactly the behavior previously seen for esters (Section 16-6). The mechanism of the Claisen condensation reaction is shown in **FIGURE 17.10**.

FIGURE 17.10 Mechanism of the Claisen condensation reaction.



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If the starting ester has more than one acidic α hydrogen, the product β -keto ester has a highly acidic, doubly activated hydrogen atom that can be abstracted by base. This deprotonation of the product requires that a full equivalent of base rather than a catalytic amount be used in the reaction. Furthermore, the deprotonation serves to drive the equilibrium completely to the product side so that high yields are usually obtained in Claisen condensations.

Predicting the Product of a Claisen Condensation Reaction

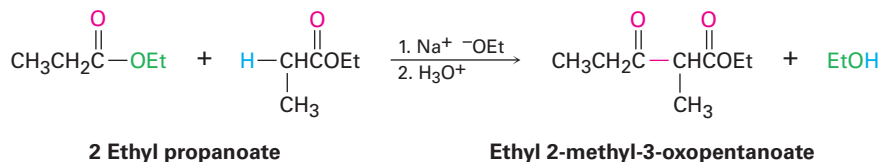
WORKED EXAMPLE 17.7

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy

The Claisen condensation of an ester results in loss of one molecule of alcohol and formation of a product in which an acyl group of one reactant bonds to the α carbon of the second reactant. The product is a β -keto ester.

Solution



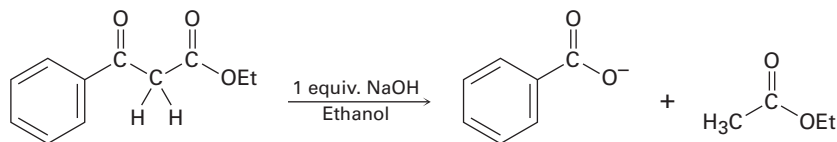
PROBLEM 17.22

Show the products you would expect to obtain by Claisen condensation of the following esters:

(a) $(\text{CH}_3)_2\text{CHCH}_2\text{CO}_2\text{Et}$ (b) Ethyl phenylacetate (c) Ethyl cyclohexylacetate

PROBLEM 17.23

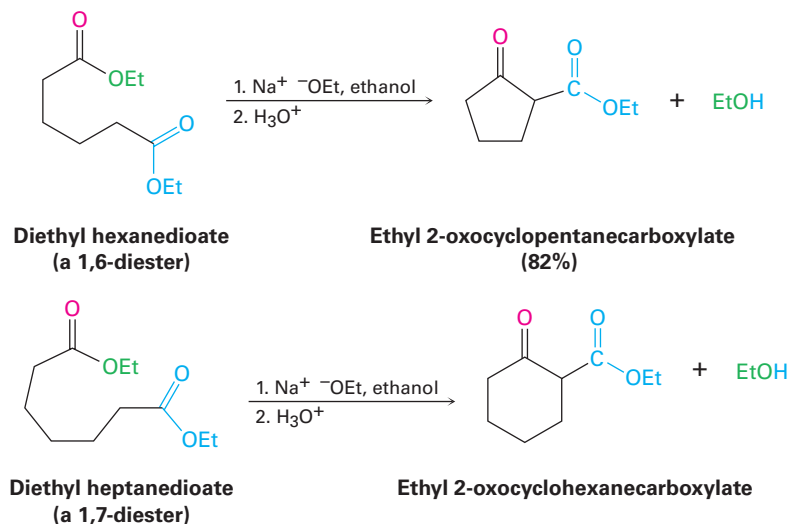
As shown in Figure 17.10, the Claisen reaction is reversible. That is, a β -keto ester can be cleaved by base into two fragments. Using curved arrows to indicate electron flow, show the mechanism by which this cleavage occurs.



17-10 Intramolecular Claisen Condensations: The Dieckmann Cyclization

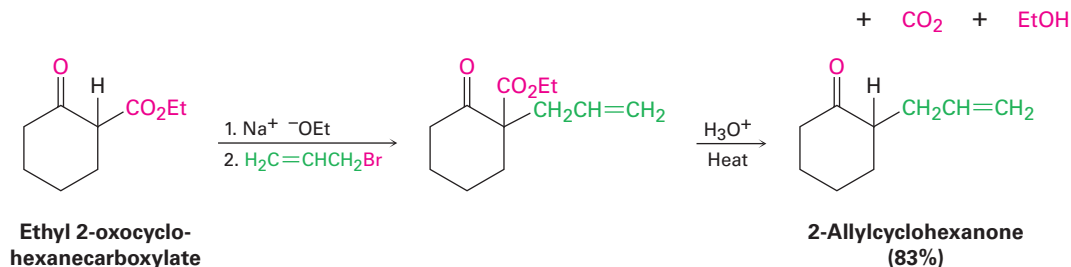
Intramolecular Claisen condensations can be carried out with diesters, just as intramolecular aldol condensations can be carried out with diketones (Section 17-8). Called the **Dieckmann cyclization**, the process works best on

1,6-diesters and 1,7-diesters. Cyclization of a 1,6-diester gives a five-membered cyclic β -keto ester, and cyclization of a 1,7-diester gives a six-membered cyclic β -keto ester.



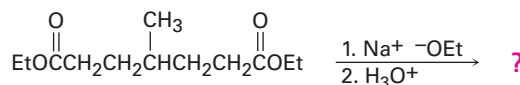
The mechanism of the intramolecular Dieckmann cyclization, shown in **FIGURE 17.11**, is the same as that of the intermolecular Claisen condensation. One of the two ester groups is converted into an enolate ion, which then carries out a nucleophilic acyl substitution on the second ester group at the other end of the molecule. A cyclic β -keto ester product results.

The cyclic β -keto ester produced in a Dieckmann cyclization can be further alkylated and decarboxylated by a series of reactions analogous to those used in the acetoacetic ester synthesis (Section 17-5). Alkylation and subsequent decarboxylation of ethyl 2-oxocyclohexanecarboxylate, for instance, yields a 2-alkylcyclohexanone. The overall sequence of (1) Dieckmann cyclization, (2) β -keto ester alkylation, and (3) decarboxylation is a powerful method for preparing 2-substituted cyclohexanones and cyclopentanones.



PROBLEM 17.24

What product would you expect from the following reaction?



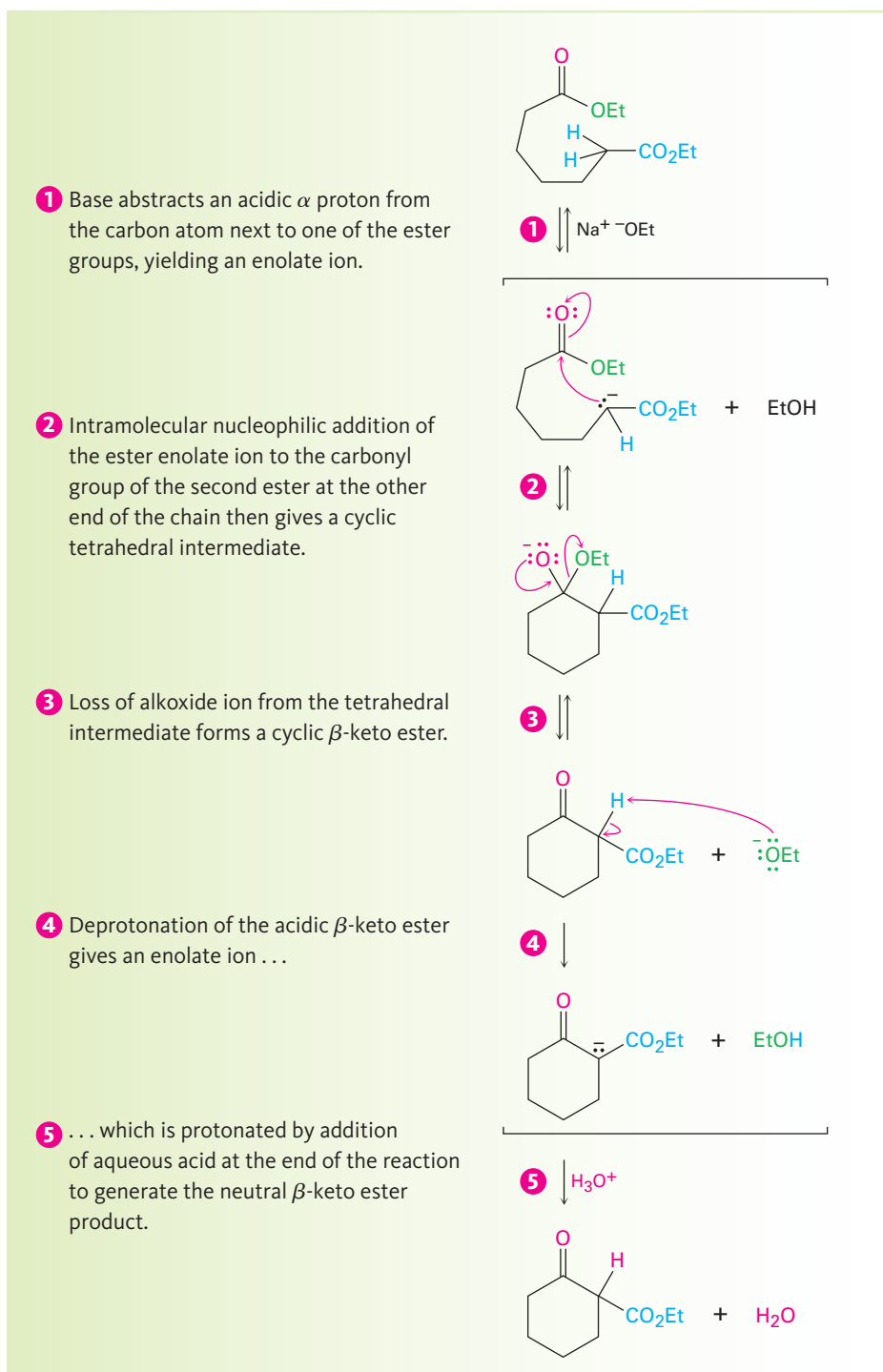


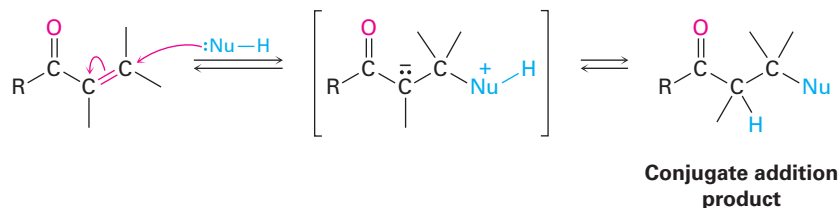
FIGURE 17.11 Mechanism of the Dieckmann cyclization of a 1,7-diester to yield a cyclic β -keto ester product.

PROBLEM 17.25

Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β -keto ester products. What are their structures, and why is a mixture formed?

17-11 Conjugate Carbonyl Additions: The Michael Reaction

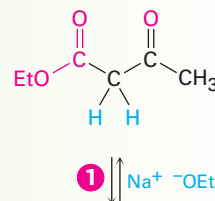
We saw in Section 14-11 that certain nucleophiles, such as amines, react with α,β -unsaturated aldehydes and ketones to give the conjugate addition product, rather than the direct addition product:



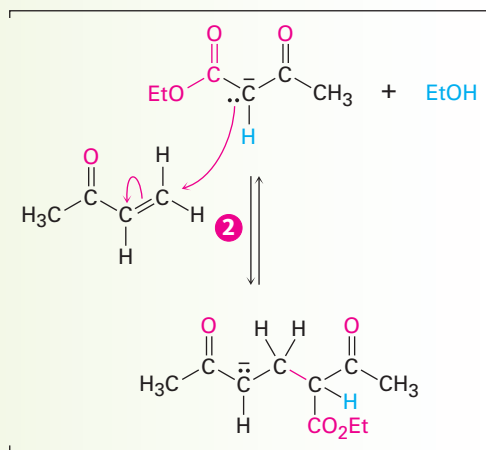
Exactly the same kind of conjugate addition can occur when a nucleophilic enolate ion reacts with an α,β -unsaturated carbonyl compound—a process known as the **Michael reaction**.

FIGURE 17.12 Mechanism of the Michael reaction between a β -keto ester and an α,β -unsaturated ketone. The reaction is a conjugate addition of an enolate ion to the unsaturated carbonyl compound.

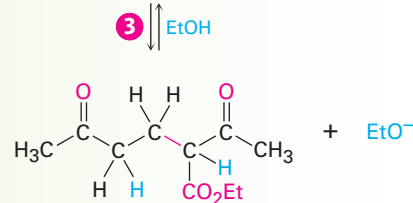
- 1 The base catalyst removes an acidic alpha proton from the starting β -keto ester to generate a stabilized enolate ion nucleophile.



- 2 The nucleophile adds to the α,β -unsaturated ketone electrophile in a Michael reaction to generate a new enolate as product.

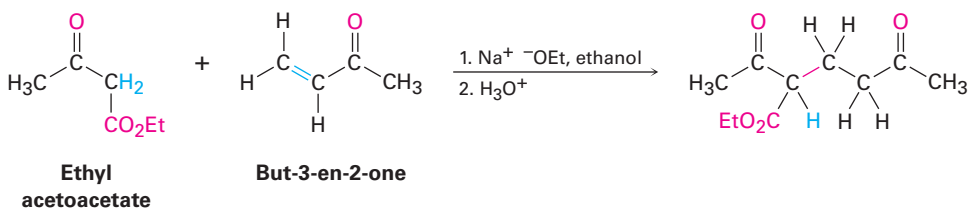


- 3 The enolate product abstracts an acidic proton, either from solvent or from starting keto ester, to yield the final addition product.



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The best Michael reactions are those that take place when a particularly stable enolate ion such as that derived from a β -keto ester or other 1,3-dicarbonyl compound adds to an unhindered α,β -unsaturated ketone. For example, ethyl acetoacetate reacts with but-3-en-2-one in the presence of sodium ethoxide to yield the conjugate addition product.



Michael reactions take place by addition of a nucleophilic enolate ion donor to the β carbon of an α,β -unsaturated carbonyl acceptor, according to the mechanism shown in **FIGURE 17.12**.

The Michael reaction occurs with a variety of α,β -unsaturated carbonyl compounds, not just conjugated ketones. Unsaturated aldehydes, esters, thioesters, nitriles, and amides can all act as the electrophilic acceptor component in Michael reactions (**TABLE 17.2**). Similarly, a variety of different donors can be used, including β -diketones, β -keto esters, malonic esters, and β -keto nitriles.

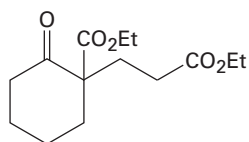
TABLE 17.2 Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
$\text{H}_2\text{C}=\text{CHCHO}$	Propenal	$\text{RCOCH}_2\text{CR}'$	β -Diketone
$\text{H}_2\text{C}=\text{CHCOCH}_3$	But-3-en-2-one	$\text{RCOCH}_2\text{COEt}$	β -Keto ester
$\text{H}_2\text{C}=\text{CHCOEt}$	Ethyl propenoate	$\text{EtOCOCCH}_2\text{COEt}$	Diethyl malonate
$\text{H}_2\text{C}=\text{CHCONH}_2$	Propenamide	$\text{RCOCH}_2\text{C}\equiv\text{N}$	β -Keto nitrile
$\text{H}_2\text{C}=\text{CHC}\equiv\text{N}$	Propenenitrile		

Using the Michael Reaction

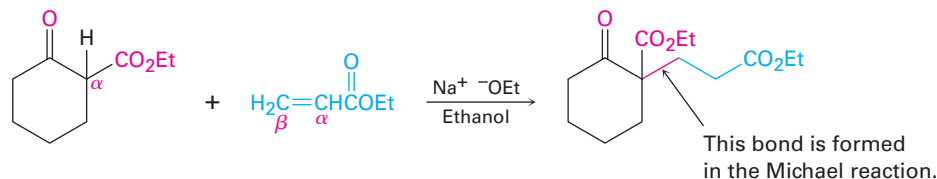
WORKED EXAMPLE 17.8

How might you obtain the following compound using a Michael reaction?



Strategy

A Michael reaction involves the conjugate addition of a stable enolate ion donor to an α,β -unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a β -diketone, β -keto ester, malonic ester, or similar compound. The C–C bond made in the conjugate addition step is the one between the α carbon of the acidic donor and the β carbon of the unsaturated acceptor.

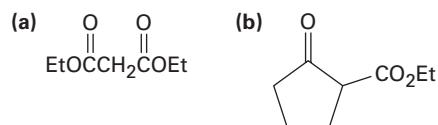
Solution**PROBLEM 17.26**

What product would you obtain from a base-catalyzed Michael reaction of pentane-2,4-dione with each of the following α,β -unsaturated acceptors?

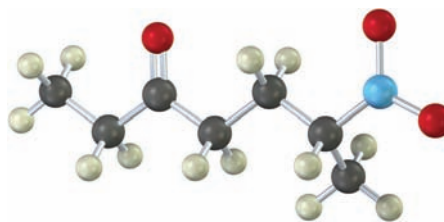
- (a) Cyclohex-2-enone (b) Propenenitrile (c) Ethyl but-2-enoate

PROBLEM 17.27

What product would you obtain from a base-catalyzed Michael reaction of but-3-en-2-one with each of the following nucleophilic donors?

**PROBLEM 17.28**

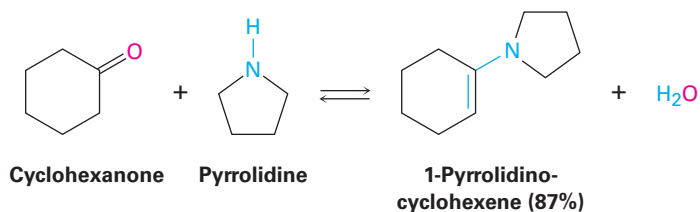
How would you prepare the following compound using a Michael reaction?



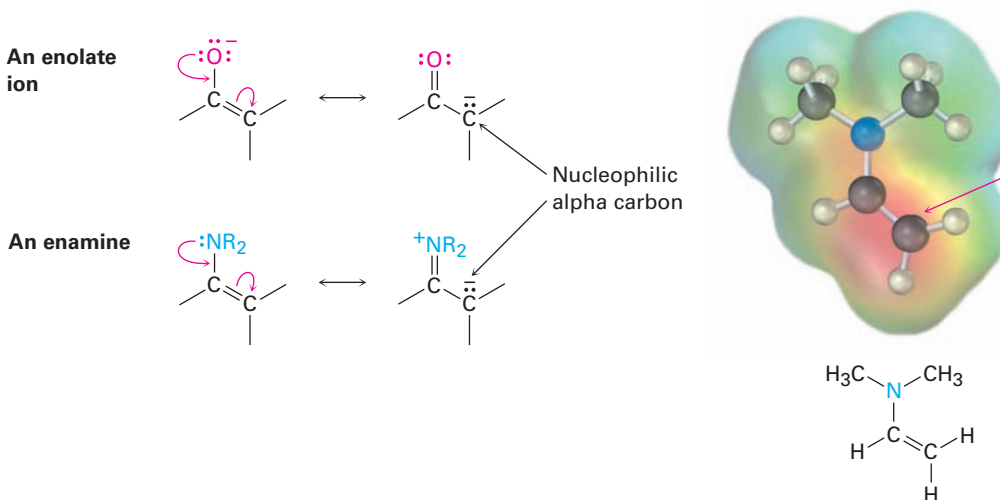
17-12 Carbonyl Condensations with Enamines: The Stork Reaction

In addition to enolate ions, other kinds of carbon nucleophiles also add to α,β -unsaturated acceptors in Michael-like reactions. Among the most important such nucleophiles, particularly in biological chemistry, are *enamines*,

which are readily prepared by reaction between a ketone and a secondary amine, as we saw in Section 14-7. For example:



As the following resonance structures indicate, enamines are electronically similar to enolate ions. Overlap of the nitrogen lone-pair orbital with the double-bond p orbitals leads to an increase in electron density on the α carbon atom, making that carbon nucleophilic. An electrostatic potential map of N,N -dimethylaminoethylene shows this shift of electron density (red) toward the α position.



Enamines behave in much the same way as enolate ions and enter into many of the same kinds of reactions. In the *Stork reaction*, for example, an enamine adds to an α,β -unsaturated carbonyl acceptor in a Michael-like process. The initial product is then hydrolyzed by aqueous acid (Section 14-7) to yield a 1,5-dicarbonyl compound. The overall reaction is thus a three-step sequence of (1) enamine formation from a ketone, (2) Michael addition to an α,β -unsaturated carbonyl compound, and (3) enamine hydrolysis back to a ketone.

The net effect of the Stork reaction is a Michael addition of a ketone to an α,β -unsaturated carbonyl compound. For example, cyclohexanone reacts with the cyclic amine pyrrolidine to yield an enamine; further reaction with an enone such as but-3-en-2-one yields a Michael adduct; and aqueous hydrolysis completes the sequence to give a 1,5-diketone (**FIGURE 17.13**).

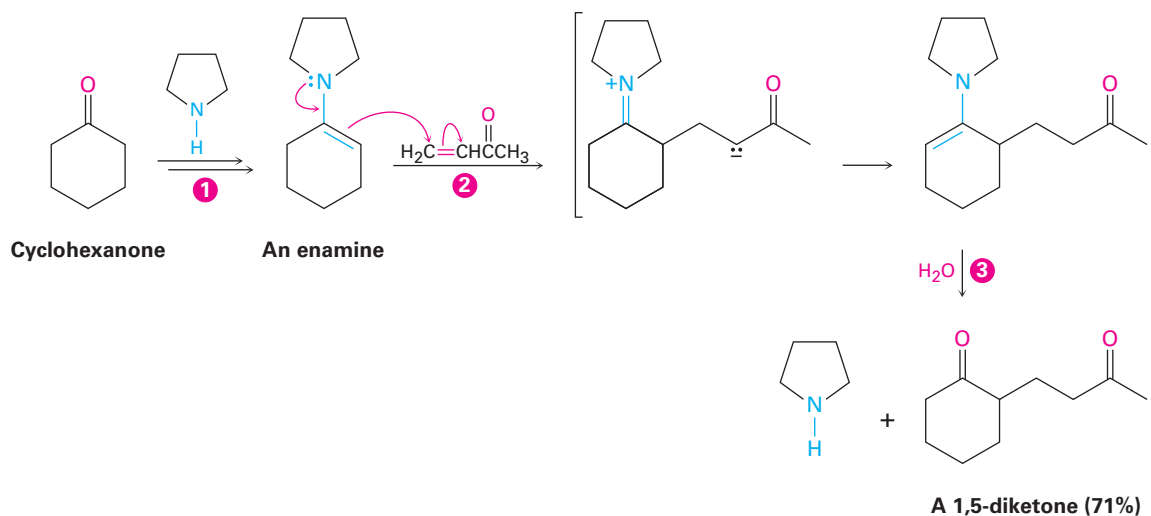


FIGURE 17.13 The Stork reaction between cyclohexanone and but-3-en-2-one.

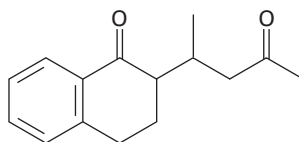
① Cyclohexanone is first converted into an enamine, ② the enamine adds to the α,β -unsaturated ketone in a Michael reaction, and ③ the conjugate addition product is hydrolyzed to yield a 1,5-diketone.

The enamine–Michael reaction has two advantages over the enolate–Michael reaction that make enamines so useful in biological pathways. First, an enamine is neutral, easily prepared, and easily handled, while an enolate ion is charged, sometimes difficult to prepare, and must be handled with care. Second, an enamine from a monoketone can be used in the Michael addition, whereas enolate ions from only β -dicarbonyl compounds can be used.

WORKED EXAMPLE 17.9

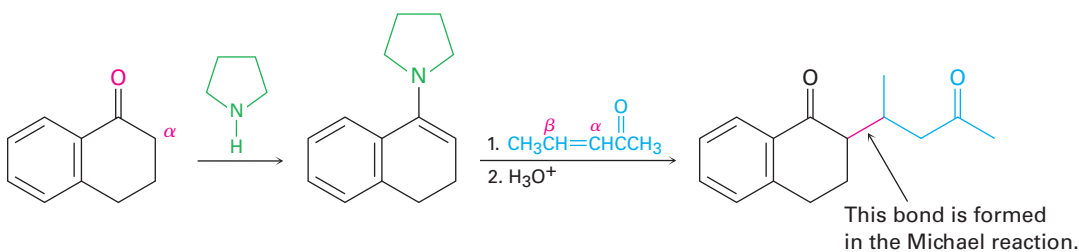
Using the Stork Enamine Reaction

How might you use an enamine reaction to prepare the following compound?



Strategy

The overall result of an enamine reaction is the Michael addition of a ketone as donor to an α,β -unsaturated carbonyl compound as acceptor, yielding a 1,5-dicarbonyl product. The C–C bond made in the Michael addition step is the one between the α carbon of the ketone donor and the β carbon of the unsaturated acceptor.

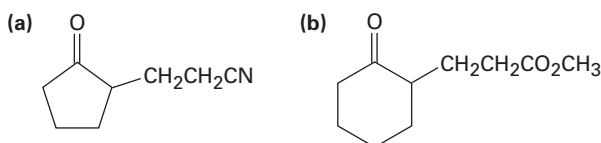
Solution**PROBLEM 17.29**

What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine with the following α,β -unsaturated acceptors?

- (a) $\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$ (b) $\text{H}_2\text{C}=\text{CHCHO}$ (c) $\text{CH}_3\text{CH}=\text{CHCOCH}_3$

PROBLEM 17.30

Show how you might use an enamine reaction to prepare each of the following compounds:

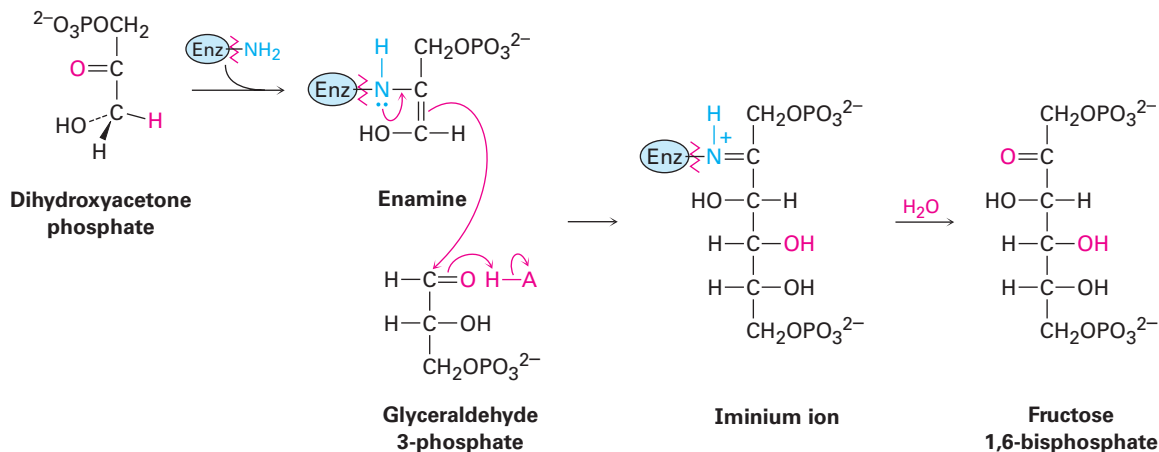
**17-13 Biological Carbonyl Condensation Reactions****Biological Aldol Reactions**

Aldol reactions occur in many biological pathways but are particularly common in carbohydrate metabolism, where enzymes called *aldolases* catalyze the addition of a ketone enolate ion to an aldehyde. Aldolases occur in all organisms and are of two types. Type I aldolases occur primarily in animals and higher plants; type II aldolases occur primarily in fungi and bacteria. Both types catalyze the same kind of reaction, but type I aldolases operate through an enamine, while type II aldolases require a metal ion (usually Zn^{2+}) as Lewis acid and operate through an enolate ion.

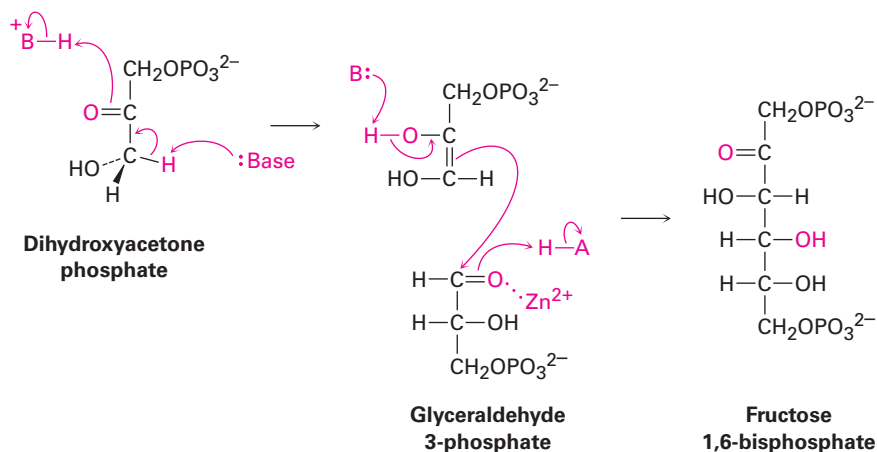
An example of an aldolase-catalyzed reaction occurs in glucose biosynthesis when dihydroxyacetone phosphate reacts with glyceraldehyde 3-phosphate to give fructose 1,6-bisphosphate. In animals and higher plants, dihydroxyacetone phosphate is first converted into an enamine by reaction with the $-\text{NH}_2$ group on a lysine amino acid in the enzyme. The enamine then adds to glyceraldehyde 3-phosphate, and the iminium ion that results is hydrolyzed. In bacteria and fungi, the aldol reaction occurs directly, with the

ketone carbonyl group of glyceraldehyde 3-phosphate complexed to a Zn^{2+} ion to make it a better acceptor.

Type I aldolase



Type II aldolase



Note that the aldolase-catalyzed reactions shown are *mixed* aldol reactions, which take place between two different partners, as opposed to the symmetrical aldol reactions between identical partners usually carried out in the laboratory. Mixed aldol reactions between different partners often give mixtures of products in the laboratory but are successful in living systems because of the selectivity of the enzyme catalysts.

Biological Claisen Condensations

Claisen condensations, like aldol reactions, also occur in a large number of biological pathways. In fatty-acid biosynthesis, for instance, an enolate ion generated by decarboxylation (Section 17-5) of malonyl ACP adds to the carbonyl group of another acyl group bonded through a thioester linkage to a synthase enzyme. The tetrahedral intermediate that results then expels the synthase, giving acetoacetyl ACP (**FIGURE 17.14**).

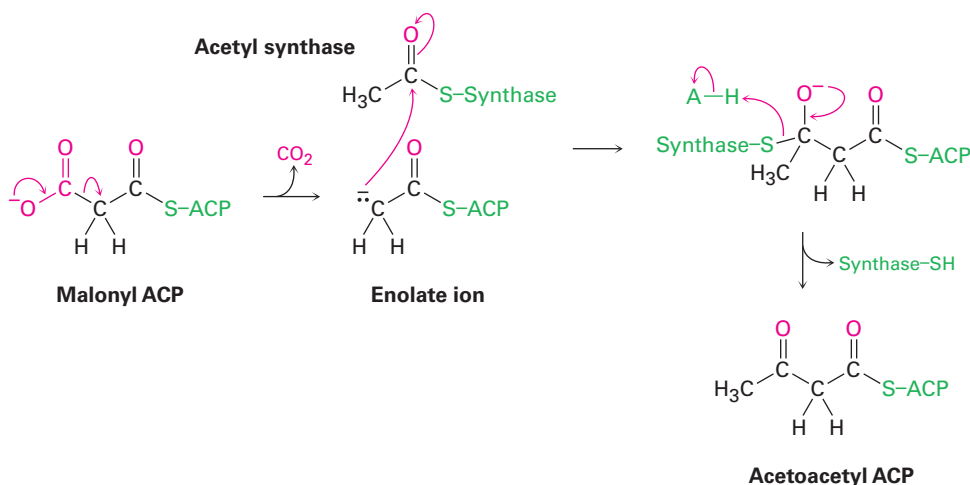
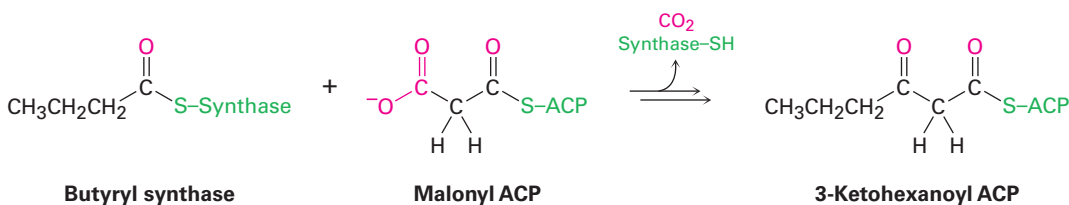


FIGURE 17.14 A Claisen condensation between two thioesters. The reaction occurs as the first step in fatty-acid biosynthesis.

Like the aldolase-catalyzed mixed aldol reaction, mixed Claisen condensations also occur frequently in living organisms, particularly in the pathway for fatty-acid biosynthesis that we'll discuss in Section 23-6. Butyryl synthase, for instance, reacts with malonyl ACP in a mixed Claisen condensation to give 3-ketohexanoyl ACP.



SOMETHING EXTRA

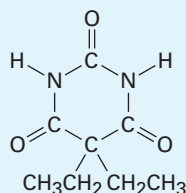
Barbiturates

The use of herbal remedies to treat illness and disease goes back thousands of years, but the medical use of chemicals prepared in the laboratory has a much shorter history. Barbiturates, a large class of drugs with a wide variety of uses, constitute one of the earliest successes of medicinal chemistry. The synthesis and medical use of barbiturates goes back to 1904 when Bayer, a German chemical company, first marketed a compound called barbital, trade named Veronal, as a treatment for insomnia. Since that time, more than 2500 different barbiturate analogs have been synthesized by drug companies, more than 50 have been used medicinally, and about a



Barbiturates come in a multitude of colors, giving rise to similarly colorful street names when the drugs are abused.

dozen are still in use as anesthetics, anticonvulsants, sedatives, and anxiolytics.



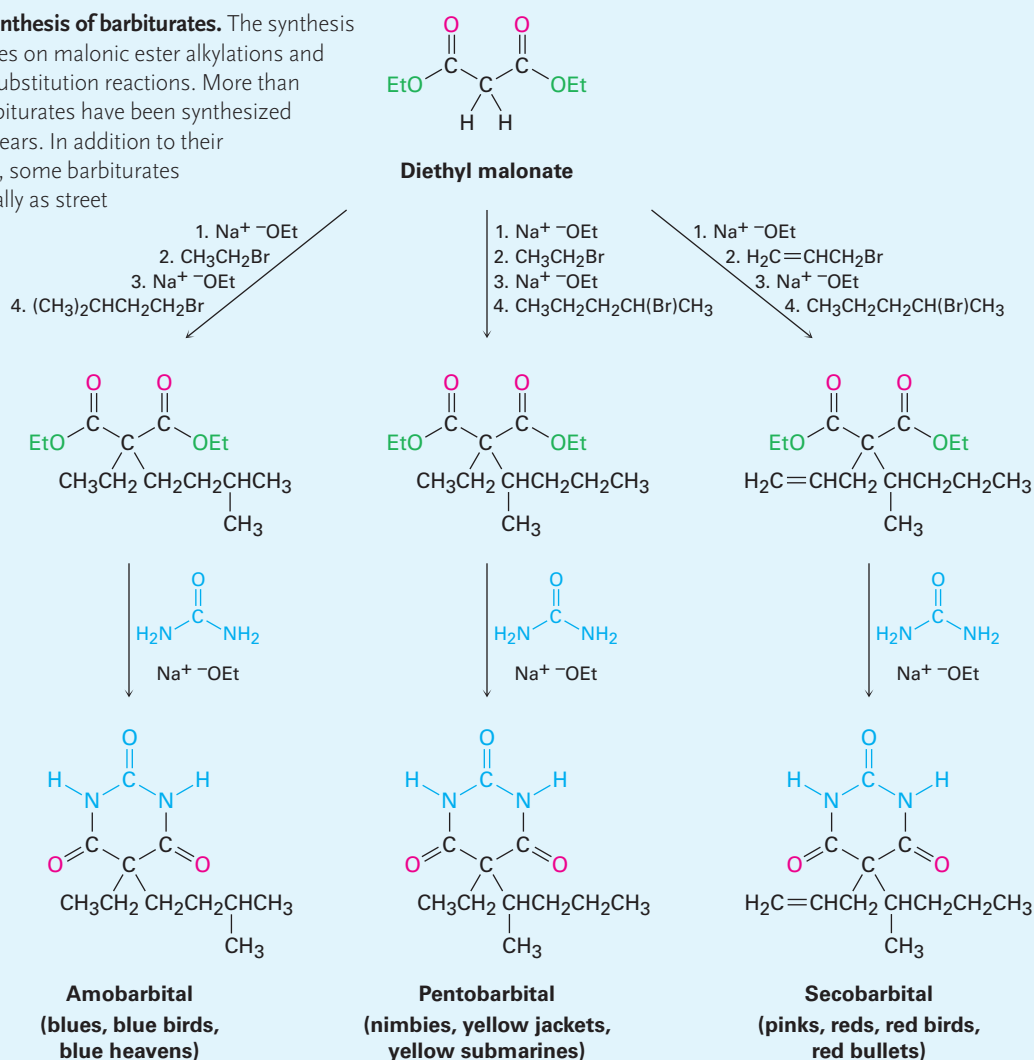
**Barbital (Veronal),
the first barbiturate**

The synthesis of barbiturates is relatively simple and relies on reactions that are now familiar: enolate alkylations and nucleophilic acyl substitutions. Starting with diethyl malonate, or malonic ester, alkylation of the corresponding enolate ion with simple alkyl

halides provides a wealth of different disubstituted malonic esters. Reaction with urea, $(\text{H}_2\text{N})_2\text{C}=\text{O}$, then gives the product barbiturates by a twofold nucleophilic acyl substitution reaction of the ester groups with the $-\text{NH}_2$ groups of urea (FIGURE 17.15). Amobarbital (Amytal), pentobarbital (Nembutal), and secobarbital (Seconal) are typical examples.

In addition to their prescribed medical uses, many barbiturates have also found widespread illegal use as street drugs. Each barbiturate comes as a tablet of regulated size, shape, and color, and their street names often mimic those colors. Although still used today, most barbiturates have been replaced by safer, more potent alternatives with markedly different structures.

FIGURE 17.15 Synthesis of barbiturates. The synthesis of barbiturates relies on malonic ester alkylations and nucleophilic acyl substitution reactions. More than 2500 different barbiturates have been synthesized over the past 100 years. In addition to their legal medical uses, some barbiturates are also used illegally as street drugs under many colorful names.



SUMMARY

Biochemical pathways make frequent use of α -substitution and carbonyl condensation reactions. In fact, practically every biosynthetic pathway for building up larger molecules from smaller precursors uses carbonyl condensation reactions for the purpose. In this chapter, we saw how and why these reactions occur.

Carbonyl compounds are in an equilibrium with their **enols**, a process called keto–enol tautomerism. Although enol **tautomers** are normally present to only a small extent at equilibrium and usually can't be isolated pure, they nevertheless contain a highly nucleophilic double bond and react with electrophiles in an **α -substitution reaction**. An example is the α halogenation of ketones on treatment with Cl_2 or Br_2 in acid solution. Alpha bromination of carboxylic acids can be similarly accomplished by the Hell–Volhard–Zelinskii (HVZ) reaction, in which an acid is treated with Br_2 and PBr_3 .

Alpha hydrogen atoms of carbonyl compounds are weakly acidic and can be removed by strong bases, such as lithium diisopropylamide (LDA), to yield strongly nucleophilic **enolate ions**. Among the most useful reactions of enolate ions is $\text{S}_{\text{N}}2$ alkylation with alkyl halides. The **malonic ester synthesis** converts an alkyl halide into a carboxylic acid with the addition of two carbon atoms ($\text{RX} \rightarrow \text{RCH}_2\text{CO}_2\text{H}$), and the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone ($\text{RX} \rightarrow \text{RCH}_2\text{COCH}_3$). In addition, many carbonyl compounds, including ketones, esters, and nitriles, can be directly alkylated by treatment with LDA and an alkyl halide.

A **carbonyl condensation reaction** takes place between two carbonyl partners and involves both nucleophilic addition and α -substitution processes. One carbonyl partner is converted by base into a nucleophilic enolate ion, which then adds to the electrophilic carbonyl group of the second partner. The first partner thus undergoes an α substitution, while the second undergoes a nucleophilic addition.

The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone molecules. Aldol reactions are reversible, leading first to β -hydroxy aldehydes/ketones and then to α,β -unsaturated products after dehydration. Intramolecular aldol condensations of 1,4- and 1,5-diketones are also successful and provide a good way to make five- and six-membered rings.

The **Claisen condensation reaction** is a carbonyl condensation that occurs between two ester components and gives a β -keto ester product. Intramolecular Claisen condensations, called **Dieckmann cyclizations**, yield five- and six-membered cyclic β -keto esters starting from 1,6- and 1,7-diester.

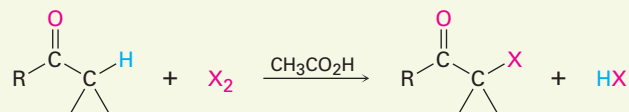
The conjugate addition of a carbon nucleophile to an α,β -unsaturated acceptor is known as the **Michael reaction**. The best Michael reactions take place between relatively acidic donors (β -keto esters or β -diketones) and unhindered α,β -unsaturated acceptors. Enamines, prepared by reaction of a ketone with a disubstituted amine, are also good Michael donors.

KEY WORDS

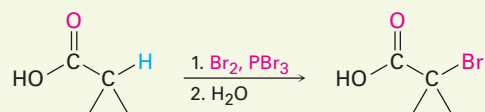
acetoacetic ester synthesis,	614
aldol reaction,	620
α -substitution reaction,	599
carbonyl condensation reaction,	599
Claisen condensation reaction,	627
Dieckmann cyclization reaction,	629
enol,	600
enolate ion,	601
malonic ester synthesis,	611
Michael reaction,	632
tautomer,	600

SUMMARY OF REACTIONS

1. Aldehyde/ketone halogenation (Section 17-2)

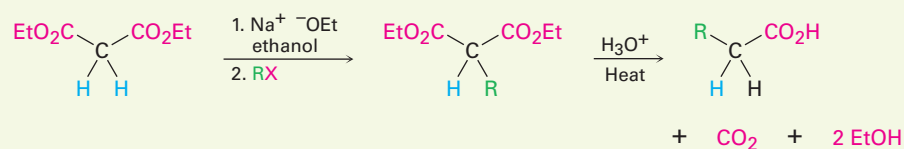


2. Hell-Volhard-Zelinskii bromination of acids (Section 17-3)

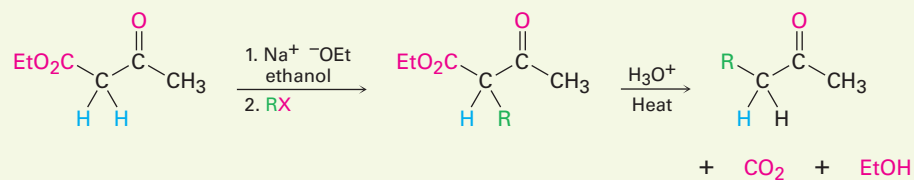


3. Alkylation of enolate ions (Section 17-5)

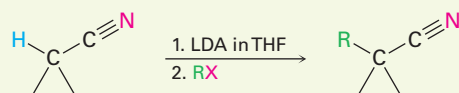
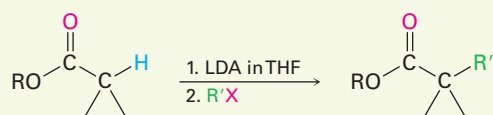
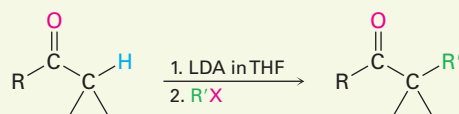
(a) Malonic ester synthesis



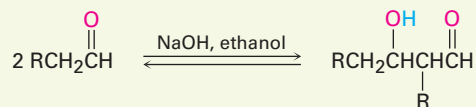
(b) Acetoacetic ester synthesis



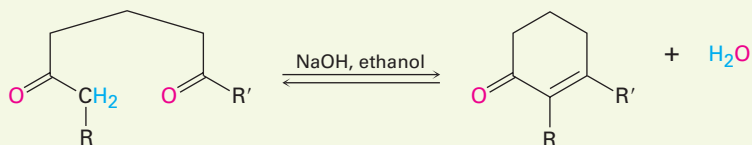
(c) Direct alkylation of ketones, esters, and nitriles



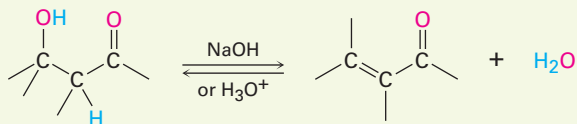
4. Aldol reaction (Section 17-6)



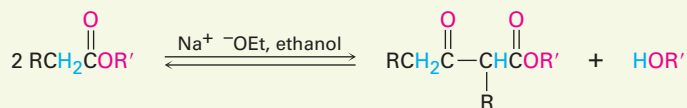
5. Intramolecular aldol reaction (Section 17-8)



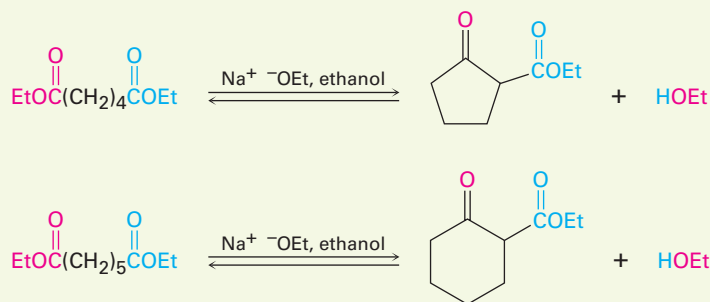
6. Dehydration of aldol products (Section 17-7)



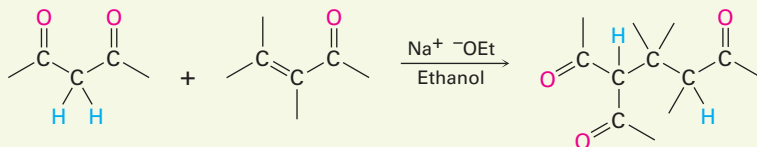
7. Claisen condensation reaction (Section 17-9)



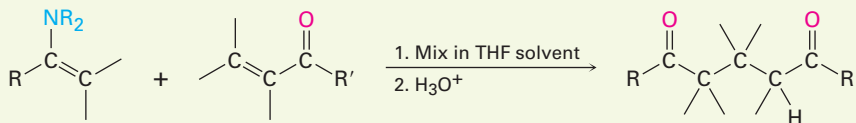
8. Intramolecular Claisen condensation (Dieckmann cyclization; Section 17-10)



9. Michael reaction (Section 17-11)



10. Carbonyl condensations with enamines (Stork reaction; Section 17-12)

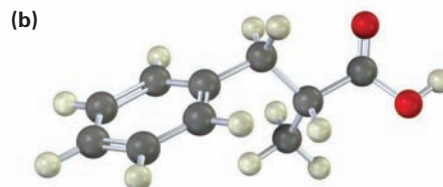
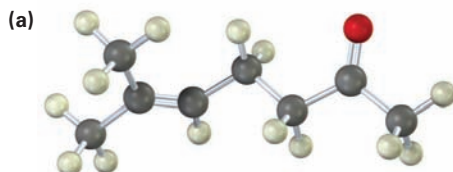


EXERCISES

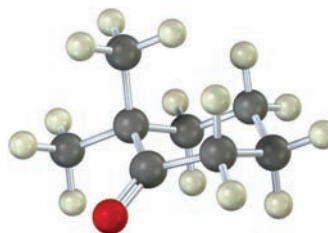
VISUALIZING CHEMISTRY

(Problems 17.1–17.30 appear within the chapter.)

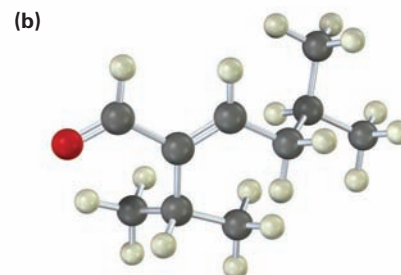
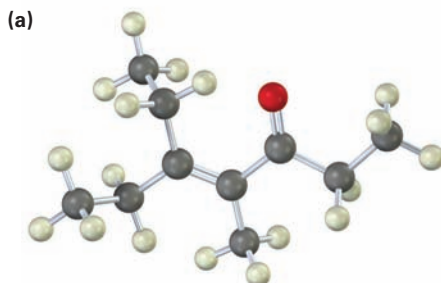
17.31 Show the steps in preparing each of the following substances, using either a malonic ester synthesis or an acetoacetic ester synthesis:



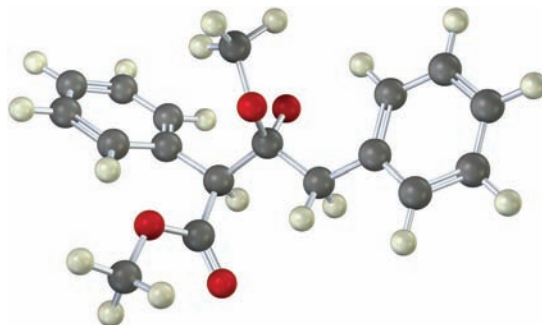
17.32 For a given α hydrogen atom to be acidic, the C–H bond must be parallel to the p orbitals of the C=O bond, that is, perpendicular to the plane of the adjacent carbonyl group. Identify the most acidic hydrogen atom in the following structure. Is it axial or equatorial?



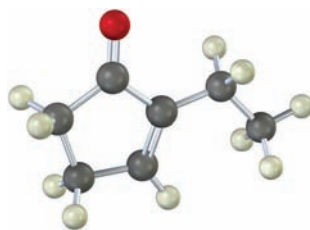
17.33 What ketones or aldehydes might the following enones have been prepared from by aldol reaction?



- 17.34 The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



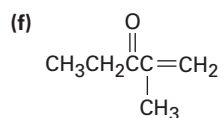
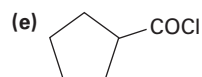
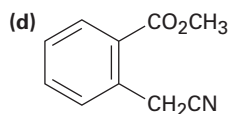
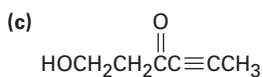
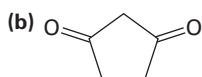
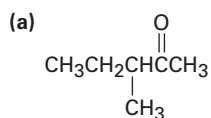
- 17.35 The following molecule was formed by an intramolecular aldol reaction. What dicarbonyl precursor was used for its preparation?



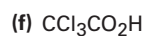
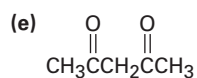
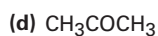
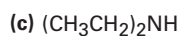
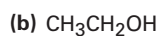
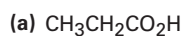
ADDITIONAL PROBLEMS

Acidity and Tautomerism

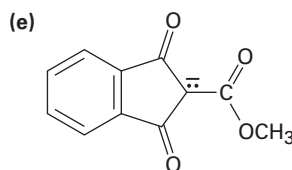
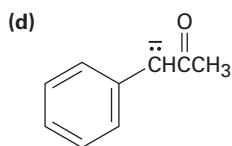
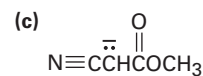
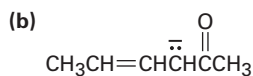
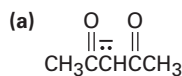
- 17.36 Identify all the acidic hydrogens ($pK_a < 25$) in the following molecules:



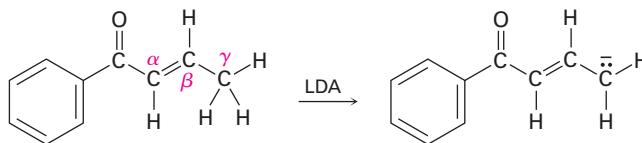
- 17.37 Rank the following compounds in order of increasing acidity:



17.38 Write resonance structures for the following anions:



17.39 Base treatment of the following α,β -unsaturated carbonyl compound yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?

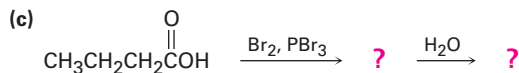
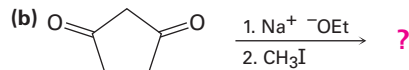
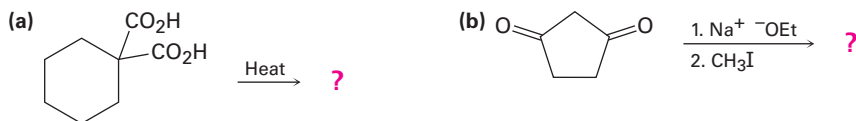


17.40 When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

17.41 Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (Problem 17.40)? Explain.

α -Substitution Reactions

17.42 Predict the product(s) of the following reactions:



17.43 Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.

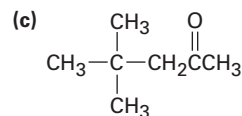
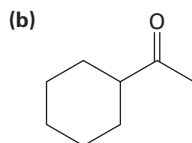
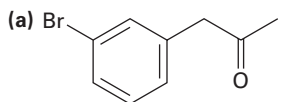
(a) Ethyl pentanoate

(b) Ethyl 3-methylbutanoate

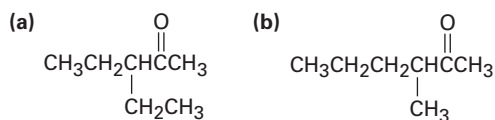
(c) Ethyl 2-methylbutanoate

(d) Ethyl 2,2-dimethylpropanoate

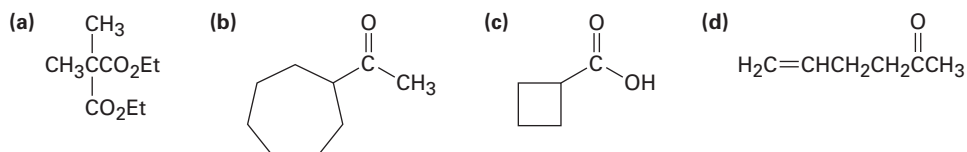
17.44 Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.



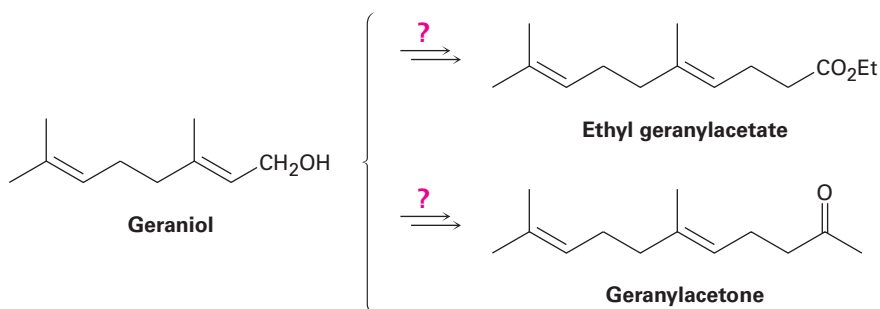
17.45 How would you prepare the following ketones using an acetoacetic ester synthesis?



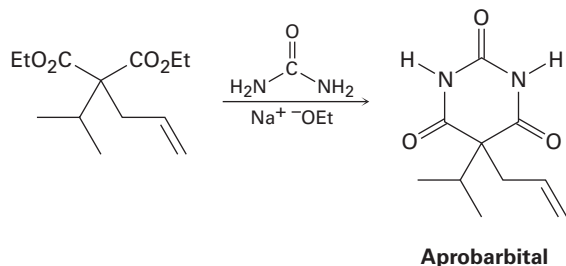
17.46 How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis?



17.47 How might you convert geraniol into either ethyl geranylacetate or geranylacetone?



17.48 Aprobarbital, a barbiturate once used in treating insomnia, is synthesized in three steps from diethyl malonate. Show how you would synthesize the necessary dialkylated intermediate, and then propose a mechanism for the reaction of that intermediate with urea to give aprobarbital.

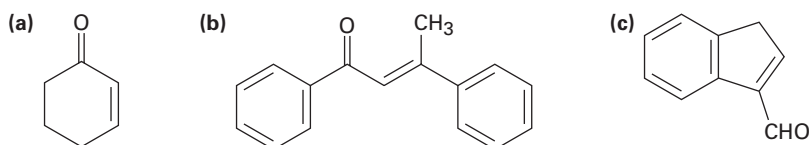


Aldol Reactions

17.49 Which of the following compounds would you expect to undergo aldol self-condensation? Show the product of each successful reaction.

- (a) Trimethylacetaldehyde (b) Cyclobutanone
 (c) Benzophenone (diphenyl ketone) (d) Pentan-3-one
 (e) Decanal (f) 3-Phenylprop-2-enal

17.50 How might you synthesize each of the following compounds using an aldol reaction? Show the structure of the starting aldehyde(s) or ketone(s) you would use in each case.



17.51 What product would you expect to obtain from aldol cyclization of hexanedial, $\text{OHCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$?

17.52 What condensation products would you expect to obtain by treatment of the following substances with sodium ethoxide in ethanol?

- (a) 4,4-Dimethylcyclohexanone (b) Cycloheptanone
 (c) Nonane-3,7-dione (d) 3-Phenylpropanal

17.53 Intramolecular aldol cyclization of heptane-2,5-dione with aqueous NaOH yields a mixture of two enone products in the approximate ratio 9:1. Write their structures, and show how each is formed.

17.54 The major product formed by intramolecular aldol cyclization of heptane-2,5-dione (Problem 17.53) has two singlet absorptions in the ^1H NMR spectrum at 1.65 δ and 1.90 δ , and has no absorptions in the range 3 to 10 δ . What is its structure?

17.55 Treatment of the minor product formed in the intramolecular aldol cyclization of heptane-2,5-dione (Problems 17.53 and 17.54) with aqueous NaOH converts it into the major product. Propose a mechanism for this base-catalyzed isomerization.

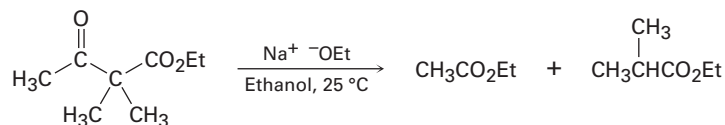
17.56 The aldol reaction is catalyzed by acid as well as by base. What is the reactive nucleophile in the acid-catalyzed aldol reaction? Propose a mechanism.

Claisen Condensations

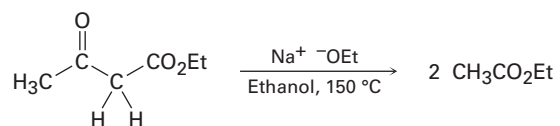
17.57 Give the structures of the possible Claisen condensation products from the following reactions. Tell which, if any, you would expect to predominate in each case.

- (a) $\text{CH}_3\text{CO}_2\text{Et} + \text{CH}_3\text{CH}_2\text{CO}_2\text{Et}$ (b) $\text{C}_6\text{H}_5\text{CO}_2\text{Et} + \text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Et}$
 (c) $\text{EtOCO}_2\text{Et} + \text{cyclohexanone}$ (d) $\text{C}_6\text{H}_5\text{CHO} + \text{CH}_3\text{CO}_2\text{Et}$

- 17.58** Ethyl dimethylacetoacetate reacts instantly at room temperature when treated with ethoxide ion to yield two products, ethyl acetate and ethyl 2-methylpropanoate. Propose a mechanism for this cleavage reaction.

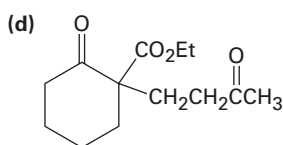
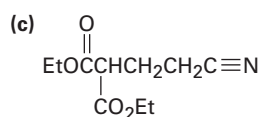
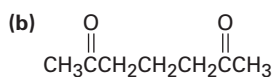
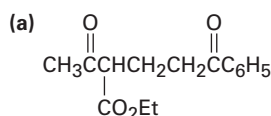


- 17.59** In contrast to the rapid reaction shown in Problem 17.58, ethyl acetoacetate requires a temperature over 150°C to undergo the same kind of cleavage reaction. How can you explain the difference in reactivity?

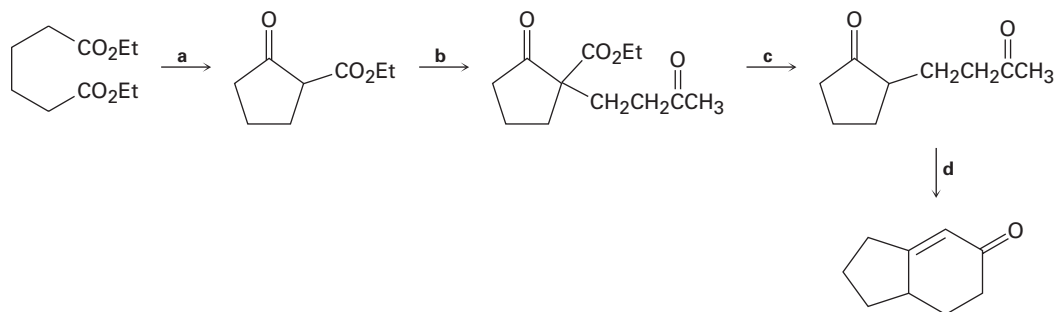


Michael and Enamine Reactions

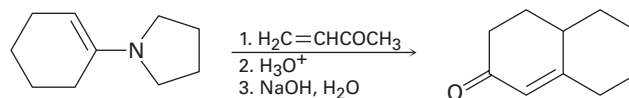
- 17.60** How might the following compounds be prepared using Michael reactions? Show the nucleophilic donor and the electrophilic acceptor in each case.



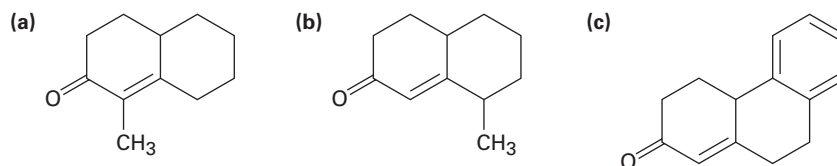
- 17.61** Fill in the missing reagents **a–d** in the following scheme:



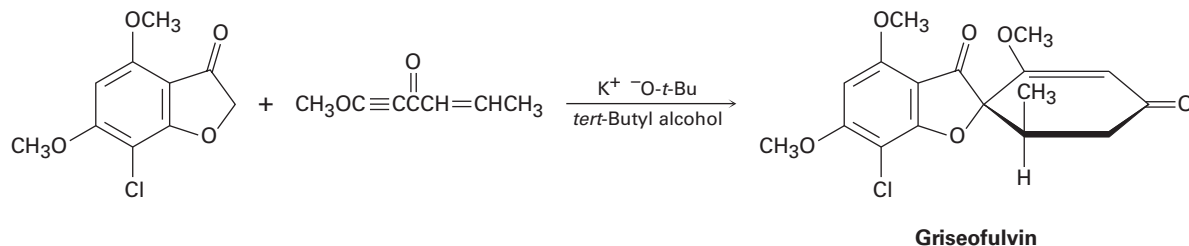
- 17.62** The Stork enamine reaction and the intramolecular aldol reaction can be carried out in sequence to allow the synthesis of cyclohexenones. For example, reaction of the pyrrolidine enamine of cyclohexanone with but-3-en-2-one, followed by enamine hydrolysis and base treatment, yields the product indicated. Write each step, and show the mechanism of each.



- 17.63** How could you prepare the following cyclohexenones by combining a Stork enamine reaction with an intramolecular aldol condensation? (See Problem 17.62.)

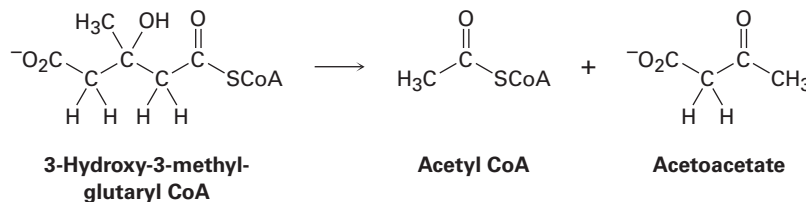


- 17.64** Griseofulvin, an antibiotic produced by the mold *Penicillium griseofulvum* (Dierckx), has been synthesized by a route that employs a twofold Michael reaction as the key step. Propose a mechanism.

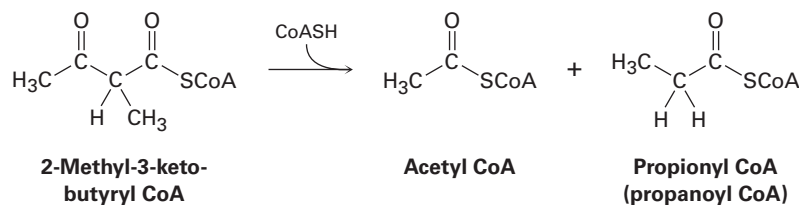


General Problems

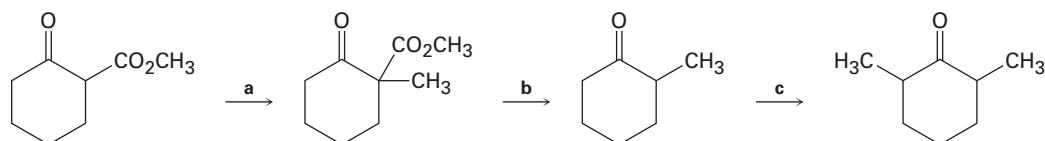
- 17.65** Butan-1-ol is prepared commercially by a route that begins with an aldol reaction. What is the likely starting material, and what steps are likely to be involved?
- 17.66** Leucine, one of the 20 amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



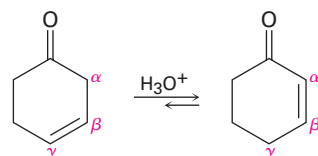
- 17.67 Isoleucine, another of the 20 amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



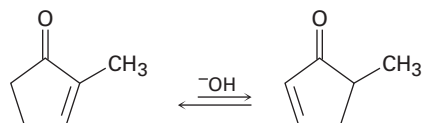
- 17.68 Fill in the reagents **a–c** that are missing from the following scheme:



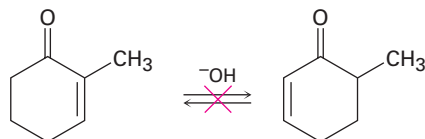
- 17.69 Nonconjugated β,γ -unsaturated ketones, such as cyclohex-3-enone, are in both an acid- and a base-catalyzed equilibrium with their conjugated α,β -unsaturated isomers. Propose a mechanism.



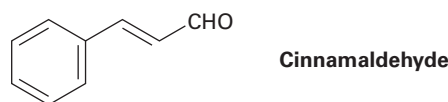
- 17.70 A consequence of the base-catalyzed isomerization of unsaturated ketones described in Problem 17.69 is that 2-substituted cyclopent-2-enones can be interconverted with 5-substituted cyclopent-2-enones. Propose a mechanism.



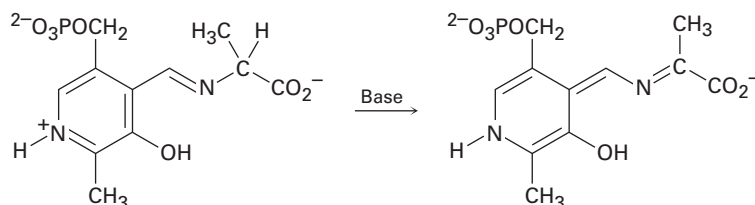
- 17.71 Although 2-substituted cyclopent-2-enones are in a base-catalyzed equilibrium with their 5-substituted cyclopent-2-enone isomers (Problem 17.70), the analogous isomerization is not observed for 2-substituted cyclohex-2-enones. Explain.



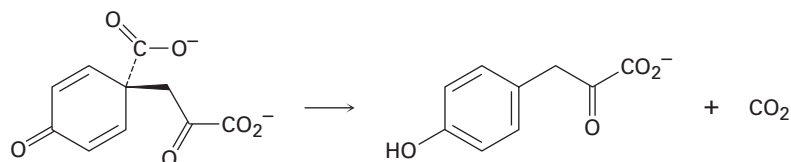
- 17.72** Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol condensation between two different carbonyl compounds. Show the starting materials you would use, and write the reaction.



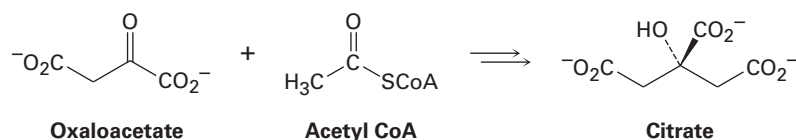
- 17.73** Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine:



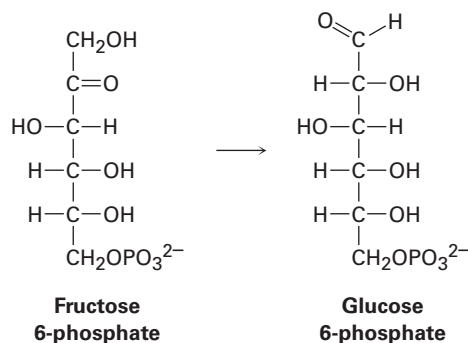
- 17.74** Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.



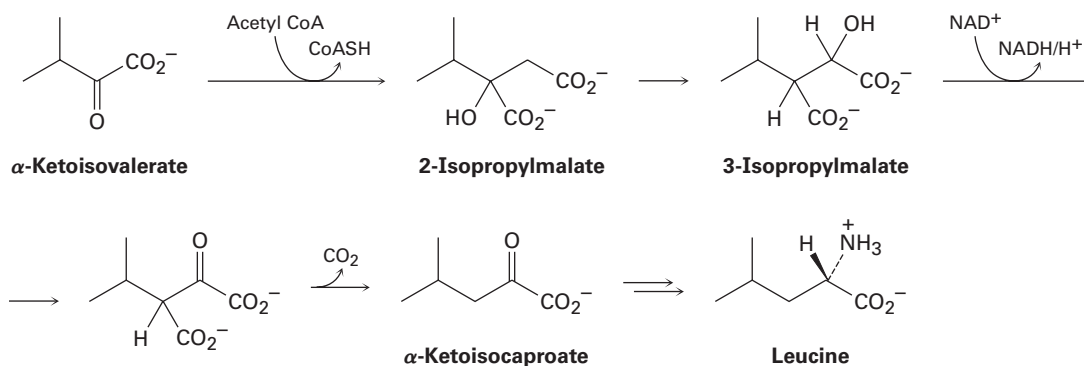
- 17.75** The first step in the citric acid cycle of food metabolism is reaction of oxaloacetate with acetyl CoA to give citrate. Propose a mechanism, using acid or base catalysis as needed.



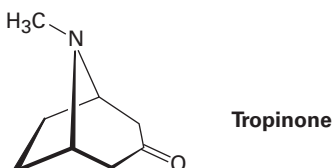
- 17.76** One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.



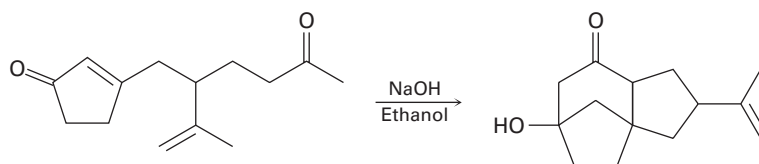
- 17.77 The amino acid leucine is biosynthesized from α -ketoisovalerate by the following sequence of steps. Show the mechanism of each.



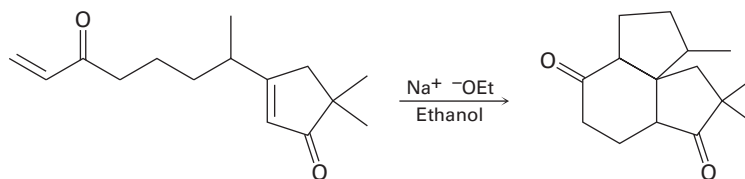
- 17.78 As far back as the 16th century, South American Incas chewed the leaves of the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of cocaine, $\text{C}_{17}\text{H}_{21}\text{NO}_4$, as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called ecgonine, $\text{C}_9\text{H}_{15}\text{NO}_3$. Oxidation of ecgonine with CrO_3 yields a keto acid that readily loses CO_2 on heating, giving tropinone.



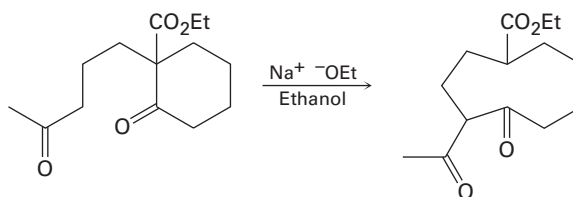
- (a) What is a likely structure for the keto acid?
- (b) What is a likely structure for ecgonine, neglecting stereochemistry?
- (c) What is a likely structure for cocaine, neglecting stereochemistry?
- 17.79 The following reaction involves an intramolecular Michael reaction followed by an intramolecular aldol reaction. Write both steps, and show their mechanisms.



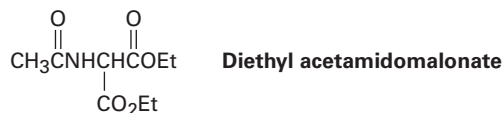
- 17.80** The following reaction involves two successive intramolecular Michael reactions. Write both steps, and show their mechanisms.



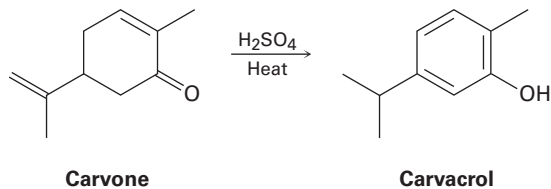
- 17.81** The following reaction involves an intramolecular aldol reaction followed by a *retro* aldol-like reaction. Write both steps, and show their mechanisms.



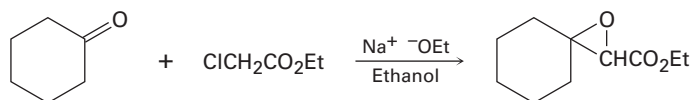
- 17.82** Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $\text{CH}_3\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$, one of the 20 amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.



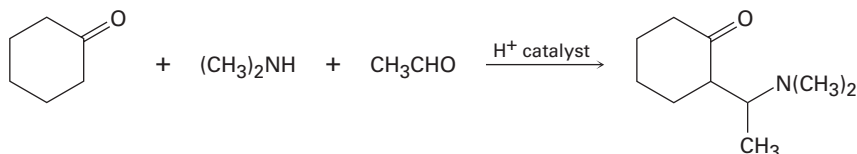
- 17.83** Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$, and identify the mechanism of the second step.
- 17.84** Heating the terpene carvone with aqueous sulfuric acid converts it into carvacrol. Propose a mechanism for the isomerization.



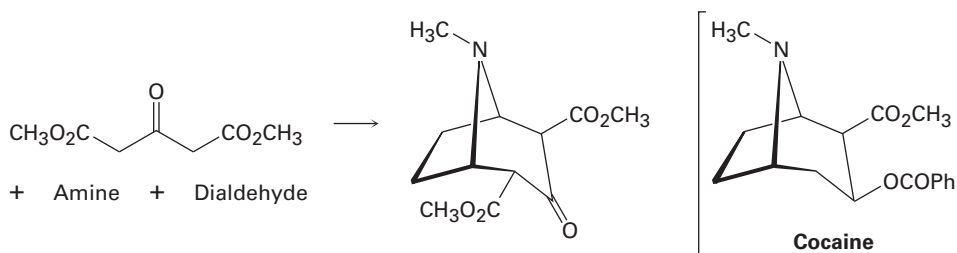
- 17.85** The *Darzens reaction* involves a two-step, base-catalyzed condensation of ethyl chloroacetate with a ketone to yield an epoxy ester. The first step is a carbonyl condensation reaction, and the second step is an S_N2 reaction. Write both steps, and show their mechanisms.



- 17.86** The *Mannich reaction* of a ketone, an amine, and an aldehyde is one of the few three-component reactions in organic chemistry. Cyclohexanone, for example, reacts with dimethylamine and acetaldehyde to yield an amino ketone. The reaction takes place in two steps, both of which are typical carbonyl-group reactions.



- (a) The first step is reaction between the aldehyde and the amine to yield an intermediate iminium ion ($R_2C=NR_2^+$) plus water. Propose a mechanism, and show the structure of the intermediate iminium ion.
- (b) The second step is reaction between the iminium ion intermediate and the ketone to yield the final product. Propose a mechanism.
- 17.87** Cocaine has been prepared by a sequence beginning with a Mannich reaction (Problem 17.86) between dimethyl acetonedicarboxylate, an amine, and a dialdehyde. Show the structures of the amine and dialdehyde.



18

Amines and Heterocycles

CONTENTS

- 18-1 Naming Amines
- 18-2 Properties of Amines
- 18-3 Basicity of Amines
- 18-4 Basicity of Arylamines
- 18-5 Biological Amines and the Henderson–Hasselbalch Equation
- 18-6 Synthesis of Amines
- 18-7 Reactions of Amines
- 18-8 Heterocyclic Amines
- 18-9 Fused-Ring Heterocycles
- 18-10 Spectroscopy of Amines

SOMETHING EXTRA
Green Chemistry



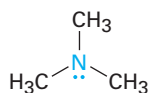
Glutamine synthase catalyzes the reductive amination of α -ketoglutarate to give glutamate, a step in amino acid metabolism.

WHY THIS CHAPTER?

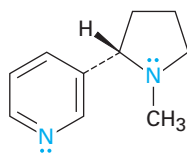
By the end of this chapter, we will have seen all the common functional groups that occur in biomolecules. Of those groups, amines and carbonyl compounds are the most abundant and have the richest chemistry. In addition to the proteins and nucleic acids already mentioned, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We'll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

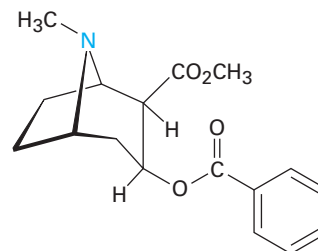
Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish, nicotine is found in tobacco, and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



Trimethylamine



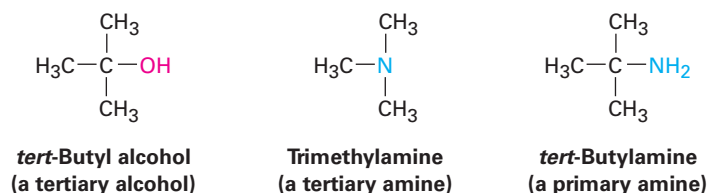
Nicotine



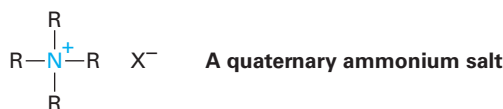
Cocaine

18-1 Naming Amines

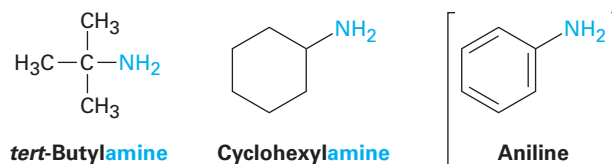
Amines can be either alkyl-substituted (**alkylamines**) or aryl-substituted (**arylamines**). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as **primary** (RNH_2), **secondary** (R_2NH), or **tertiary** (R_3N), depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary amine, dimethylamine $[(\text{CH}_3)_2\text{NH}]$ is a secondary amine, and trimethylamine $[(\text{CH}_3)_3\text{N}]$ is a tertiary amine. Note that this usage of the terms primary, secondary, and tertiary is different from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



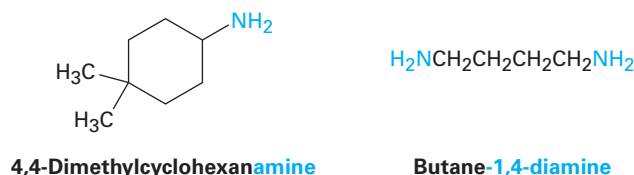
Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called **quaternary ammonium salts**.



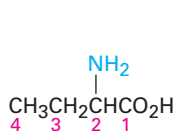
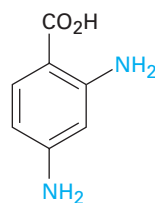
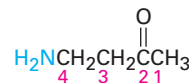
Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent. You might also recall from Chapter 9 that phenylamine, $\text{C}_6\text{H}_5\text{NH}_2$, has the common name *aniline*.



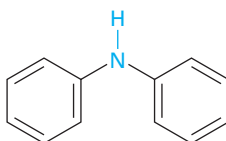
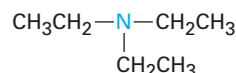
Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound:



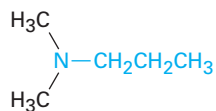
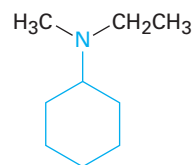
Amines with more than one functional group are named by considering the -NH_2 as an *amino* substituent on the parent molecule:

**2-Amino**butanoic acid**2,4-Diamino**benzoic acid**4-Amino**butan-2-one

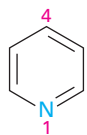
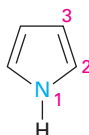
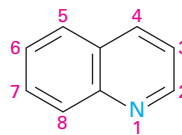
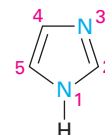
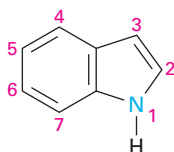
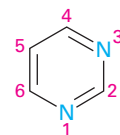
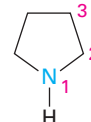
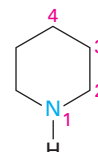
Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group:

**Diphenylamine****Triethylamine**

Unsymmetrically substituted secondary and tertiary amines are named as *N*-substituted primary amines. The largest alkyl group is chosen as the parent name, and the other alkyl groups are considered *N*-substituents on the parent (*N* because they're attached to nitrogen).

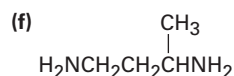
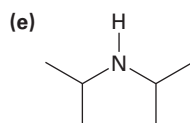
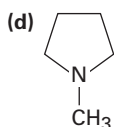
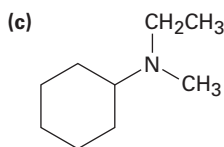
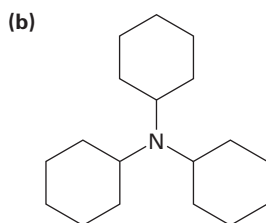
***N,N*-Dimethyl**propylamine***N*-Ethyl-*N*-methyl**cyclohexylamine

Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.

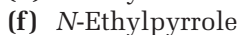
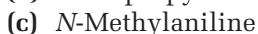
**Pyridine****Pyrrole****Quinoline****Imidazole****Indole****Pyrimidine****Pyrrolidine****Piperidine**

PROBLEM 18.1

Name the following compounds:

**PROBLEM 18.2**

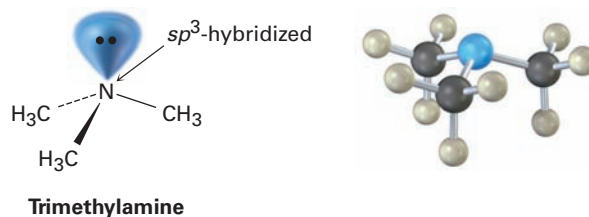
Draw structures corresponding to the following IUPAC names:

**PROBLEM 18.3**

Draw structures for the following heterocyclic amines:

**18-2 Properties of Amines**

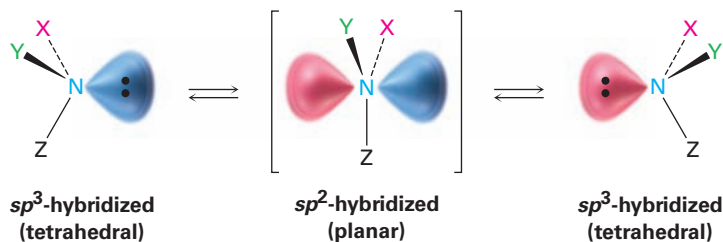
The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3 -hybridized, with the three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value— 108° in trimethylamine, for example.



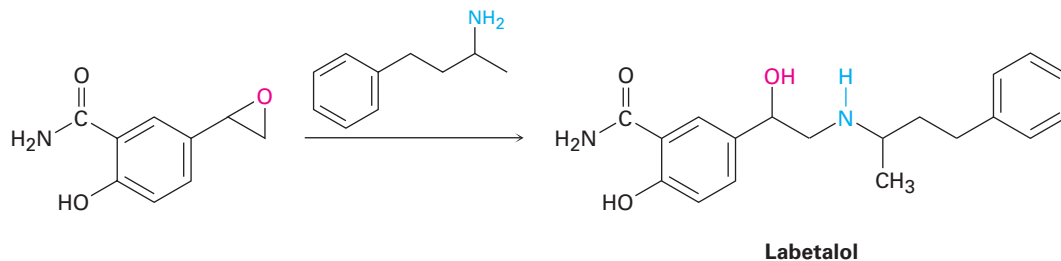
One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral, as we saw in Section 5-10. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a pyramidal

inversion, much as an alkyl halide inverts during an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry (FIGURE 18.1). The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C–C single bond.

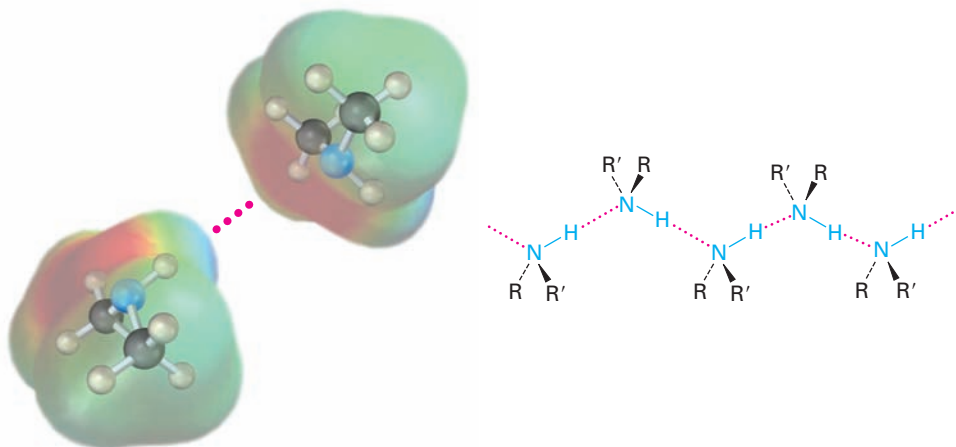
FIGURE 18.1 Pyramidal inversion of an amine. The two mirror-image (enantiomeric) forms of an amine are rapidly interconverted by pyramidal inversion.



Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. Labetalol, for instance, a so-called β -blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity derives primarily from the (*R,R*) isomer.



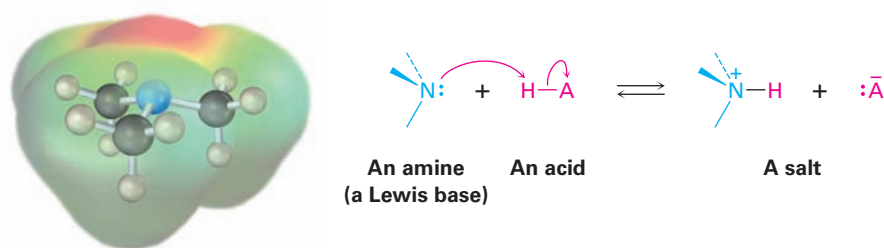
Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.



One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (pentane-1,5-diamine) and putrescine (butane-1,4-diamine) have the appalling odors you might expect from their common names. Both these diamines arise from the decomposition of proteins.

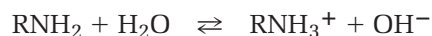
18-3 Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential map of trimethylamine how the negative (red) region corresponds to the lone pair of electrons on nitrogen.



Amines are much stronger bases than alcohols and ethers, their oxygen-containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous *basicity constant* K_b . The larger the K_b , and the smaller the pK_b , the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction:

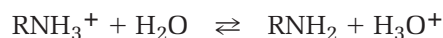


$$K_b = \frac{[\text{RNH}_3^+][\text{OH}^-]}{[\text{RNH}_2]}$$

$$pK_b = -\log K_b$$

In practice, K_b values are not often used. Instead, the most convenient way to measure the basicity of an amine (RNH_2) is to look at the acidity of the corresponding ammonium ion (RNH_3^+).

For the reaction:



$$K_a = \frac{[\text{RNH}_2][\text{H}_3\text{O}^+]}{[\text{RNH}_3^+]}$$

so

$$K_a \cdot K_b = \left[\frac{[\text{RNH}_2][\text{H}_3\text{O}^+]}{[\text{RNH}_3^+]} \right] \left[\frac{[\text{RNH}_3^+][\text{OH}^-]}{[\text{RNH}_2]} \right]$$

$$= [\text{H}_3\text{O}^+][\text{OH}^-] = K_w = 1.00 \times 10^{-14}$$

Thus, $K_a = \frac{K_w}{K_b}$ and $K_b = \frac{K_w}{K_a}$

and $\text{p}K_a + \text{p}K_b = 14$





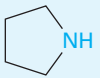
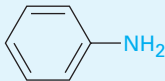
These equations say that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w , the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller $\text{p}K_a$, and a stronger base has an ammonium ion with a larger $\text{p}K_a$.

Weaker base Smaller $\text{p}K_a$ for ammonium ion

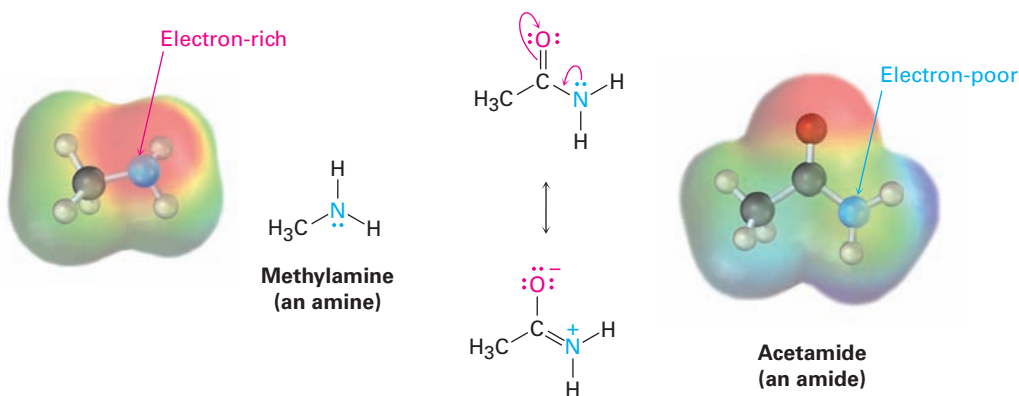
Stronger base Larger $\text{p}K_a$ for ammonium ion

TABLE 18.1 lists $\text{p}K_a$ values of the ammonium ions from a variety of amines and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with $\text{p}K_a$'s for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

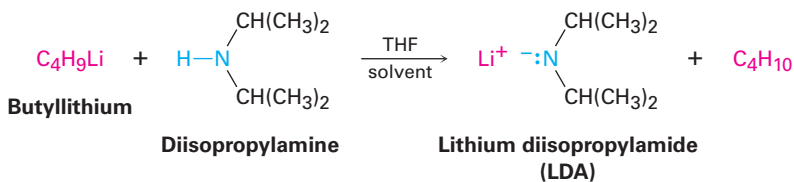
TABLE 18.1 Basicity of Some Common Amines

Name	Structure	$\text{p}K_a$ of ammonium ion	Name	Structure	$\text{p}K_a$ of ammonium ion
Ammonia	NH_3	9.26	Heterocyclic amine		
Primary alkylamine			Pyridine		5.25
Methylamine	CH_3NH_2	10.64	Pyrimidine		1.3
Ethylamine	$\text{CH}_3\text{CH}_2\text{NH}_2$	10.75	Pyrrole		0.4
Secondary alkylamine			Imidazole		6.95
Diethylamine	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	10.98			
Pyrrolidine		11.27			
Tertiary alkylamine					
Triethylamine	$(\text{CH}_3\text{CH}_2)_3\text{N}$	10.76			
Arylamine					
Aniline		4.63			

In contrast with amines, amides (RCONH_2) are nonbasic. Amides aren't protonated by aqueous acids, and they are poor nucleophiles. The main reason for this difference in basicity between amines and amides is that an amide is stabilized by delocalization of the nitrogen lone-pair electrons through orbital overlap with the carbonyl group. In resonance terms, amides are more stable and less reactive than amines because they are hybrids of two resonance forms. This amide resonance stabilization is lost when the nitrogen atom is protonated, so protonation is disfavored. Electrostatic potential maps show clearly the decreased electron density on the amide nitrogen.



In addition to their behavior as bases, primary and secondary amines can also act as very weak acids because an N–H proton can be removed by a sufficiently strong base. We've seen, for example, how diisopropylamine ($\text{p}K_{\text{a}} \approx 36$) reacts with butyllithium to yield lithium diisopropylamide (LDA; Section 17-4). Dialkylamine anions like LDA are very strong bases that are often used in laboratory organic chemistry for the generation of enolate ions from carbonyl compounds (Section 17-5). They are not, however, encountered in biological chemistry.



PROBLEM 18.4

Which compound in each of the following pairs is more basic?

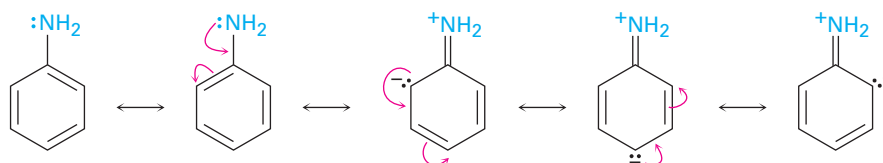
- (a) $\text{CH}_3\text{CH}_2\text{NH}_2$ or $\text{CH}_3\text{CH}_2\text{CONH}_2$ (b) NaOH or CH_3NH_2
 (c) CH_3NHCH_3 or pyridine

PROBLEM 18.5

The benzylammonium ion ($\text{C}_6\text{H}_5\text{CH}_2\text{NH}_3^+$) has $\text{p}K_{\text{a}} = 9.33$, and the propylammonium ion has $\text{p}K_{\text{a}} = 10.71$. Which is the stronger base, benzylamine or propylamine? What are the $\text{p}K_{\text{b}}$'s of benzylamine and propylamine?

18-4 Basicity of Arylamines

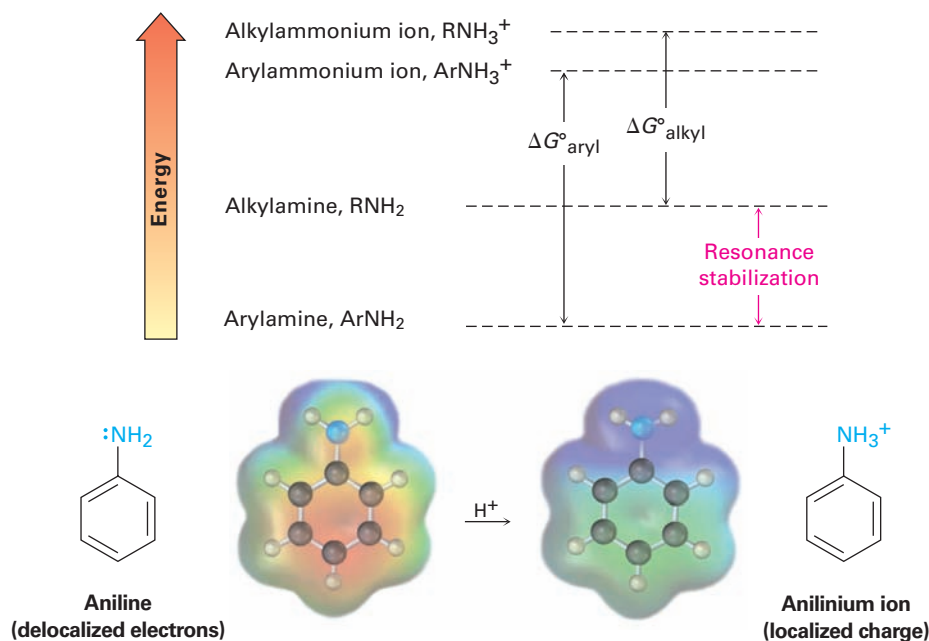
As noted previously, arylamines are generally less basic than alkylamines. Anilinium ion has $pK_a = 4.63$, for instance, whereas methylammonium ion has $pK_a = 10.64$. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring π electron system and are less available for bonding to H^+ . In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms:



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and nonprotonated forms is higher for arylamines than it is for alkylamines, making arylamines less basic.

FIGURE 18.2 illustrates the difference.


FIGURE 18.2 Comparison of arylamine and alkylamine basicities. Arylamines have a larger positive ΔG° for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.



Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $-CH_3$ and $-OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution (Section 9-8), also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as $-Cl$, $-NO_2$, and $-CN$, which decrease ring reactivity toward electrophilic substitution, also decrease

arylamine basicity. TABLE 18.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

TABLE 18.2 Base Strength of Some *p*-Substituted Anilines



	Substituent, Y	p <i>K</i> _a	
Stronger base ↑	-NH ₂	6.15	Activating groups
	-OCH ₃	5.34	
	-CH ₃	5.08	
	-H	4.63	
Weaker base ↓	-Cl	3.98	Deactivating groups
	-Br	3.86	
	-CN	1.74	
	-NO ₂	1.00	

PROBLEM 18.6

Rank the following compounds in order of increasing basicity:

- (a) *p*-Nitroaniline, *p*-aminobenzaldehyde, *p*-bromoaniline
 (b) *p*-Chloroaniline, *p*-aminoacetophenone, *p*-methylaniline
 (c) *p*-(Trifluoromethyl)aniline, *p*-methylaniline, *p*-(fluoromethyl)aniline

18-5 Biological Amines and the Henderson–Hasselbalch Equation

We saw in Section 15-3 that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO₂⁻.

Henderson–Hasselbalch equation:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad \text{so} \quad \log \frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_a$$

What about amine bases? In what form do they exist at the physiological pH inside cells—as the amine ($A^- = \text{RNH}_2$) or as the ammonium ion ($\text{HA} = \text{RNH}_3^+$)? Let's take a 0.0010 M solution of methylamine at $\text{pH} = 7.3$, for example. According to Table 18.1, the $\text{p}K_a$ of methylammonium ion is 10.64, so from the Henderson–Hasselbalch equation, we have:

$$\log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{pH} - \text{p}K_a = 7.3 - 10.64 = -3.34$$

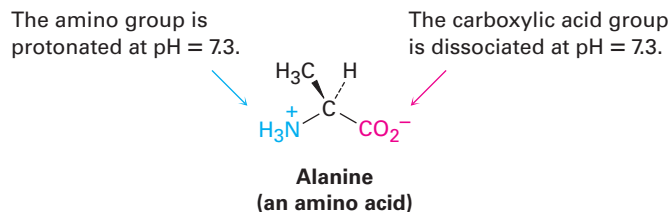
$$\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{antilog}(-3.34) = 4.6 \times 10^{-4}$$

so $[\text{RNH}_2] = (4.6 \times 10^{-4}) [\text{RNH}_3^+]$

In addition, we know that

$$[\text{RNH}_2] + [\text{RNH}_3^+] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives $[\text{RNH}_3^+] = 0.0010 \text{ M}$ and $[\text{RNH}_2] = 5 \times 10^{-7} \text{ M}$. In other words, at a physiological pH of 7.3, essentially 100% of the methylamine in a 0.0010 M solution exists in its protonated form as methylammonium ion. The same is true of other amine bases, so we always write cellular amines in their protonated form and amino acids in their ammonium carboxylate form to reflect their structures at physiological pH.



PROBLEM 18.7

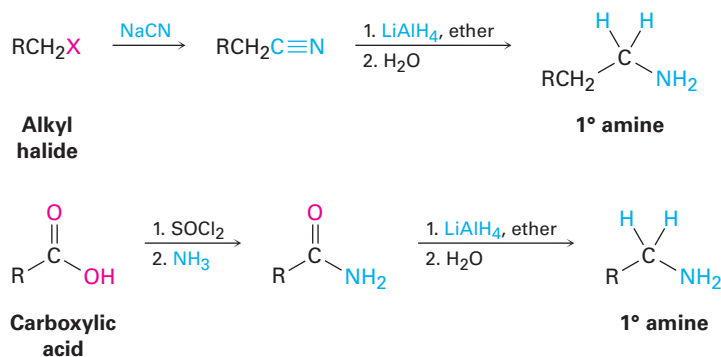
Calculate the percentages of neutral and protonated forms present in a solution of 0.0010 M pyrimidine at $\text{pH} = 7.3$. The $\text{p}K_a$ of pyrimidinium ion is 1.3.

18-6 Synthesis of Amines

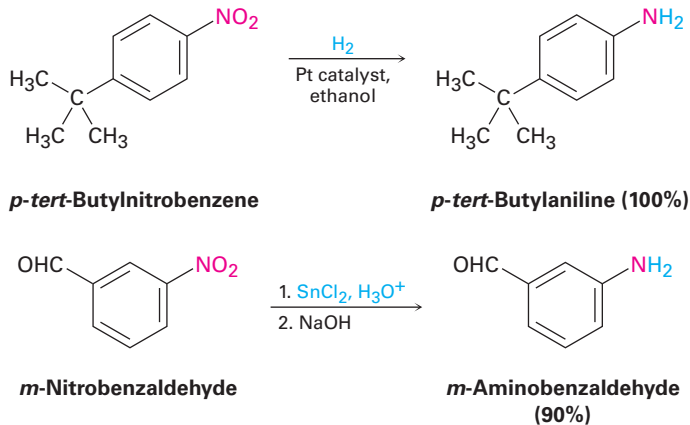
Reduction of Nitriles, Amides, and Nitro Compounds

We've already seen in Sections 15-7 and 16-7 how amines can be prepared by reduction of nitriles and amides with LiAlH_4 . The two-step sequence of $\text{S}_{\text{N}}2$ displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having one more carbon atom. Amide

reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.



Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group (Section 9-6). The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups. Iron, zinc, tin, and tin(II) chloride (SnCl₂) are also effective when used in acidic aqueous solution. Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



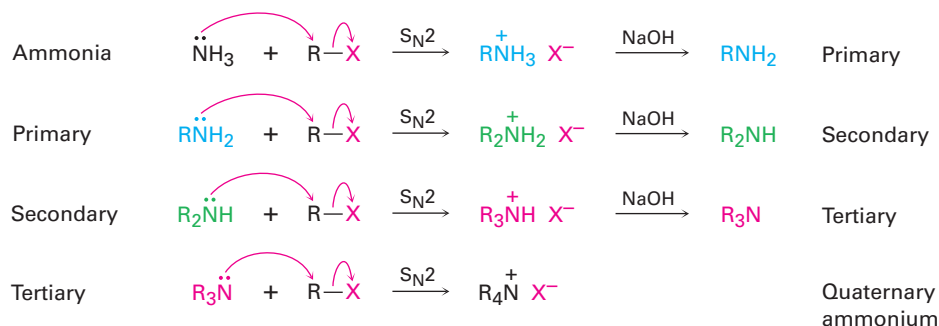
PROBLEM 18.8

Propose structures for either a nitrile or an amide that might be a precursor of each of the following amines:

- (a) CH₃CH₂CH₂NH₂ (b) (CH₃CH₂CH₂)₂NH
 (c) Benzylamine, C₆H₅CH₂NH₂ (d) *N*-Ethylaniline

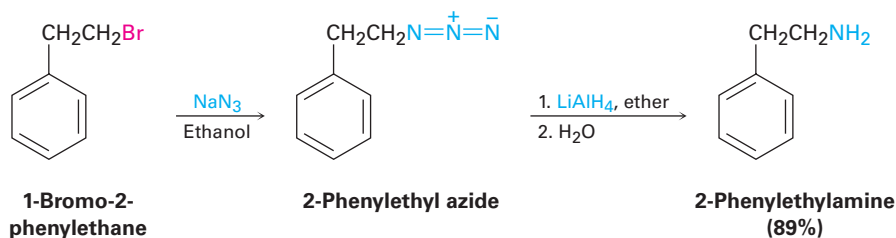
S_N2 Reactions of Alkyl Halides

Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, R₄N⁺ X⁻.



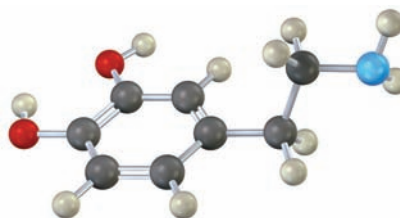
Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of mono-, di-, and trialkylated products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent.

A better method for preparing primary amines from alkyl halides is to use azide ion, N₃⁻, as the nucleophile rather than ammonia. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with LiAlH₄ leads to the desired primary amine. Although the method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.



PROBLEM 18.9

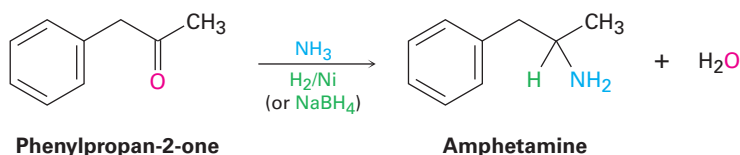
Show two methods for synthesizing dopamine, a neurotransmitter involved in regulation of the central nervous system.



Dopamine

Reductive Amination of Aldehydes and Ketones

Amines can be synthesized from an aldehyde or ketone in a single step by reaction with ammonia or an amine in the presence of a reducing agent, a process called **reductive amination**. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenylpropan-2-one with ammonia, using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, NaBH_4 is often used as the reducing agent rather than H_2 and nickel.



Reductive amination takes place by the pathway shown in **FIGURE 18.3**. An imine intermediate is first formed by a nucleophilic addition reaction (Section 14-7), and the $\text{C}=\text{N}$ bond of the imine is then reduced to the amine, much as the $\text{C}=\text{O}$ bond of a ketone can be reduced to an alcohol.

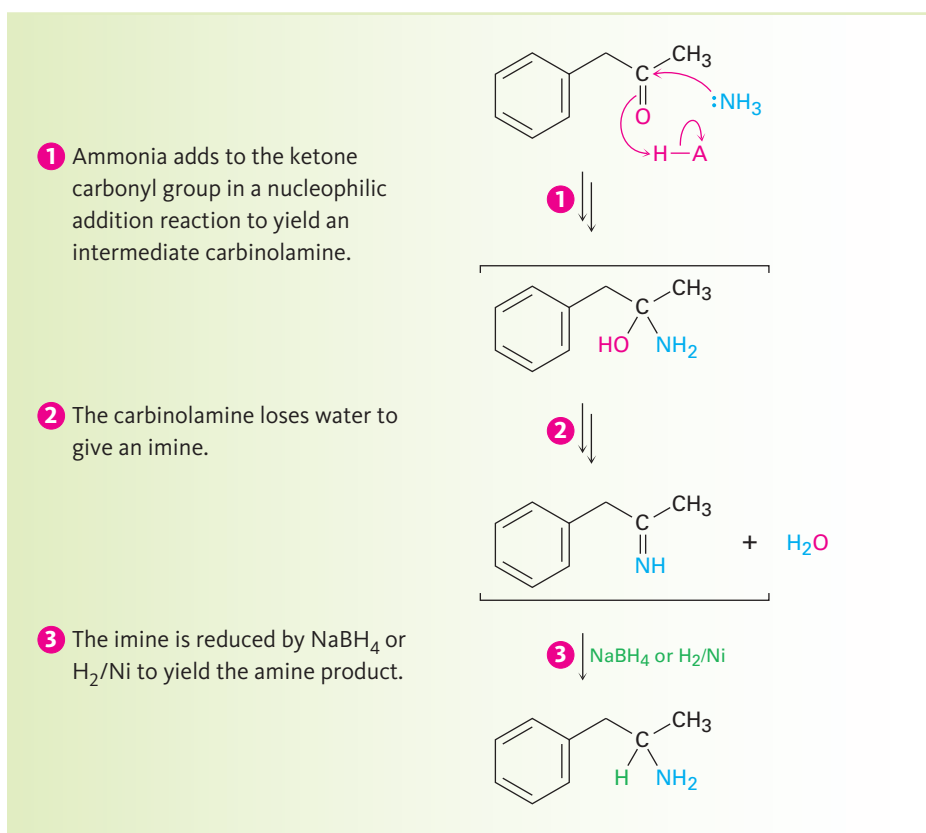
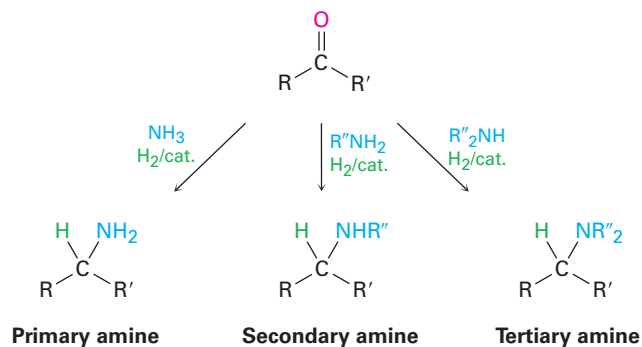
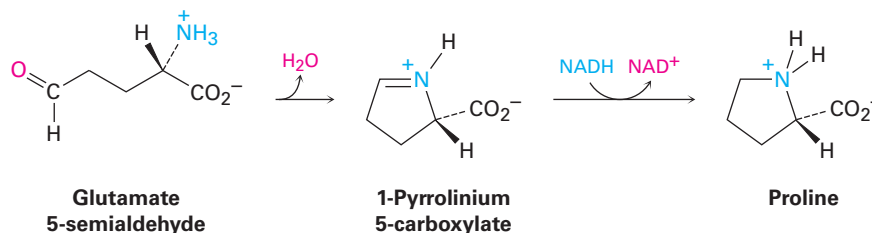


FIGURE 18.3 Mechanism of reductive amination of a ketone to yield an amine. The details of the imine-forming step were shown in Figure 14.6 on page 506.

Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.



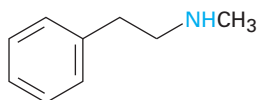
Reductive aminations also occur in various biological pathways. In the biosynthesis of the amino acid proline, for instance, glutamate 5-semialdehyde undergoes internal imine formation to give 1-pyrrolinium 5-carboxylate, which is then reduced by nucleophilic addition of hydride ion to the C=N bond. Reduced nicotinamide adenine dinucleotide, NADH, acts as the biological reducing agent.



WORKED EXAMPLE 18.1

Using a Reductive Amination Reaction

How might you prepare *N*-methyl-2-phenylethylamine using a reductive amination reaction?



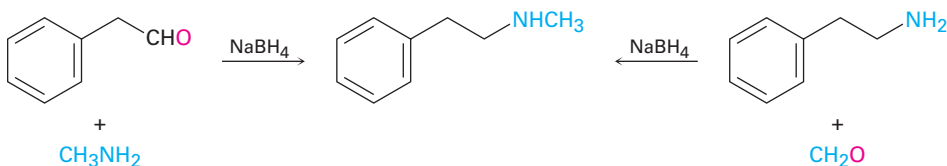
N-Methyl-2-phenylethylamine

Strategy

Look at the target molecule, and identify the groups attached to nitrogen. One of the groups must be derived from the aldehyde or ketone component, and the other must be derived from the amine component. In the case of *N*-methyl-2-phenylethylamine, there are two combinations that can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. It's usually better to choose the combination with the simpler amine

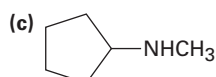
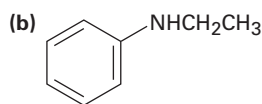
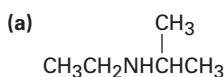
component—methylamine in this case—and to use an excess of that amine as reactant.

Solution



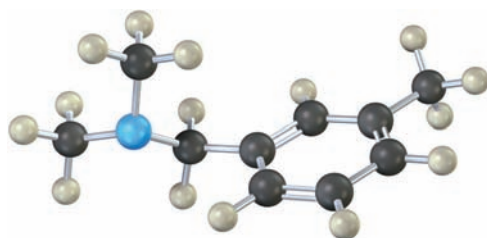
PROBLEM 18.10

How might the following amines be prepared using reductive amination reactions? Show all precursors if more than one is possible.



PROBLEM 18.11

How could you prepare the following amine using a reductive amination reaction?

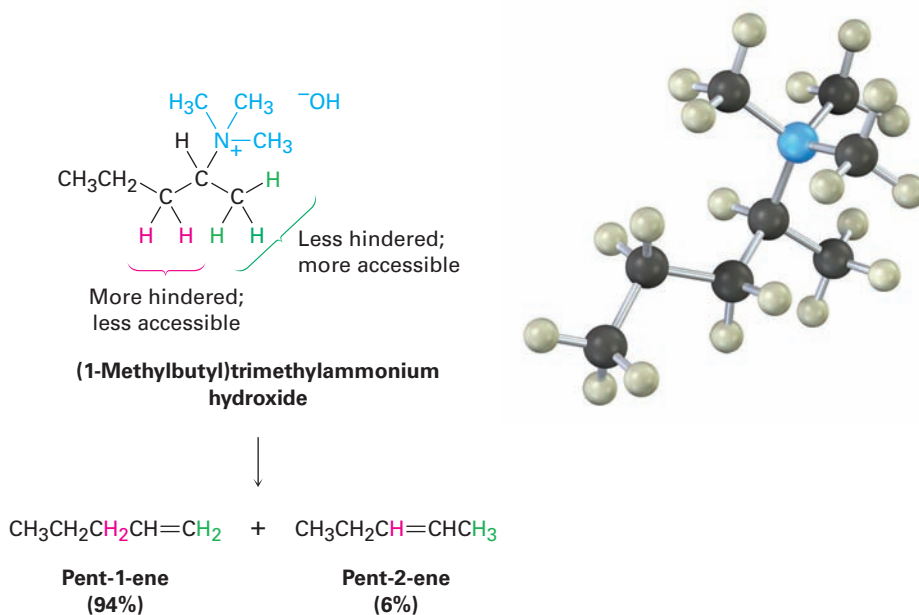


18-7 Reactions of Amines

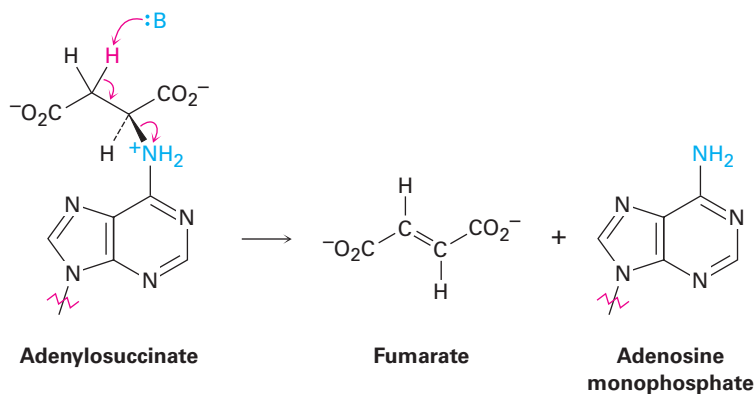
Alkylation and Acylation

We've already studied the two most general reactions of amines—alkylation and acylation. As we saw in the previous section, primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide (Sections 16-4 and 16-5). Note that overacylation of the nitrogen does not occur because

Unlike what happens in other E2 reactions, the major product of the Hofmann elimination is the *less* highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl)trimethylammonium hydroxide to give pent-1-ene rather than the alternative pent-2-ene. The reason for this non-Zaitsev result is probably steric. Because of the large size of the trialkylamine leaving group, the base must abstract a hydrogen from the more accessible, least hindered position.

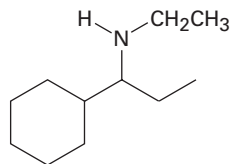


The Hofmann elimination reaction is not often used today in the laboratory, but analogous biological eliminations occur frequently, although usually with protonated ammonium ions rather than quaternary ammonium salts. In the biosynthesis of nucleic acids, for instance, a substance called adenylosuccinate undergoes an elimination of a positively charged nitrogen to give fumarate plus adenosine monophosphate.

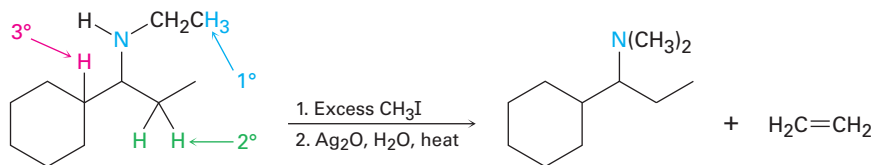


WORKED EXAMPLE 18.2 Predicting the Product of a Hofmann Elimination

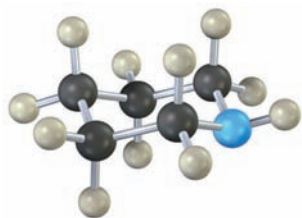
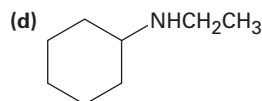
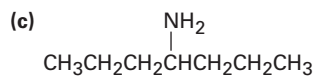
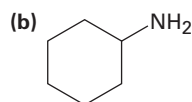
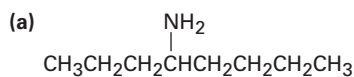
What product would you expect from Hofmann elimination of the following amine?

**Strategy**

The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the least highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons removed from nitrogen). Then carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

Solution**PROBLEM 18.12**

What products would you expect from Hofmann elimination of the following amines? If more than one product is formed, tell which is major.



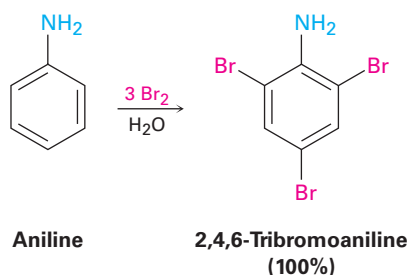
Piperidine

PROBLEM 18.13

What product would you expect from Hofmann elimination of a heterocyclic amine such as piperidine? Write all the steps.

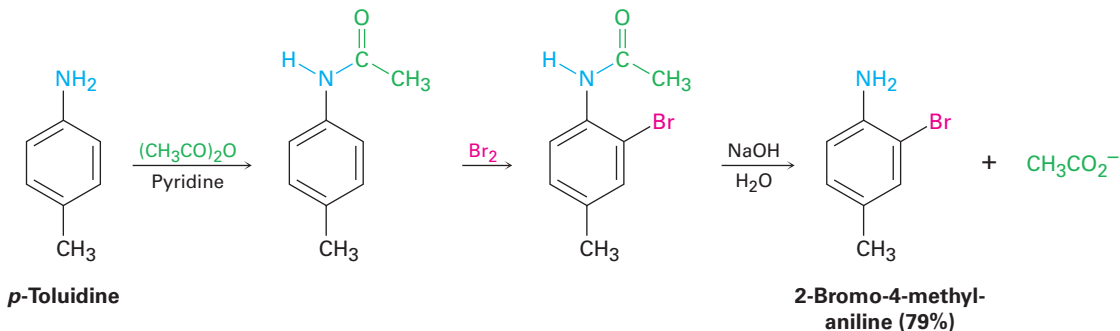
Electrophilic Aromatic Substitution of Arylamines

An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions (Section 9-8). This high reactivity of amino-substituted benzenes can be a drawback at times because it's often difficult to prevent polysubstitution. Reaction of aniline with Br_2 for instance, takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the monobromo stage.



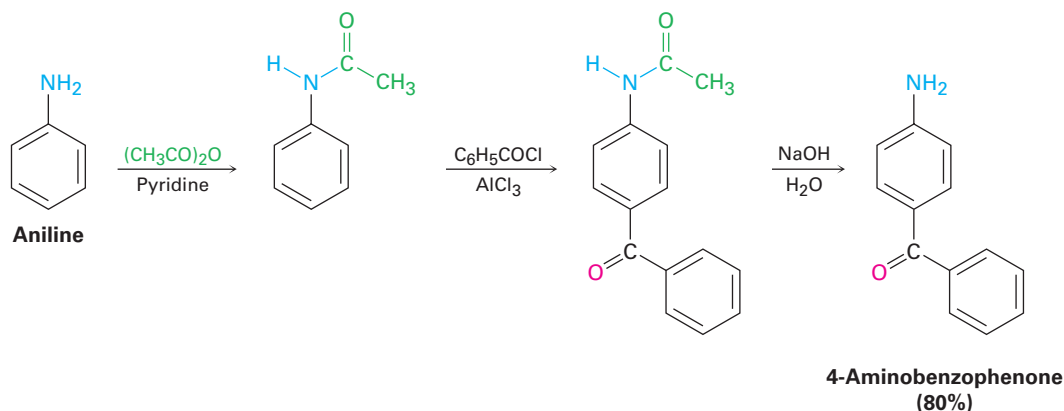
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful (Section 9-7). The amino group forms an acid–base complex with the AlCl_3 catalyst, which prevents further reaction from occurring. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

As we saw in Section 16-5, treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents ($-\text{NHCOR}$) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



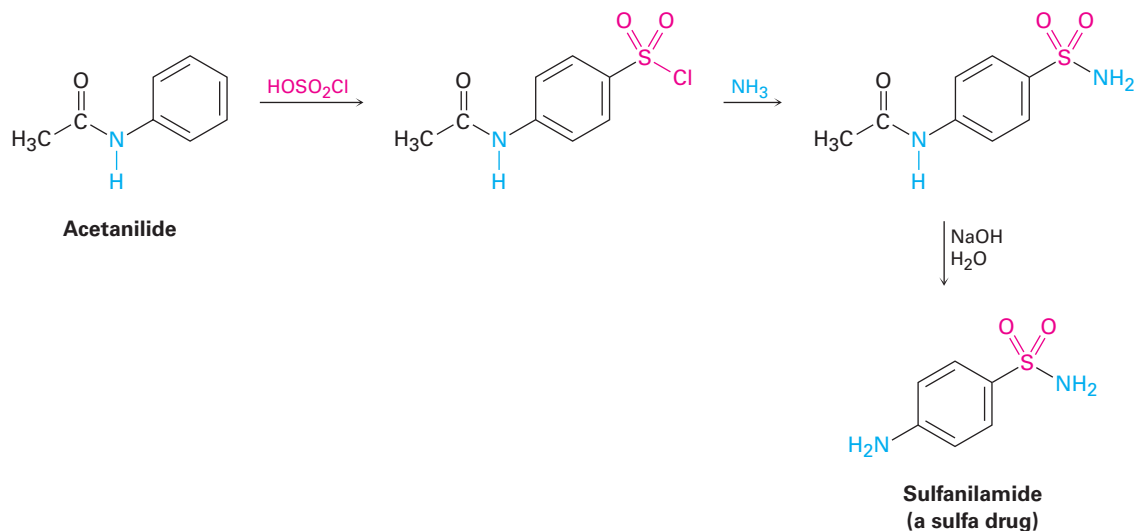
Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under

Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



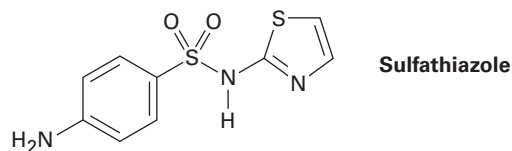
Modulating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. An example is the preparation of the sulfa drugs, such as sulfanilamide.

Sulfa drugs were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced today by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II and are still prescribed for urinary-tract infections. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino)benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that hydrolysis of the amide can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.



PROBLEM 18.14

Propose a synthesis of the drug sulfathiazole from benzene and any necessary amine.

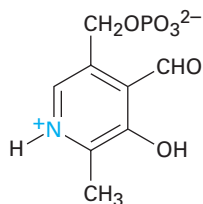
**PROBLEM 18.15**

Propose syntheses of the following compounds from benzene:

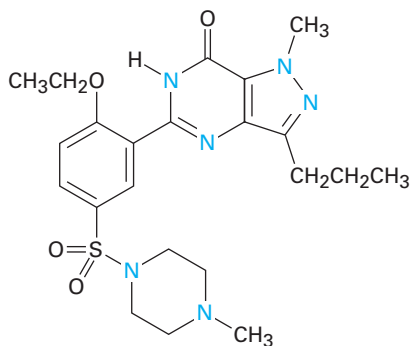
(a) *N,N*-Dimethylaniline (b) *p*-Chloroaniline (c) *m*-Chloroaniline

18-8 Heterocyclic Amines

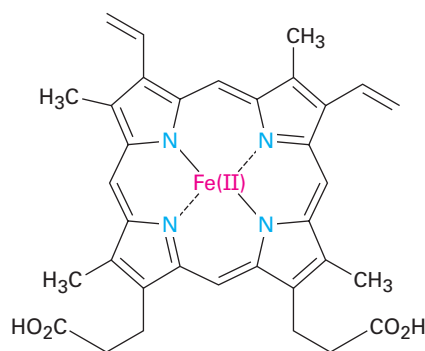
As noted in Section 9-4 in connection with a discussion of aromaticity, a cyclic organic compound that contains atoms of two or more elements in its ring is called a *heterocycle*. Heterocyclic amines are particularly common, and many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra), a well-known pharmaceutical; and heme, the oxygen carrier in blood, are examples.



Pyridoxal phosphate
(a coenzyme)



Sildenafil
(Viagra)

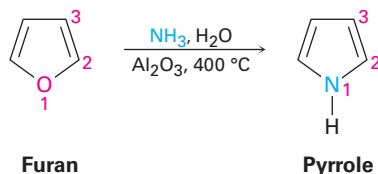


Heme

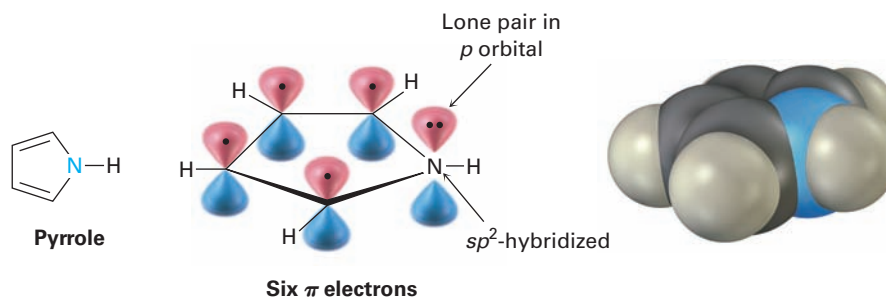
Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

Pyrrole and Imidazole

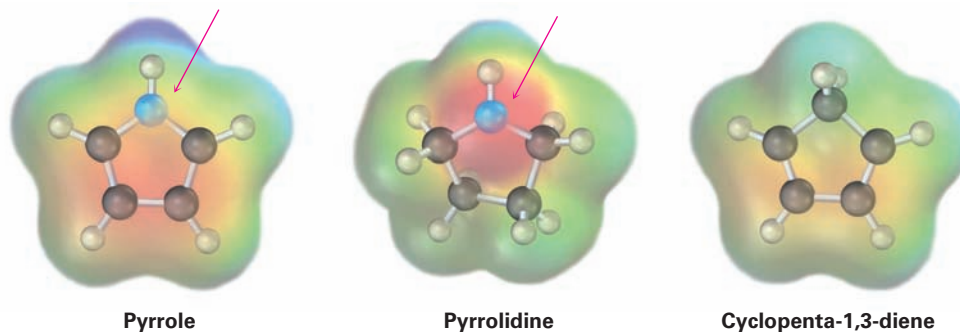
Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



Although pyrrole appears to be both an amine and a conjugated diene, its chemical properties are not consistent with either of these structural features. Unlike most other amines, pyrrole is not basic—the pK_a of the pyrrolinium ion is 0.4; unlike most other conjugated dienes, pyrrole undergoes electrophilic substitution reactions rather than additions. The reason for both these properties, as noted previously in Section 9-4, Figure 9.7, is that pyrrole has six π electrons and is aromatic. Each of the four carbons contributes one π electron, and the sp^2 -hybridized nitrogen contributes two more from its lone pair.



Because the nitrogen lone pair is a part of the aromatic sextet, protonation on nitrogen would destroy the aromaticity of the ring. The nitrogen atom in pyrrole is therefore less electron-rich, less basic, and less nucleophilic than the nitrogen in an aliphatic amine. By the same token, the carbon atoms of pyrrole are more electron-rich and more nucleophilic than typical double-bond carbons. The pyrrole ring is therefore reactive toward electrophiles in the same way that enamines are (Section 17-12). Electrostatic potential maps show how the pyrrole nitrogen is electron-poor (less red) compared with the nitrogen in its saturated counterpart pyrrolidine, while the pyrrole carbon atoms are electron-rich (more red) compared with the carbons in cyclopenta-1,3-diene.



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PROBLEM 18.16

Draw an orbital picture of thiazole. Assume that both the nitrogen and sulfur atoms are sp^2 -hybridized, and show the orbitals that the lone pairs occupy.

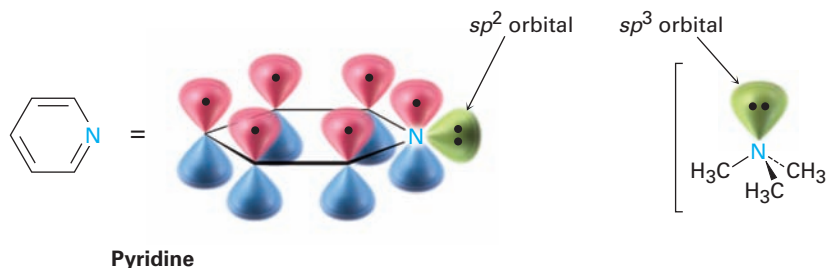
PROBLEM 18.17

What is the percent protonation of the imidazole nitrogen atom in histidine at a physiological pH of 7.3? (See Section 18-5.)

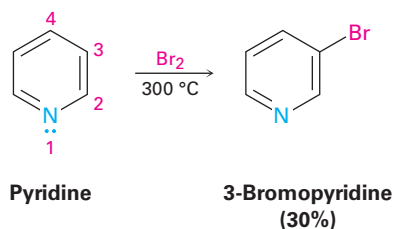
Pyridine and Pyrimidine

Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like benzene, pyridine is a flat, aromatic molecule, with bond angles of 120° and C–C bond lengths of 139 pm, intermediate between typical single and double bonds. The five carbon atoms and the sp^2 -hybridized nitrogen atom each contribute one π electron to the aromatic sextet, and the lone-pair electrons occupy an sp^2 orbital in the plane of the ring (Section 9-4, Figure 9.6).

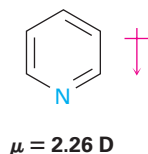
As shown previously in Table 18.1, pyridine ($pK_a = 5.25$) is a stronger base than pyrrole but a weaker base than alkylamines. The diminished basicity of pyridine compared with that of alkylamines is due to the fact that the lone-pair electrons on the pyridine nitrogen are in an sp^2 orbital, while those on an alkylamine nitrogen are in an sp^3 orbital. Because s orbitals have their maximum electron density at the nucleus but p orbitals have a node at the nucleus, electrons in an orbital with more s character are held more closely to the positively charged nucleus and are less available for bonding. As a result, the sp^2 -hybridized nitrogen atom (33% s character) in pyridine is less basic than the sp^3 -hybridized nitrogen in an alkylamine (25% s character).



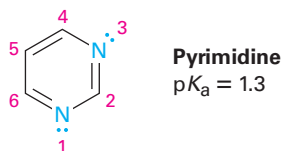
Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with difficulty. Halogenation can be carried out under drastic conditions, but nitration occurs in very low yield and Friedel–Crafts reactions are not successful. Reactions usually give the 3-substituted product.



The low reactivity of pyridine toward electrophilic aromatic substitution is caused by a combination of factors. One is that acid–base complexation between the basic ring nitrogen atom and the incoming electrophile places a positive charge on the ring, thereby deactivating it. Equally important is that the electron density of the ring is decreased by the electron-withdrawing inductive effect of the electronegative nitrogen atom. Thus, pyridine has a substantial dipole moment ($\mu = 2.26$ D), with the ring carbons acting as the positive end of the dipole. Reaction of an electrophile with the positively polarized carbon atoms is therefore difficult.



In addition to pyridine, the six-membered diamine pyrimidine is also found commonly in biological molecules, particularly as a constituent of nucleic acids. With a pK_a of 1.3, pyrimidine is substantially less basic than pyridine because of the inductive effect of the second nitrogen.



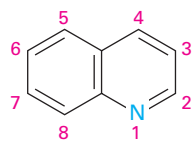
PROBLEM 18.18

Electrophilic aromatic substitution reactions of pyridine normally occur at C3. Draw the carbocation intermediates resulting from reaction of an electrophile at C2, C3, and C4, and explain the observed result.

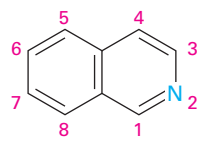
18-9 Fused-Ring Heterocycles

As we saw in Section 9-5, quinoline, isoquinoline, indole, and purine are common *fused-ring heterocycles*. The first three contain both a benzene ring and a heterocyclic aromatic ring, while purine contains two heterocyclic rings fused together. All four ring systems occur commonly in nature, and many compounds with these rings have pronounced physiological activity. The quinoline alkaloid quinine, for instance, is widely used as an antimalarial

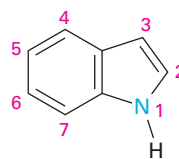
drug; tryptophan is a common amino acid; and the purine adenine is a constituent of nucleic acids.



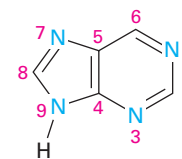
Quinoline



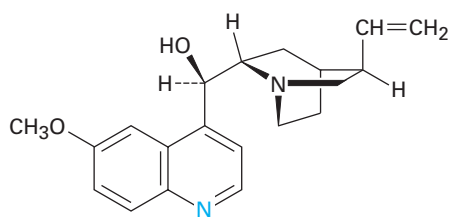
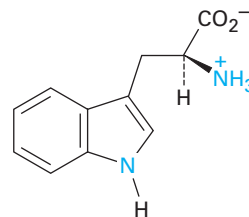
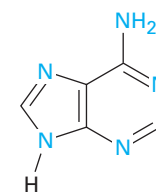
Isoquinoline



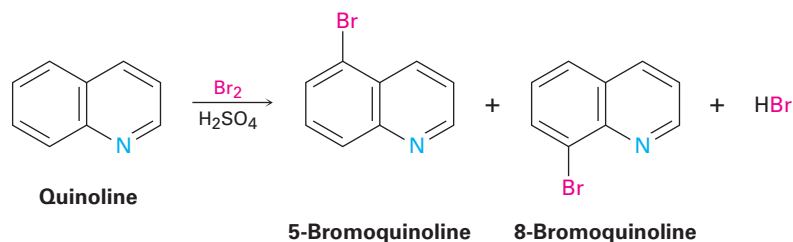
Indole



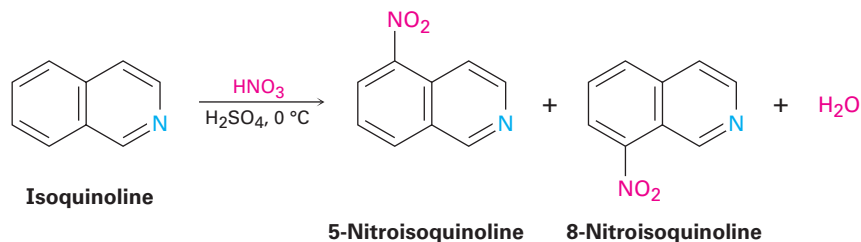
Purine

Quinine
(antimalarial)Tryptophan
(amino acid)Adenine
(DNA constituent)

The chemistry of these fused-ring heterocycles is just what you might expect from a knowledge of the simpler heterocycles pyridine and pyrrole. Quinoline and isoquinoline both have basic, pyridine-like nitrogen atoms, and both undergo electrophilic substitutions, although less easily than benzene. Reaction occurs on the benzene ring rather than on the pyridine ring, and a mixture of substitution products is obtained.

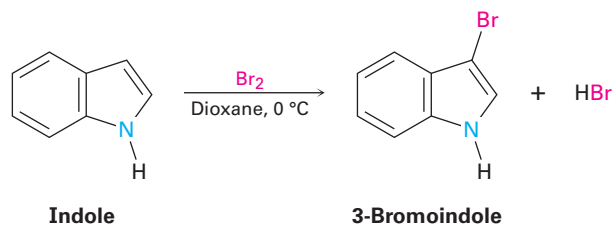


A 51 : 49 ratio

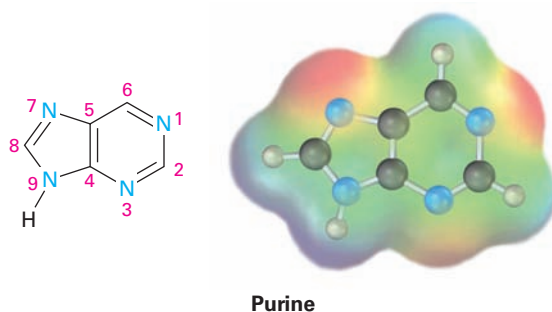


A 90 : 10 ratio

Indole has a nonbasic, pyrrole-like nitrogen and undergoes electrophilic substitution more easily than benzene. Substitution occurs at C3 of the electron-rich pyrrole ring, rather than on the benzene ring.

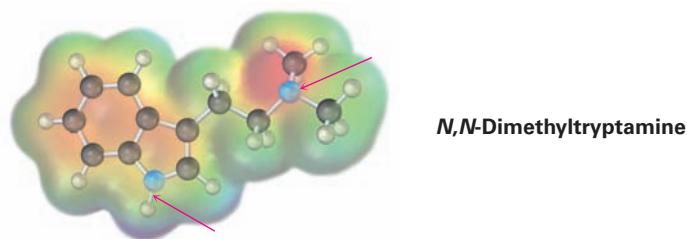


Purine has three basic, pyridine-like nitrogens with lone-pair electrons in sp^2 orbitals in the plane of the ring. The remaining purine nitrogen is nonbasic and pyrrole-like, with its lone-pair electrons as part of the aromatic π electron system.



PROBLEM 18.19

Which nitrogen atom in the hallucinogenic indole alkaloid *N,N*-dimethyltryptamine is more basic? Explain.



PROBLEM 18.20

Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

18-10 Spectroscopy of Amines

Infrared Spectroscopy

Primary and secondary amines can be identified by a characteristic N–H stretching absorption in the 3300 to 3500 cm^{-1} range of the IR spectrum. Alcohols also absorb in this range (Section 13-13), but amine absorption bands are generally sharper and less intense than hydroxyl bands. Primary amines show a pair of bands at about 3350 and 3450 cm^{-1} , and secondary amines show a single band at 3350 cm^{-1} . Tertiary amines have no absorption in this region because they have no N–H bonds. An IR spectrum of cyclohexylamine is shown in **FIGURE 18.5**.

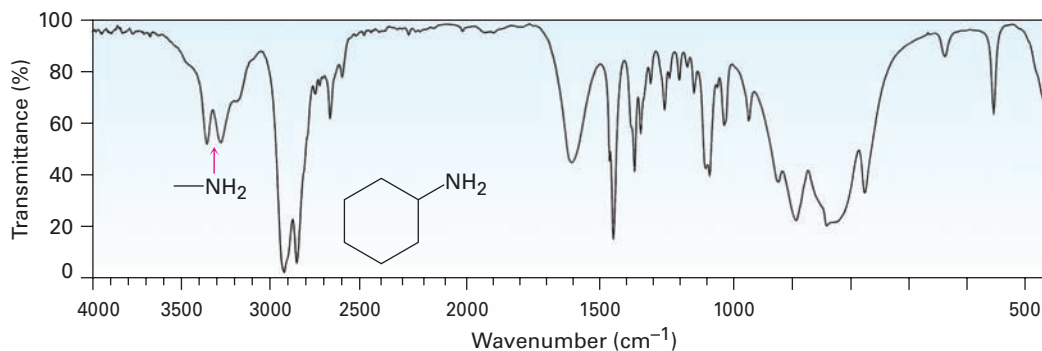
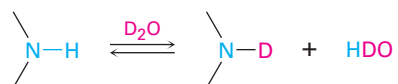


FIGURE 18.5 IR spectrum of cyclohexylamine.

Nuclear Magnetic Resonance Spectroscopy

Amines are difficult to identify solely by ^1H NMR spectroscopy because N–H hydrogens tend to appear as broad signals without well-defined coupling to neighboring C–H hydrogens. As with O–H absorptions (Section 13-13), amine N–H absorptions can appear over a wide range and are best identified by adding a small amount of D_2O to the sample tube. Exchange of N–D for N–H occurs, and the N–H signal disappears from the NMR spectrum.



Hydrogens on the carbon next to nitrogen are deshielded because of the electron-withdrawing effect of the nitrogen, and they therefore absorb at lower field than alkane hydrogens. *N*-Methyl groups are particularly distinctive because they absorb as a sharp three-proton singlet at 2.2 to 2.6 δ . The *N*-methyl resonance at 2.42 δ is easily seen in the ^1H NMR spectrum of *N*-methylcyclohexylamine (**FIGURE 18.6**).

Carbons next to amine nitrogens are slightly deshielded in the ^{13}C NMR spectrum and absorb about 20 ppm downfield from where they would absorb

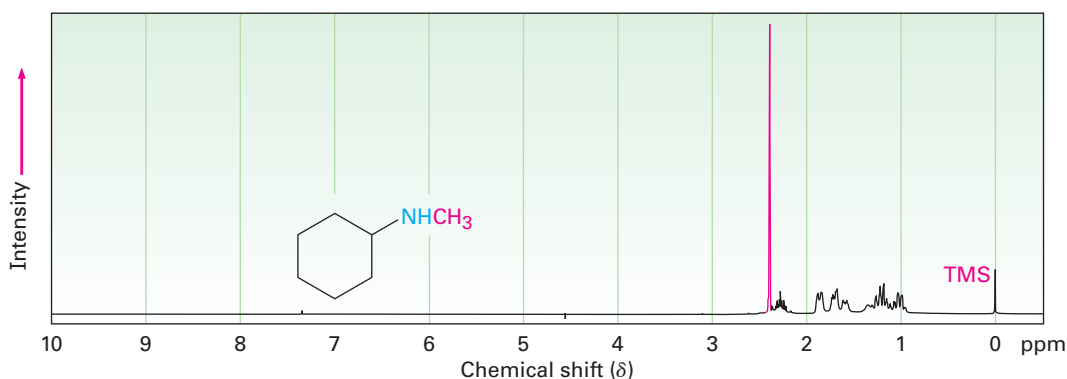
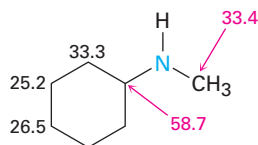


FIGURE 18.6 ^1H NMR spectrum of *N*-methylcyclohexylamine.

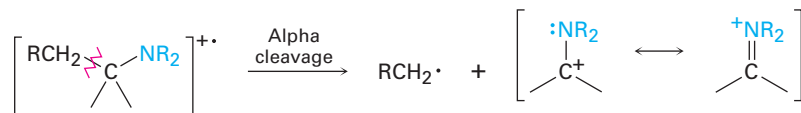
in an alkane of similar structure. In *N*-methylcyclohexylamine, for example, the ring carbon to which nitrogen is attached absorbs at a position 24 ppm lower than that of any other ring carbon.



Mass Spectrometry

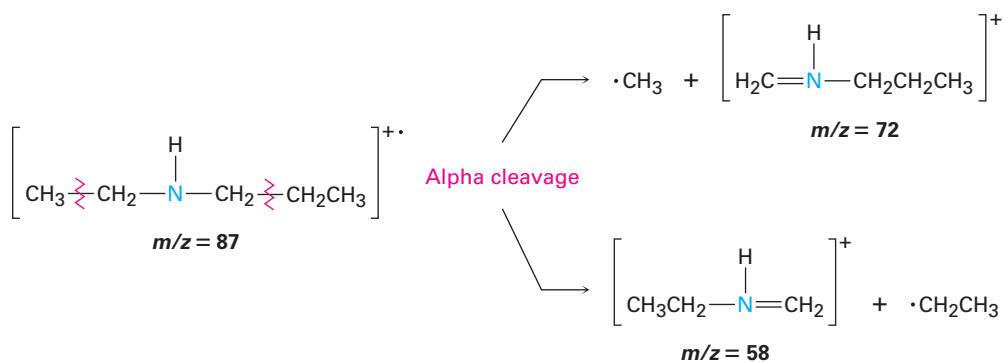
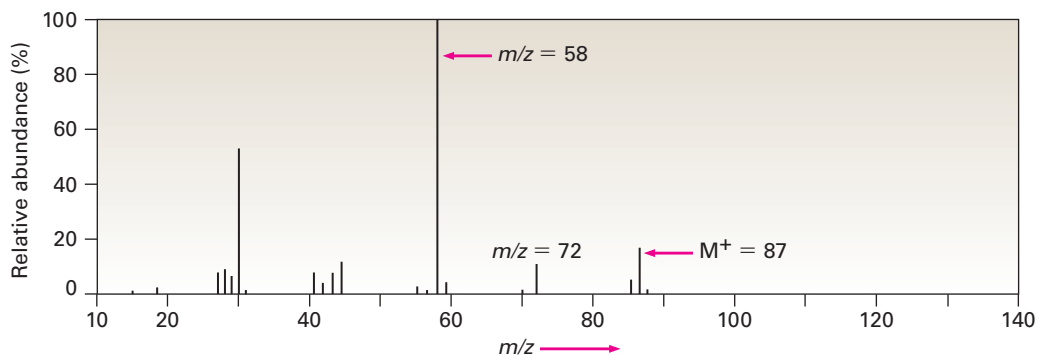
The *nitrogen rule* of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. Thus, the presence of nitrogen in a molecule is detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms. The logic behind the rule derives from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. For example, morphine has the formula $\text{C}_{17}\text{H}_{19}\text{NO}_3$ and a molecular weight of 285 amu.

Alkylamines undergo a characteristic α cleavage in the mass spectrometer, similar to the cleavage observed for alcohols (Section 13-13). A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a nitrogen-containing cation:



As an example, the mass spectrum of *N*-ethylpropylamine shown in **FIGURE 18.7** has peaks at $m/z = 58$ and $m/z = 72$, corresponding to the two possible modes of α cleavage.

FIGURE 18.7 Mass spectrum of *N*-ethylpropylamine. The two possible modes of α cleavage lead to the observed fragment ions at $m/z = 58$ and $m/z = 72$.



SOMETHING EXTRA

Green Chemistry

Organic chemistry in the 20th century changed the world, giving us new medicines, insecticides, adhesives, textiles, dyes, building materials, composites, and all manner of polymers. But these advances did not come without a cost: every chemical process produces wastes that must be dealt with, including reaction solvents and toxic by-products that might evaporate into the air or be leached into groundwater if not disposed of properly. Even apparently harmless by-products must be safely buried or otherwise sequestered. As always, there's no such thing as a free lunch; with the good also comes the bad.

It may never be possible to make organic chemistry completely benign, but awareness of the environmental problems caused by many chemical processes has grown dramatically in recent years, giving rise to a movement called *green chemistry*. Green chemistry is the design and implementation of chemical products

and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry:



Robert Brook / Alamy

and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry:

Prevent waste—Waste should be prevented rather than treated or cleaned up after it has been created.

Maximize atom economy—Synthetic methods should maximize the incorporation of all materials used in a process into the final product so that waste is minimized.

Use less hazardous processes—Synthetic methods should use reactants and generate wastes with minimal toxicity to health and the environment.

Design safer chemicals—Chemical products should be designed to have minimal toxicity.

Use safer solvents—Minimal use should be made of solvents, separation agents, and other auxiliary substances in a reaction.

Design for energy efficiency—Energy requirements for chemical processes should be minimized, with reactions carried out at room temperature if possible.

Use renewable feedstocks—Raw materials should come from renewable sources when feasible.

Minimize derivatives—Syntheses should be designed with minimal use of protecting groups to avoid extra steps and reduce waste.

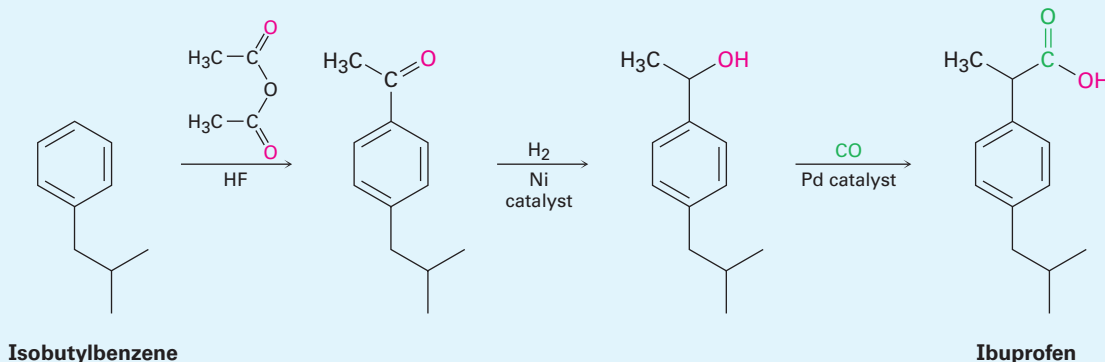
Use catalysis—Reactions should be catalytic rather than stoichiometric.

Design for degradation—Products should be designed to be biodegradable at the end of their useful lifetimes.

Monitor pollution in real time—Processes should be monitored in real time for the formation of hazardous substances.

Prevent accidents—Chemical substances and processes should minimize the potential for fires, explosions, or other accidents.

The foregoing 12 principles won't all be met in most real-world applications, but they provide a worthy goal to aim for and they can make chemists think more carefully about the environmental implications of their work. Real success stories are already occurring, and more are in progress. Approximately 7 million pounds per year of ibuprofen (6 billion tablets!) is now made by a “green” process that produces approximately 99% less waste than the process it replaces. Only three steps are needed, the anhydrous HF solvent used in the first step is recovered and reused, and the second and third steps are catalytic.



SUMMARY

We've now seen all the common functional groups that occur in biomolecules. Of those groups, amines are among the most abundant and have among the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups and many of the common coenzymes necessary for biological reactions are amines.

Amines are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix *-amine* to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which make amines both basic and nucleophilic. The base strength of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the

KEY WORDS

- alkylamine, 645
- amine, 644
- arylamines, 645
- heterocyclic amine, 646
- Hofmann elimination reaction, 660
- primary amine (RNH₂), 645
- quaternary ammonium salt, 645
- reductive amination, 657
- secondary amine (R₂NH), 645
- tertiary amine (R₃N), 645

basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3 inside cells.

Heterocyclic amines are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

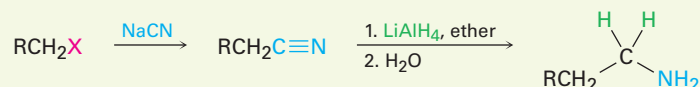
Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by S_N2 reaction of ammonia or an amine with an alkyl halide as well as by a number of reductive methods, including $LiAlH_4$ reduction of amides and nitriles. Also important is the **reductive amination** reaction in which an aldehyde or ketone is treated with an amine in the presence of a reducing agent.

Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo $E2$ elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

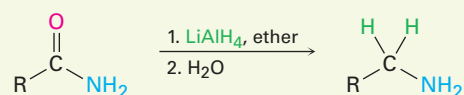
SUMMARY OF REACTIONS

1. Synthesis of amines (Section 18-6)

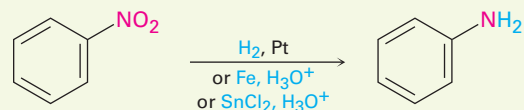
(a) Reduction of nitriles

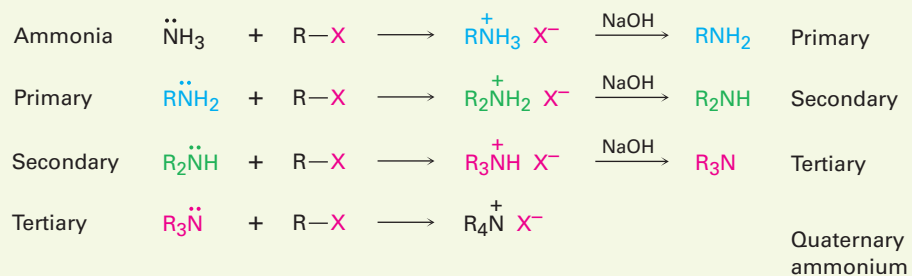
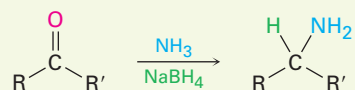
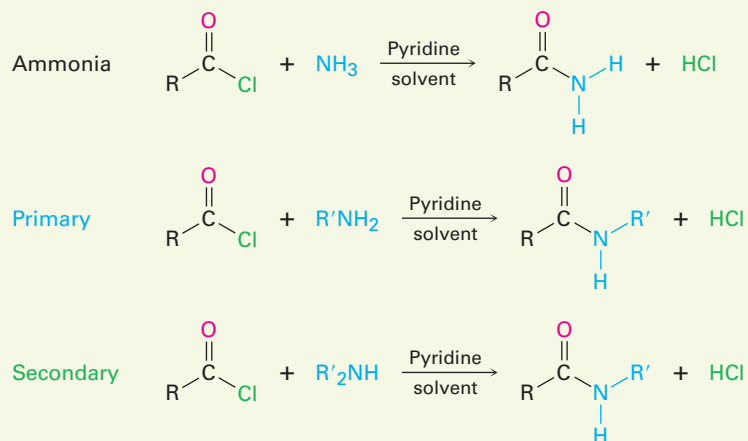
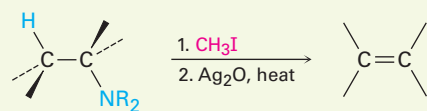


(b) Reduction of amides



(c) Reduction of nitrobenzenes



(d) S_N2 Alkylation of alkyl halides**(e)** Reductive amination of aldehydes/ketones**2.** Reactions of amines (Section 18-7)**(a)** Alkylation with alkyl halides; see reaction 1(d)**(b)** Acylation with acid chlorides**(c)** Hofmann elimination

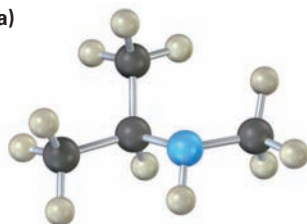
EXERCISES

VISUALIZING CHEMISTRY

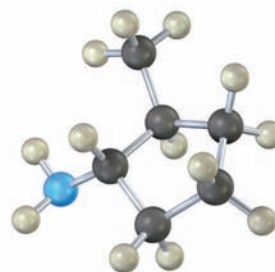
(Problems 18.1–18.20 appear within the chapter.)

18.21 Name the following amines, and identify each as primary, secondary, or tertiary:

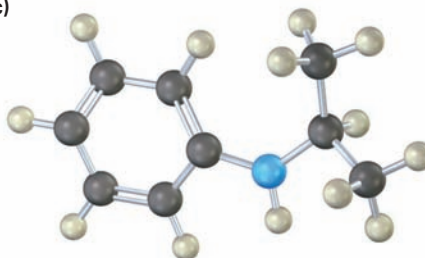
(a)



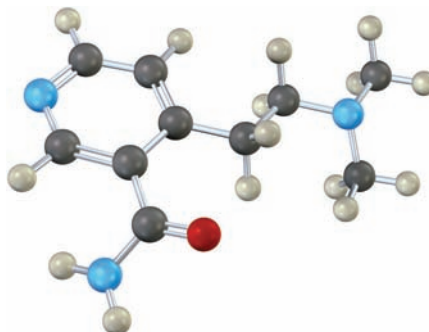
(b)



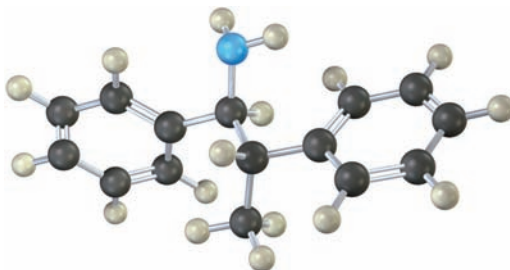
(c)



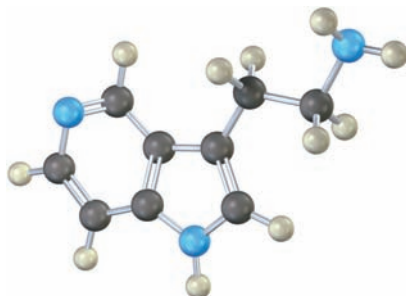
18.22 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



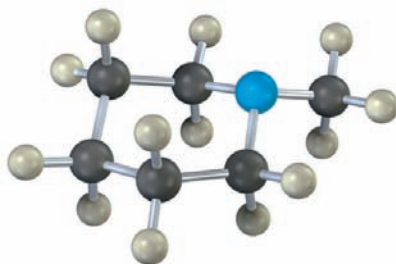
- 18.23 Name the following amine, including *R,S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.



- 18.24 The following molecule has three nitrogen atoms. List them in order of increasing basicity, and explain your ordering.



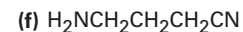
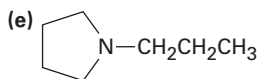
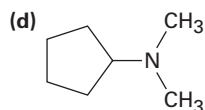
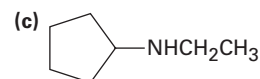
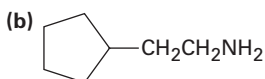
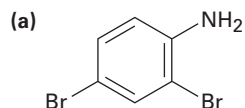
- 18.25 The following molecule can be prepared by reaction between a primary amine and a *dihalide*. Identify the two reactants, and write the reaction.



ADDITIONAL PROBLEMS

Naming Amines

18.26 Name the following compounds:



18.27 Draw structures corresponding to the following IUPAC names:

(a) *N,N*-Dimethylaniline

(b) (Cyclohexylmethyl)amine

(c) *N*-Methylcyclohexylamine

(d) (2-Methylcyclohexyl)amine

(e) 3-(*N,N*-Dimethylamino)propanoic acid

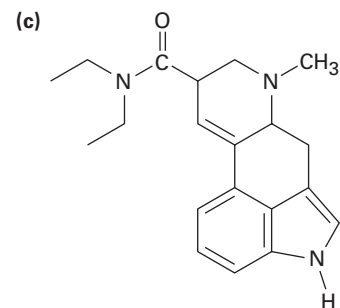
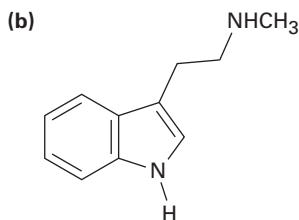
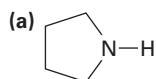
18.28 Propose structures for substances that fit the following descriptions:

(a) A chiral quaternary ammonium salt

(b) A six-membered heterocyclic diamine

(c) A secondary amine, $\text{C}_6\text{H}_{11}\text{N}$

18.29 Classify each of the amine (not amide) nitrogen atoms in the following substances as primary, secondary, or tertiary:

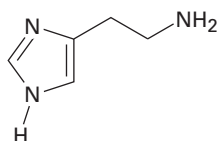


Lysergic acid diethylamide

18.30 There are eight isomeric amines with the formula $\text{C}_4\text{H}_{11}\text{N}$. Draw them, name them, and classify each as primary, secondary, or tertiary.

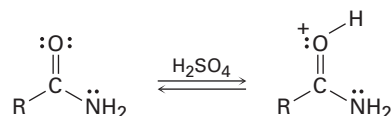
Amine Basicity

- 18.31** Which compound do you think is more basic, $\text{CH}_3\text{CH}_2\text{NH}_2$ or $\text{CF}_3\text{CH}_2\text{NH}_2$? Explain.
- 18.32** Which compound do you think is more basic, *p*-aminobenzaldehyde or aniline? Explain.
- 18.33** Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($\text{p}K_{\text{a}} \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H proton is readily abstracted by base to yield the pyrrole anion, $\text{C}_4\text{H}_4\text{N}^-$. Explain.
- 18.34** Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity, and explain your ordering.



Histamine

- 18.35** Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.

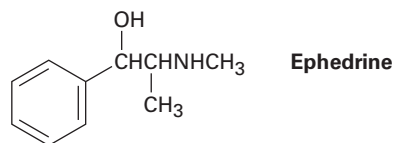


- 18.36** *p*-Nitroaniline ($\text{p}K_{\text{a}} = 1.0$) is less basic than *m*-nitroaniline ($\text{p}K_{\text{a}} = 2.5$) by a factor of 30. Explain, using resonance structures. (The $\text{p}K_{\text{a}}$ values refer to the corresponding ammonium ions.)

Synthesis of Amines

- 18.37** How would you prepare the following amines from butan-1-ol?
(a) Butylamine **(b)** Dibutylamine **(c)** Pentylamine **(d)** Butanamide
- 18.38** How would you prepare benzylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, from benzene? More than one step is needed.
- 18.39** How might you prepare pentylamine from the following starting materials?
(a) Pentanamide **(b)** Pentanenitrile **(c)** But-1-ene
(d) Butan-1-ol **(e)** Pentanoic acid

- 18.40 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that is widely used for the treatment of bronchial asthma?



Reactions of Amines

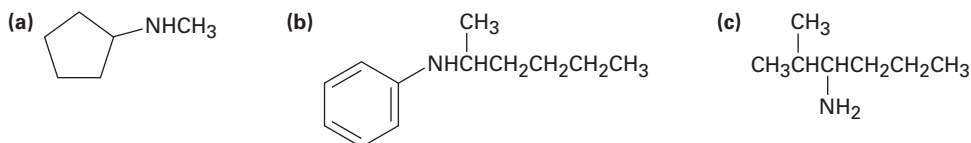
- 18.41 Give the structures of the major organic products you would expect from reaction of *m*-toluidine (*m*-methylaniline) with the following reagents:

(a) Br_2 (1 equivalent) (b) CH_3I (excess)
 (c) CH_3COCl in pyridine (d) The product of (c), then HSO_3Cl

- 18.42 Show the products from reaction of *p*-bromoaniline with the following reagents:

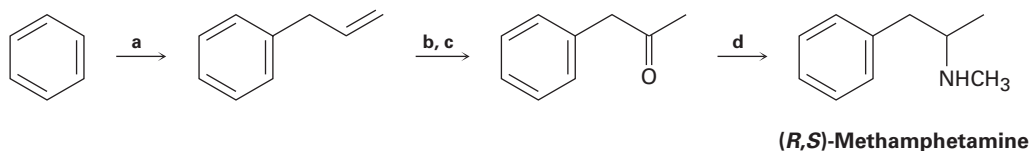
(a) CH_3I (excess) (b) HCl (c) CH_3COCl (d) CH_3MgBr

- 18.43 What are the major products you would expect from Hofmann elimination of the following amines?

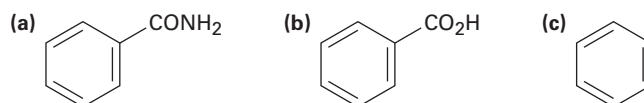


- 18.44 Show the mechanism of reductive amination of cyclohexanone and dimethylamine with NaBH_4 .

- 18.45 Fill in the missing reagents **a–d** in the following synthesis of racemic methamphetamine from benzene:

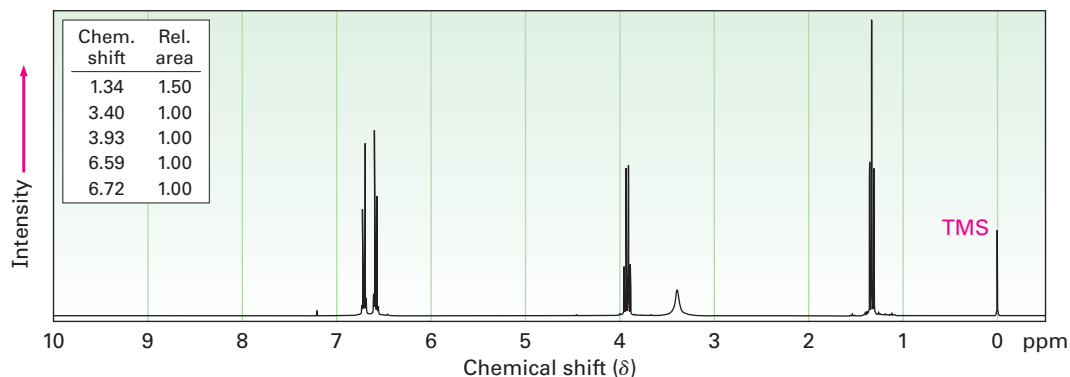


- 18.46 How would you prepare benzylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, from each of the following starting materials?



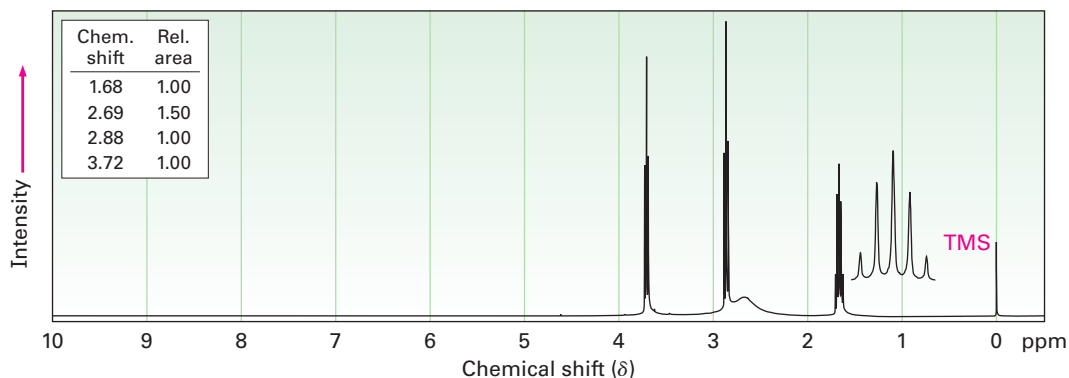
Spectroscopy of Amines

18.47 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose 1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO . What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?

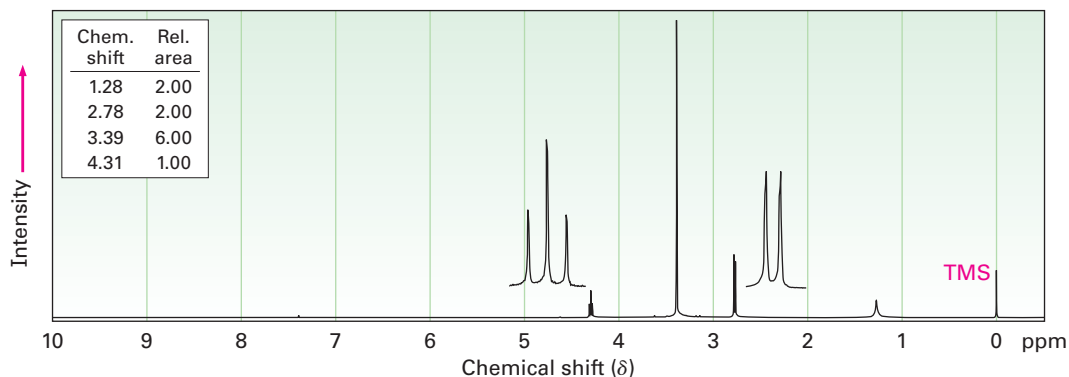


18.48 Propose structures for amines with the following 1H NMR spectra:

(a) C_3H_9NO

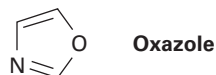


(b) $C_4H_{11}NO_2$

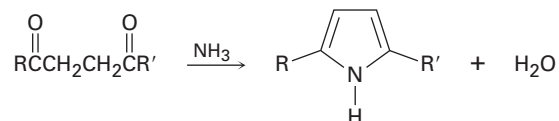


General Problems

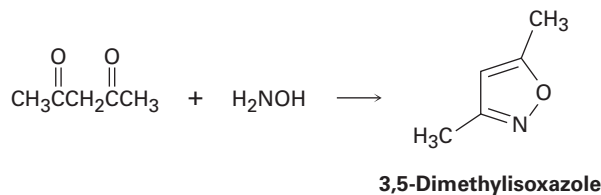
- 18.49 Oxazole is a five-membered aromatic heterocycle. Draw an orbital picture of oxazole, showing all p orbitals and all lone-pair orbitals. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.



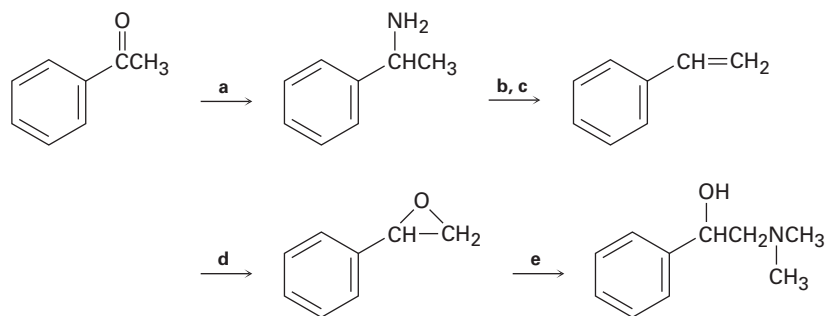
- 18.50 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Suggest a mechanism.



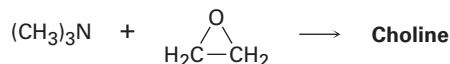
- 18.51 3,5-Dimethylisoxazole is prepared by reaction of pentane-2,4-dione with hydroxylamine. Propose a mechanism.



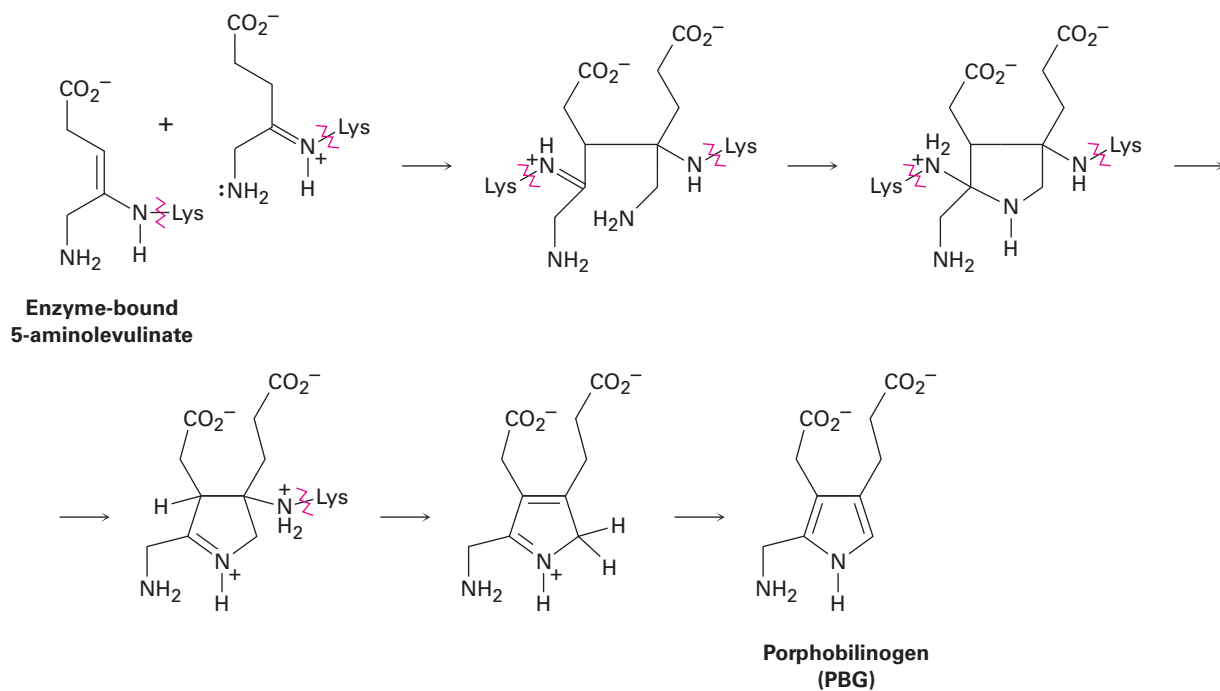
- 18.52 Fill in the missing reagents **a–e** in the following scheme:



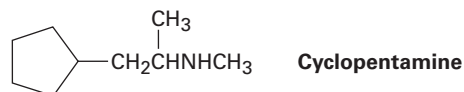
- 18.53 Pyrrole has a dipole moment $\mu = 1.8$ D, with the *nitrogen* atom at the positive end of the dipole. Explain.
- 18.54 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.
- 18.55 Choline, a component of the phospholipids in cell membranes, can be prepared by $\text{S}_{\text{N}}2$ reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



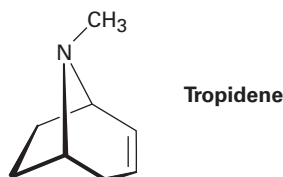
- 18.56** Chlorophyll, heme, vitamin B₁₂, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Using curved arrows, show the mechanism of each step.



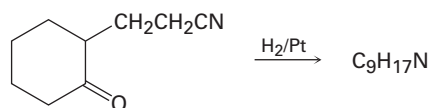
- 18.57** Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



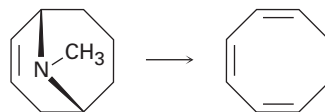
- 18.58** Atropine, C₁₇H₂₃NO₃, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10⁻⁹ g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, C₆H₅CH(CH₂OH)CO₂H, and tropine, C₈H₁₅NO. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H₂SO₄. Propose a structure for atropine.



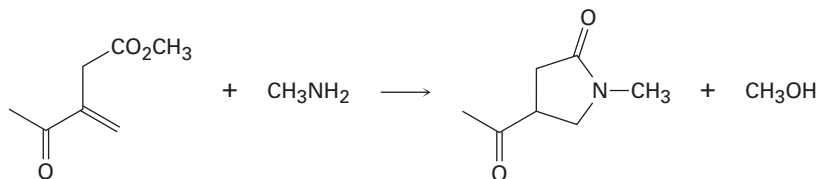
- 18.59** Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



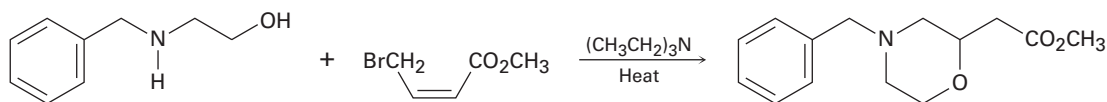
- 18.60** Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N,N*-dimethylamino)oct-1-ene. If coniine is a secondary amine, what is its structure?
- 18.61** How would you synthesize coniine (Problem 18.60) from acrylonitrile ($H_2C=CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (See Problem 18.59.)
- 18.62** Cycloocta-1,3,5,7-tetraene was first synthesized in 1911 by a route that involved the following transformation. How would you accomplish this reaction?



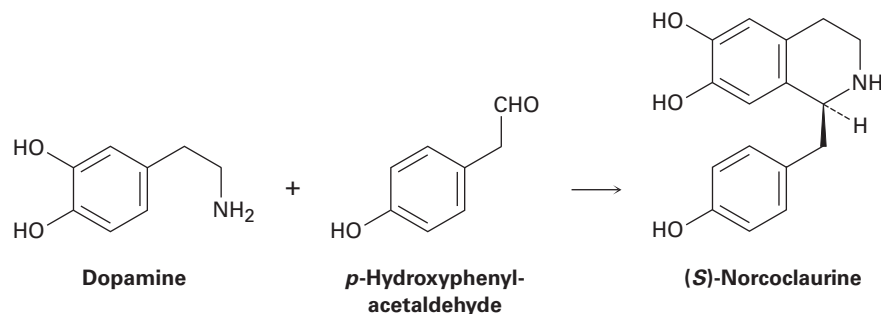
- 18.63** The following transformation involves a conjugate nucleophilic addition reaction (Section 14-11) followed by an intramolecular nucleophilic acyl substitution reaction (Section 16-2). Show the mechanism.



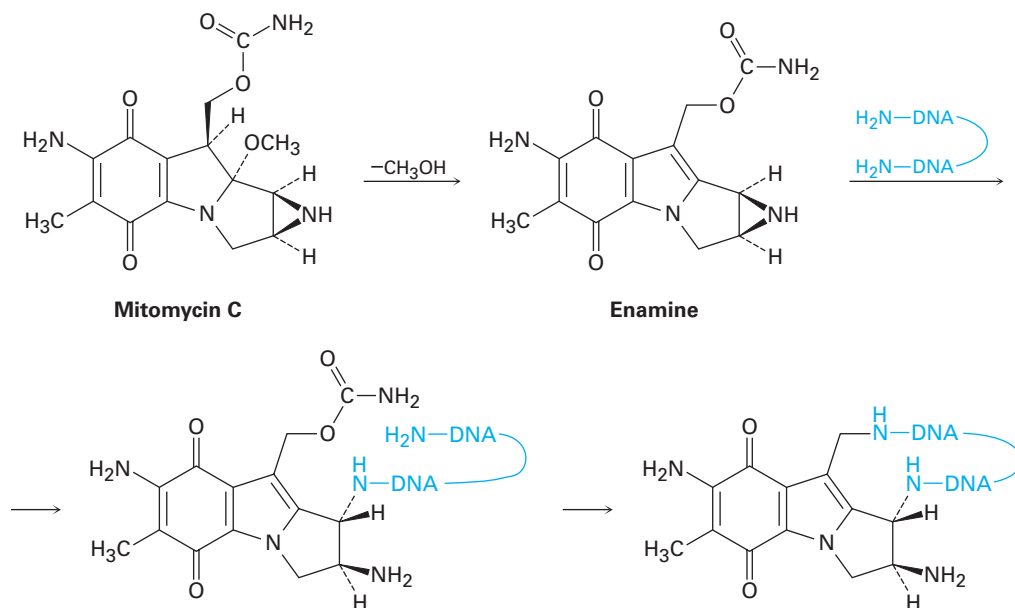
- 18.64** Propose a mechanism for the following reaction:



- 18.65** One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.

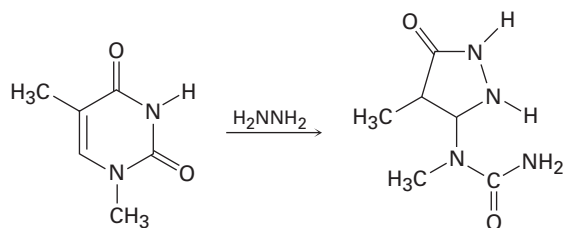


- 18.66** The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.

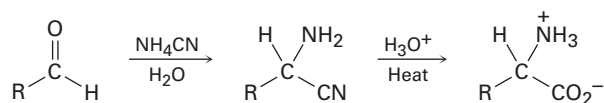


- (a) The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.
- (b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.
- (c) The third step is loss of carbamate (NH_2CO_2^-) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

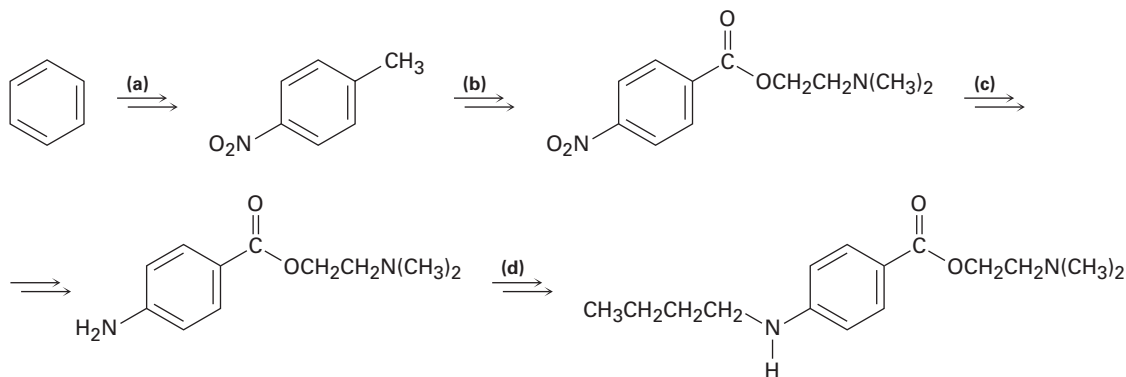
- 18.67** One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation:



- 18.68** α -Amino acids can be prepared by the *Strecker synthesis*, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.

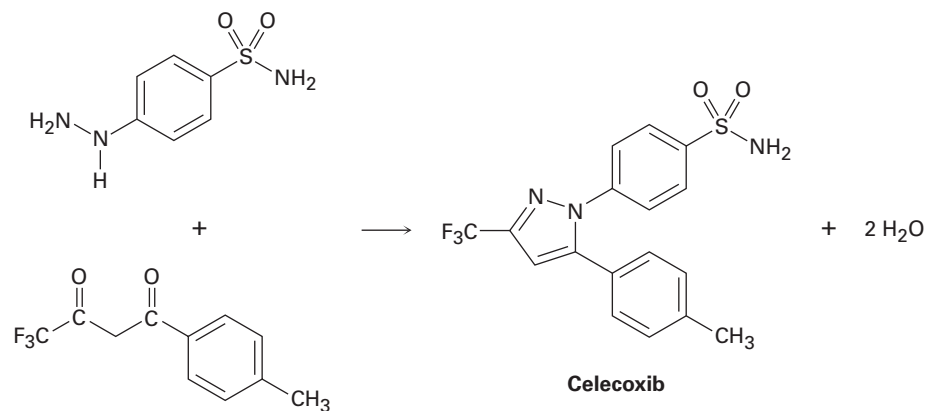
An α -amino acid

- 18.69** Tetracaine, a substance used as a spinal anesthetic, can be prepared from benzene by the following route. Show how you could accomplish each of the transformations (a) through (d).



Tetracaine

- 18.70 The anti-inflammatory drug celecoxib, marketed as Celebrex, is widely used for treatment of rheumatoid arthritis. Draw a mechanism for the following step used in celecoxib synthesis.



19

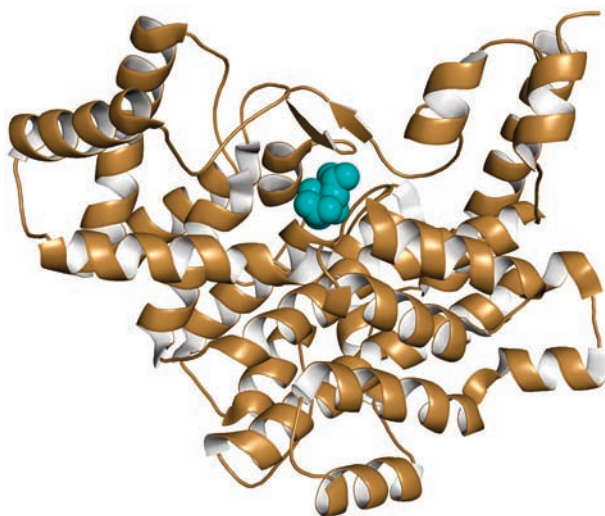
Biomolecules: Amino Acids, Peptides, and Proteins

CONTENTS

- 19-1** Structures of Amino Acids
- 19-2** Amino Acids and the Henderson–Hasselbalch Equation: Isoelectric Points
- 19-3** Synthesis of Amino Acids
- 19-4** Peptides and Proteins
- 19-5** Amino Acid Analysis of Peptides
- 19-6** Peptide Sequencing: The Edman Degradation
- 19-7** Peptide Synthesis
- 19-8** Protein Structure
- 19-9** Enzymes and Coenzymes
- 19-10** How Do Enzymes Work? Citrate Synthase

SOMETHING EXTRA

The Protein Data Bank



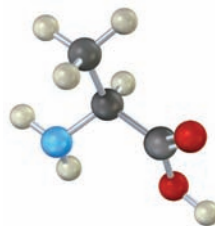
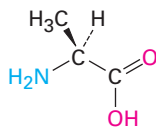
Citrate synthase catalyzes the reaction of acetyl CoA with oxaloacetate to give citrate, the first step in the citric acid cycle of food metabolism.

WHY THIS CHAPTER?

We've now seen the major functional groups and the common reaction types that occur in biological chemistry and have reached the heart of this book. Beginning in this chapter with amino acids and proteins, and continuing for the remainder of the text, we'll look at each of the main classes of biomolecules to see what their primary biological functions are, how they're biosynthesized, and how they're metabolized in the body.

Proteins occur in every living organism, are of many different types, and have many different biological functions. The keratin of skin and fingernails, the fibroin of silk and spider webs, and the estimated 50,000 or so enzymes that catalyze the biological reactions in our bodies are all proteins. Regardless of their function, all proteins have a fundamentally similar structure and are made up of many *amino acids* linked together in a long chain.

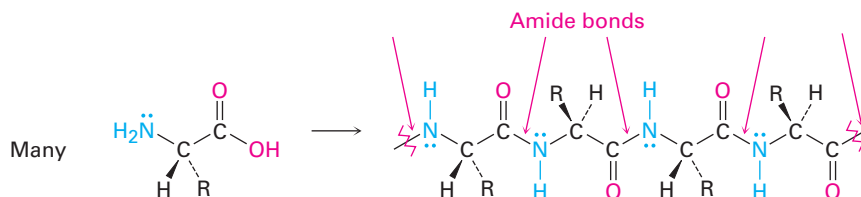
Amino acids, as their name implies, are difunctional. They contain both a basic amino group and an acidic carboxyl group:



Alanine, an amino acid

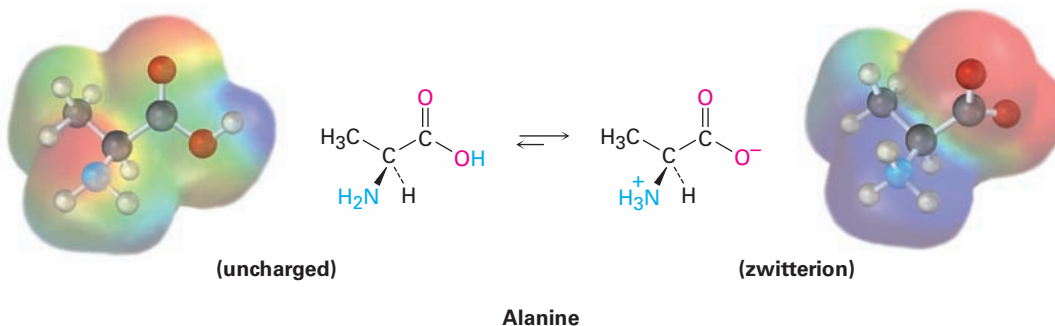
Their value as building blocks to make proteins stems from the fact that amino acids can join together into long chains by forming amide bonds between the $-\text{NH}_2$ of one amino acid and the $-\text{CO}_2\text{H}$ of another.

For classification purposes, chains with fewer than 50 amino acids are often called **peptides**, while the term **protein** is generally used for larger chains.

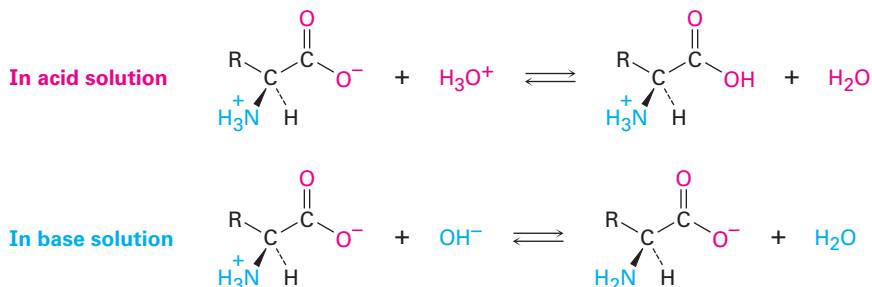


19-1 Structures of Amino Acids

We saw in Sections 15-3 and 18-5 that a carboxyl group is deprotonated and exists as the carboxylate anion at a pH of 7.3 in the body (the *physiological* pH), while an amino group is protonated and exists as the ammonium cation. Thus, an amino acid exists in aqueous solution primarily in the form of a dipolar ion, or **zwitterion** (German *zwitter*, meaning “hybrid”).

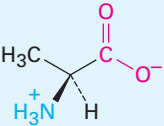
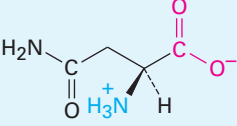
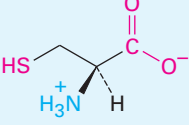
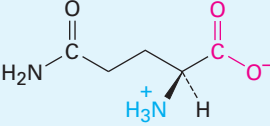
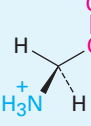
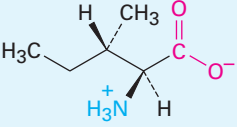
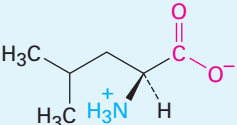
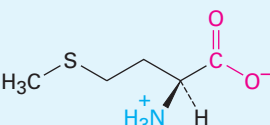
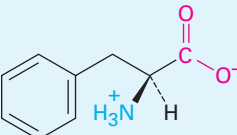
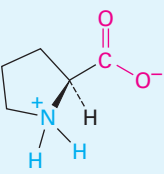


Amino acid zwitterions are internal salts and therefore have many of the physical properties associated with salts. They have large dipole moments, are relatively soluble in water but insoluble in hydrocarbons, and are crystalline with relatively high melting points. In addition, amino acids are *amphiprotic*: they can react either as acids or as bases, depending on the circumstances. In aqueous acid solution, an amino acid zwitterion is a base that accepts a proton onto its CO_2^- group to yield a cation. In aqueous base solution, the zwitterion is an acid that loses a proton from its NH_3^+ group to form an anion.



The structures, abbreviations (both three- and one-letter), and pK_a values of the 20 amino acids commonly found in proteins are shown in **TABLE 19.1**.

TABLE 19.1 The 20 Common Amino Acids in Proteins

Name	Abbreviations	MW	Structure	pK _a α-CO ₂ H	pK _a α-NH ₃ ⁺	pK _a side chain	pI	
Neutral Amino Acids								
Alanine	Ala	A	89		2.34	9.69	—	6.01
Asparagine	Asn	N	132		2.02	8.80	—	5.41
Cysteine	Cys	C	121		1.96	10.28	8.18	5.07
Glutamine	Gln	Q	146		2.17	9.13	—	5.65
Glycine	Gly	G	75		2.34	9.60	—	5.97
Isoleucine	Ile	I	131		2.36	9.60	—	6.02
Leucine	Leu	L	131		2.36	9.60	—	5.98
Methionine	Met	M	149		2.28	9.21	—	5.74
Phenylalanine	Phe	F	165		1.83	9.13	—	5.48
Proline	Pro	P	115		1.99	10.60	—	6.30

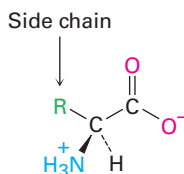
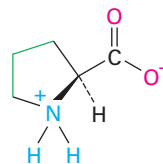
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TABLE 19.1 The 20 Common Amino Acids in Proteins *continued*

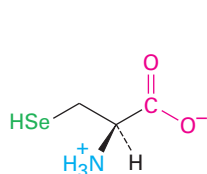
Name	Abbreviations	MW	Structure	pK _a α-CO ₂ H	pK _a α-NH ₃ ⁺	pK _a side chain	pI	
Neutral Amino Acids <i>continued</i>								
Serine	Ser	S	105		2.21	9.15	—	5.68
Threonine	Thr	T	119		2.09	9.10	—	5.60
Tryptophan	Trp	W	204		2.83	9.39	—	5.89
Tyrosine	Tyr	Y	181		2.20	9.11	10.07	5.66
Valine	Val	V	117		2.32	9.62	—	5.96
Acidic Amino Acids								
Aspartic acid	Asp	D	133		1.88	9.60	3.65	2.77
Glutamic acid	Glu	E	147		2.19	9.67	4.25	3.22
Basic Amino Acids								
Arginine	Arg	R	174		2.17	9.04	12.48	10.76
Histidine	His	H	155		1.82	9.17	6.00	7.59
Lysine	Lys	K	146		2.18	8.95	10.53	9.74

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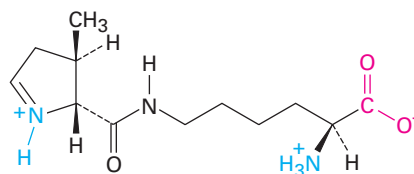
All are **α -amino acids**, meaning that the amino group in each is a substituent on the α carbon—the one next to the carbonyl group. Nineteen of the twenty amino acids are primary amines, RNH_2 , and differ only in the nature of the **side chain**—the substituent attached to the α carbon. Proline is a secondary amine whose nitrogen and α carbon atoms are part of a five-membered pyrrolidine ring.

A primary α -amino acidProline, a secondary α -amino acid

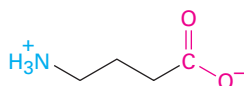
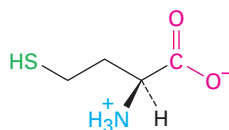
In addition to the twenty amino acids commonly found in proteins, two others—selenocysteine and pyrrolysine—are found in some organisms, and more than 700 nonprotein amino acids are also found in nature. γ -Aminobutyric acid (GABA), for instance, is found in the brain and acts as a neurotransmitter; homocysteine is found in blood and is linked to coronary heart disease; and thyroxine is found in the thyroid gland, where it acts as a hormone.



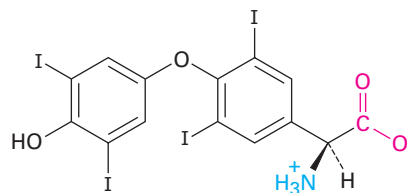
Selenocysteine



Pyrrolysine

 γ -Aminobutyric acid

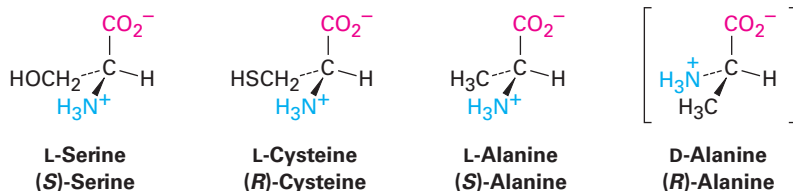
Homocysteine



Thyroxine

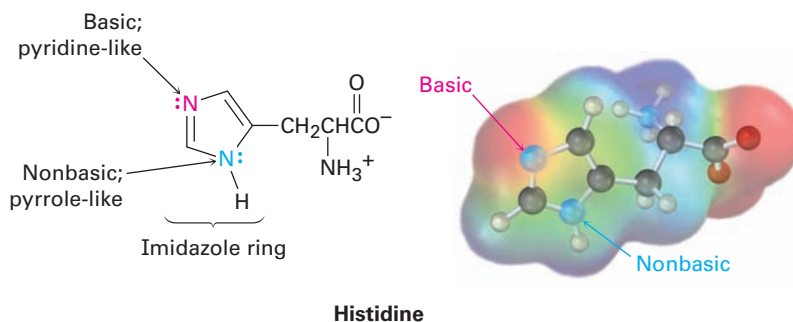
Except for glycine, $^+\text{H}_3\text{NCH}_2\text{CO}_2^-$, the α carbons of amino acids are chirality centers. Two enantiomers of each are therefore possible, but nature uses only one to build proteins. Because of their stereochemical similarity to

L sugars, which we'll look at in Section 21-3, the naturally occurring α -amino acids are often referred to as L amino acids. The nonnaturally occurring enantiomers are called D amino acids.



The 20 common amino acids can be further classified as neutral, acidic, or basic, depending on the structure of their side chains. Fifteen of the twenty have neutral side chains, two (aspartic acid and glutamic acid) have an extra carboxylic acid function in their side chains, and three (lysine, arginine, and histidine) have basic amino groups in their side chains. Note that both cysteine (a thiol) and tyrosine (a phenol), although usually classified as neutral, nevertheless have weakly acidic side chains that can be deprotonated in a sufficiently basic solution.

At the physiological pH of 7.3 within cells, the side-chain carboxyl groups of aspartic acid and glutamic acid are deprotonated and the basic side-chain nitrogens of lysine and arginine are protonated. Histidine, however, which contains a heterocyclic imidazole ring in its side chain, is not quite basic enough to be protonated at pH 7.3. Note that only the pyridine-like, doubly bonded nitrogen in histidine is basic. The pyrrole-like singly bonded nitrogen is nonbasic because its lone pair of electrons is part of the six- π -electron aromatic imidazole ring (Section 18-8).



Humans are able to synthesize only 11 of the 20 protein amino acids, called nonessential amino acids. The other 9, called essential amino acids, are biosynthesized only in plants and microorganisms and must be obtained in our diet. The division between essential and nonessential amino acids is not clear-cut, however. Tyrosine, for instance, is sometimes considered nonessential because humans can produce it from phenylalanine, but phenylalanine itself is essential and must be obtained in the diet. Arginine can be synthesized by humans, but much of the arginine we need also comes from our diet.

PROBLEM 19.1

How many of the α -amino acids shown in Table 19.1 contain aromatic rings? How many contain sulfur? How many contain alcohols? How many contain hydrocarbon side chains?

PROBLEM 19.2

Of the 19 L amino acids, 18 have the *S* configuration at the α carbon. Cysteine is the only L amino acid that has an *R* configuration. Explain.

PROBLEM 19.3

The amino acid threonine, (2*S*,3*R*)-2-amino-3-hydroxybutanoic acid, has two chirality centers.

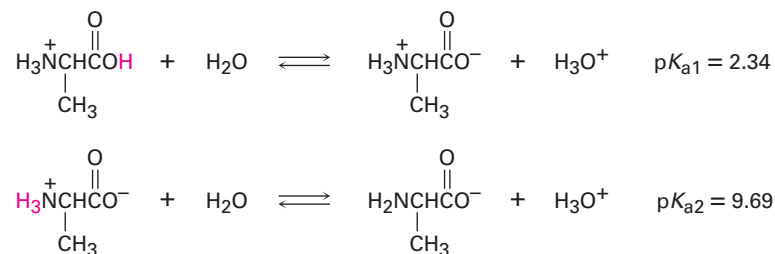
- (a) Draw threonine, using normal, wedged, and dashed lines to show dimensionality.
 (b) Draw a diastereomer of threonine, and label its chirality centers as *R* or *S*.

19-2 Amino Acids and the Henderson–Hasselbalch Equation: Isoelectric Points

According to the Henderson–Hasselbalch equation (Sections 15-3 and 18-5), if we know both the pH of a solution and the pK_a of an acid HA, we can calculate the ratio of $[A^-]$ to $[HA]$ in the solution. Furthermore, when $pH = pK_a$, the two forms A^- and HA are present in equal amounts because $\log 1 = 0$.

$$pH = pK_a = \log \frac{[A^-]}{[HA]} \quad \text{or} \quad \log \frac{[A^-]}{[HA]} = pH - pK_a$$

To apply the Henderson–Hasselbalch equation to an amino acid, let's find out what species are present in a 1.00 M solution of alanine at $pH = 9.00$. According to Table 19.1, protonated alanine [$^+H_3NCH(CH_3)CO_2H$] has $pK_{a1} = 2.34$ and neutral zwitterionic alanine [$^+H_3NCH(CH_3)CO_2^-$] has $pK_{a2} = 9.69$:



Since the pH of the solution is much closer to pK_{a2} than to pK_{a1} , we need to use pK_{a2} for the calculation. From the Henderson–Hasselbalch equation, we have:

$$\log \frac{[A^-]}{[HA]} = pH - pK_a = 9.00 - 9.69 = -0.69$$

so

$$\frac{[A^-]}{[HA]} = \text{antilog}(-0.69) = 0.20 \quad \text{and} \quad [A^-] = 0.20 [HA]$$

In addition, we know that

$$[A^-] + [HA] = 1.00 \text{ M}$$

Solving the two simultaneous equations gives $[HA] = 0.83$ and $[A^-] = 0.17$. In other words, at $\text{pH} = 9.00$, 83% of alanine molecules in a 1.00 M solution are neutral (zwitterionic) and 17% are deprotonated. Similar calculations can be done at any other pH and the results plotted to give the titration curve shown in **FIGURE 19.1**.

Each leg of the titration curve is calculated separately. The first leg, from pH 1 to 6, corresponds to the dissociation of protonated alanine, H_2A^+ . The second leg, from pH 6 to 11, corresponds to the dissociation of zwitterionic alanine, HA. It's as if we started with H_2A^+ at low pH and then titrated with NaOH. When 0.5 equivalent of NaOH is added, the deprotonation of H_2A^+ is 50% done; when 1.0 equivalent of NaOH is added, the deprotonation of H_2A^+ is complete and HA predominates; when 1.5 equivalent of NaOH is added, the deprotonation of HA is 50% done; and when 2.0 equivalents of NaOH is added, the deprotonation of HA is complete.

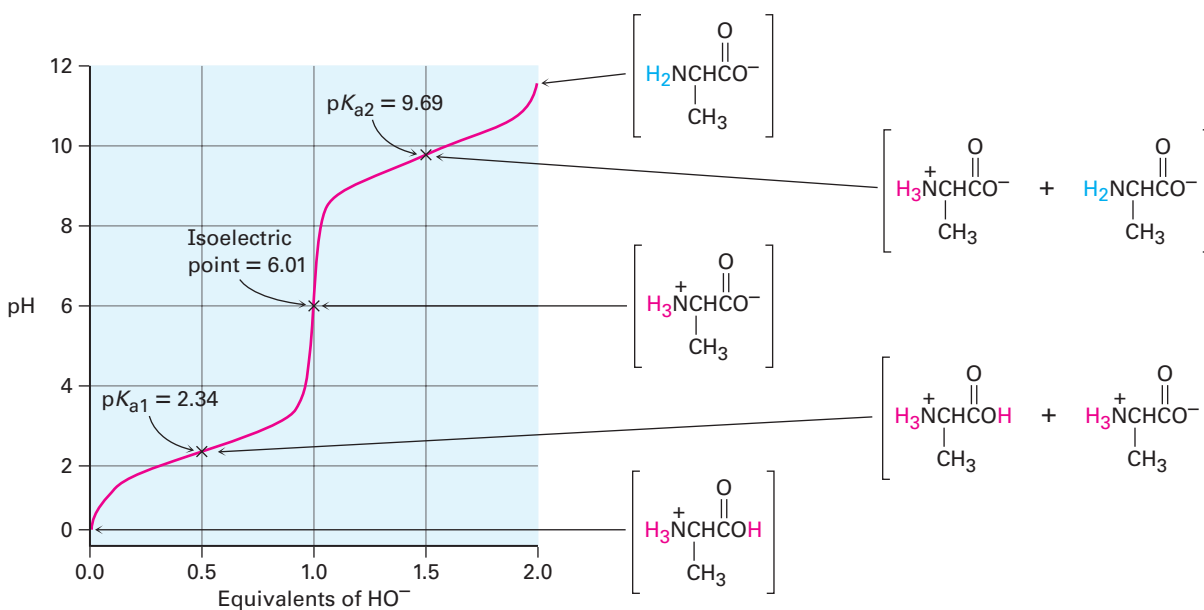
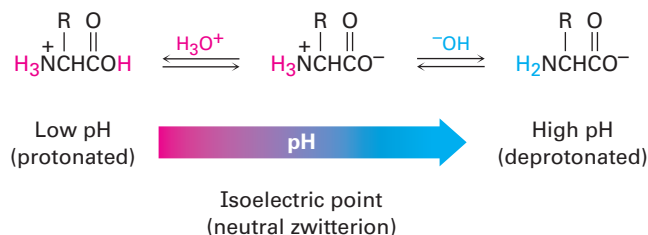


FIGURE 19.1 A titration curve for alanine, plotted using the Henderson–Hasselbalch equation. Each of the two legs is plotted separately. At $\text{pH} < 1$, alanine is entirely protonated; at $\text{pH} = 2.34$, alanine is a 50:50 mix of protonated and neutral forms; at $\text{pH} 6.01$, alanine is entirely neutral; at $\text{pH} = 9.69$, alanine is a 50:50 mix of neutral and deprotonated forms; at $\text{pH} > 11.5$, alanine is entirely deprotonated.

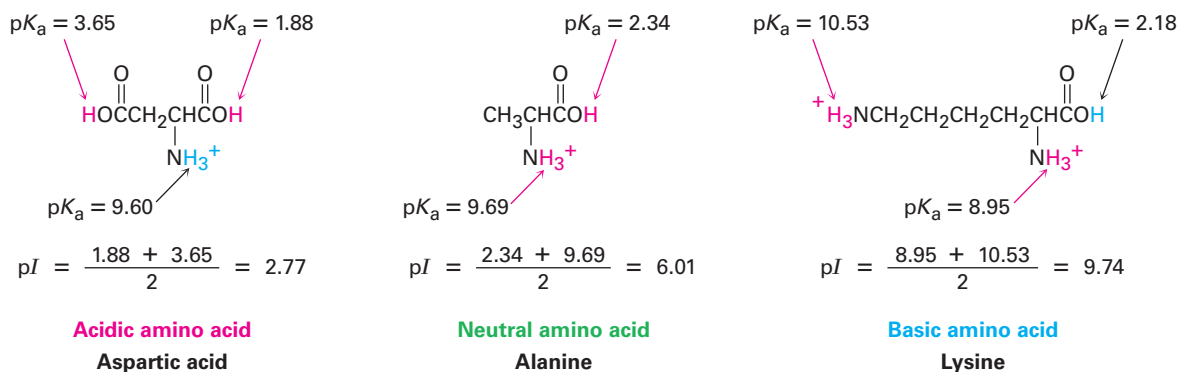
Look carefully at the titration curve in Figure 19.1. In acid solution, an amino acid is protonated and exists primarily as a cation. In basic solution, an amino acid is deprotonated and exists primarily as an anion. In between the

two is an intermediate pH at which the amino acid is exactly balanced between anionic and cationic forms and exists primarily as the neutral zwitterion. This pH is called the amino acid's **isoelectric point (pI)** and has a value of 6.01 for alanine.



The isoelectric point of an amino acid depends on its structure, with values for the 20 common amino acids given in Table 19.1. The 15 neutral amino acids have isoelectric points near neutrality, in the pH range 5.0 to 6.5. The two acidic amino acids have isoelectric points at lower pH so that deprotonation of the side-chain $-\text{CO}_2\text{H}$ does not occur at their pI, and the three basic amino acids have isoelectric points at higher pH so that protonation of the side-chain amino group does not occur at their pI.

More specifically, the pI of any amino acid is the average of the two acid-dissociation constants that involve the neutral zwitterion. For the 13 amino acids with a neutral side chain, pI is the average of $\text{pK}_{\text{a}1}$ and $\text{pK}_{\text{a}2}$. For the four amino acids with either a strongly or weakly acidic side chain, pI is the average of the two lowest pK_{a} values. For the three amino acids with a basic side chain, pI is the average of the two highest pK_{a} values.



Just as individual amino acids have isoelectric points, proteins have an overall pI because of the cumulative effect of all the acidic or basic amino acids they may contain. The enzyme lysozyme, for instance, has a preponderance of basic amino acids and thus has a high isoelectric point ($\text{pI} = 11.0$). Pepsin, however, has a preponderance of acidic amino acids and a low isoelectric point ($\text{pI} \sim 1.0$). Not surprisingly, the solubilities and properties of proteins with different pI's are strongly affected by the pH of the medium. Solubility in water is usually lowest at the isoelectric point, where the protein has no net charge, and is higher both above and below the pI, where the protein is charged.

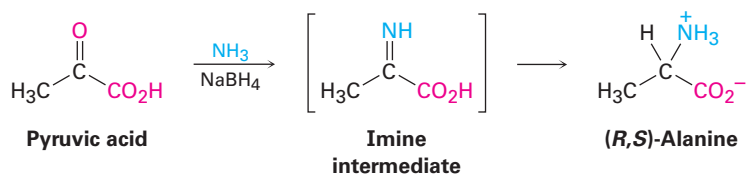
PROBLEM 19.5

What alkyl halides would you use to prepare the following α -amino acids by the amidomalonate method?

(a) Leucine (b) Histidine (c) Tryptophan (d) Methionine

Reductive Amination of α -Keto Acids

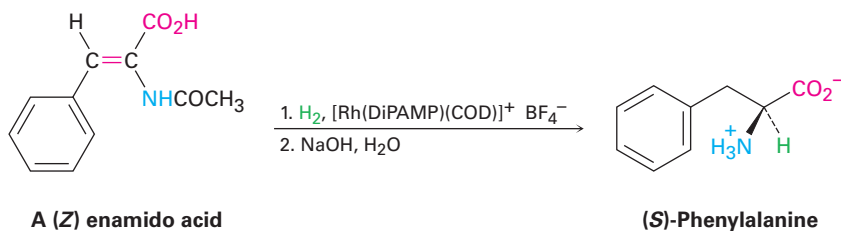
Another method for the synthesis of α -amino acids is by reductive amination of an α -keto acid with ammonia and a reducing agent. Alanine, for instance, is prepared by treatment of pyruvic acid with ammonia in the presence of NaBH_4 . As described in Section 18-6, the reaction proceeds through formation of an intermediate imine that is then reduced.

**Enantioselective Synthesis**

The synthesis of an α -amino acid from an achiral precursor by either of the methods just described yields a racemic mixture, with equal amounts of *S* and *R* enantiomers. To use an amino acid in the laboratory synthesis of a naturally occurring protein, however, the pure *S* enantiomer must be obtained.

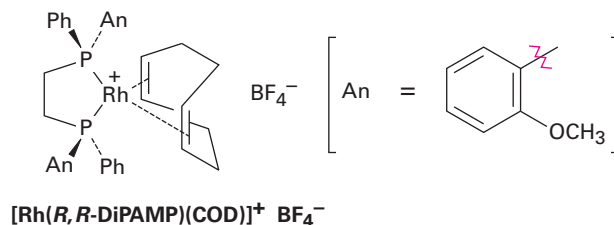
Two methods are used in practice to obtain enantiomerically pure amino acids. One way is to resolve the racemate into its pure enantiomers, as discussed in Section 5-8. A more efficient approach, however, is to use an enantioselective synthesis to prepare only the desired *S* enantiomer directly. As discussed in the Chapter 14 *Something Extra*, the idea behind enantioselective synthesis is to find a chiral reaction catalyst that will temporarily hold a substrate molecule in an unsymmetrical chiral environment. While in that chiral environment, the substrate may be more open to reaction on one side than on another, leading to an excess of one enantiomeric product over another.

William Knowles at the Monsanto Company discovered some years ago that α -amino acids can be prepared enantioselectively by hydrogenation of a *Z* enamido acid with a chiral hydrogenation catalyst. (*S*)-Phenylalanine, for instance, is prepared in 98.7% purity contaminated by only 1.3% of the (*R*) enantiomer when a chiral rhodium catalyst is used. For this discovery, Knowles shared the 2001 Nobel Prize in Chemistry.



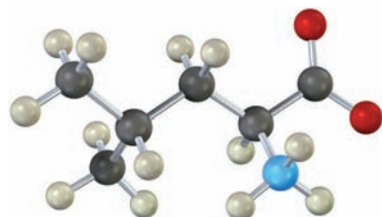
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The most effective catalysts for enantioselective amino acid synthesis are coordination complexes of rhodium(I) with cycloocta-1,5-diene (COD) and a chiral diphosphine such as (*R,R*)-1,2-bis(*o*-anisylphenylphosphino)ethane, the so-called DiPAMP ligand. The complex owes its chirality to the presence of the trisubstituted phosphorus atoms (Section 5-10).



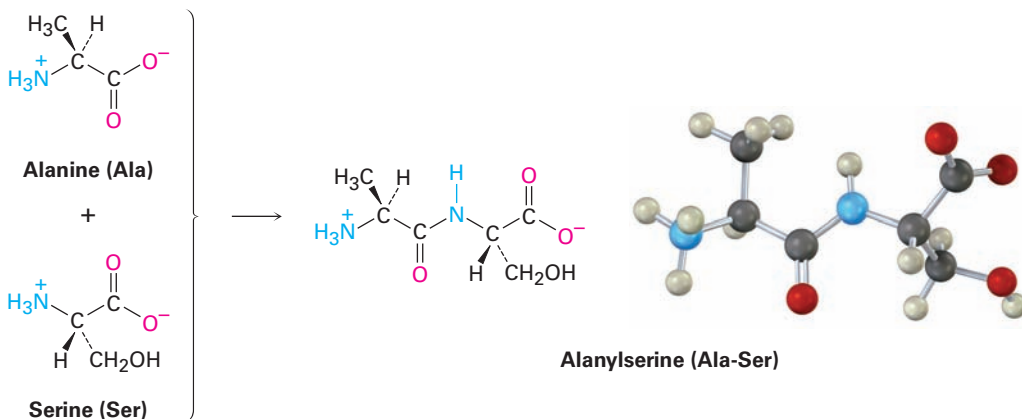
PROBLEM 19.6

Show how you could prepare the following amino acid enantioselectively:

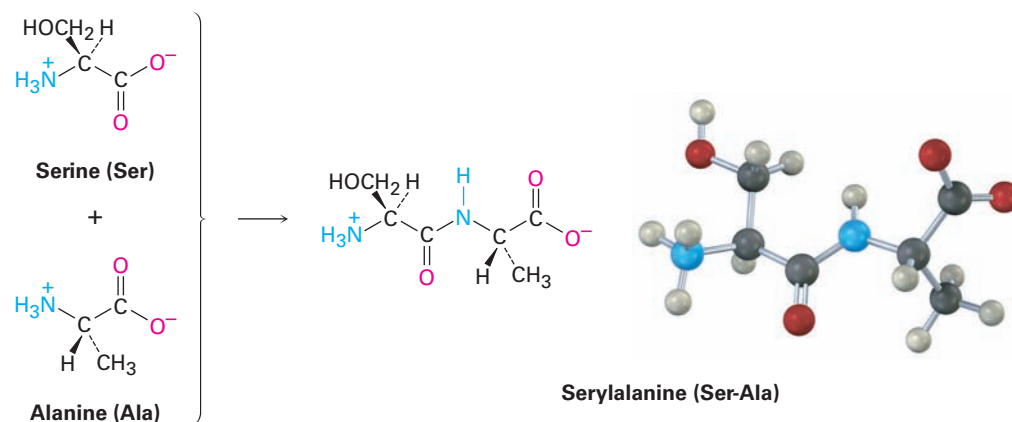


19-4 Peptides and Proteins

Proteins and peptides are amino acid polymers in which the individual amino acids, called **residues**, are joined together by amide bonds, or *peptide bonds*. An amino group from one residue forms an amide bond with the carboxyl of a second residue, the amino group of the second forms an amide bond with the carboxyl of a third, and so on. For example, alanylserine is the dipeptide that results when an amide bond forms between the alanine carboxyl and the serine amino group:

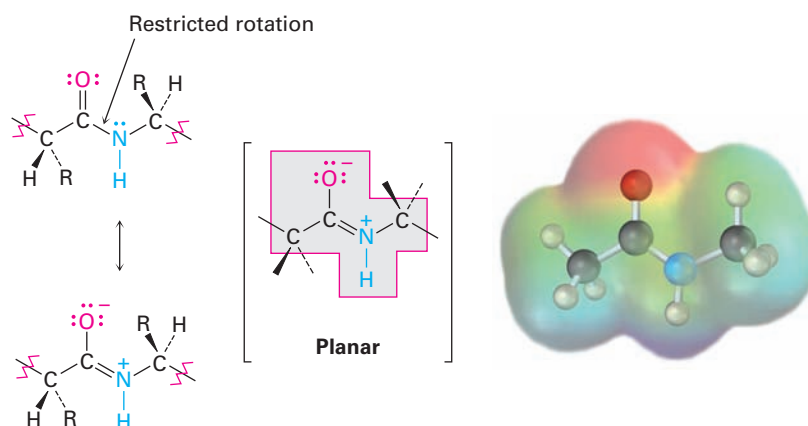


Note that two dipeptides can result from reaction between alanine and serine, depending on which carboxyl group reacts with which amino group. If the alanine amino group reacts with the serine carboxyl, serylalanine results:



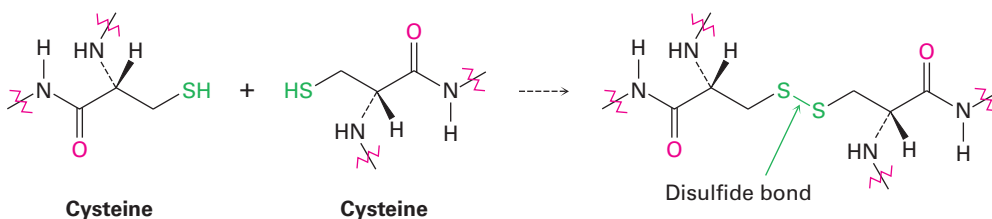
The long, repetitive sequence of -N-CH-CO- atoms that makes up a continuous chain is called the protein's **backbone**. By convention, peptides are written with the **N-terminal amino acid** (the one with the free -NH_3^+ group) on the left and the **C-terminal amino acid** (the one with the free -CO_2^- group) on the right. The name of the peptide is indicated by using the abbreviations listed in Table 19.1 for each amino acid. Thus, alanylserine is abbreviated Ala-Ser or A-S, and serylalanine is abbreviated Ser-Ala or S-A. Needless to say, the one-letter abbreviations are more convenient, though less immediately recognizable, than the three-letter abbreviations.

The amide bond that links different amino acids together in peptides is no different from any other amide bond (Sections 16-7 and 18-3). An amide nitrogen is nonbasic because its unshared electron pair is delocalized by interaction with the carbonyl group. This overlap of the nitrogen p orbital with the p orbitals of the carbonyl group imparts a certain amount of double-bond character to the C–N bond and restricts rotation around it. The amide bond is therefore planar, and the N–H is oriented 180° to the C=O.

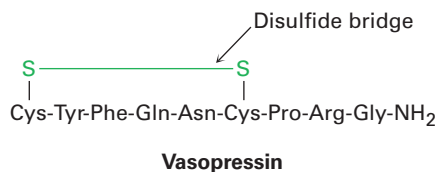


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A second kind of covalent bonding in peptides occurs when a disulfide linkage, RS–SR, is formed between two cysteine residues. As we saw in Section 13-7, a disulfide is formed by mild oxidation of a thiol, RSH, and is cleaved by mild reduction.



A disulfide bond between cysteine residues in different peptide chains links the otherwise separate chains together, while a disulfide bond between cysteine residues in the same chain forms a loop. The antidiuretic hormone vasopressin, for instance, contains a disulfide bridge between cysteine residues at positions 1 and 6 in the chain. Note that the C-terminal end of vasopressin occurs as the amide rather than as the carboxylate.



PROBLEM 19.7

There are six isomeric tripeptides containing valine, tyrosine, and glycine. Name them using both three- and one-letter abbreviations.

PROBLEM 19.8

Draw the structure of M-P-V-G, and indicate the amide bonds.

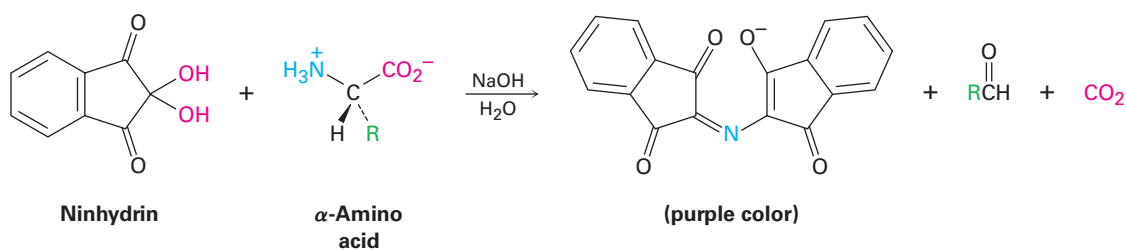
19-5 Amino Acid Analysis of Peptides

To determine the structure of a protein or peptide, we need to answer three questions: What amino acids are present? How much of each is present? In what sequence do the amino acids occur in the peptide chain? The answers to the first two questions are provided by an automated instrument called an amino acid analyzer.

In preparation for analysis, the peptide is broken into its constituent amino acids by reducing all disulfide bonds, capping the –SH groups of cysteine residues by S_N2 reaction with iodoacetic acid, and hydrolyzing the amide bonds by heating with aqueous 6 M HCl at 110 °C for 24 hours. The resultant amino acid mixture is then separated into its components by a technique called *chromatography*, either high-pressure liquid chromatography (HPLC) or a related technique called ion-exchange chromatography.

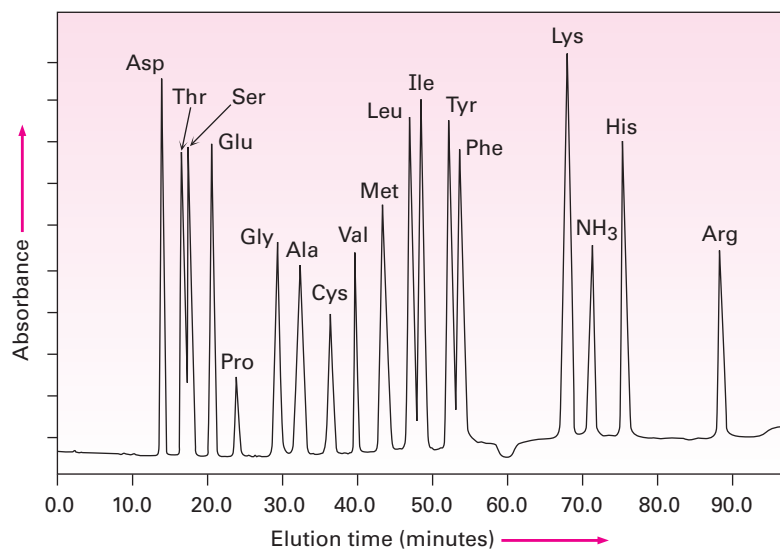
In both HPLC and ion-exchange chromatography, the mixture to be separated is dissolved in a solvent, called the *mobile phase*, and passed through a metal tube or glass column that contains an adsorbent material, called the *stationary phase*. Because different compounds adsorb to the stationary phase to different extents, they migrate through the chromatography column at different rates and are separated as they emerge (*elute*) from the end.

In the ion-exchange technique, separated amino acids eluting from the chromatography column mix with a solution of a substance called ninhydrin and undergo a rapid reaction that produces an intense purple color. The color is detected by a spectrometer, and a plot of elution time versus spectrometer absorbance is obtained.



Because the time required for a given amino acid to elute from a standard column is reproducible, the identities of the amino acids in a peptide can be determined. The amount of each amino acid in the sample is determined by measuring the intensity of the purple color resulting from its reaction with ninhydrin. **FIGURE 19.3** shows the results of amino acid analysis of a standard equimolar mixture of 17 α -amino acids. Typically, amino acid analysis requires about 100 picomoles (2–3 μg) of sample for a protein containing about 200 residues.

FIGURE 19.3 Amino acid analysis of an equimolar mixture of 17 amino acids.



PROBLEM 19.9

Show the structure of the product you would expect to obtain by S_N2 reaction of a cysteine residue with iodoacetic acid.

PROBLEM 19.10

Show the structures of the products obtained on reaction of valine with ninhydrin.

19-6 Peptide Sequencing: The Edman Degradation

With the identities and relative amounts of amino acids known, the peptide is sequenced to find out in what order the amino acids are linked together. Much peptide sequencing is now done by mass spectrometry, using either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI) linked to a time-of-flight (TOF) mass analyzer, as described in Section 10-4. Also in common use is a chemical method of peptide sequencing called the Edman degradation.

The general idea of peptide sequencing by Edman degradation is to cleave one amino acid at a time from an end of the peptide chain. That terminal amino acid is then separated and identified, and the cleavage reactions are repeated on the chain-shortened peptide until the entire peptide sequence is known. Automated protein sequencers are available that allow as many as 50 repetitive sequencing cycles to be carried out before a buildup of unwanted by-products interferes with the results. So efficient are these instruments that sequence information can be obtained from as little as 1 to 5 picomoles of sample—less than $0.1 \mu\text{g}$.

Edman degradation involves treatment of a peptide with phenyl isothiocyanate (PITC), $\text{C}_6\text{H}_5\text{-N}=\text{C}=\text{S}$, followed by reaction with trifluoroacetic acid, as shown in **FIGURE 19.4**. The first step attaches the PITC to the $-\text{NH}_2$ group of the N-terminal amino acid, and the second step splits the N-terminal residue from the peptide chain, yielding an anilinothiazolinone (ATZ) derivative plus the chain-shortened peptide. Further acid-catalyzed rearrangement of the ATZ derivative with aqueous acid converts it into a phenylthiohydantoin (PTH), which is identified chromatographically by comparison of its elution time with the known elution times of PTH derivatives of the 20 common amino acids. The chain-shortened peptide is then automatically resubmitted to another round of Edman degradation.

Complete sequencing of large proteins by Edman degradation is impractical because of the buildup of unwanted by-products. To get around the problem, a large peptide chain is first cleaved by partial hydrolysis into a number of smaller fragments, the sequence of each fragment is determined, and the individual fragments are fitted together by matching the overlapping ends. In this way, protein chains with more than 400 amino acids have been sequenced.

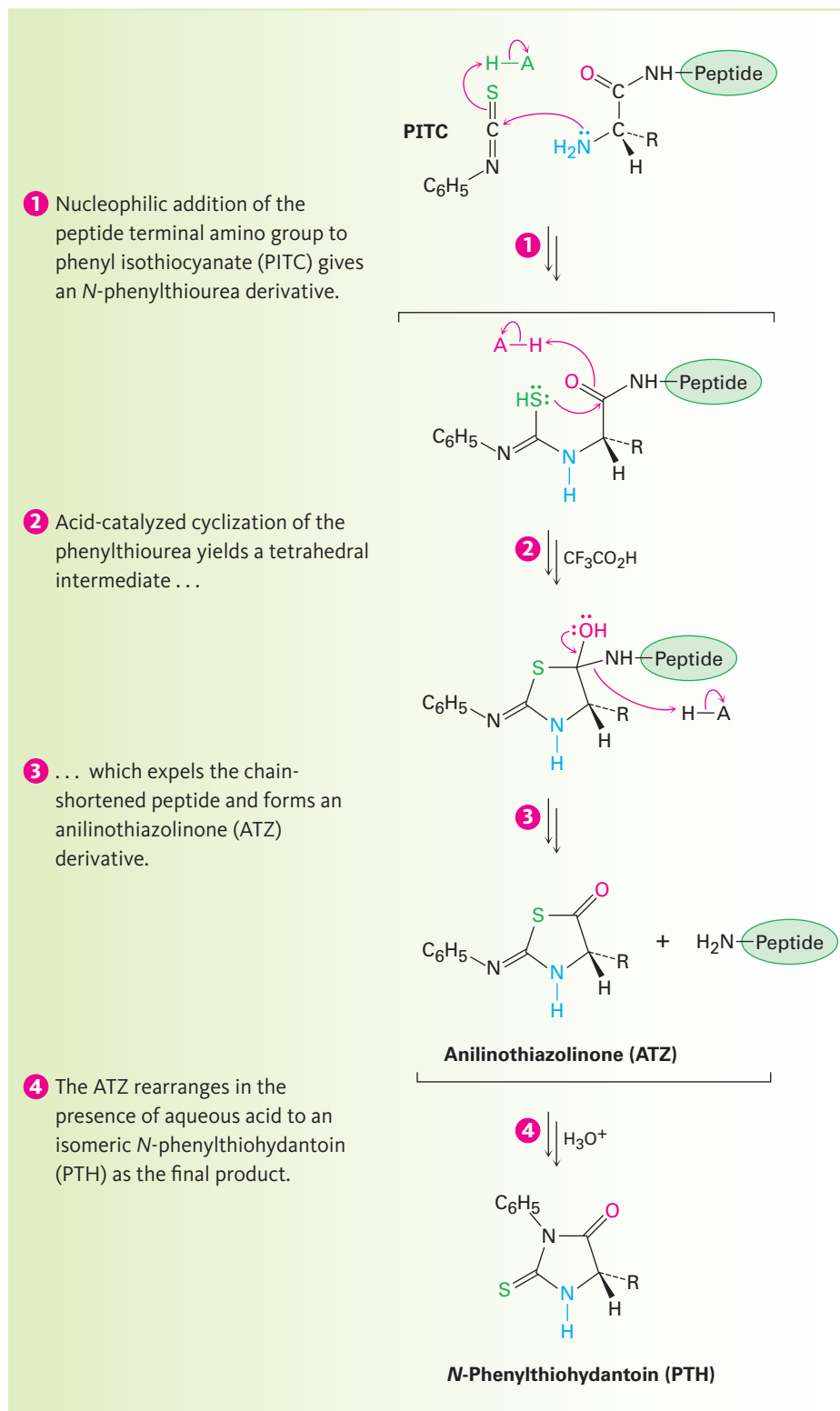
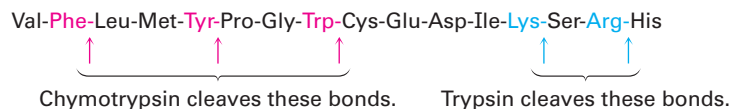


FIGURE 19.4 Mechanism of the Edman degradation for N-terminal analysis of peptides.

Partial hydrolysis of a peptide can be carried out either chemically, using aqueous acid, or enzymatically. Acid hydrolysis is unselective and leads to a more-or-less random mixture of small fragments, but enzymatic hydrolysis is quite specific. The enzyme trypsin, for instance, catalyzes hydrolysis of peptides only at the carboxyl side of the basic amino acids arginine and lysine; chymotrypsin cleaves only at the carboxyl side of the aryl-substituted amino acids phenylalanine, tyrosine, and tryptophan.

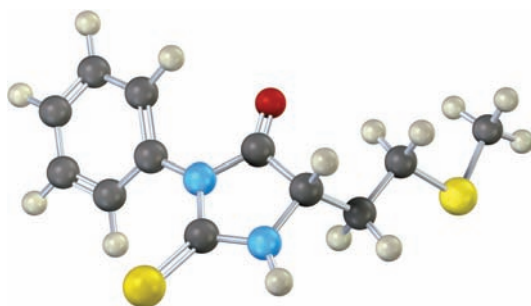


PROBLEM 19.11

The octapeptide angiotensin II has the sequence Asp-Arg-Val-Tyr-Ile-His-Pro-Phe. What fragments would result if angiotensin II were cleaved with trypsin? With chymotrypsin?

PROBLEM 19.12

What N-terminal residue on a peptide gives the following PTH derivative on Edman degradation?



PROBLEM 19.13

Draw the structure of the PTH derivative that would be formed on Edman degradation of angiotensin II (Problem 19.11).

PROBLEM 19.14

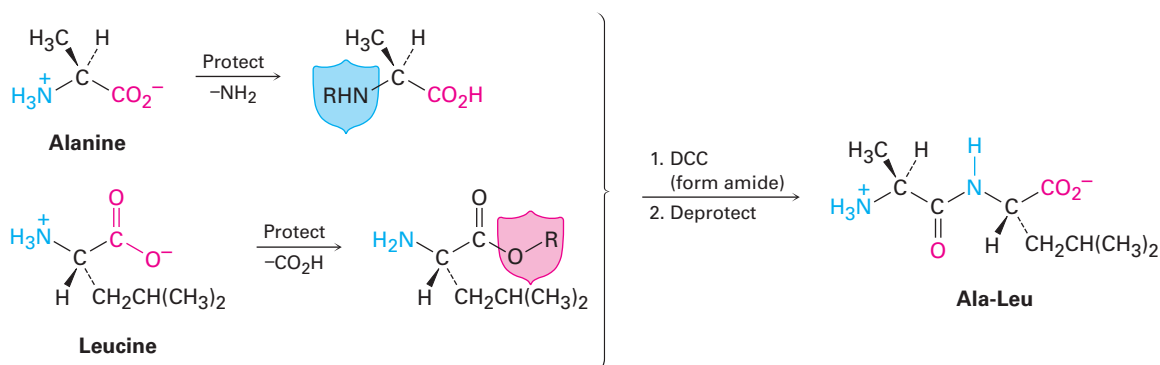
Give the amino acid sequence of hexapeptides that produce the following sets of fragments on partial acid hydrolysis:

- (a) Arg, Gly, Ile, Leu, Pro, Val gives Pro-Leu-Gly, Arg-Pro, Gly-Ile-Val
 (b) N, L, M, W, V₂ gives V-L, V-M-W, W-N-V

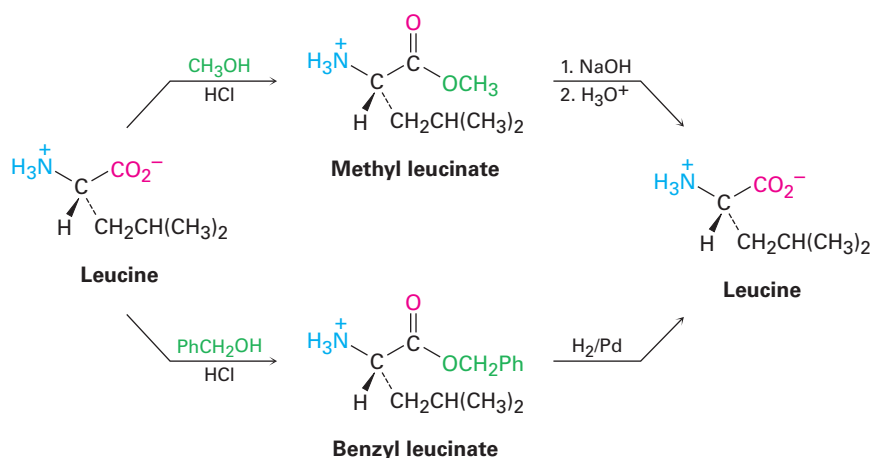
19-7 Peptide Synthesis

Once the structure of a peptide is known, its synthesis can be undertaken—perhaps to obtain a larger amount for biological evaluation. A simple amide can be formed by treating an amine and a carboxylic acid with dicyclohexylcarbodiimide (DCC; Section 16-3), but peptide synthesis is a more difficult problem because many different amide bonds must be formed in a specific order rather than at random.

The solution to the specificity problem is protection (Sections 13-6 and 14-8). If we want to couple alanine with leucine to synthesize Ala-Leu, for instance, we could protect the $-\text{NH}_2$ group of alanine and the $-\text{CO}_2\text{H}$ group of leucine to shield them from reacting, then form the desired Ala-Leu amide bond by reaction with DCC, and then remove the protecting groups.

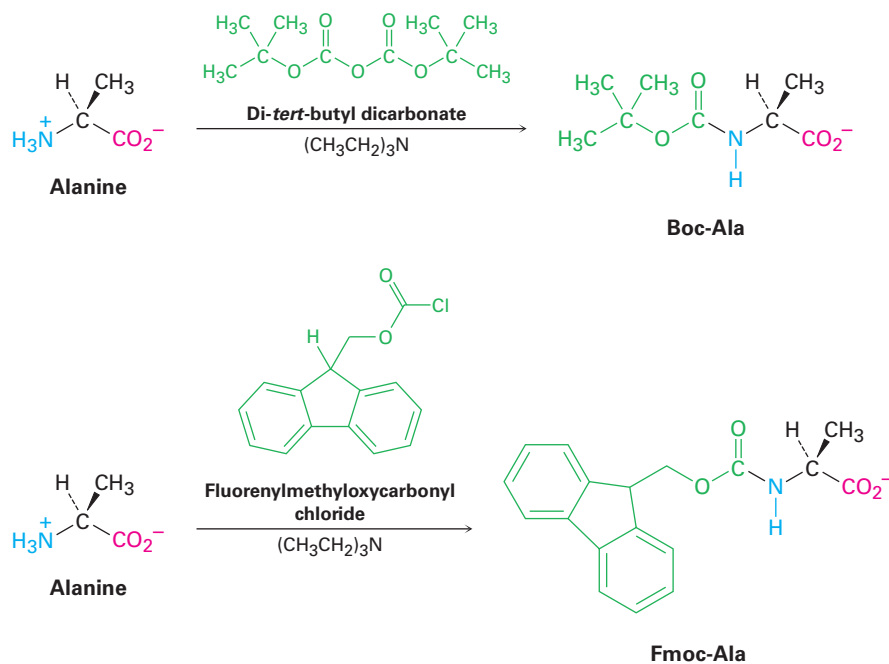


Many different amino- and carboxyl-protecting groups have been devised, but only a few are widely used. Carboxyl groups are often protected simply by converting them into methyl or benzyl esters. Both groups are easily introduced by standard methods of ester formation and are easily removed by mild hydrolysis with aqueous NaOH. Benzyl esters can also be cleaved by catalytic *hydrogenolysis* of the weak benzylic C–O bond ($\text{RCO}_2\text{---CH}_2\text{Ph} + \text{H}_2 \rightarrow \text{RCO}_2\text{H} + \text{PhCH}_3$).

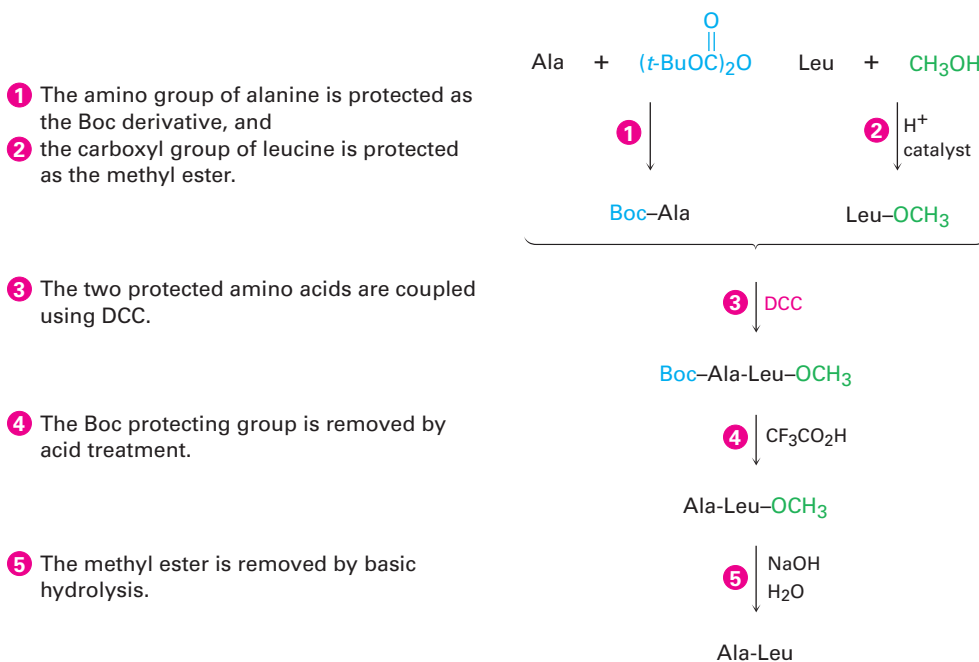


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Amino groups are often protected as their *tert*-butyloxycarbonyl amide (Boc) or fluorenylmethyloxycarbonyl amide (Fmoc) derivatives. The Boc protecting group is introduced by reaction of the amino acid with di-*tert*-butyl dicarbonate in a nucleophilic acyl substitution reaction and is removed by brief treatment with a strong acid such as trifluoroacetic acid, $\text{CF}_3\text{CO}_2\text{H}$. The Fmoc protecting group is introduced by reaction with an acid chloride and is removed by treatment with base.

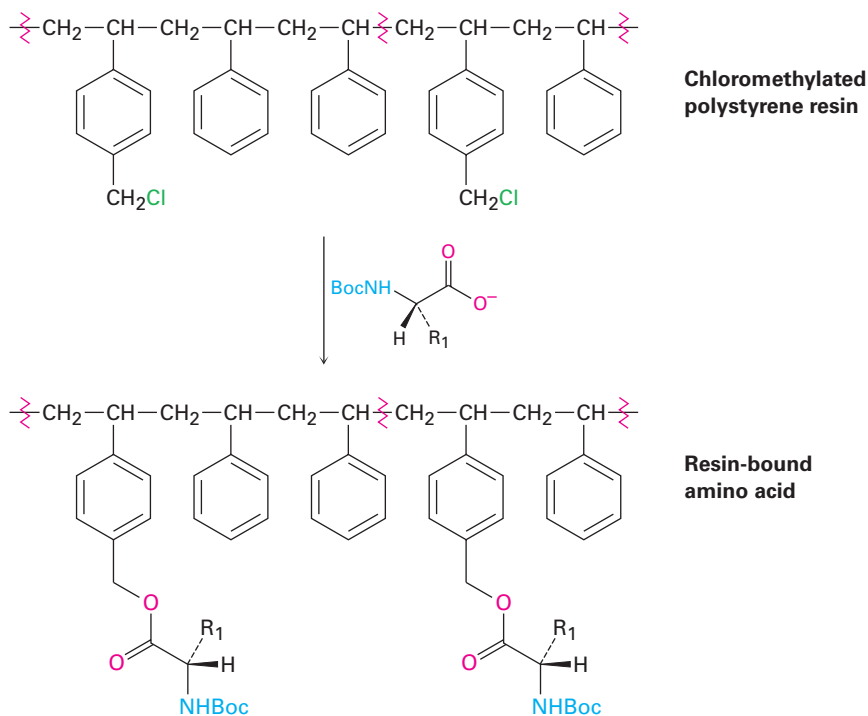


Thus, five steps are needed to synthesize a dipeptide such as Ala-Leu:

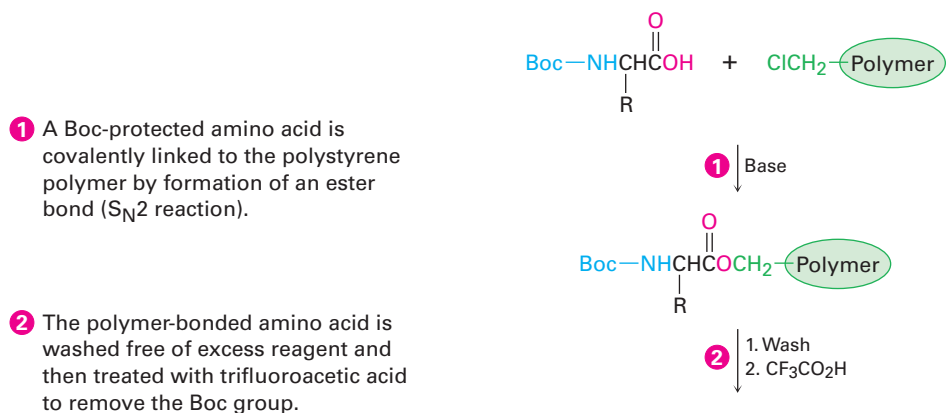


Although the steps just shown can be repeated to add one amino acid at a time to a growing chain, the synthesis of a large peptide by this sequential addition is long and arduous. An immense simplification is possible, however, using methods introduced by R. Bruce Merrifield, who received the 1984 Nobel Prize in Chemistry for his work. In the Merrifield solid-phase method, peptide synthesis is carried out with the growing amino acid chain covalently bonded to small beads of a polymer resin rather than in solution.

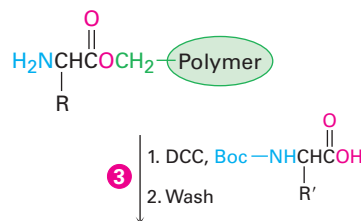
In the original procedure, polystyrene resin was used, prepared so that 1 of every 100 or so benzene rings contained a chloromethyl ($-\text{CH}_2\text{Cl}$) group. A Boc-protected C-terminal amino acid was then attached to the resin through an ester bond formed by $\text{S}_{\text{N}}2$ reaction.



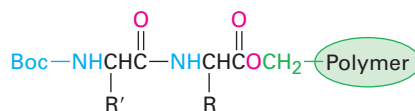
Once the first amino acid was bonded to the resin, a repeating series of four steps was carried out to build a peptide:



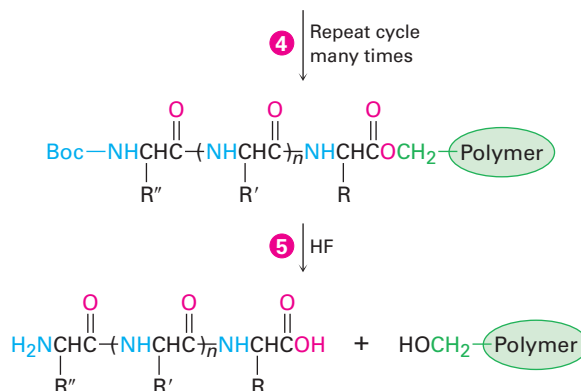
- 3 A second Boc-protected amino acid is coupled to the first by reaction with DCC. Excess reagents are removed by washing them from the insoluble polymer.



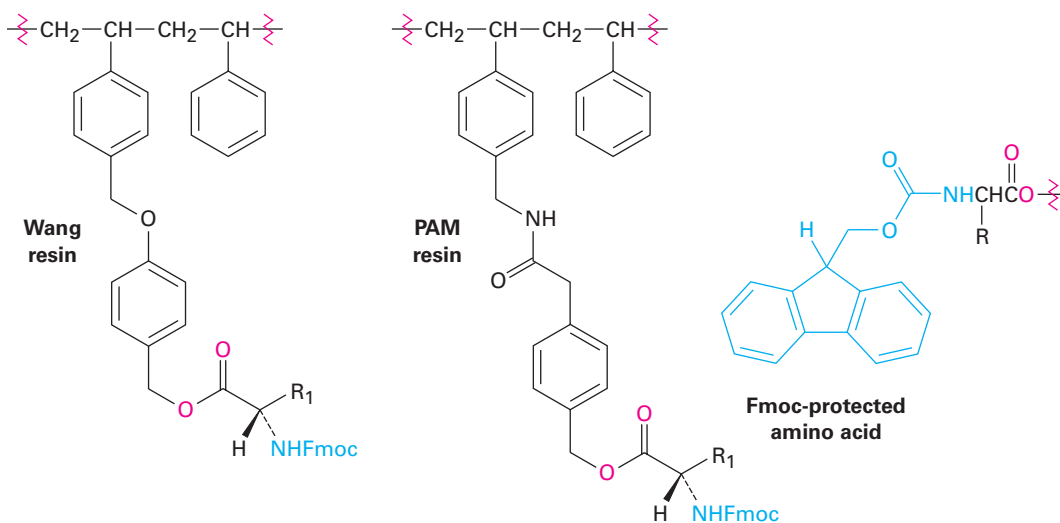
- 4 The cycle of deprotection, coupling, and washing is repeated as many times as desired to add amino acid units to the growing chain.



- 5 After the desired peptide has been made, treatment with anhydrous HF removes the final Boc group and cleaves the ester bond to the polymer, yielding the free peptide.



The solid-phase technique has been improved substantially over the years, but the fundamental idea remains the same. The most commonly used resins at present are either the Wang resin or the PAM (phenylacetamidomethyl) resin, and the most commonly used N-protecting group is the Fmoc group, rather than Boc.



Robotic peptide synthesizers are now used to automatically repeat the coupling, washing, and deprotection steps with different amino acids. Each

step occurs in high yield, and mechanical losses are minimized because the peptide intermediates are never removed from the insoluble polymer until the final step. Using this procedure, up to 30 mg of a peptide with 20 amino acids can be routinely prepared in a few hours.

PROBLEM 19.15

Show the mechanism for formation of a Boc derivative by reaction of an amino acid with di-*tert*-butyl dicarbonate.

PROBLEM 19.16

Write all five steps required for the synthesis of Leu-Ala from alanine and leucine.

19-8 Protein Structure

Proteins are usually classified as either fibrous or globular, according to their three-dimensional shape. **Fibrous proteins**, such as the collagen in tendons and connective tissue and the myosin in muscle tissue, consist of polypeptide chains arranged side by side in long filaments. Because these proteins are tough and insoluble in water, they are used in nature for structural materials. **Globular proteins**, by contrast, are usually coiled into compact, roughly spherical shapes. These proteins are generally soluble in water and are mobile within cells. Most of the 3000 or so enzymes that have been characterized to date are globular proteins.

Proteins are so large that the word *structure* takes on a broader meaning than it does with simpler organic compounds. In fact, chemists speak of four different levels of structure when describing proteins:

- The **primary structure** of a protein is simply the amino acid sequence.
- The **secondary structure** of a protein describes how *segments* of the peptide backbone orient into a regular pattern.
- The **tertiary structure** describes how the *entire* protein molecule coils into an overall three-dimensional shape.
- The **quaternary structure** describes how different protein molecules come together to yield large aggregate structures.

Primary structure is determined, as we've seen, by sequencing the protein. Secondary, tertiary, and quaternary structures are determined either by NMR or by X-ray crystallography (Chapter 10 *Something Extra*).

The most common secondary structures are the α helix and the β -pleated sheet. An **α helix** is a right-handed coil of the protein backbone, much like the coil of a spiral staircase (**FIGURE 19.5a**). Each turn of the helix contains 3.6 amino acid residues, with a distance between coils of 540 pm, or 5.4 Å. The structure is stabilized by hydrogen bonds between amide N–H groups and C=O groups four residues away, with an N–H \cdots O distance of 2.8 Å. The α helix is an extremely common secondary structure, and almost all globular proteins contain many helical segments. Myoglobin, a small globular

protein containing 153 amino acid residues in a single chain, is an example (FIGURE 19.5b).

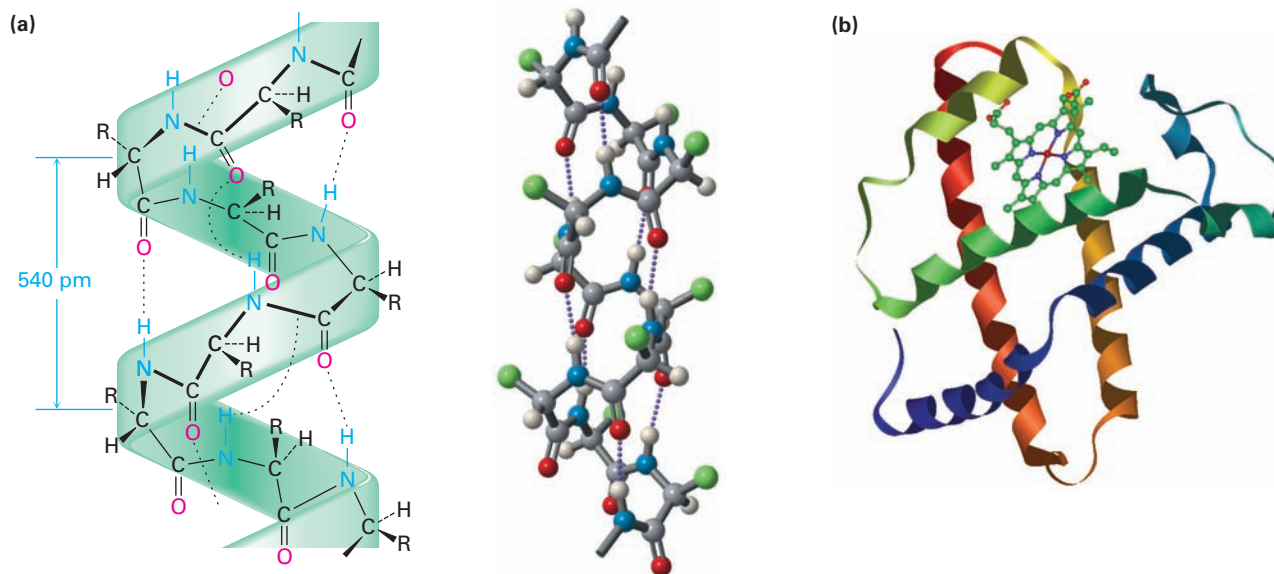


FIGURE 19.5 The α -helical secondary structure of proteins. (a) The helix is stabilized by hydrogen bonds between the N–H group of one residue and the C=O group four residues away. (b) The structure of myoglobin, a globular protein with extensive helical regions that are shown as coiled ribbons in this representation.

A β -pleated sheet differs from an α helix in that the peptide chain is fully extended rather than coiled and the hydrogen bonds occur between residues in adjacent chains (FIGURE 19.6a). The neighboring chains can run either in the same direction (parallel) or in opposite directions (antiparallel), although the antiparallel arrangement is more common and energetically somewhat more favorable. Concanavalin A, for instance, consists of two identical chains of 237 residues with extensive regions of antiparallel β sheets (FIGURE 19.6b).

What about tertiary structure? Why does a protein adopt the shape it does? The forces that determine the tertiary structure of a protein are the same forces that act on all molecules, regardless of size, to provide maximum stability. Particularly important are the hydrophilic (water-loving; Section 2-12) interactions of the polar side chains on acidic or basic amino acids and the hydrophobic (water-fearing) interactions of nonpolar side chains. Those acidic or basic amino acids with charged side chains tend to congregate on the exterior of the protein, where they can be solvated by water. Those amino acids with neutral, nonpolar side chains tend to congregate on the hydrocarbon-like interior of a protein molecule, away from the aqueous medium.

Also important for stabilizing a protein's tertiary structure are the formation of disulfide bridges between cysteine residues, the formation of hydrogen bonds between nearby amino acid residues, and the presence of ionic attractions, called *salt bridges*, between positively and negatively charged sites on various amino acid side chains within the protein.

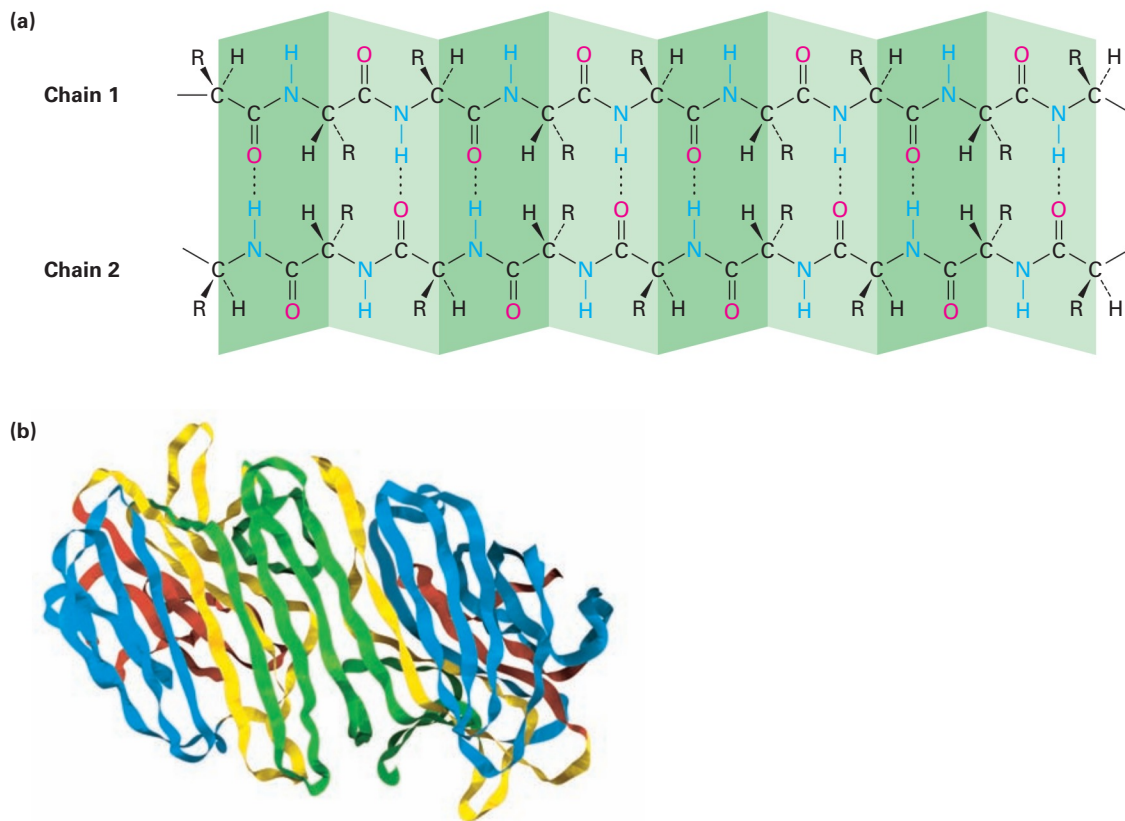
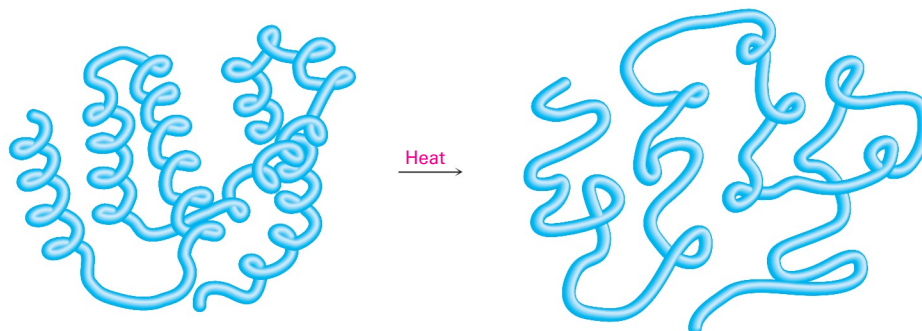


FIGURE 19.6 The β -pleated sheet secondary structure of proteins. (a) The sheet is stabilized by hydrogen bonds between parallel or antiparallel chains. (b) The structure of concanavalin A, a protein with extensive regions of antiparallel β sheets, shown as ribbons.

Because the tertiary structure of a globular protein is delicately held together by weak intramolecular attractions, a modest change in temperature or pH is often enough to disrupt that structure and cause the protein to become **denatured**. Denaturation occurs under such mild conditions that the primary structure remains intact but the tertiary structure unfolds from a specific globular shape to a randomly looped chain (**FIGURE 19.7**).

FIGURE 19.7 A representation of protein denaturation. A globular protein loses its specific three-dimensional shape and becomes randomly looped.



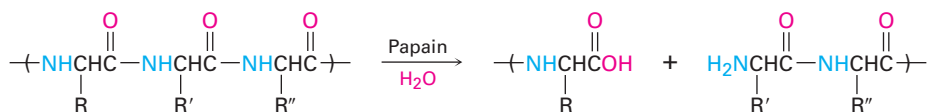
Denaturation is accompanied by changes in both physical and biological properties. Solubility is drastically decreased, as occurs when egg white is cooked and the albumins unfold and coagulate. Most enzymes also lose their catalytic activity when denatured, since a precisely defined tertiary structure is required for their action. Although most denaturation is irreversible, cases are also known where spontaneous renaturation of an unfolded protein to its stable tertiary structure occurs, accompanied by a full recovery of biological activity.

19-9 Enzymes and Coenzymes

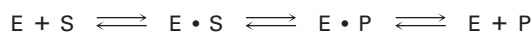
An **enzyme** is a substance—usually a large protein—that acts as a catalyst for a biological reaction. Like all catalysts, an enzyme doesn't affect the equilibrium constant of a reaction and can't bring about a chemical change that is otherwise unfavorable. An enzyme acts only to lower the activation energy for a reaction, thereby making the reaction take place more rapidly. Sometimes, in fact, the rate acceleration brought about by enzymes is extraordinary. Millionfold rate increases are common, and the glycosidase enzymes that hydrolyze polysaccharides increase the reaction rate by a factor of more than 10^{17} , changing the time required for the reaction from millions of years to milliseconds!

Unlike many of the catalysts that chemists use in the laboratory, enzymes are usually specific in their action. Often, in fact, an enzyme will catalyze only a single reaction of a single compound, called the enzyme's *substrate*. For example, the enzyme amylase, found in the human digestive tract, catalyzes only the hydrolysis of starch to yield glucose. Cellulose and other polysaccharides are untouched by amylase.

Different enzymes have different specificities. Some, such as amylase, are specific for a single substrate, but others operate on a range of substrates. Papain, for instance, a globular protein of 212 amino acids isolated from papaya fruit, catalyzes the hydrolysis of many kinds of peptide bonds. In fact, it's this ability to hydrolyze peptide bonds that makes papain useful as a cleaner for contact lenses.



Enzymes function through a pathway that involves initial formation of an enzyme-substrate complex $E \cdot S$, followed by a multistep chemical conversion of the enzyme-bound substrate into enzyme-bound product $E \cdot P$ and final release of product from the complex.

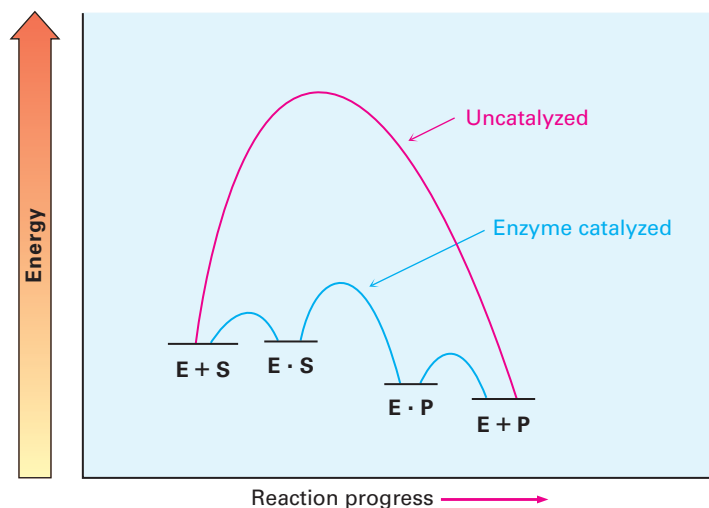


The overall rate constant for conversion of the $E \cdot S$ complex to products $E + P$ is called the *turnover number* because it represents the number of substrate molecules a single enzyme molecule turns over into product per unit time. A value of about 10^3 per second is typical although carbonic anhydrase can reach a value of up to 600,000.

The extraordinary rate accelerations achieved by enzymes are due to a combination of several factors. One important factor is simple geometry: an enzyme will adjust its shape to hold the substrate, other reactants, and various catalytic sites on acidic or basic residues in the precise geometry needed for reaction. In addition, the wrapping of the enzyme around the substrate can create specialized microenvironments that protect the substrate from the aqueous medium and can dramatically change the behavior of acid–base catalytic residues in the active site.

But perhaps most important is that the enzyme stabilizes and thus lowers the energy of the rate-limiting transition state for reaction. That is, it's not the ability of the enzyme to bind the *substrate* that matters but rather its ability to bind and stabilize the *transition state*. Often, in fact, the enzyme binds the transition structure as much as 10^{12} times more tightly than it binds the substrate or products. An energy diagram for an enzyme-catalyzed process might look like that in **FIGURE 19.8**.

FIGURE 19.8 Energy diagrams for **uncatalyzed** and **enzyme-catalyzed** processes. The enzyme makes available an alternative, lower-energy pathway. Rate enhancement is due to the ability of the enzyme to bind to the transition state for product formation, thereby lowering its energy.



Enzymes are classified into six categories depending on the kind of reaction they catalyze, as shown in **TABLE 19.2**. *Oxidoreductases* catalyze oxidations and reductions; *transferases* catalyze the transfer of a group from one substrate to another; *hydrolases* catalyze hydrolysis reactions of esters, amides, and related substrates; *lyases* catalyze the elimination or addition of a small molecule such as H_2O from or to a substrate; *isomerases* catalyze isomerizations; and *ligases* catalyze the bonding together of two molecules, often coupled with the hydrolysis of ATP. The systematic name of an enzyme has two parts, ending with *-ase*. The first part identifies the enzyme's substrate, and the second part identifies its

class. For example, hexose kinase is a transferase that catalyzes the transfer of a phosphate group from ATP to a hexose sugar.

TABLE 19.2 Classification of Enzymes

Class	Some subclasses	Function
Oxidoreductases	Dehydrogenases	Introduction of a double bond
	Oxidases	Oxidation
	Reductases	Reduction
Transferases	Kinases	Transfer of a phosphate group
	Transaminases	Transfer of an amino group
Hydrolases	Lipases	Hydrolysis of an ester
	Nucleases	Hydrolysis of a phosphate
	Proteases	Hydrolysis of an amide
Lyases	Decarboxylases	Loss of CO ₂
	Dehydrases	Loss of H ₂ O
Isomerases	Epimerases	Isomerization of a chirality center
Ligases	Carboxylases	Addition of CO ₂
	Synthetases	Formation of a new bond

In addition to their protein part, most enzymes also contain a small non-protein part called a **cofactor**. A cofactor can be either an inorganic ion, such as Zn²⁺, or a small organic molecule, called a **coenzyme**. A coenzyme is not a catalyst but is a reactant that undergoes chemical change during the reaction and requires an additional step or series of steps to return to its initial state.

Many coenzymes are derived from vitamins—substances that an organism requires in small amounts for growth but is unable to synthesize and must receive in its diet. Coenzyme A from pantothenate (vitamin B₃), NAD⁺ from niacin, FAD from riboflavin (vitamin B₂), tetrahydrofolate from folic acid, pyridoxal phosphate from pyridoxine (vitamin B₆), and thiamin diphosphate from thiamin (vitamin B₁) are examples (TABLE 19.3). We'll discuss the chemistry and mechanisms of coenzyme reactions at appropriate points later in the text.

PROBLEM 19.17

To what classes do the following enzymes belong?

- (a) Pyruvate decarboxylase (b) Chymotrypsin
(c) Alcohol dehydrogenase

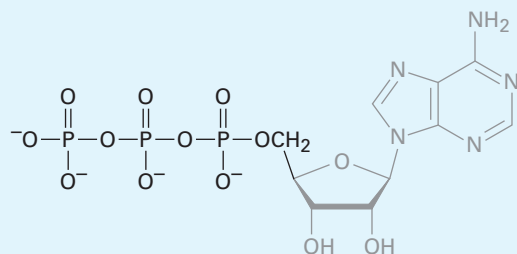
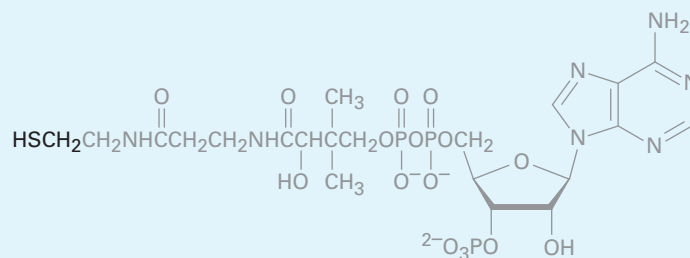
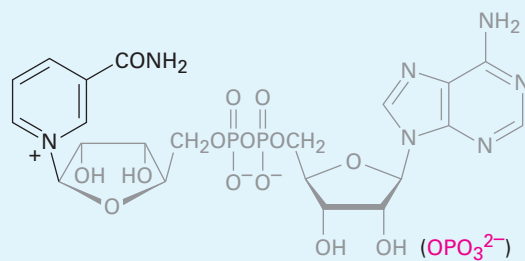
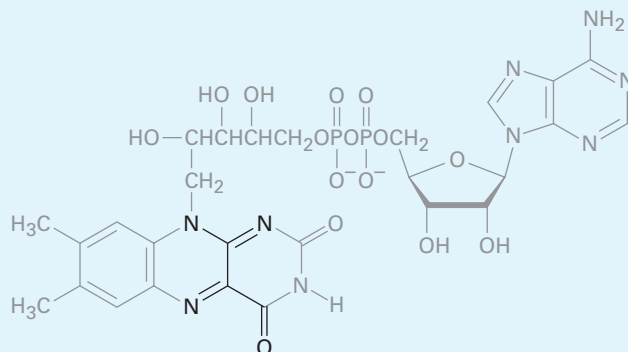
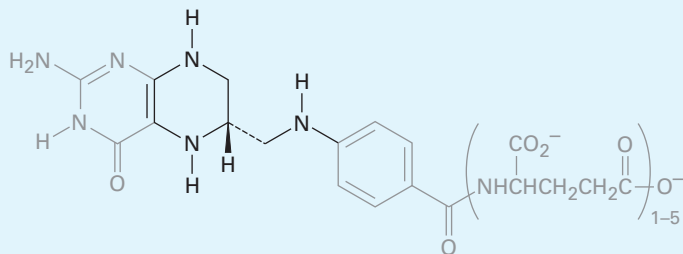
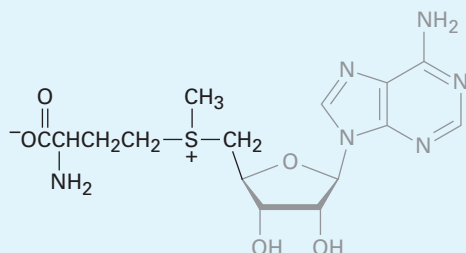
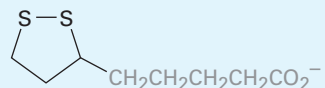
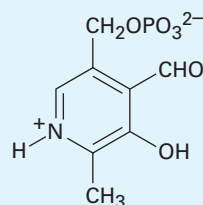
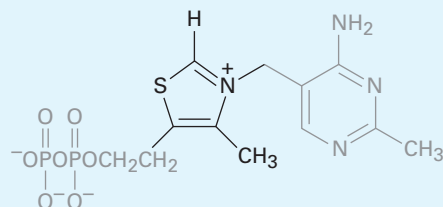
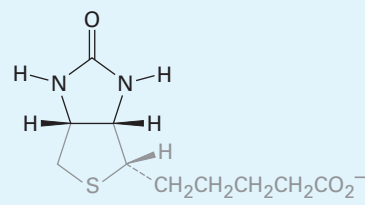
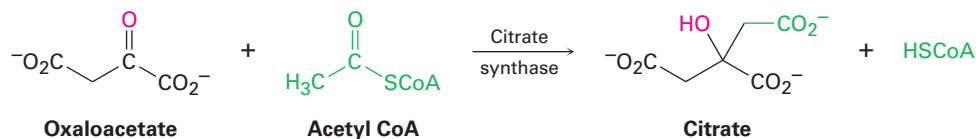
TABLE 19.3 Structures and Functions of Some Common Coenzymes**Adenosine triphosphate—ATP (phosphorylation)****Coenzyme A (acyl transfer)****Nicotinamide adenine dinucleotide—NAD⁺ (oxidation/reduction)
(NADP⁺)****Flavin adenine dinucleotide—FAD (oxidation/reduction)**

TABLE 19.3 Structures and Functions of Some Common Coenzymes *continued***Tetrahydrofolate (transfer of C₁ units)****S-Adenosylmethionine (methyl transfer)****Lipoic acid (acyl transfer)****Pyridoxal phosphate (amino acid metabolism)****Thiamin diphosphate (decarboxylation)****Biotin (carboxylation)****19-10 How Do Enzymes Work? Citrate Synthase**

As we saw in the previous section, enzymes work by bringing substrate and other reactant molecules together, holding them in the orientation necessary for reaction, providing any necessary acidic or basic sites to catalyze specific

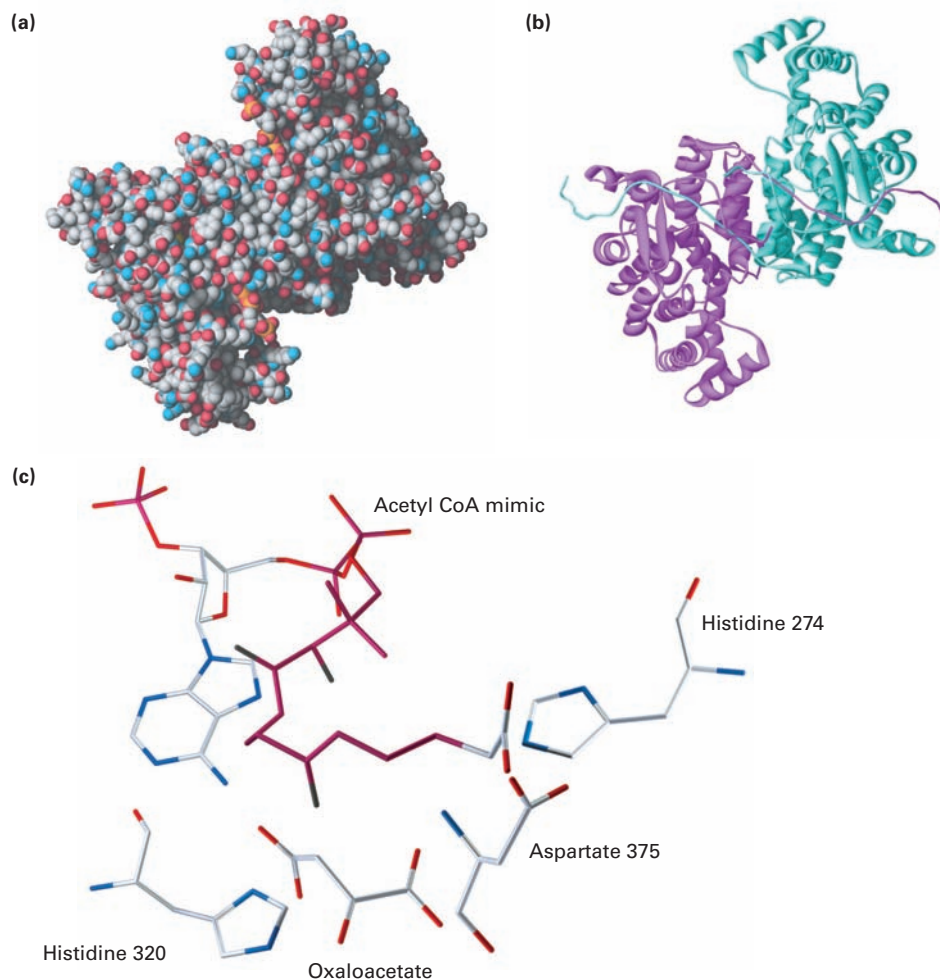
steps, and stabilizing the transition state for reaction. As an example, let's look at citrate synthase, an enzyme that catalyzes the aldol-like addition of acetyl CoA to oxaloacetate to give citrate. The reaction is the first step in the citric acid cycle, in which acetyl groups produced by degradation of food molecules are metabolized to yield CO_2 and H_2O . We'll look at the details of the citric acid cycle in Section 22-4.



Citrate synthase is a globular protein of 433 amino acids with a deep cleft lined by an array of functional groups that can bind to the substrate, oxaloacetate. On binding oxaloacetate, the original cleft closes and another opens up nearby to bind acetyl CoA. This second cleft is also lined by appropriate functional groups, including a histidine at position 274 and an aspartic acid at position 375. The two reactants are now held by the enzyme in close proximity and with a suitable orientation for reaction. **FIGURE 19.9** shows the structure of citrate synthase as determined by X-ray crystallography, along with a close-up of the active site.

FIGURE 19.9 X-ray crystal structure of citrate synthase.

Part (a) is a space-filling model and part (b) is a ribbon model, which emphasizes the α -helical segments of the protein chain and indicates that the enzyme is dimeric; that is, it consists of two identical chains held together by hydrogen bonds and other intermolecular attractions. Part (c) is a close-up of the active site, in which oxaloacetate and an unreactive acetyl CoA mimic are bound.



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As shown in **FIGURE 19.10**, the first step in the aldol reaction is generation of the enol of acetyl CoA. The side-chain carboxyl of an aspartate residue acts as base to abstract an acidic α proton, while at the same time the side-chain imidazole ring of a histidine donates H^+ to the carbonyl oxygen. The enol thus produced then does a nucleophilic addition to the ketone carbonyl group of oxaloacetate. The first histidine acts as a base to remove the $-OH$ hydrogen from the enol, while a second histidine residue simultaneously donates a proton to the oxaloacetate carbonyl group, giving citryl CoA. Water then hydrolyzes the thioester group in citryl CoA in a nucleophilic acyl substitution reaction, releasing citrate and coenzyme A as the final products. We'll look in similar detail at other enzyme mechanisms in later chapters.

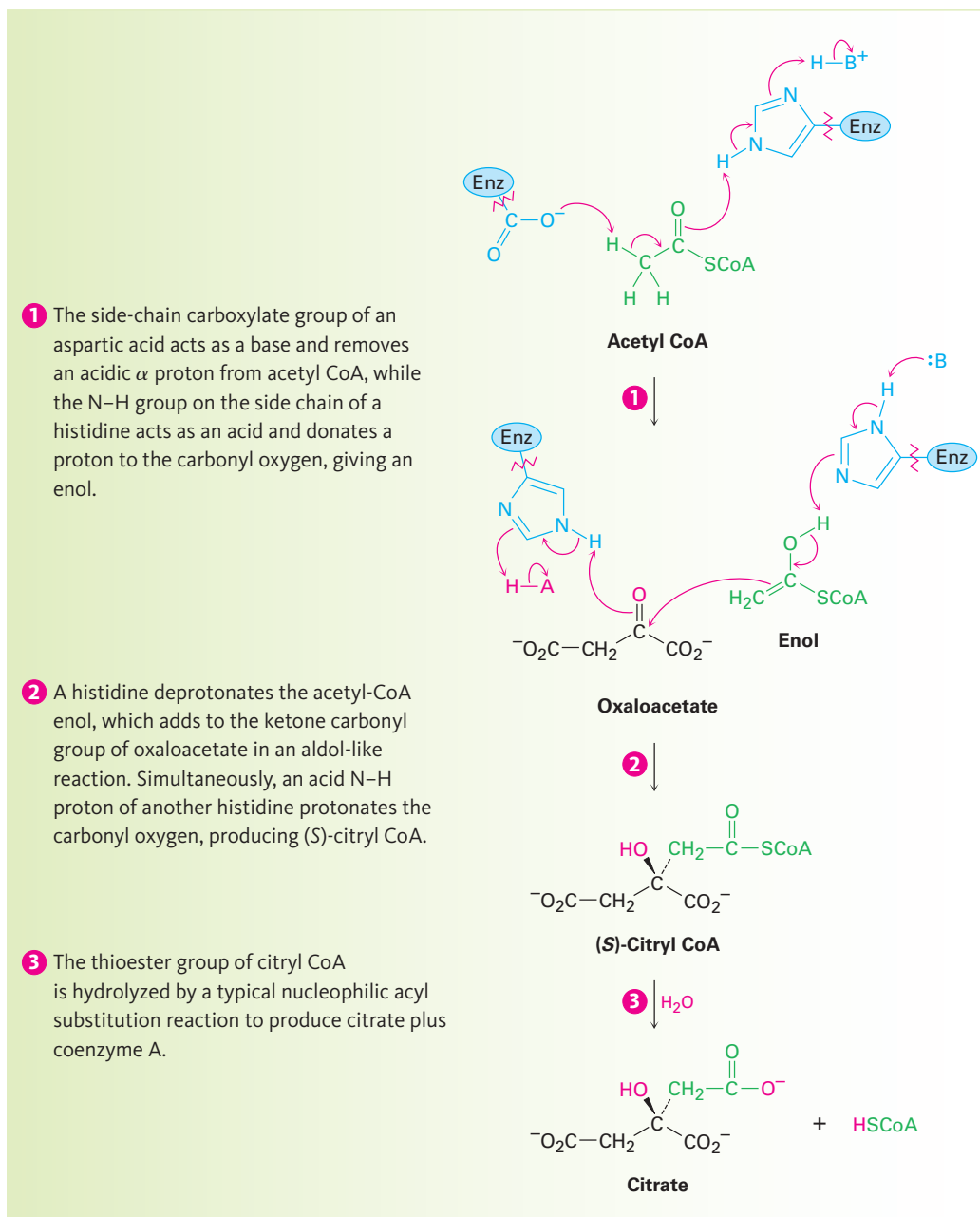


FIGURE 19.10
Mechanism of the addition of acetyl CoA to oxaloacetate to give (S)-citryl CoA. The reaction is catalyzed by citrate synthase.

SOMETHING EXTRA

The Protein Data Bank

Enzymes are so large, so structurally complex, and so numerous that the use of computer databases and molecular visualization programs has become an essential tool for studying biological chemistry. Of the various databases available online, the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (<http://www.genome.ad.jp/kegg>), maintained by the Kanehisa Laboratory of Kyoto University Bioinformatics Center, is useful for obtaining information on biosynthetic pathways of the sort we'll be describing in the next few chapters. For obtaining information on a specific enzyme, the

BRENDA database (<http://www.brenda.uni-koeln.de>), maintained by the Institute of Biochemistry at the University of Cologne, Germany, is particularly valuable.

Perhaps the most useful of all biological databases is the Protein Data Bank (PDB) operated by the Research Collaboratory for Structural Bioinformatics (RCSB). The PDB is a worldwide repository of X-ray and NMR structural data for biological macromolecules. In late 2013, data for more than 94,000 structures were available, with 9,000 new ones being added yearly. To access the Protein Data Bank, go to <http://www.rcsb.org/pdb/> and a home page like that shown in **FIGURE 19.11** will appear. As with much that is available online, however, the PDB site is changing rapidly, so you may not see quite the same thing.

The screenshot shows the PDB website interface. At the top, it says 'An Information Portal to Biological Macromolecular Structures' and 'As of Tuesday Oct 29, 2013 at 5 PM PDT there are 95113 Structures'. The search bar contains 'PDB-101'. The main content area is titled 'Biological Macromolecular Resource' and features several sections: 'Learn: Featured Molecules' with a 'Structural View of Biology' section for 'PDB-101', 'Molecule of the Month: Proteasome' with a 3D model and text describing proteasomes as 'the cell's protein recyclers', and 'Protein Structure Initiative Featured System: G Proteins and Cancer' with a 3D model and text about cancer communication. There are also sections for 'Explore Archive' and 'Latest Structures'. The page is cluttered with various links, buttons, and informational text.

FIGURE 19.11 The Protein Data Bank home page.

Protein Data Bank

To learn how to use the PDB, begin by checking the “PDB-101” blackboard at the top of the screen and choosing “Understanding PDB Data.” Then start exploring. Let’s say you want to view citrate synthase, the enzyme shown previously in Figure 19.9 that catalyzes the addition of acetyl CoA to oxaloacetate to give citrate. Type “citrate synthase” into the small search window on the top line, click on “Site Search,” and a list of more than 300(!) structures will appear. Scroll down until you find the entry with a PDB code of 5CTS and the title “Proposed Mechanism for the Condensation Reaction of Citrate Synthase: 1.9 Angstrom Structure of the Ternary Complex with Oxaloacetate and Carboxymethyl Coenzyme A.” Alternatively, if you know the code of the enzyme you want, you can enter it directly into the search window. Click on the PDB code of entry 5CTS, and a new page containing information about the enzyme will open.

If you choose, you can download the structure file to your computer and open it with any of numerous molecular graphics programs to see an image like that in **FIGURE 19.12**. The biologically active molecule is a dimer of two identical subunits consisting primarily of

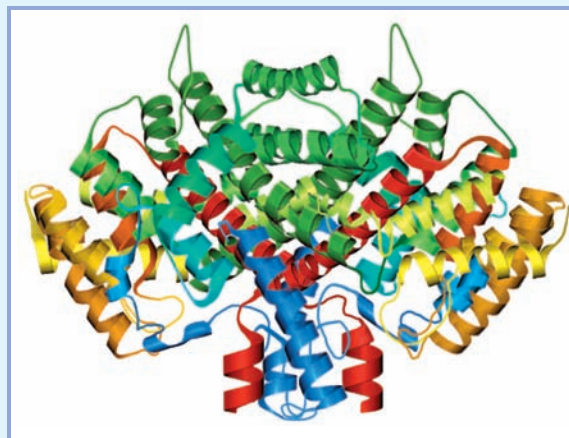


FIGURE 19.12 An image of citrate synthase, downloaded from the Protein Data Bank. Bound enzyme substrate is visible in gray toward the bottom on each subunit.

α -helical regions displayed as coiled ribbons. For now, just look at the image in the upper right of the screen to see some of the tools for visualizing and further exploring the enzyme. We’ll look at some of these tools in the Chapter 20 *Something Extra*.

SUMMARY

We’ve now reached the heart of this book. Beginning in this chapter with a look at amino acids and proteins, and continuing for the remainder of the text, we’ll examine each of the main classes of biomolecules to see what their primary biological functions are, how they’re biosynthesized, and how they’re metabolized in the body.

Proteins and **peptides** are large biomolecules made up of **α -amino acid residues** linked together by amide, or peptide, bonds. Twenty amino acids are commonly found in proteins, all are α -amino acids, and all except glycine have stereochemistry similar to that of L sugars. In neutral solution, amino acids exist as dipolar **zwitterions**.

Amino acids can be synthesized in racemic form by several methods, including alkylation of diethyl acetamidomalonate and reductive amination of an α -keto acid. Alternatively, an enantioselective synthesis of amino acids can be carried out using a chiral hydrogenation catalyst.

Determining the structure of a peptide or protein begins with amino acid analysis. The peptide is hydrolyzed to its constituent α -amino acids, which are separated and identified. Next, the peptide is sequenced. **Edman degradation** by treatment with phenyl isothiocyanate (PITC) cleaves one residue from the N terminus of the peptide and forms an easily identifiable phenylthiohydantoin

KEY WORDS

α -amino acid,	682
α helix,	700
backbone,	690
β -pleated sheet,	701
C-terminal amino acid,	690
coenzyme,	705
cofactor,	705
denatured,	702
Edman degradation,	693
enzyme,	703
fibrous protein,	700
globular protein,	700
isoelectric point, (pI),	686
N-terminal amino acid,	690
peptide,	679

primary structure,	700
protein,	679
quaternary structure,	700
residue,	689
secondary structure,	700
side chain,	682
tertiary structure,	700
zwitterion,	679

(PTH) derivative of the **N-terminal amino acid**. An automated series of Edman degradations can sequence peptide chains up to 50 residues in length.

Peptide synthesis involves the use of protecting groups. An N-protected amino acid with a free $-\text{CO}_2\text{H}$ group is coupled using DCC to an O-protected amino acid with a free $-\text{NH}_2$ group. Amide formation occurs, the protecting groups are removed, and the sequence is repeated. Amines are usually protected as their *tert*-butyloxycarbonyl (Boc) or fluorenylmethyloxycarbonyl (Fmoc) derivatives; acids are usually protected as esters. The synthesis is often carried out by the Merrifield solid-phase method, in which the peptide is bonded to insoluble polymer beads.

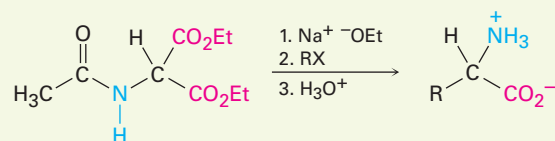
Proteins have four levels of structure. **Primary structure** describes a protein's amino acid sequence, **secondary structure** describes how segments of the protein chain orient into regular patterns—either α -helix or β -pleated sheet, **tertiary structure** describes how the entire protein molecule coils into an overall three-dimensional shape, and **quaternary structure** describes how individual protein molecules aggregate into larger structures.

Proteins are classified as either globular or fibrous. **Fibrous proteins** such as α -keratin are tough, rigid, and water-insoluble; **globular proteins** such as myoglobin are water-soluble and roughly spherical in shape. Many globular proteins are **enzymes**—substances that act as catalysts for biological reactions. Enzymes are grouped into six classes according to the kind of reaction they catalyze. They function by bringing reactant molecules together, holding them in the orientation necessary for reaction, and providing any necessary acidic or basic sites to catalyze specific steps. In addition to their protein part, many enzymes contain **cofactors**, which can be either metal ions or small organic molecules called **coenzymes**.

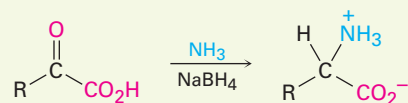
SUMMARY OF REACTIONS

1. Amino acid synthesis (Section 19-3)

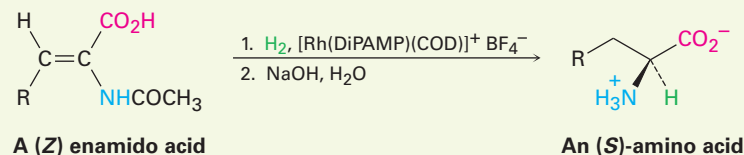
(a) Diethyl acetamidomalonate synthesis



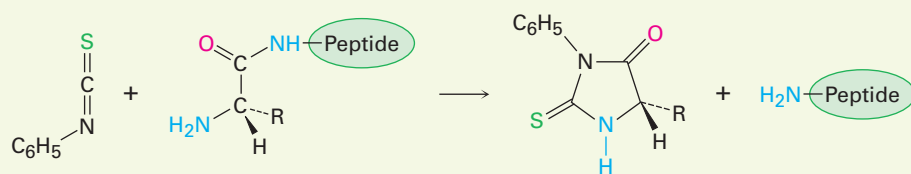
(b) Reductive amination of an α -keto acid



(c) Enantioselective synthesis

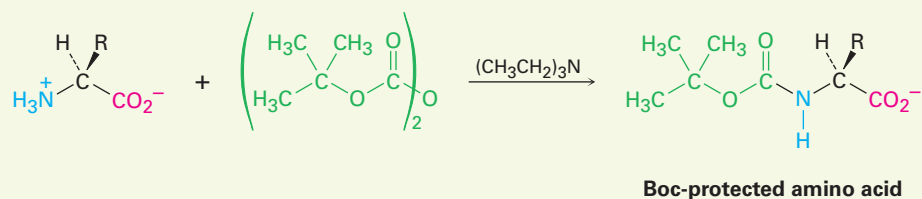


2. Peptide sequencing by Edman degradation (Section 19-6)

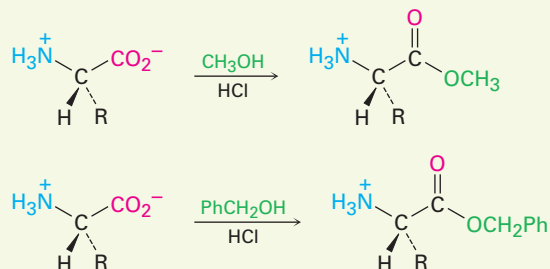


3. Peptide synthesis (Section 19-7)

(a) Amine protection



(b) Carboxyl protection

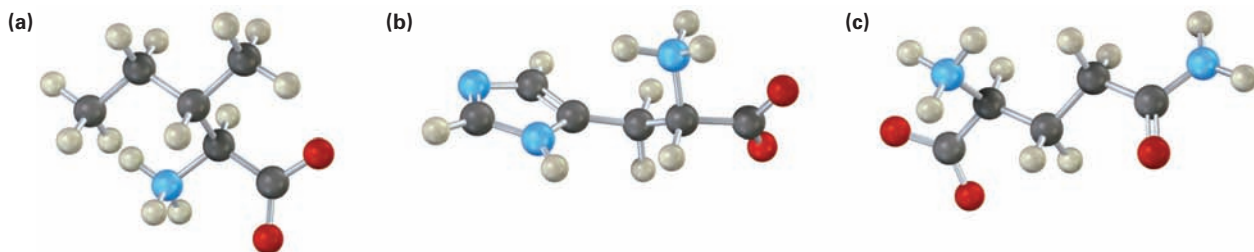


EXERCISES

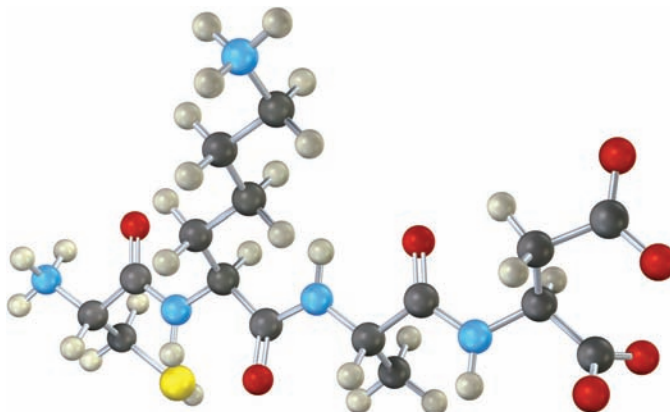
VISUALIZING CHEMISTRY

(Problems 19.1–19.17 appear within the chapter.)

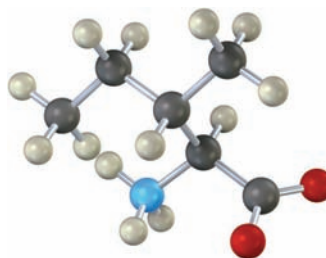
19.18 Identify the following amino acids:



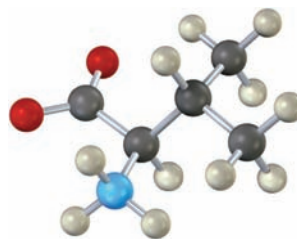
19.19 Give the sequence of the following tetrapeptide (yellow = S):



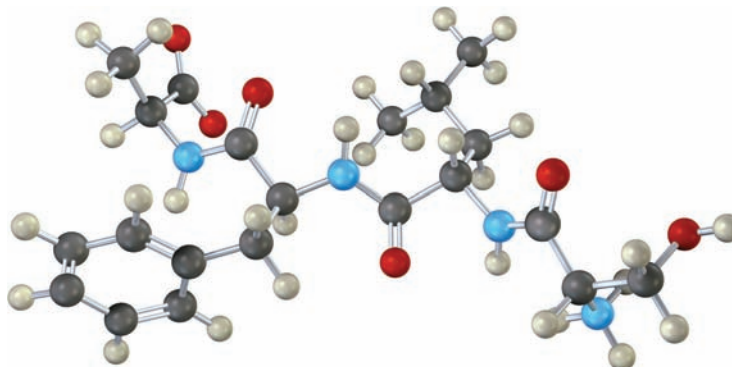
19.20 Isoleucine and threonine are the only two amino acids with two chirality centers. Assign *R* or *S* configuration to the methyl-bearing carbon atom of isoleucine:



19.21 Is the following structure a D amino acid or an L amino acid? Identify it.



19.22 Give the sequence of the following tetrapeptide:



ADDITIONAL PROBLEMS

Amino Acids

- 19.23 What does the prefix “ α ” mean when referring to an α -amino acid?
- 19.24 What amino acids do the following abbreviations stand for?
(a) Ser (b) Thr (c) Pro (d) F (e) Q (f) D
- 19.25 Why is cysteine such an important amino acid for determining the tertiary structure of a protein?
- 19.26 Except for cysteine, only *S* amino acids occur in proteins. Several *R* amino acids are also found in nature, however. (*R*)-Serine is found in earthworms, and (*R*)-alanine is found in insect larvae. Draw the structures of (*R*)-serine and (*R*)-alanine. Are these *D* or *L* amino acids?
- 19.27 Cysteine is the only amino acid that has *L* stereochemistry but an *R* configuration. Make up a structure for another *L* amino acid of your own creation that also has an *R* configuration.
- 19.28 Draw the structure of (*S*)-proline.
- 19.29 Show the structures of the following amino acids in their zwitterionic forms:
(a) Trp (b) Ile (c) Cys (d) His
- 19.30 Proline has $pK_{a1} = 1.99$ and $pK_{a2} = 10.60$. Use the Henderson–Hasselbalch equation to calculate the ratio of protonated and neutral forms at $pH = 2.50$. Calculate the ratio of neutral and deprotonated forms at $pH = 9.70$.
- 19.31 The amino acid threonine, (*2S,3R*)-2-amino-3-hydroxybutanoic acid, has two chirality centers. Draw the structure using plain, wedged, and dashed lines to indicate stereochemistry.

Synthesis and Reactions of Amino Acids

- 19.32 Show how you could use the acetamidomalonate method to prepare the following amino acids:
(a) Leucine (b) Tryptophan
- 19.33 Show how you could prepare the following amino acids using a reductive amination:
(a) Methionine (b) Isoleucine
- 19.34 Show how you could prepare the following amino acids enantioselectively:
(a) Pro (b) Val
- 19.35 Serine can be synthesized by a simple variation of the amidomalonate method using formaldehyde rather than an alkyl halide. How might this be done?

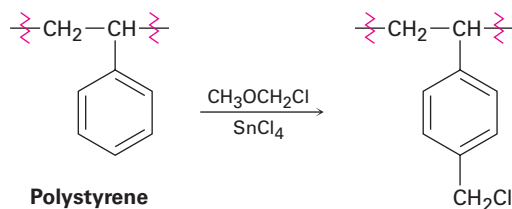
- 19.36** Predict the product of the reaction of valine with the following reagents:
(a) $\text{CH}_3\text{CH}_2\text{OH}$, acid (b) Di-*tert*-butyl dicarbonate
(c) KOH , H_2O (d) CH_3COCl , pyridine; then H_2O
- 19.37** The amino acid analysis data in Figure 19.3 indicate that proline is not easily detected by reaction with ninhydrin. Suggest a reason.

Peptides, Proteins, and Enzymes

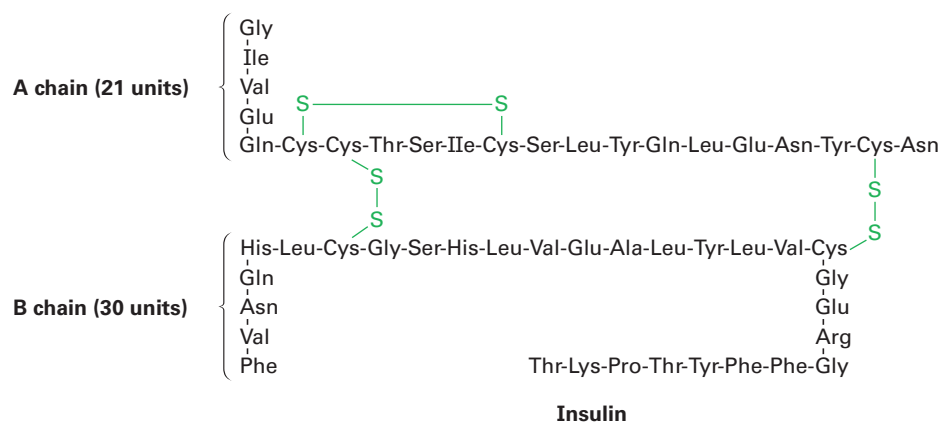
- 19.38** Using both three- and one-letter codes for amino acids, write the structures of all possible peptides containing the following amino acids:
(a) Val, Ser, Leu (b) Ser, Leu₂, Pro
- 19.39** Write full structures for the following peptides:
(a) C-H-E-M (b) E-A-S-Y (c) P-E-P-T-I-D-E
- 19.40** Propose two structures for a tripeptide that gives Leu, Ala, and Phe on hydrolysis but does not react with phenyl isothiocyanate.
- 19.41** Show the steps involved in a synthesis of Phe-Ala-Val using the Merrifield procedure.
- 19.42** Draw the structure of the PTH derivative product you would obtain by Edman degradation of the following peptides:
(a) I-L-P-F (b) D-T-S-G-A
- 19.43** The α -helical parts of myoglobin and other proteins stop whenever a proline residue is encountered in the chain. Why do you think a proline is never present in a protein α helix?
- 19.44** Which amide bonds in the following polypeptide are cleaved by trypsin? By chymotrypsin?
Phe-Leu-Met-Lys-Tyr-Asp-Gly-Gly-Arg-Val-Ile-Pro-Tyr
- 19.45** What kinds of reactions do the following classes of enzymes catalyze?
(a) Hydrolases (b) Lyases (c) Transferases
- 19.46** Which of the following amino acids are more likely to be found on the outside of a globular protein, and which on the inside? Explain.
(a) Valine (b) Aspartic acid (c) Phenylalanine (d) Lysine

General Problems

- 19.47** The chloromethylated polystyrene resin used for Merrifield solid-phase peptide synthesis is prepared by treatment of polystyrene with chloromethyl methyl ether and a Lewis acid catalyst. Propose a mechanism for the reaction.



- 19.48** Human insulin is composed of two chains totaling 51 amino acids and linked to disulfide bridges. Indicate where in each chain the molecule is cleaved by trypsin and by chymotrypsin.

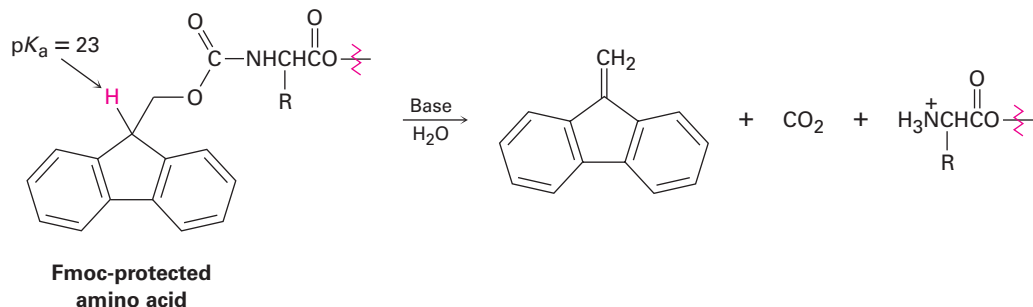


- 19.49** Look at the side chains of the 20 amino acids in Table 19.1, and then think about what is not present. None of the 20 contain either an aldehyde or a ketone carbonyl group, for instance. Is this just one of nature's oversights, or is there a likely chemical reason? What complications might an aldehyde or ketone carbonyl group cause?
- 19.50** What is the structure of a nonapeptide that gives the following fragments when cleaved?

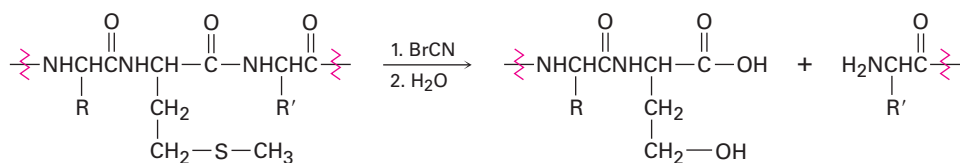
Trypsin cleavage: Val-Val-Pro-Tyr-Leu-Arg, Ser-Ile-Arg

Chymotrypsin cleavage: Leu-Arg, Ser-Ile-Arg-Val-Val-Pro-Tyr

- 19.51** An Fmoc amine protecting group is removed by treatment with aqueous base. The mechanism involves initial removal of the relatively acidic hydrogen on the five-membered ring, followed by elimination of the adjacent leaving group and loss of CO₂. Write the mechanism, and explain why the Fmoc group is acidic. (See Section 9-4.)



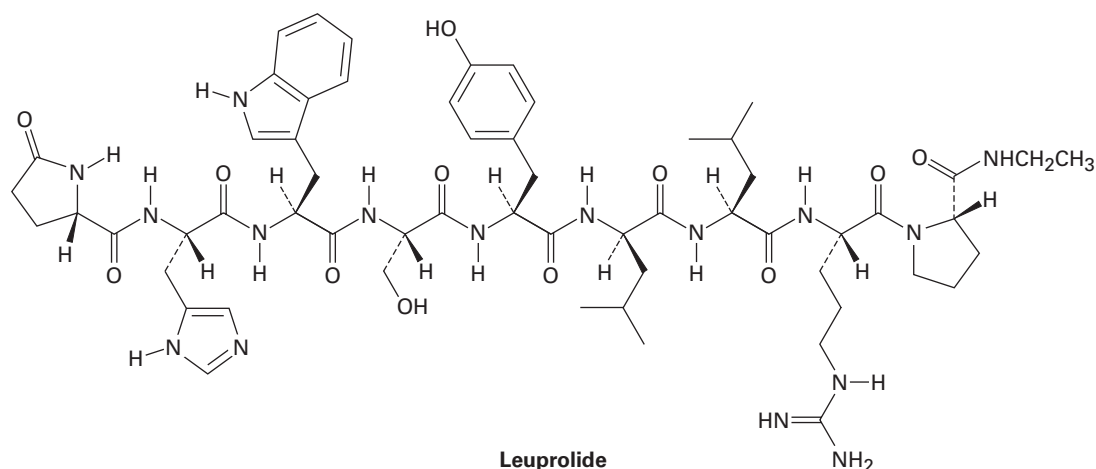
- 19.52** Proteins can be cleaved specifically at the amide bond on the carboxyl side of methionine residues by reaction with cyanogen bromide, BrC≡N:



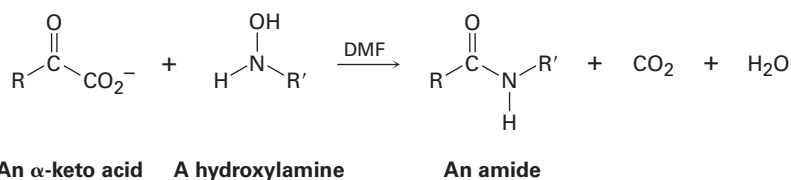
The reaction occurs in several steps:

- The first step is a nucleophilic substitution reaction of the sulfur on the methionine side chain with BrCN to give a cyanosulfonium ion, R₂SCN⁺. Show the structure of the product, and propose a mechanism for the reaction.
- The second step is an internal S_N2 reaction, with the carbonyl oxygen of the methionine residue displacing the positively charged sulfur leaving group and forming a five-membered ring product. Show the structure of the product and the mechanism of its formation.
- The third step is a hydrolysis reaction to split the peptide chain. The carboxyl group of the former methionine residue is now part of a lactone (cyclic ester) ring. Show the structure of the lactone product and the mechanism of its formation.
- The final step is a hydrolysis of the lactone to give the product shown. Write the mechanism of the reaction.

- 19.53** Leuprolide is a synthetic nonapeptide used to treat both endometriosis in women and prostate cancer in men.

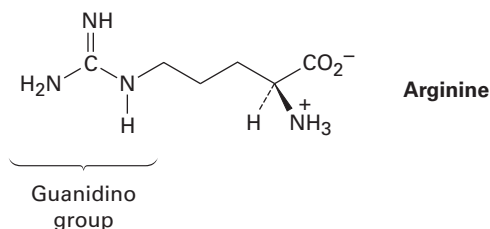


- (a) Both C-terminal and N-terminal amino acids in leuprolide have been structurally modified. Identify the modifications.
- (b) One of the nine amino acids in leuprolide has D stereochemistry rather than the usual L. Which one?
- (c) Write the structure of leuprolide using both one- and three-letter abbreviations.
- (d) What charge would you expect leuprolide to have at neutral pH?
- 19.54** A recent method of peptide synthesis involves formation of an amide bond by reaction of an α -keto acid with an *N*-alkylhydroxylamine:

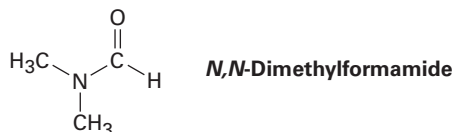


The reaction is thought to occur by nucleophilic addition of the *N*-alkylhydroxylamine to the keto acid as if forming an imine (see Section 14-7), followed by decarboxylation and elimination of water. Show the mechanism.

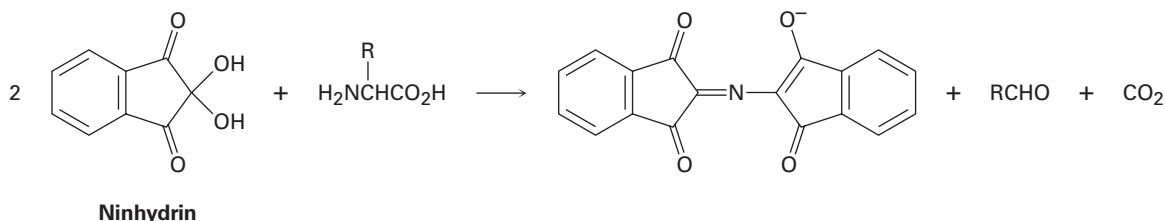
- 19.55** Arginine, the most basic of the 20 common amino acids, contains a *guanidino* functional group in its side chain. Explain, using resonance structures to show how the protonated guanidino group is stabilized.



- 19.56** Cytochrome *c* is an enzyme found in the cells of all aerobic organisms. Elemental analysis of cytochrome *c* shows that it contains 0.43% iron. What is the minimum molecular weight of this enzyme?
- 19.57** Evidence for restricted rotation around amide CO–N bonds comes from NMR studies. At room temperature, the ^1H NMR spectrum of *N,N*-dimethylformamide shows three peaks: 2.9 δ (singlet, 3 H), 3.0 δ (singlet, 3 H), 8.0 δ (singlet, 1 H). As the temperature is raised, however, the two singlets at 2.9 δ and 3.0 δ slowly merge. At 180 $^\circ\text{C}$, the ^1H NMR spectrum shows only two peaks: 2.95 δ (singlet, 6 H) and 8.0 δ (singlet, 1 H). Explain this temperature-dependent behavior.



- 19.58** The reaction of ninhydrin with an α -amino acid occurs in several steps:
- The first step is formation of an imine by reaction of the amino acid with ninhydrin. Show its structure and the mechanism of its formation.
 - The second step is a decarboxylation. Show the structure of the product and the mechanism of the decarboxylation reaction.
 - The third step is hydrolysis of an imine to yield an amine and an aldehyde. Show the structures of both products and the mechanism of the hydrolysis reaction.
 - The final step is formation of the purple anion. Show the mechanism of the reaction.



- 19.59** Draw resonance forms for the purple anion obtained by reaction of ninhydrin with an α -amino acid (Problem 19.58).

19.60 Oxytocin, a nonapeptide hormone secreted by the pituitary gland, functions by stimulating uterine contraction and lactation during childbirth. Its sequence was determined from the following evidence:

1. Oxytocin is a cyclic compound containing a disulfide bridge between two cysteine residues.
2. When the disulfide bridge is reduced, oxytocin has the constitution N, C₂, Q, G, I, L, P, Y.
3. Partial hydrolysis of reduced oxytocin yields seven fragments: D-C, I-E, C-Y, L-G, Y-I-E, E-D-C, C-P-L
4. Gly is the C-terminal group.
5. Both E and D are present as their side-chain amides (Q and N) rather than as free side-chain acids.

What is the amino acid sequence of reduced oxytocin? What is the structure of oxytocin itself?

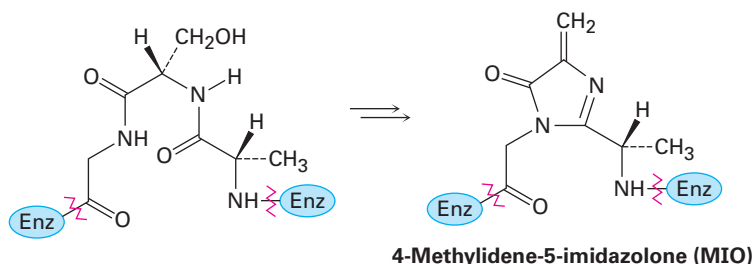
19.61 *Aspartame*, a nonnutritive sweetener marketed under the trade name NutraSweet, is the methyl ester of a simple dipeptide, Asp-Phe-OCH₃.

- (a) Draw the structure of aspartame.
- (b) The isoelectric point of aspartame is 5.9. Draw the principal structure present in aqueous solution at this pH.
- (c) Draw the principal form of aspartame present at physiological pH = 7.3.

19.62 Refer to Figure 19.3 and propose a mechanism for the final step in the Edman degradation—the acid-catalyzed rearrangement of the ATZ derivative to the PTH derivative.

19.63 Amino acids are metabolized by a transamination reaction in which the -NH₂ group of the amino acid changes places with the keto group of an α -keto acid. The products are a new amino acid and a new α -keto acid. Show the product from transamination of isoleucine.

19.64 The first step in the biological degradation of histidine is formation of a 4-methylideneimidazol-5-one (MIO) by cyclization of a segment of the peptide chain in the histidine ammonia lyase enzyme. Propose a mechanism.



20

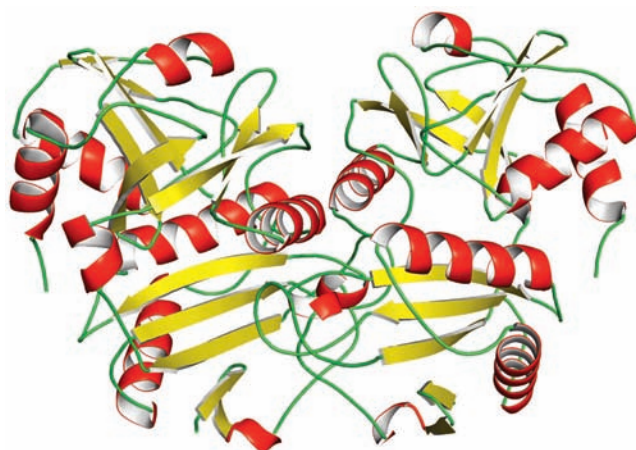
Amino Acid Metabolism

CONTENTS

- 20-1 An Overview of Metabolism and Biochemical Energy
- 20-2 Catabolism of Amino Acids: Deamination
- 20-3 The Urea Cycle
- 20-4 Catabolism of Amino Acids: The Carbon Chains
- 20-5 Biosynthesis of Amino Acids

SOMETHING EXTRA

Visualizing Enzyme Structures



D-Amino-acid aminotransferase catalyzes the deamination of amino acids, the first step in amino acid metabolism.

WHY THIS CHAPTER?

Anyone who wants to understand or contribute to the revolution now taking place in the biological sciences must first understand life processes at the molecular level. This understanding, in turn, must be based on a detailed knowledge of the chemical reactions and paths used by living organisms. Just knowing *what* occurs is not enough; it's also necessary to understand *how* and *why* organisms use the chemistry they do.

In this chapter, we'll begin a study of biological reactions, looking first at a general overview of metabolism and then focusing on amino acids. We'll see both how amino acids are biosynthesized for incorporation into proteins and how they are ultimately degraded when proteins are broken down.

Biochemical reactions are not mysterious. It's true that many of the biological reactions occurring in even the simplest living organism are more complex than those carried out in any laboratory, yet they follow the same rules of reactivity as laboratory reactions and they take place by the same mechanisms. In past chapters, we've seen many biological reactions used as examples, but it's now time to focus specifically on those reactions, paying particular attention to the metabolic pathways that organisms use to synthesize and degrade biomolecules.

A word of caution: some of the molecules we'll be encountering are substantially larger and more complex than any we've been dealing with up to this point. As always, keep your focus on the functional groups in those parts of the molecules where changes occur. The reactions themselves are the same sorts of additions, eliminations, substitutions, carbonyl condensations, and so forth, that we've been dealing with all along. Biological chemistry *is* organic chemistry.



20-1 An Overview of Metabolism and Biochemical Energy

The many reactions that go on in the cells of living organisms are collectively called **metabolism**. The pathways that break down larger molecules into smaller ones are called **catabolism**, and the pathways that synthesize larger biomolecules from smaller ones are known as **anabolism**. Catabolic reaction pathways are usually exergonic and release energy, while anabolic pathways are often endergonic and absorb energy. Catabolism can be divided into the four stages shown in **FIGURE 20.1**.

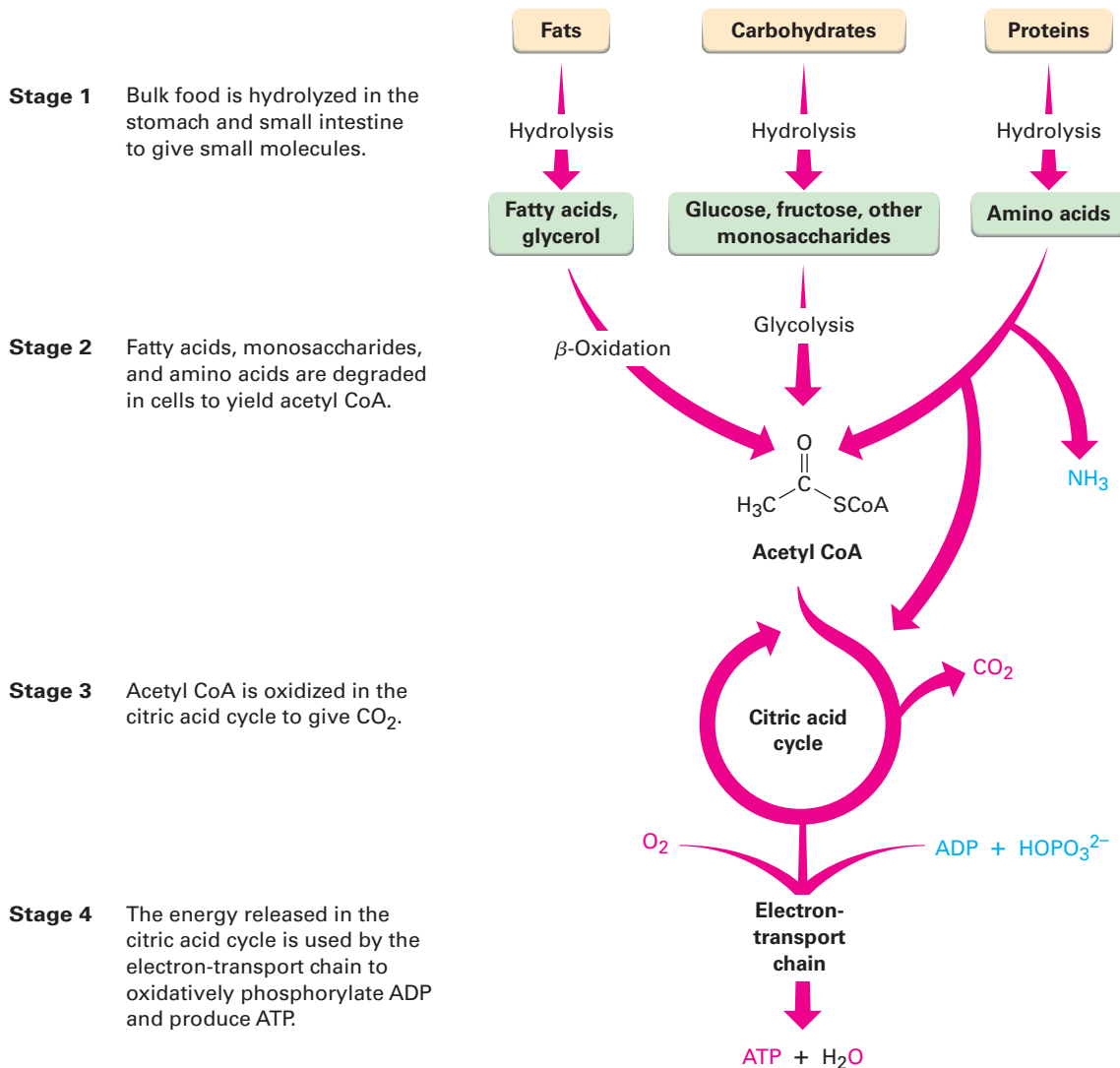
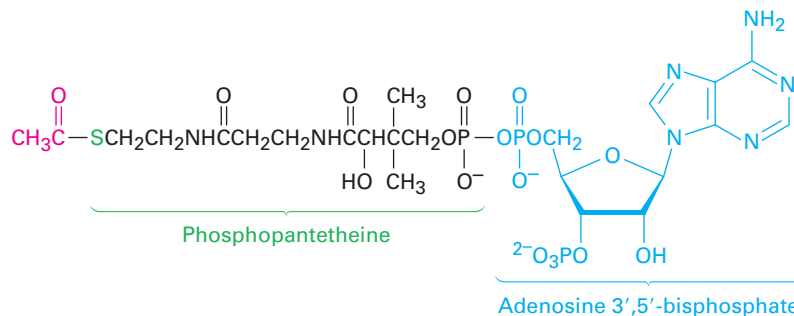


FIGURE 20.1 An overview of catabolic pathways for the degradation of food and the production of biochemical energy. The ultimate products of food catabolism are CO_2 and H_2O , with the energy released in the citric acid cycle used to drive the endergonic synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) plus phosphate ion, HOPO_3^{2-} .

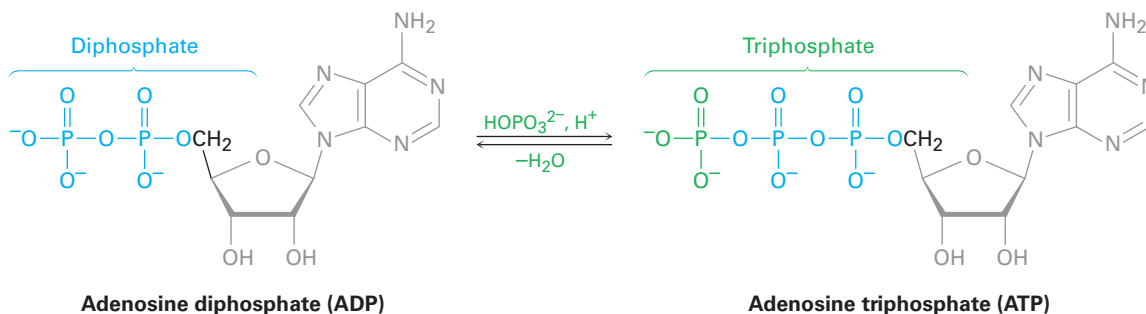
In *digestion*, the first catabolic stage, food is broken down in the mouth, stomach, and small intestine by hydrolysis of ester, glycoside (acetal), and peptide (amide) bonds to yield primarily fatty acids, glycerol, simple sugars, and amino acids. These smaller molecules are further degraded in the cytoplasm of cells in the second stage of catabolism to yield acetyl groups attached by a thioester bond to the large carrier molecule coenzyme A. The resultant compound, acetyl coenzyme A (acetyl CoA), is a key substance in the metabolism of food molecules and in many other biological pathways. As noted in Section 16-8, the acetyl group in acetyl CoA is linked to the sulfur atom of phosphopantetheine, which is itself linked to adenosine 3',5'-bisphosphate.



Acetyl CoA—a thioester

Acetyl groups are oxidized inside cellular mitochondria in the third stage of catabolism, the *citric acid cycle*, to yield CO_2 . (We'll see the details of the process in Section 22-4.) Like most oxidations, this stage releases a large amount of energy, which is used in the fourth stage, the *electron-transport chain*, to accomplish the endergonic phosphorylation of adenosine diphosphate (ADP) with hydrogen phosphate ion (HOPO_3^{2-} , abbreviated P_i) to give adenosine triphosphate (ATP).

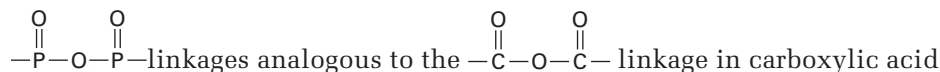
ATP, the final result of food catabolism, has been called the “energy currency” of the cell. Catabolic reactions “buy” ATP with the energy released in synthesizing it from ADP plus hydrogen phosphate ion. Anabolic reactions then spend the ATP by transferring a phosphate group to another molecule, thereby regenerating ADP. Energy production and use in living organisms thus revolves around the $\text{ATP} \rightleftharpoons \text{ADP}$ interconversion.



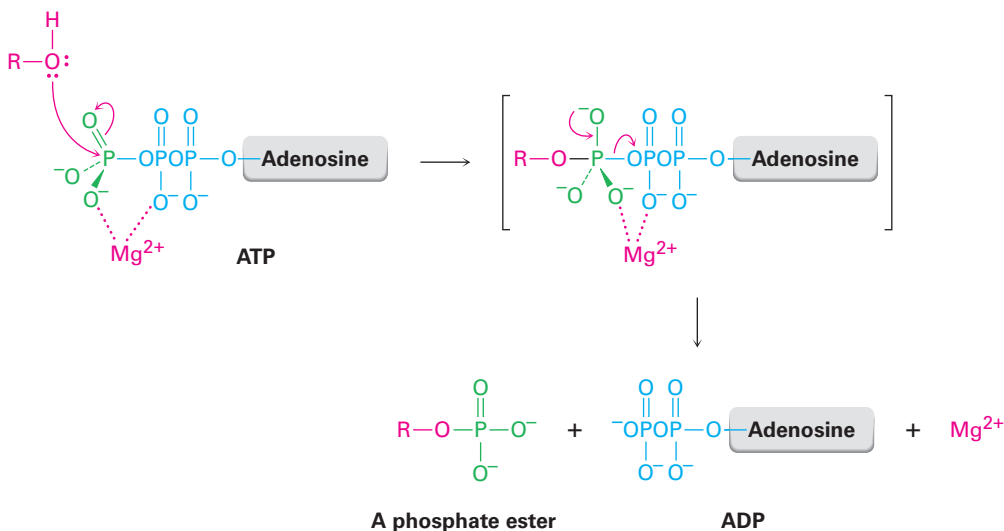
Adenosine diphosphate (ADP)

Adenosine triphosphate (ATP)

ADP and ATP are both phosphoric acid anhydrides, which contain



anhydrides. Just as carboxylic acid anhydrides react with alcohols by breaking a C–O bond and forming a carboxylic ester, ROCOR' (Section 16-5), phosphoric acid anhydrides react with alcohols by breaking a P–O bond and forming a phosphate ester, ROPO₃²⁻. The reaction is, in effect, a nucleophilic acyl substitution at phosphorus. Note that phosphorylation reactions with ATP generally require the presence of a divalent metal cation in the enzyme, usually Mg²⁺, to form a Lewis acid–base complex with the phosphate oxygen atoms and neutralize some negative charge.



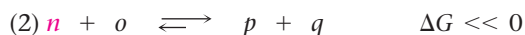
How does the body use ATP? Recall from Section 6-7 that the free-energy change ΔG must be negative and energy must be released for a reaction to be favorable and occur spontaneously. If ΔG is positive, the reaction is energetically unfavorable and the process can't occur spontaneously.

For an energetically unfavorable reaction to occur, it must be “coupled” to an energetically favorable reaction so that the overall free-energy change for the two reactions together is favorable. To understand what it means for reactions to be coupled, imagine that reaction 1 does not occur to any reasonable extent because it has a small equilibrium constant and is energetically unfavorable; that is, the reaction has $\Delta G > 0$.



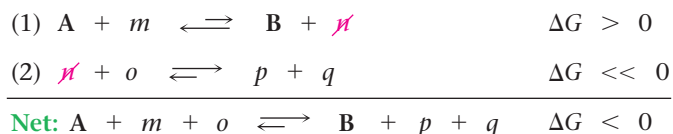
where **A** and **B** are the biochemically “interesting” substances undergoing transformation, while *m* and *n* are enzyme cofactors, H₂O, or other substances.

Imagine also that product *n* can react with substance *o* to yield *p* and *q* in a second, strongly favorable reaction that has a large equilibrium constant and $\Delta G \ll 0$:

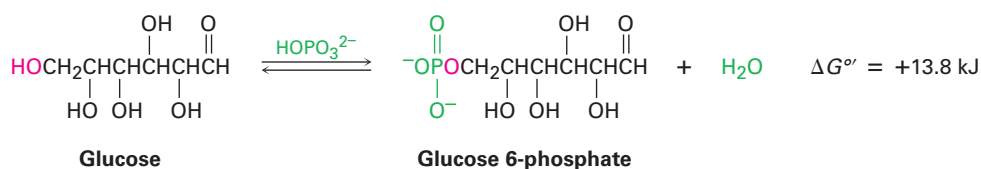


Taking the two reactions together, they share, or are coupled through, the common intermediate *n*, which is produced in the first reaction and consumed in the second. When even a tiny amount of *n* is formed in reaction 1, it undergoes essentially complete conversion in reaction 2, thereby removing

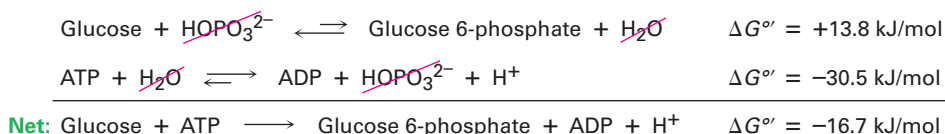
it from the first equilibrium and forcing reaction 1 to continually replenish n until the reactant **A** is gone. That is, the two reactions added together have a favorable $\Delta G < 0$, and we say that the favorable reaction 2 “drives” the unfavorable reaction 1. Because the two reactions are coupled through n , the transformation of **A** to **B** becomes favorable.



As an example of two reactions that are coupled, look at the phosphorylation of glucose to yield glucose 6-phosphate plus water, the first step in the breakdown of dietary carbohydrates.



The reaction of glucose with HOPO_3^{2-} does not occur spontaneously because it's energetically unfavorable, with $\Delta G^{\circ'} = +13.8 \text{ kJ/mol}$. (As noted in Section 6-7, the standard free-energy change for a biological reaction is denoted $\Delta G^{\circ'}$ and refers to a process in which reactants and products have a concentration of 1.0 M in a solution with $\text{pH} = 7.0$.) At the same time, however, the reaction of water with ATP to yield ADP plus HOPO_3^{2-} is strongly favorable, with $\Delta G^{\circ'} = -30.5 \text{ kJ/mol}$. When the two reactions are coupled, glucose reacts with ATP to yield glucose 6-phosphate plus ADP in a reaction that is favorable by about 16.7 kJ/mol (4.0 kcal/mol). That is, ATP drives the phosphorylation reaction of glucose.



It's this ability to drive otherwise unfavorable phosphorylation reactions that makes ATP so useful. The resultant phosphates are much more reactive as leaving groups in nucleophilic substitutions and eliminations than the alcohols they're derived from and are therefore more chemically useful.

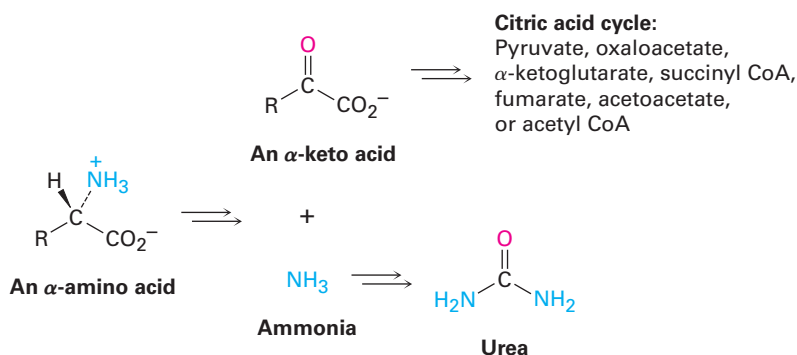
PROBLEM 20.1

One of the early steps in the urea cycle by which ammonia is excreted from the body is the reaction of bicarbonate ion (HCO_3^-) with ATP to yield carboxy phosphate. Write the reaction, and draw the structure of carboxy phosphate. You can check your answer in Figure 20.4.

20-2 Catabolism of Amino Acids: Deamination

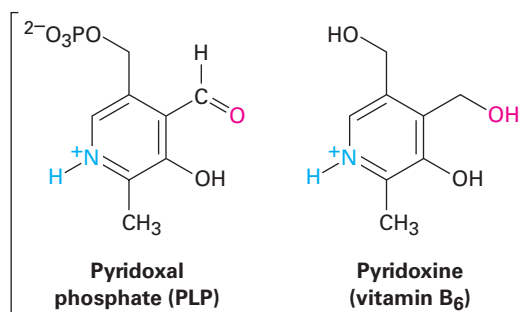
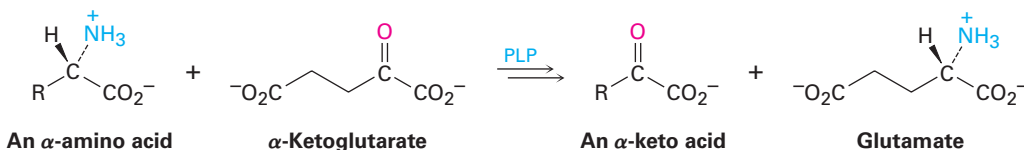
Let's now begin a study of some common metabolic pathways by starting with amino acid catabolism. Although the subject is complicated by the fact that each of the 20 α -amino acids in proteins is biologically degraded by its own unique pathway, there are some common themes that tie the different pathways together.

Amino acid catabolism occurs in three stages: (1) removal of the α amino group as ammonia, (2) conversion of the ammonia into urea, and (3) conversion of the remaining amino acid carbon skeleton (usually an α -keto acid) into an intermediate that can enter the citric acid cycle.



Transamination

The first stage in the metabolic degradation of most α -amino acids is **deamination**, the removal of the α amino group. Deamination is usually accomplished by a **transamination** reaction, in which the $-\text{NH}_2$ group of the amino acid is exchanged with the keto group of α -ketoglutarate, forming a new α -keto acid plus glutamate. The overall process occurs in two parts, is catalyzed by enzymes called aminotransferases, and involves participation of the coenzyme pyridoxal phosphate, abbreviated PLP. PLP, in turn, is a derivative of pyridoxine, or vitamin B_6 . Various aminotransferases differ in their specificity for amino acids, but the mechanism remains the same.



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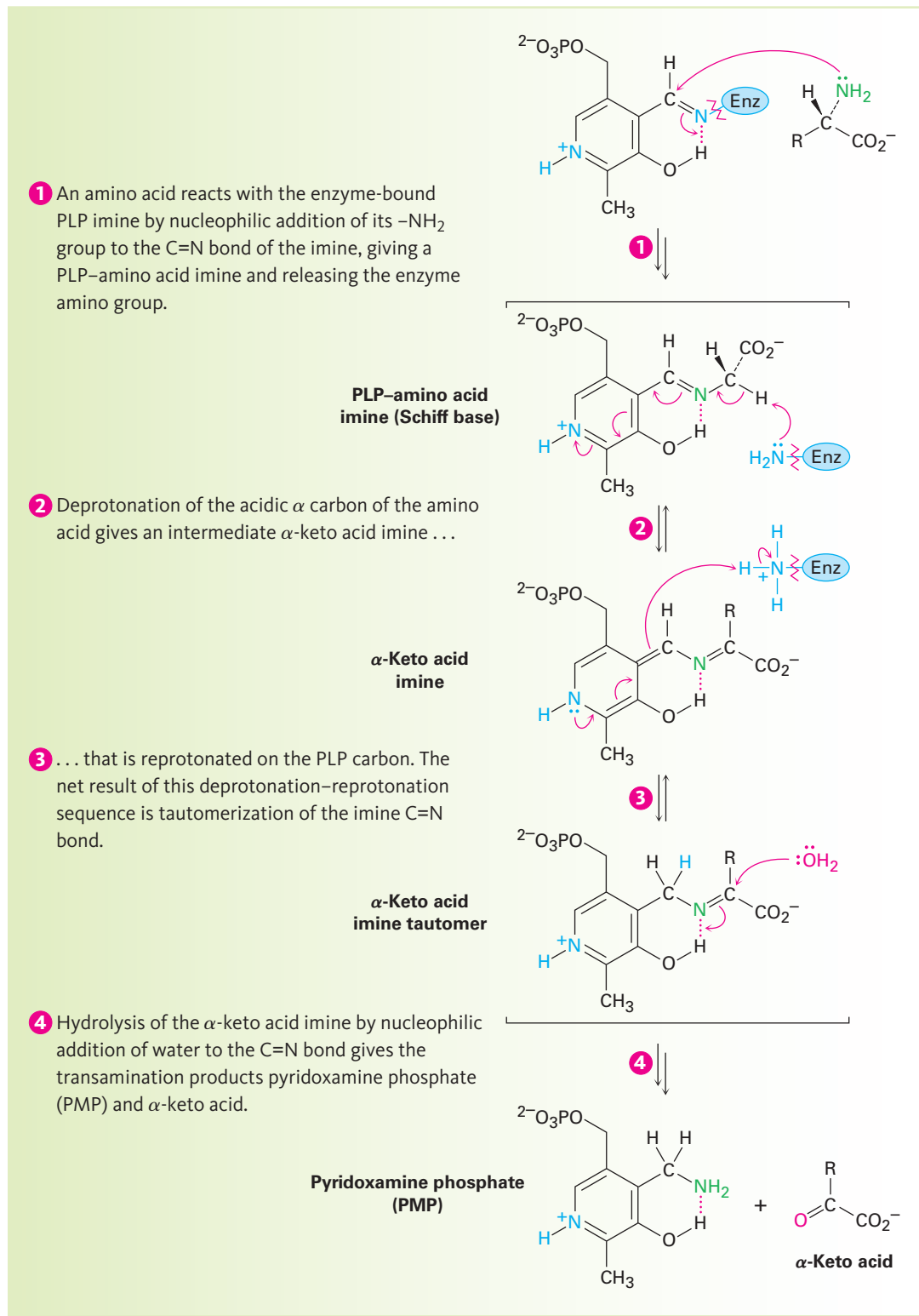
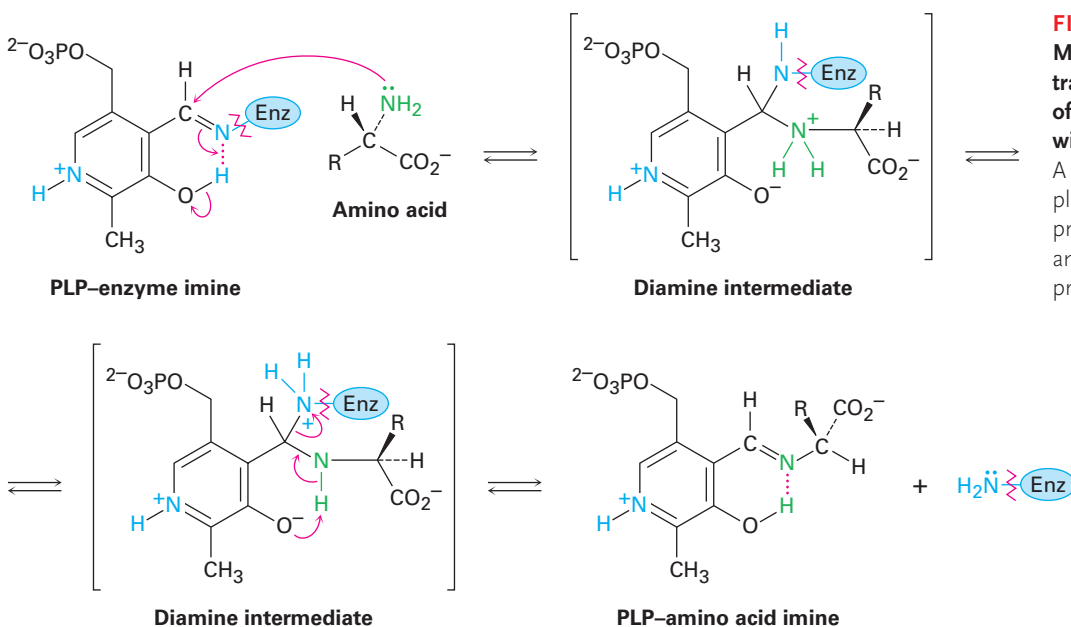


FIGURE 20.2 Overall mechanism of the enzyme-catalyzed, PLP-dependent transamination of an α -amino acid to give an α -keto acid. Individual steps are explained in the text.

The mechanism of the first part of transamination is shown in **FIGURE 20.2** and occurs through steps that use some familiar reactions we've seen in previous chapters. The process begins with reaction between the α -amino acid and PLP, which is covalently bonded to the aminotransferase by an imine linkage (Section 14-7) between the PLP aldehyde group and the side-chain $-\text{NH}_2$ group of a lysine residue in the enzyme. Following formation of a PLP–amino acid imine in step 1, deprotonation–reprotonation of the imine in steps 2 and 3 effects tautomerization of the $\text{C}=\text{N}$ bond, and hydrolysis of the tautomerized imine in step 4 gives an α -keto acid plus pyridoxamine phosphate (PMP).

STEP 1 OF FIGURE 20.2: TRANSIMINATION The first step in *transamination* is *transimination*—the reaction of the PLP–enzyme imine with an α -amino acid to give a PLP–amino acid imine plus expelled enzyme as the leaving group. The reaction occurs by nucleophilic addition of the amino acid $-\text{NH}_2$ group to the $\text{C}=\text{N}$ bond of the PLP imine, much as an amine adds to the $\text{C}=\text{O}$ bond of a ketone or aldehyde in a nucleophilic addition reaction (Figure 14.6 on page 506). The protonated diamine intermediate undergoes a proton transfer and then expels the amino group in the enzyme to complete the step (**FIGURE 20.3**).

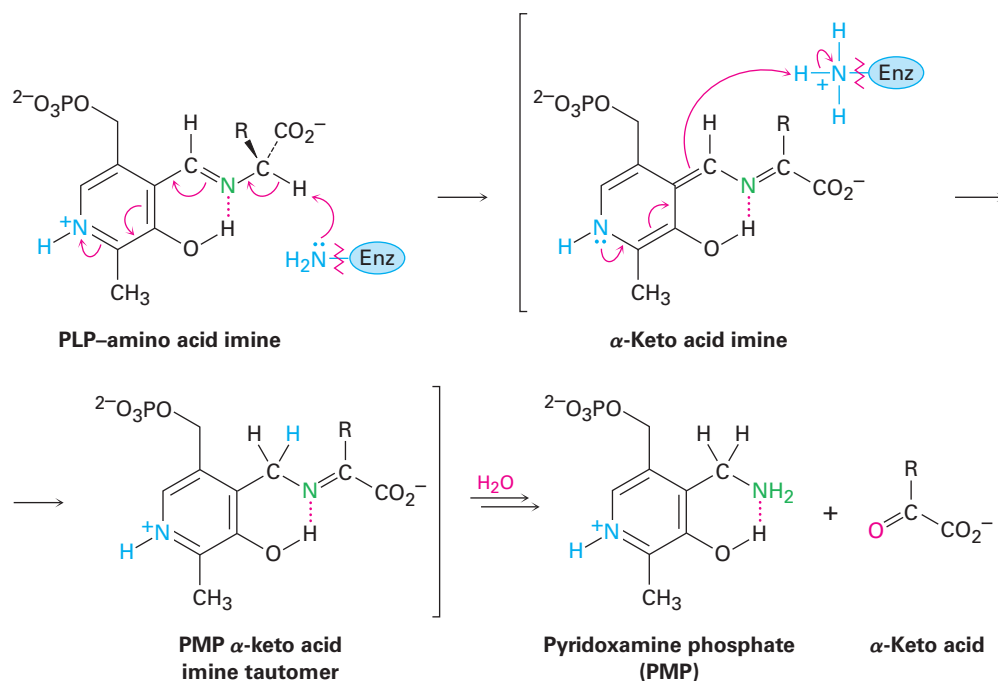


STEPS 2–4 OF FIGURE 20.2: TAUTOMERIZATION AND HYDROLYSIS

Following formation of the PLP–amino acid imine in step 1, a tautomerization of the $\text{C}=\text{N}$ bond occurs in step 2. The basic lysine residue in the enzyme that was expelled as a leaving group during transimination deprotonates the acidic α position of the amino acid, with the protonated pyridine ring of PLP acting as the electron acceptor. In step 3, reprotonation occurs on the carbon atom next to the ring, generating a tautomeric product that is the imine of an α -keto acid with pyridoxamine phosphate, abbreviated PMP.

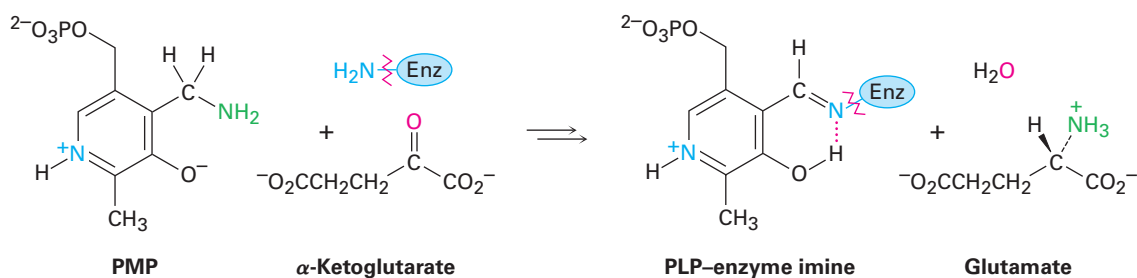
Hydrolysis of this PMP– α -keto acid imine in step 4 then completes the first part of the deamination reaction. The hydrolysis is the exact mechanistic reverse of imine formation (Figure 14.6) and occurs by nucleophilic addition

of water to the imine, followed by proton transfer and expulsion of PMP as leaving group.



Regeneration of PLP from PMP

With PLP plus the α -amino acid now converted into PMP plus an α -keto acid, PMP must be transformed back into PLP to complete the catalytic cycle. The conversion occurs by another transamination reaction, this one between PMP and an α -keto acid, usually α -ketoglutarate. The products are PLP plus glutamate, and the mechanism of the process is the exact reverse of that shown in Figure 20.2. That is, PMP and α -ketoglutarate give an imine; the PMP- α -ketoglutarate imine undergoes tautomerization of the C=N bond to give a PLP-glutamate imine; and the PLP-glutamate imine reacts with a lysine residue on the enzyme in a transamination process to yield PLP-enzyme imine plus glutamate.



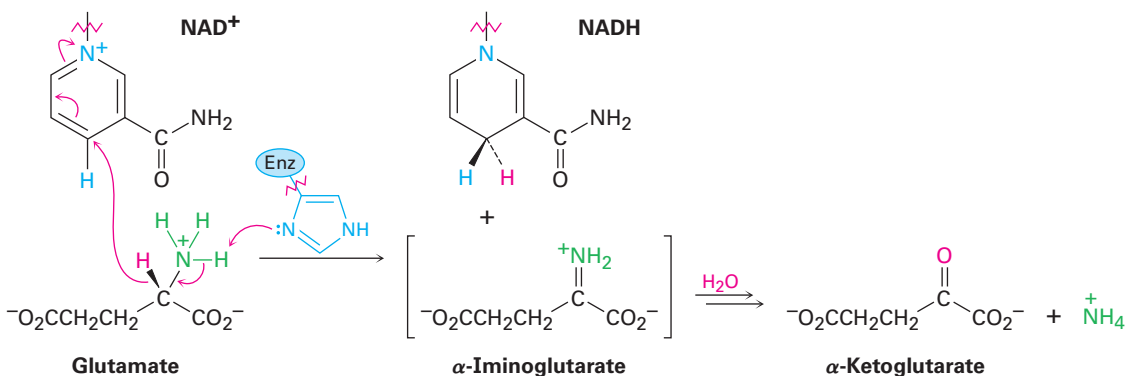
PROBLEM 20.2

Write all the steps in the mechanism of the transamination reaction of PMP with α -ketoglutarate plus a lysine residue in the enzyme to give the

PLP–enzyme imine plus glutamate. The process is the reverse of that shown in Figure 20.2.

Oxidative Deamination of Glutamate

Following transferral of the -NH_2 group from an amino acid to PLP and then to α -ketoglutarate, the glutamate product undergoes **oxidative deamination** by glutamate dehydrogenase to give ammonia plus regenerated α -ketoglutarate. The reaction occurs by oxidation of the primary amine to an imine, followed by hydrolysis. The mechanism of this biological amine oxidation is analogous to that of biological alcohol oxidation, as shown previously in Figure 13.7 on page 458. That is, a basic histidine residue in the enzyme removes a proton from nitrogen at the same time that the adjacent hydrogen on the α carbon of glutamate is transferred as hydride ion to an oxidizing coenzyme. Either NAD^+ or NADP^+ can function as the oxidizing coenzyme, depending on the organism.

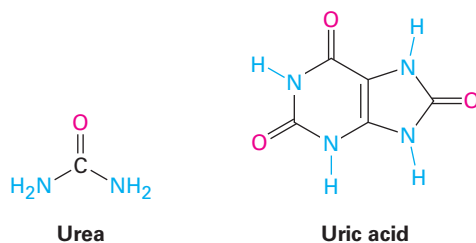


PROBLEM 20.3

In the oxidative deamination of glutamate, is the hydride ion transferred to the *Re* face or the *Si* face of NAD^+ ? (Review Section 5-11.)

20-3 The Urea Cycle

The ammonia resulting from amino acid deamination is eliminated in one of three ways depending on the organism. Fish and other aquatic animals simply excrete the ammonia to their aqueous surroundings, but terrestrial organisms must first convert the ammonia into a nontoxic substance—either urea for mammals or uric acid for birds and reptiles.



The conversion of ammonia into urea begins with its reaction with bicarbonate ion and ATP to give carbamoyl phosphate. The reaction is catalyzed by carbamoyl phosphate synthetase I and occurs by initial activation of HCO_3^- by ATP to give carboxy phosphate, followed by nucleophilic acyl substitution with ammonia to produce carbamate plus phosphate ion (P_i) as the leaving group. Subsequent phosphorylation of carbamate by a second equivalent of ATP then gives carbamoyl phosphate (FIGURE 20.4). As noted in Section 20-1, the reaction requires Mg^{2+} to form a Lewis acid–base complex with the phosphate oxygen atoms.

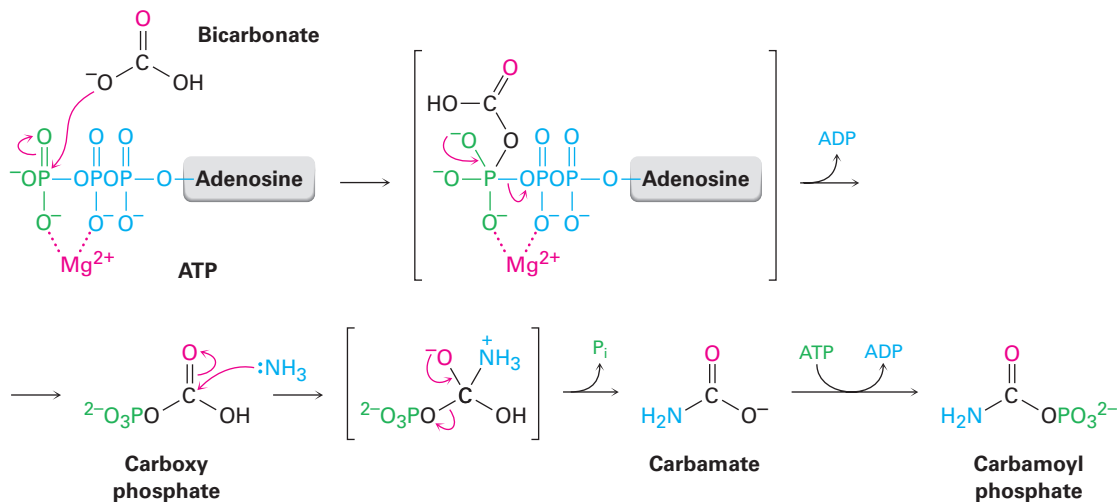
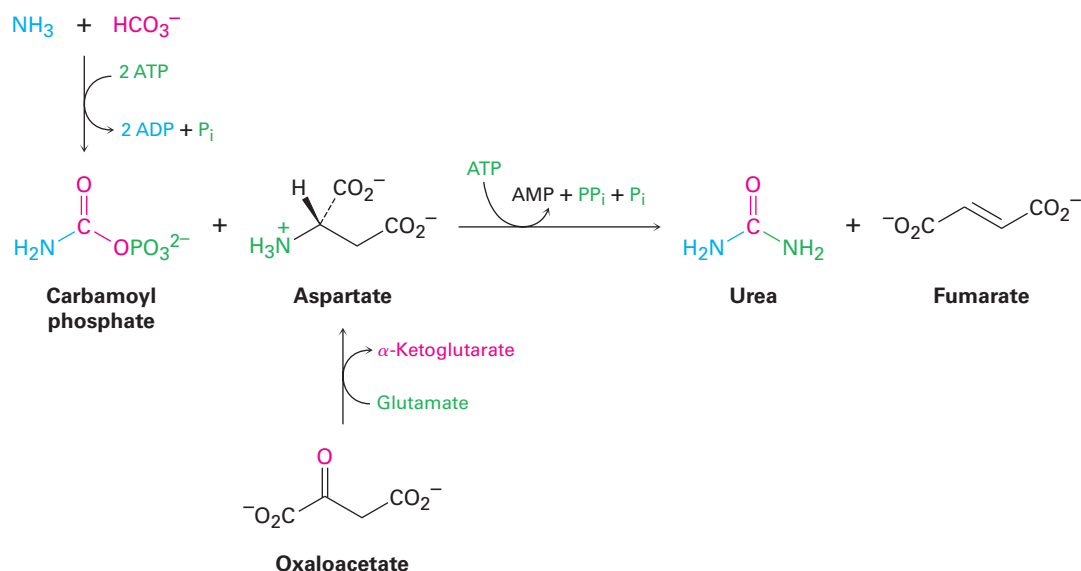


FIGURE 20.4 Mechanism of the formation of carbamoyl phosphate from bicarbonate.

Bicarbonate ion is first activated by phosphorylation with ATP, and a nucleophilic acyl substitution with ammonia then occurs.

Carbamoyl phosphate next enters the four-step **urea cycle**, whose overall result can be summarized as



Note that only one of the two nitrogen atoms in urea comes from ammonia; the other nitrogen comes from aspartate, which is itself produced from glutamate by transamination with oxaloacetate, $^{-}\text{O}_2\text{CCOCH}_2\text{CO}_2^{-}$. The reactions of the urea cycle are shown in **FIGURE 20.5**.

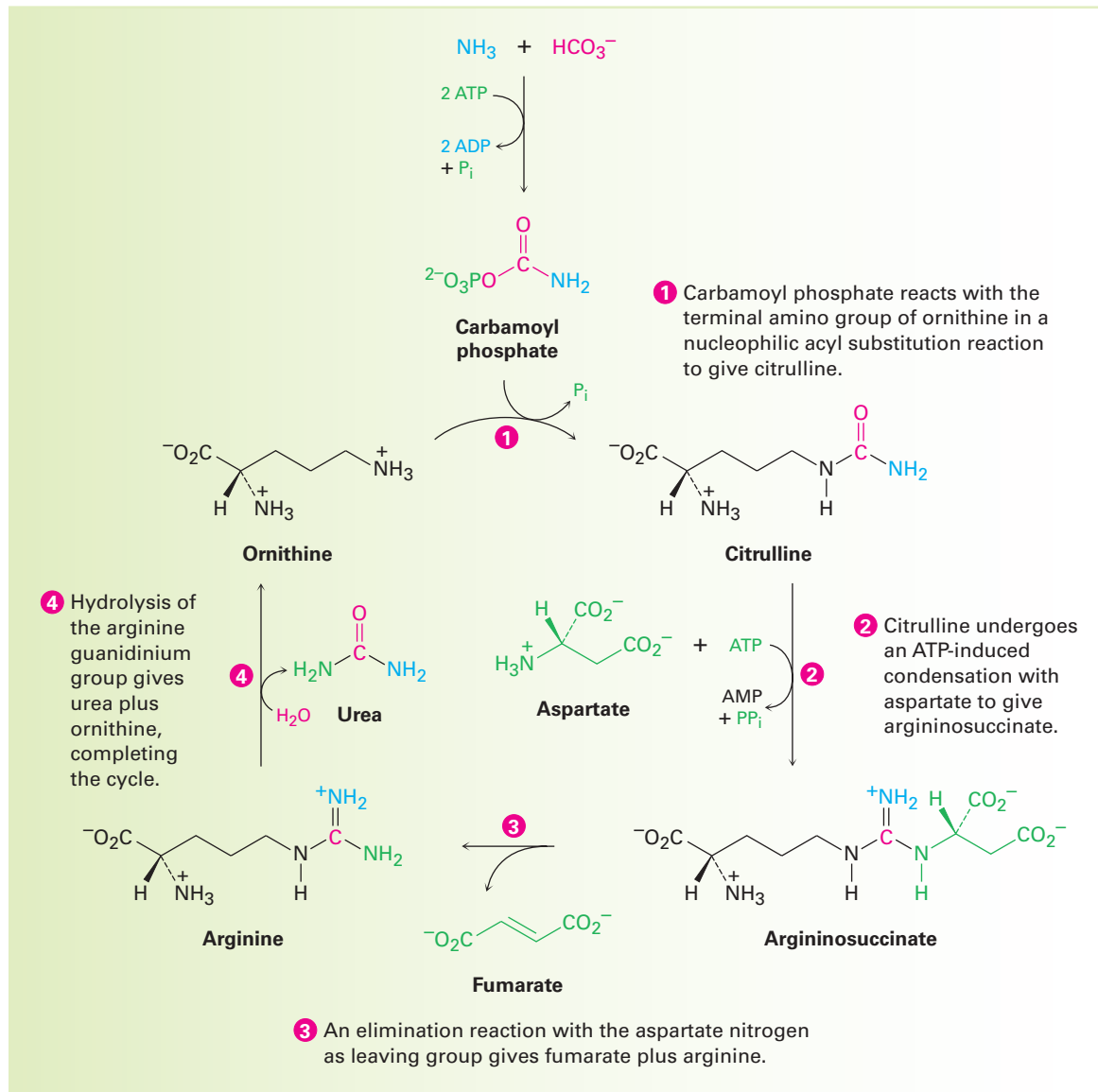
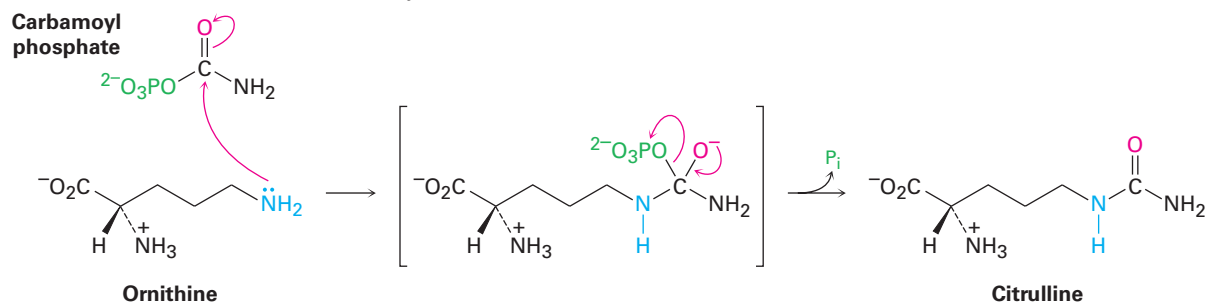


FIGURE 20.5 The urea cycle, a four-step series of reactions that converts ammonia into urea. Individual steps are explained in the text.

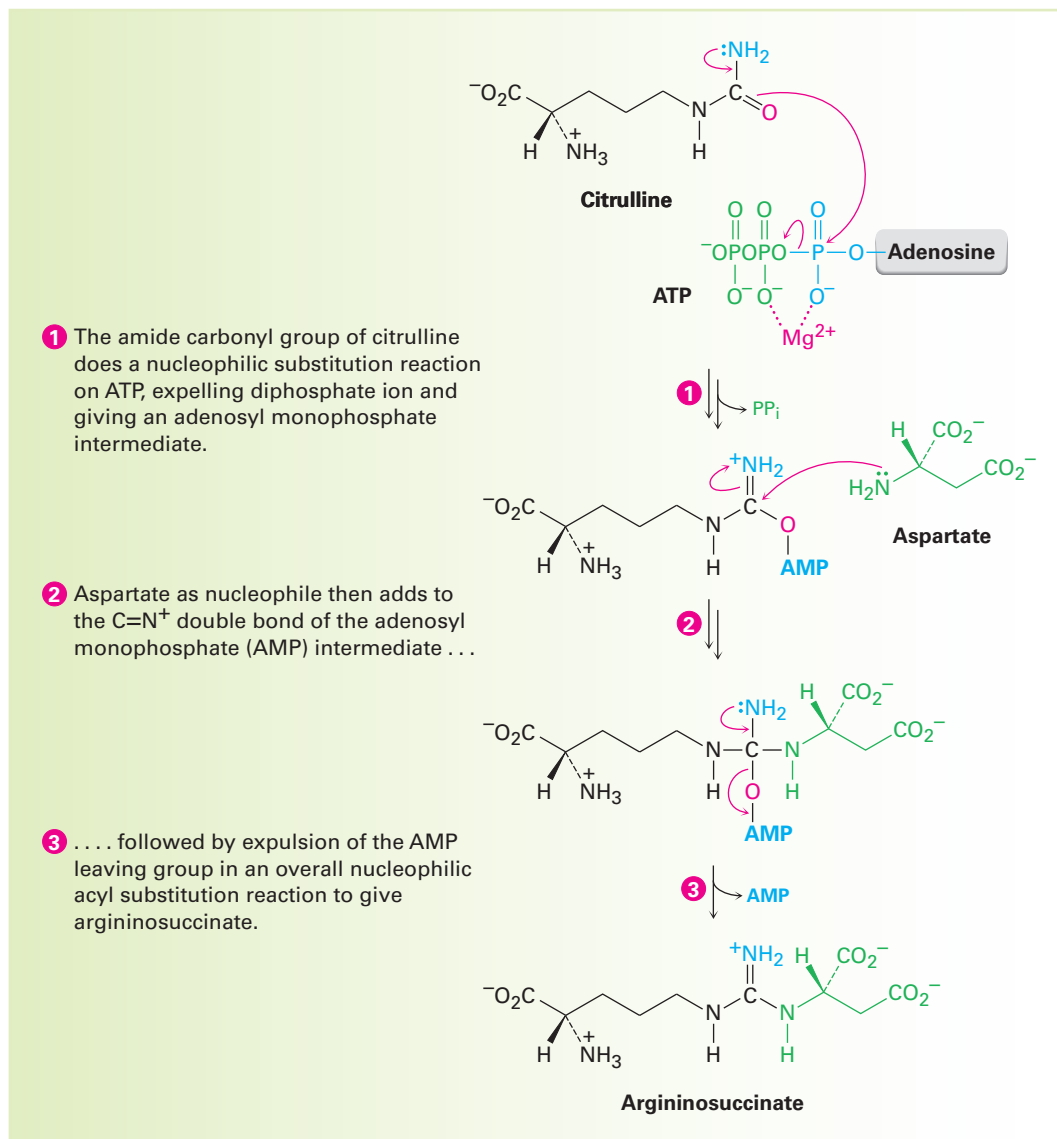
STEPS 1–2 OF FIGURE 20.5: ARGININOSUCCINATE SYNTHESIS The urea cycle begins with a nucleophilic acyl substitution reaction of the nonprotein amino acid ornithine with carbamoyl phosphate to produce citrulline. The side-chain $-\text{NH}_2$ group of ornithine is the nucleophile, phosphate ion is the leaving group, and the reaction is catalyzed by ornithine transcarbamoylase.

Note that ornithine, although not one of the 20 amino acids in proteins, is similar to lysine but contains one less carbon in its side chain.



Citrulline reacts with aspartate in step 2 to yield argininosuccinate. The reaction is catalyzed by argininosuccinate synthetase and occurs by the mechanism shown in **FIGURE 20.6**. The process is essentially a nucleophilic acyl

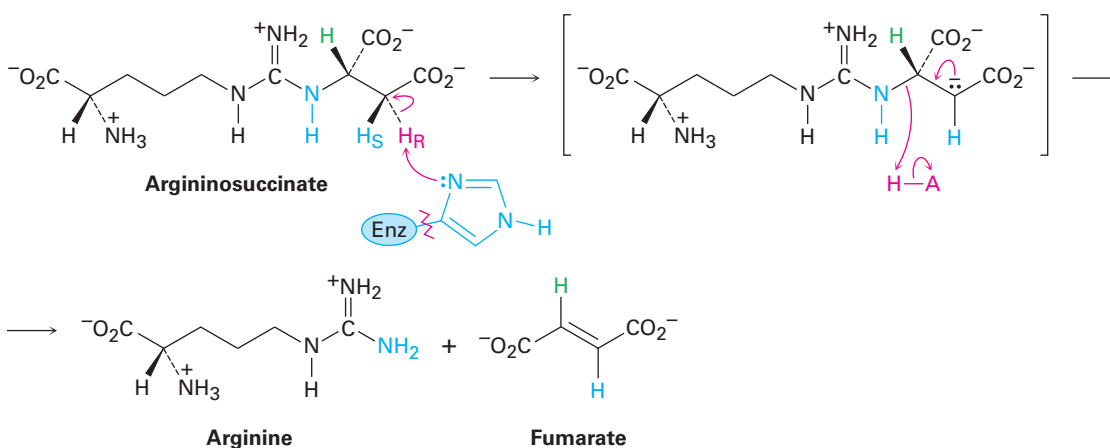
FIGURE 20.6
Mechanism of step 2 in the urea cycle. Reaction of citrulline with aspartate gives argininosuccinate.



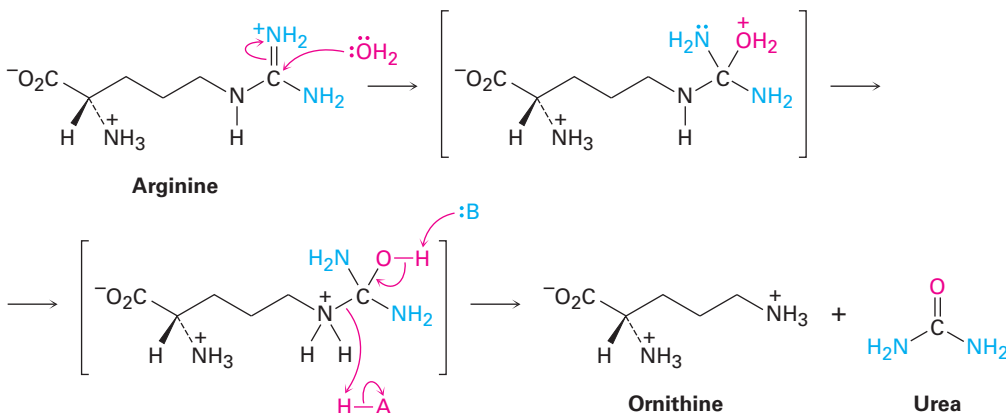
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substitution reaction in which the amide group of citrulline is first activated by reaction with ATP to give an adenosyl monophosphate (AMP) derivative with loss of diphosphate ion (abbreviated PP_i) as the leaving group. Nucleophilic addition of the aspartate amino group to the $\text{C}=\text{N}^+$ bond then gives a typical tetrahedral intermediate, which expels AMP as the leaving group.

STEP 3 OF FIGURE 20.5: FUMARATE ELIMINATION The third step in the urea cycle, conversion of argininosuccinate to arginine plus fumarate, is an elimination reaction catalyzed by argininosuccinate lyase. The process occurs by an E1cB mechanism (Section 17-7), with a histidine residue on the enzyme acting as the base to carry out the deprotonation and form the anion intermediate. Note that the *pro-R* hydrogen on argininosuccinate is specifically abstracted in the elimination. Such specificity is typical for enzyme-catalyzed reactions, although it's not usually possible to predict the stereochemistry nor is it something for you to be concerned with at this point.



STEP 4 OF FIGURE 20.5: ARGININE HYDROLYSIS The final step to complete the urea cycle is hydrolysis of arginine to give ornithine and urea. The reaction is catalyzed by the Mn^{2+} -containing enzyme arginase and occurs by addition of H_2O to the $\text{C}=\text{N}^+$ bond, followed by proton transfer and elimination of ornithine from the tetrahedral intermediate.



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PROBLEM 20.4

Draw the full structure of the adenosyl monophosphate intermediate formed by reaction of citrulline with ATP (Figure 20.6).

20-4 Catabolism of Amino Acids: The Carbon Chains

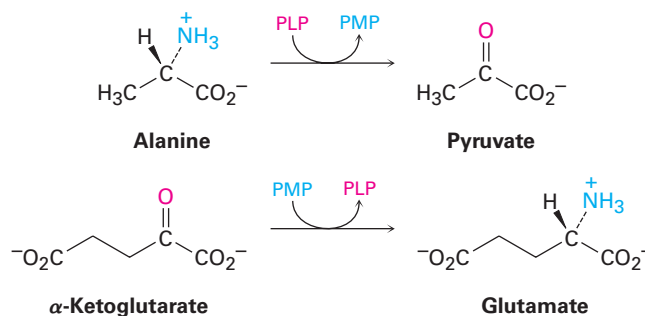
With the amino group removed by transamination and the resultant ammonia converted into urea, the third and final stage of amino acid catabolism is the degradation of the carbon chains. As indicated in **FIGURE 20.7**, the carbon chains of α -amino acids are commonly converted into one of seven intermediates that enter the citric acid cycle for final degradation.

Those amino acids (red in Figure 20.7) that are converted into either acetoacetate or acetyl CoA are called *ketogenic* because they can also enter the fatty-acid biosynthesis pathway (Section 23-6) or be converted into so-called *ketone bodies*—acetoacetate, β -hydroxybutyrate, and acetone. Those amino acids (blue in Figure 20.7) that are converted either to pyruvate or directly to an intermediate in the citric acid cycle are called *glucogenic* because they can also enter the *gluconeogenesis* pathway by which glucose is synthesized (Section 22-5). Several amino acids are both ketogenic and glucogenic, either because they can be catabolized by alternative pathways or because their carbon chains are broken down to give several different products.

A detailed coverage of the catabolic pathways for all 20 protein amino acids would take far too much space—tryptophan catabolism alone requires 14 steps—and would be far too complex for this book. The mechanisms of these pathways *are* understandable and occur by typical organic mechanisms, but we won't attempt to cover them. Instead, we'll just look at several fairly straightforward schemes to see the kinds of chemistry involved in amino acid catabolism.

Alanine Catabolism

Alanine is one of the six amino acids that are catabolized to give pyruvate. The pathway is a straightforward PLP-dependent transamination reaction, as discussed in Section 20-2, with the PMP intermediate then converted back to PLP by reaction with α -ketoglutarate.



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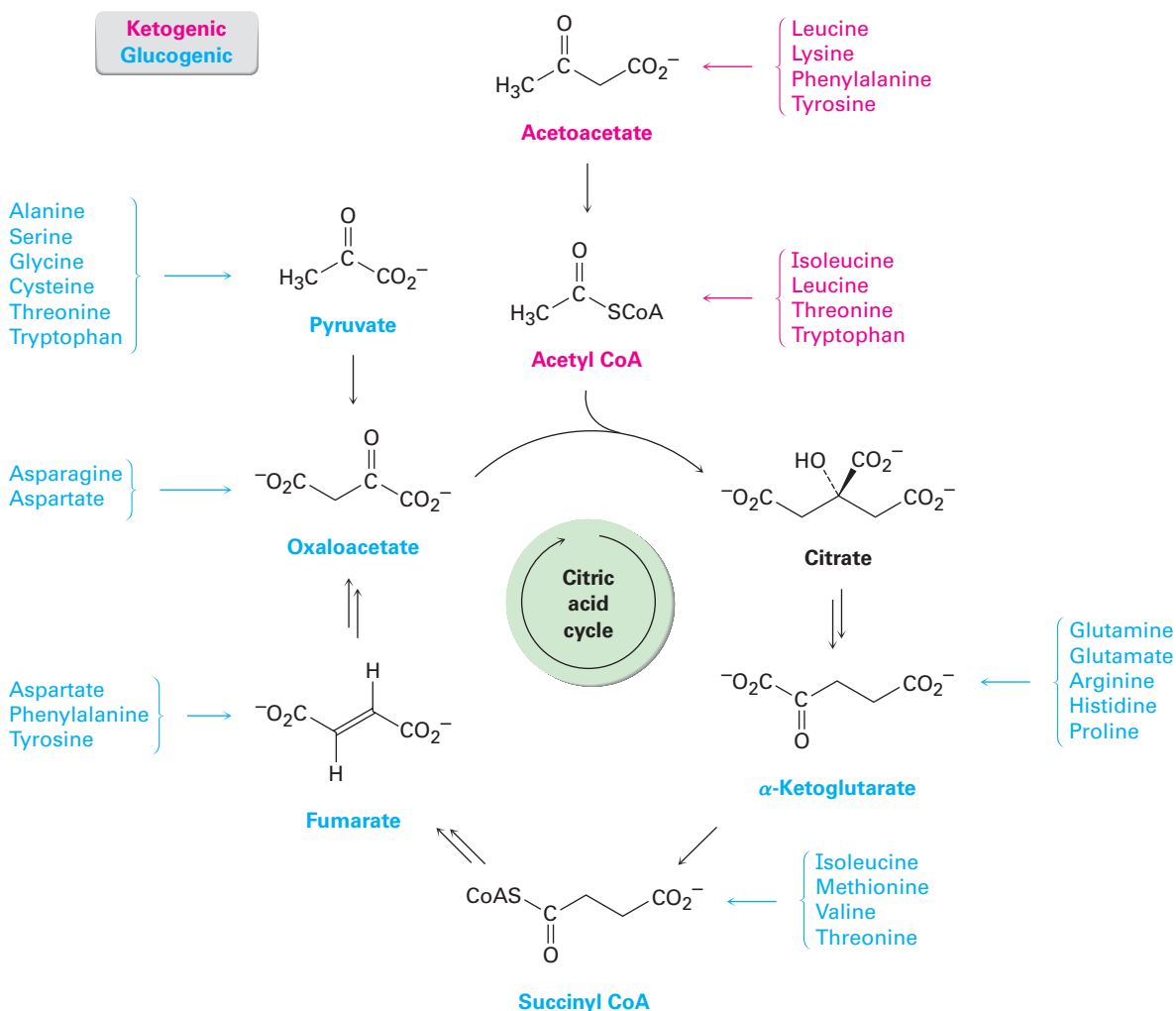


FIGURE 20.7 Intermediates in the metabolism of amino acids. Carbon chains of the 20 common amino acids are converted into one of seven intermediates for further breakdown in the citric acid cycle. **Ketogenic amino acids** can also enter the pathway for fatty-acid biosynthesis; **glucogenic amino acids** can also enter the gluconeogenesis pathway for glucose biosynthesis.

PROBLEM 20.5

Review Section 20-2, and write all the steps in the PLP-dependent transamination reaction of alanine plus α -ketoglutarate to give pyruvate plus glutamate.

Serine Catabolism

Serine, like alanine, is converted into pyruvate by a PLP-dependent pathway, but the two reaction sequences are not the same. Whereas alanine catabolism involves a PLP-dependent *transamination*, serine catabolism

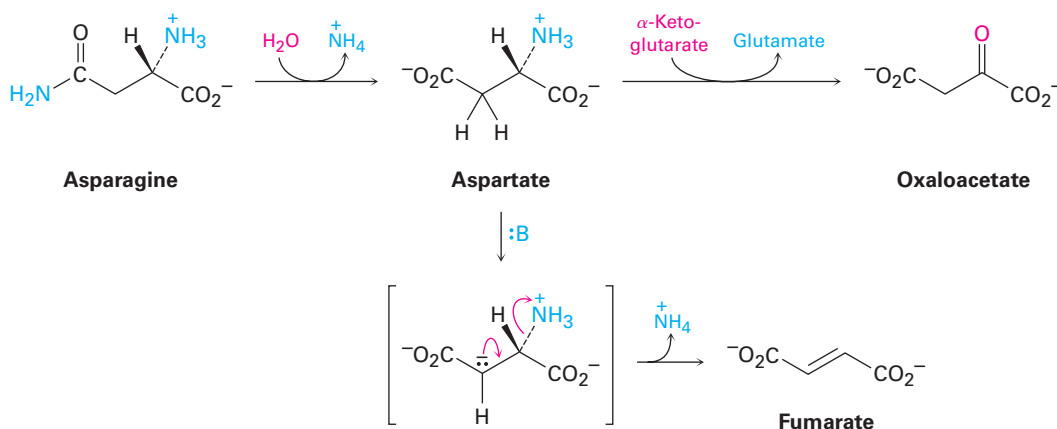


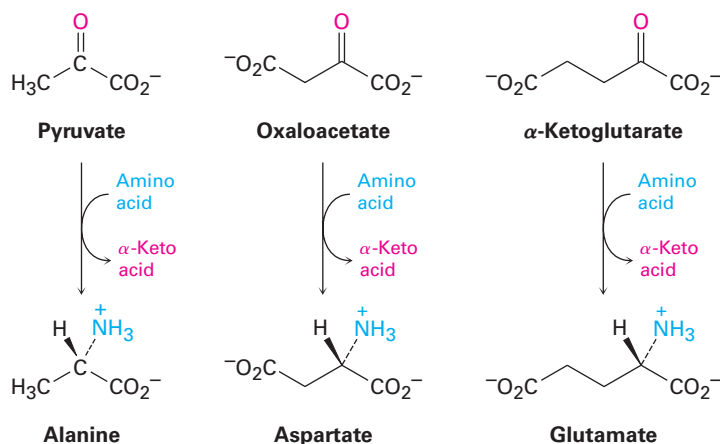
FIGURE 20.9
Mechanism of the conversion of asparagine and aspartate to oxaloacetate and fumarate. Initial PLP-dependent transamination is followed by an E1cB elimination of ammonium ion.

20-5 Biosynthesis of Amino Acids

As discussed in Section 19-1, we humans are able to synthesize only 11 of the 20 amino acids in proteins, called nonessential amino acids. The other 9, called essential amino acids, are biosynthesized only in plants and microorganisms and must be obtained in our foods. **FIGURE 20.10** shows the common biosynthetic precursors of the 20 protein amino acids. As with amino acid catabolic pathways, a detailed coverage of the biosynthetic pathways for all 20 amino acids would take far too much space. We'll therefore look only at several representative schemes.

Alanine, Aspartate, and Glutamate Biosynthesis

Seven of the eleven nonessential amino acids are synthesized either from pyruvate or from the citric acid cycle intermediates oxaloacetate and α-ketoglutarate. Alanine is biosynthesized by transamination of pyruvate, aspartate from oxaloacetate, and glutamate from α-ketoglutarate. The mechanisms of these PLP-dependent transaminations were discussed in Section 20-2 and shown in Figure 20.2.



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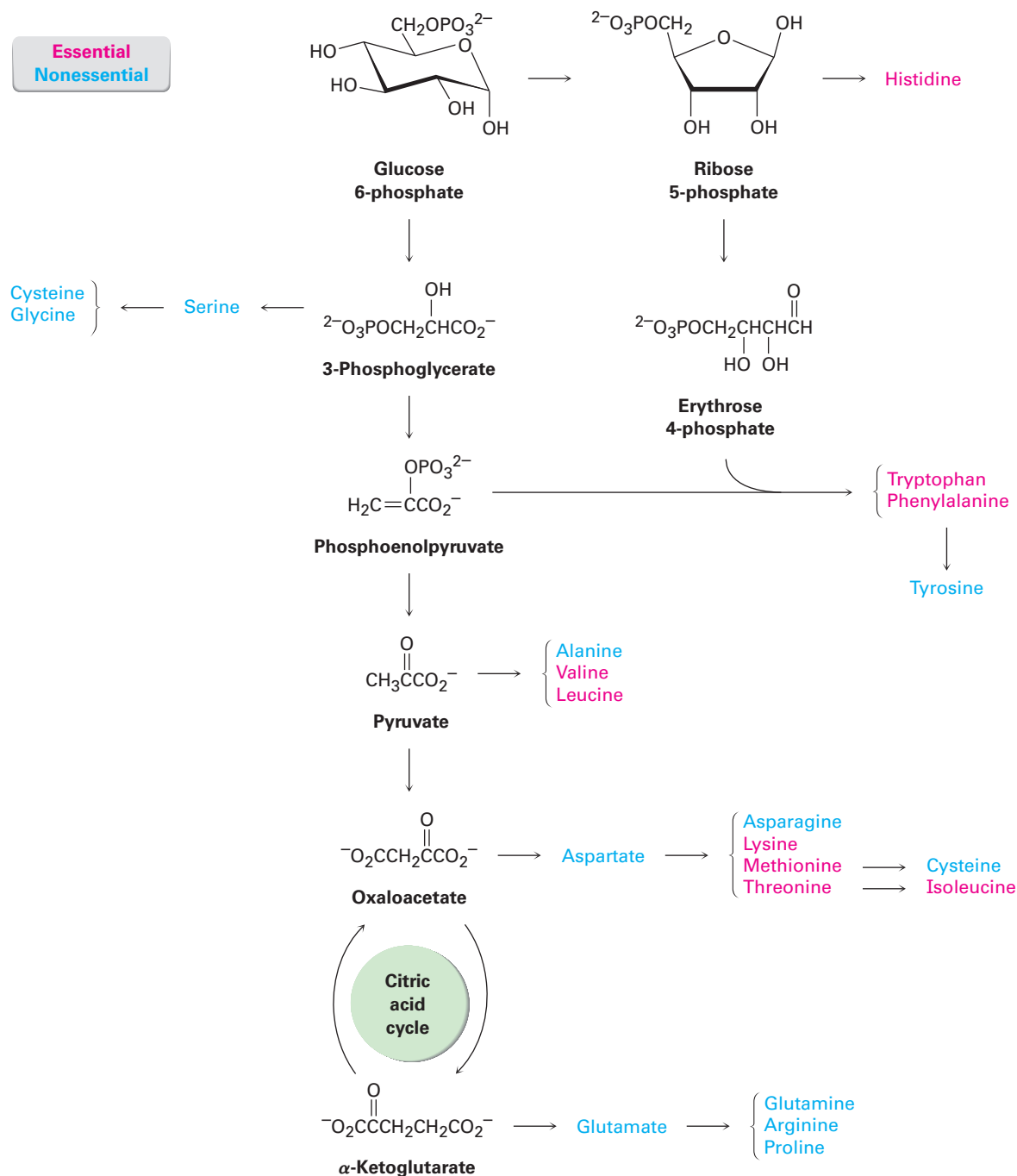


FIGURE 20.10 Biosynthesis of the 20 protein amino acids. Essential amino acids (red) are synthesized in plants and bacteria and must be obtained in our diet. Humans can synthesize only the nonessential amino acids (blue).

PROBLEM 20.7

Write the full mechanism for the PLP-dependent biosynthesis of alanine from pyruvate.

Asparagine and Glutamine Biosynthesis

The amides asparagine and glutamine are synthesized from aspartate and glutamate, respectively, as shown in **FIGURE 20.11**. Asparagine biosynthesis is catalyzed by asparagine synthetase and requires ATP as cofactor. The reaction proceeds through formation of an acyl adenosyl monophosphate, which undergoes nucleophilic acyl substitution by ammonia. The ammonia is itself produced from glutamine by a nucleophilic acyl substitution reaction with a cysteine residue in the enzyme.

Glutamine biosynthesis is catalyzed by glutamine synthetase and occurs by formation of the corresponding acyl phosphate followed by nucleophilic acyl substitution reaction with ammonia. The difference in activation strategies for the asparagine and glutamine pathways—acyl adenosyl phosphate for aspartate versus acyl phosphate for glutamate—is probably the result of different evolutionary histories for the two enzymes since both paths are energetically favorable.

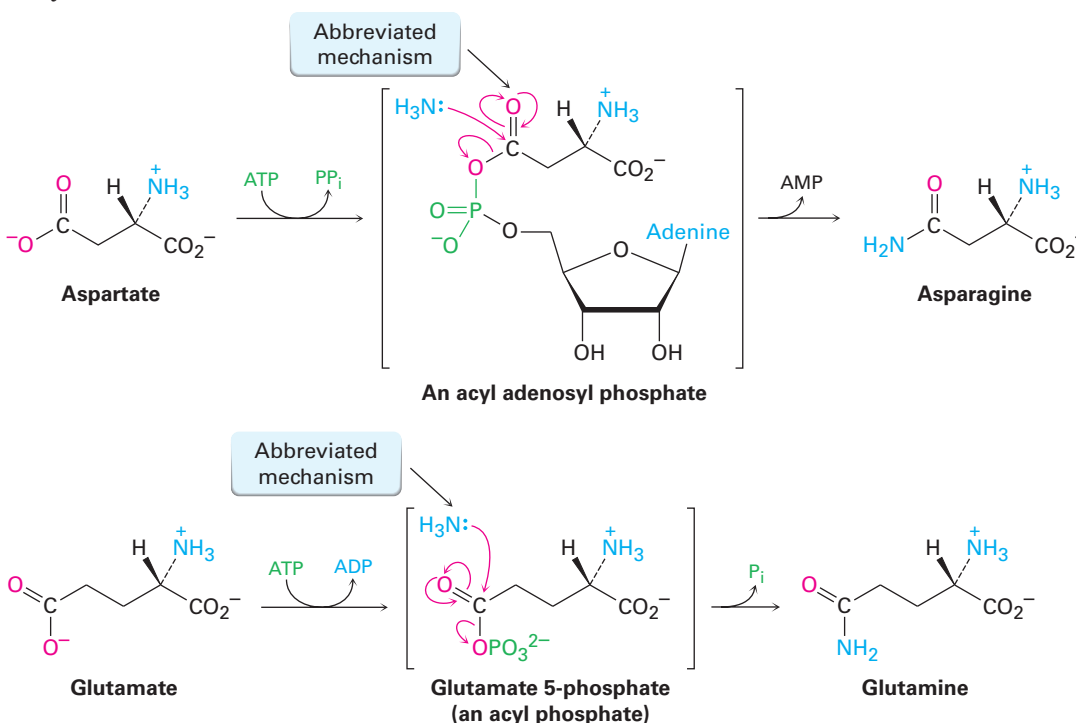


FIGURE 20.11
Biosynthetic pathways for asparagine and glutamine by amide formation from aspartate and glutamate. As explained in the text, the mechanisms of the acyl substitution reactions are given in abbreviated form without showing the tetrahedral intermediates.

Note in Figure 20.11 that the mechanisms of the nucleophilic acyl substitution steps are given in an abbreviated form that saves space by not explicitly showing the formation and subsequent collapse of tetrahedral reaction intermediates. Instead, electron movement is shown as a heart-shaped path around the carbonyl oxygen to imply the full mechanism. Biochemists use this kind of format frequently, and we'll also use it on occasion in the remaining chapters.

PROBLEM 20.8

Show the full mechanism for the formation of glutamine by reaction of glutamate 5-phosphate with ammonia, and compare that full mechanism to the abbreviated mechanism shown in Figure 20.11 to see the difference.

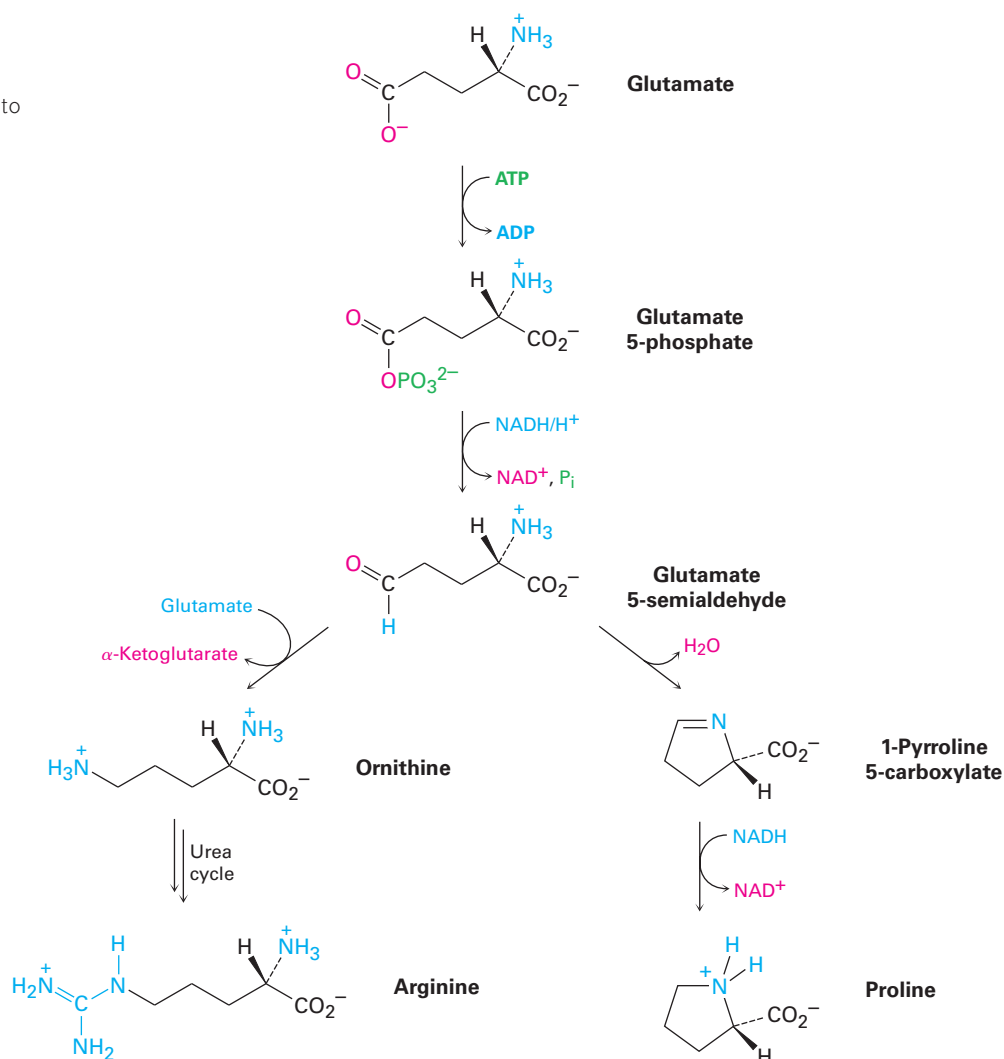
Arginine and Proline Biosynthesis

In humans, arginine is synthesized from glutamate by the pathway shown in **FIGURE 20.12**. Reaction of glutamate with ATP gives the same acyl phosphate intermediate as in glutamine biosynthesis (Figure 20.11), which is reduced by NADH in a nucleophilic acyl substitution reaction with hydride ion to yield the corresponding aldehyde, glutamate 5-semialdehyde. You might recall that a similar partial reduction of esters to aldehydes can be carried out in the laboratory by reaction of the ester with diisobutylaluminum hydride (DIBAH; Section 16-6). A related example of a partial reduction of a thioester to an aldehyde by reaction with NADPH was discussed in Section 16-8.

PLP-mediated transamination of the glutamate 5-semialdehyde carbonyl group by reaction with glutamate then gives ornithine, which is converted to arginine in the urea cycle, as discussed previously in Section 20-3 (Figure 20.5).

Proline also is synthesized from glutamate 5-semialdehyde by non-enzymatic formation of a cyclic imine followed by enzymatic reduction of the C=N bond with NADH in a nucleophilic addition reaction.

FIGURE 20.12 Biosynthesis of arginine and proline from glutamate. The key step is a partial reduction of glutamate to the corresponding aldehyde.



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PROBLEM 20.9

Review Section 16-8, and show the mechanism of the partial reduction of glutamate 5-phosphate with NADH to give glutamate 5-semialdehyde.

PROBLEM 20.10

Show the mechanisms of both the nonenzymatic cyclization of glutamate 5-semialdehyde to give 1-pyrroline 5-carboxylate and the subsequent enzymatic reduction with NADH to yield proline.

SOMETHING EXTRA

Visualizing Enzyme Structures

In the Chapter 19 *Something Extra*, we discussed how to access enzyme structural data from the Protein Data Bank. Once the data for a specific enzyme have been located, it's then possible to visualize, manipulate, and study the structure. You can do this either by downloading the data file to your own computer and opening it with a free visualization program, such as DeepView (Swiss PDB Viewer) available at <http://spdbv.vital-it.ch/>, or you can use one of display options built in to the PDB site.

Let's say that you want to study one of the more complex and interesting amino acid catabolic pathways and that you need to view urocanase, a key enzyme in histidine catabolism that catalyzes the addition of water to *trans*-urocanate.

Go to the PDB site at <http://rcsb.org/pdb/>, type "urocanase" into the search window, and choose the structure with a PDB code of 1UWK. After clicking on

the code, a screen with information on the selected structure appears, and several display options are presented in the visualization box on the right of the screen. An image of urocanase downloaded from the PDB is shown in **FIGURE 20.13**, with helical regions of the dimeric protein represented as coiled ribbons and pleated-sheet regions as flat ribbons.

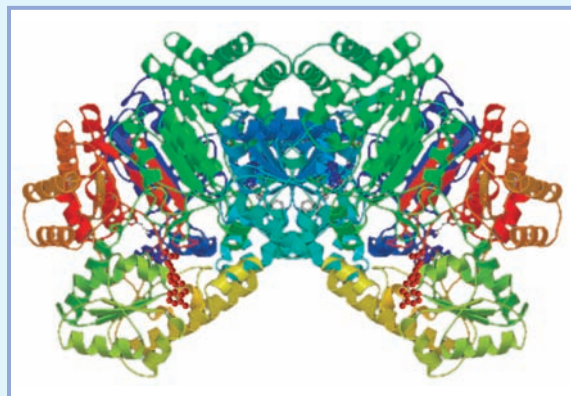
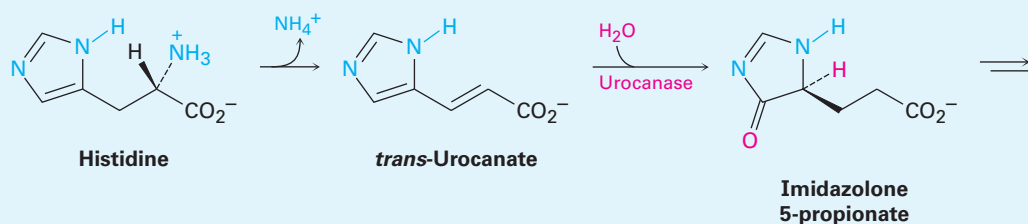


FIGURE 20.13 An image of urocanase, downloaded from the Protein Data Bank. Urocanase is a dimer composed of two identical subunits.



Among the display options available on the PDB site, one of the more useful lets you obtain detailed information on an enzyme's active site. Scroll down the 1UWK information screen until you come to a blue box titled "Ligand Chemical Component." Clicking on the [View] link under "Ligand Interaction" opens an applet called Ligand Explorer, which gives you a close-up view of the urocanate and NAD^+ ligands bound at the active site of the enzyme. You can then examine the various interactions between the ligands and amino acid residues in the enzyme. **FIGURE 20.14** shows the urocanate substrate and the pyridinium ring of NAD^+ cofactor bound at the active site. The $-\text{OH}$ group of tyrosine-52 is hydrogen bonded to the urocanate nitrogen, while arginine-362 and threonine-133 are hydrogen bonded to the urocanate carboxylate.

Explore on your own; there is an immense amount of detailed information you can learn.

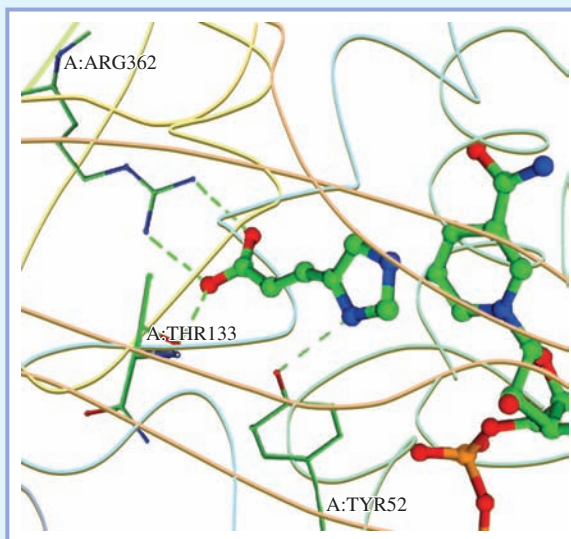


FIGURE 20.14 A view of the urocanate substrate and the pyridinium ring of NAD^+ cofactor bound at the active site of urocanase. The $-\text{OH}$ group of tyrosine-52 is hydrogen bonded to the urocanate nitrogen, while arginine-362 and threonine-133 are hydrogen bonded to the urocanate carboxylate. Note how urocanate is poised directly over the pyridinium ring of NAD^+ .

KEY WORDS

anabolism, 715
 catabolism, 715
 deamination, 719
 metabolism, 715
 oxidative deamination, 723
 transamination, 719
 urea cycle, 724

SUMMARY

In this chapter, we began a study of biological reactions, focusing specifically on amino acids, the fundamental building blocks from which the estimated 500,000 or so proteins in our bodies are made. We looked both at how amino acids are biosynthesized for incorporation into proteins and how they are ultimately degraded when proteins are broken down.

The many reactions that go on in the cells of living organisms are collectively called **metabolism**. The pathways that break down larger molecules into smaller ones are called **catabolism**, and the pathways that synthesize larger biomolecules from smaller ones are known as **anabolism**. Catabolic reaction pathways are usually exergonic, while anabolic reaction pathways are often endergonic. Catabolism is carried out in four stages: (1) digestion, in which food is hydrolyzed to fatty acids, simple sugars, and amino acids; (2) degradation of small molecules to give acetyl CoA; (3) oxidation of acetyl CoA in the citric acid cycle to give CO_2 and release energy; and (4) energy utilization by the electron-transport chain to phosphorylate ADP and give ATP. The ATP then drives many other biological reactions.

Amino acid catabolism occurs in three stages: (1) removal of the α amino group as ammonia, (2) conversion of the ammonia into urea, and (3) conversion of the remaining amino acid carbon skeleton, usually an α -keto acid, into an intermediate that can enter the citric acid cycle.

Deamination of an α -amino acid is accomplished by a pyridoxal phosphate (PLP)-dependent **transamination** reaction in which the $-\text{NH}_2$ group of the amino acid is exchanged with the keto group of α -ketoglutarate, forming a new α -keto acid plus glutamate. The glutamate is then oxidatively deaminated to give ammonia plus regenerated α -ketoglutarate, and the ammonia is converted into urea in the four-step **urea cycle**. Once the amino acids have been deaminated, their carbon chains are converted into one of seven intermediates that are further degraded in the citric acid cycle. Each amino acid has its own unique degradation pathway.

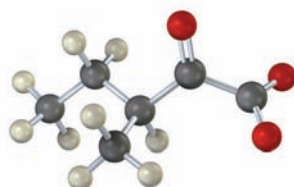
Humans synthesize only 11 of the 20 amino acids in proteins, called non-essential amino acids. The other 9, called essential amino acids, are biosynthesized only in plants and microorganisms and must be obtained in the diet. Each amino acid is biosynthesized by a unique pathway.

EXERCISES

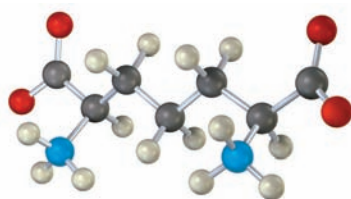
VISUALIZING CHEMISTRY

(Problems 20.1–20.10 appear within the chapter.)

20.11 What amino acid is the following α -keto acid derived from?

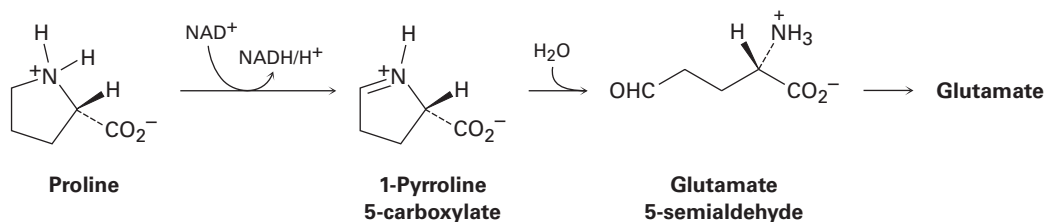


20.12 The following compound is an intermediate in the biosynthesis of one of the twenty common α -amino acids. Which one is it likely to be, and what kind of chemical change must take place to complete the biosynthesis?



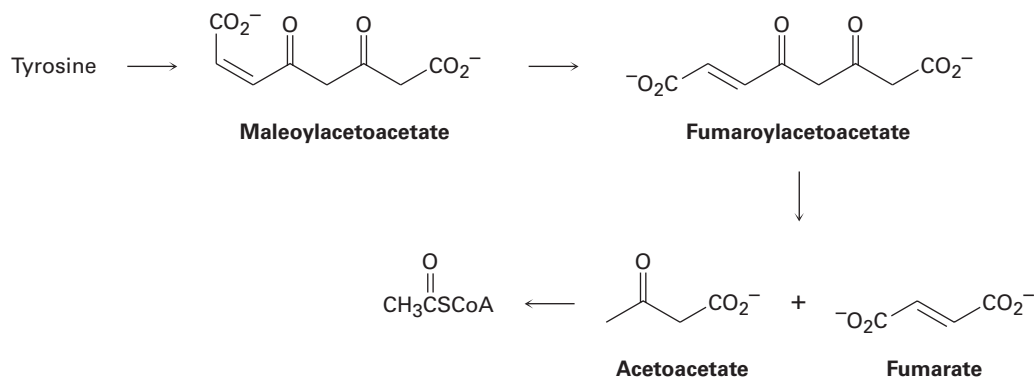
ADDITIONAL PROBLEMS

- 20.13** What general kind of reaction does ATP carry out?
- 20.14** Draw the structure of adenosine 5'-*monophosphate* (AMP), an intermediate in numerous biochemical pathways.
- 20.15** Cyclic adenosine monophosphate (cyclic AMP), a modulator of hormone action, is related to AMP (Problem 20.14) but has its phosphate group linked to *two* hydroxyl groups, at C3' and C5' of the sugar. Draw the structure of cyclic AMP.
- 20.16** In addition to the dehydration pathway giving pyruvate (Figure 20.8), serine is also catabolized by an alternative PLP-dependent pathway that gives glycine. Write mechanisms for the key step: a base-catalyzed loss of CH_2O from the PLP-serine imine to give the PLP-glycine imine.
- 20.17** Proline is catabolized by conversion to glutamate 5-semialdehyde, followed by oxidation to glutamate and oxidative deamination to α -ketoglutarate.

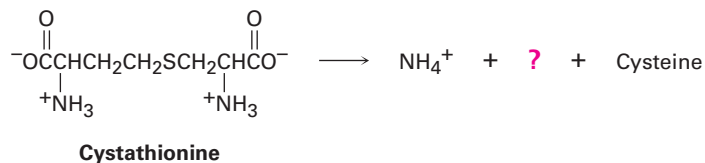


- (a)** The oxidation of proline to 1-pyrroline 5-carboxylate is analogous to what occurs in the oxidative deamination of glutamate to α -ketoglutarate (Section 20-2). Propose a mechanism.
- (b)** Show the mechanism of the hydrolysis of 1-pyrroline 5-carboxylate to give glutamate 5-semialdehyde.
- (c)** What coenzyme is probably required for the oxidation of glutamate 5-semialdehyde to glutamate?

- 20.18** Tyrosine is catabolized by a series of steps that include the following transformations:

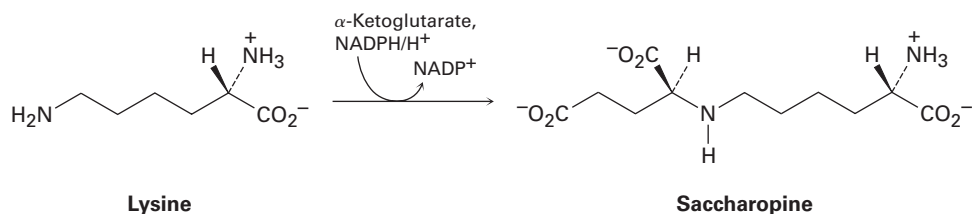


- (a) The double-bond isomerization of maleoylacetoacetate to fumaroylacetoacetate is catalyzed by practically any nucleophile, $:\text{Nu}^-$. Review Section 14-11, and then propose a mechanism.
- (b) Propose a mechanism for the biological conversion of fumaroylacetoacetate to fumarate plus acetoacetate.
- 20.19** Cysteine, $\text{C}_3\text{H}_7\text{NO}_2\text{S}$, is biosynthesized from a substance called cystathionine by a multistep pathway:

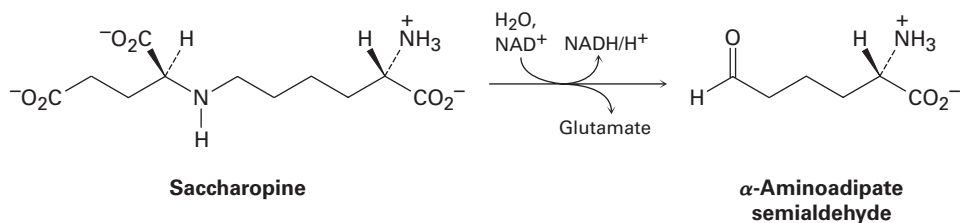


- (a) The first step is a transamination. What is the product?
- (b) The second step is an E1cB reaction. Show the products and the mechanism of the reaction.
- (c) The final step is a double-bond reduction. What product is represented by the question mark in the equation?

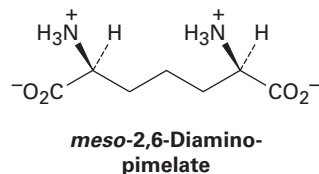
20.20 Lysine catabolism begins with reductive amination of α -ketoglutarate to give saccharopine. Show the mechanism.



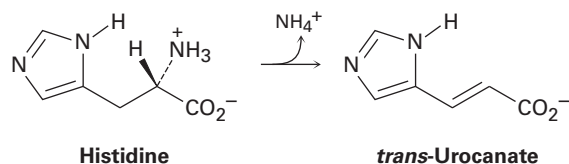
20.21 The second step in lysine catabolism is oxidative deamination of saccharopine to give α -aminoadipate semialdehyde. Show the mechanism.



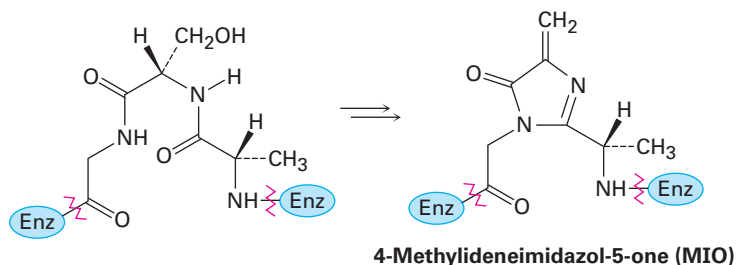
20.22 The final step in lysine biosynthesis is decarboxylation of *meso*-2,6-diaminopimelate. The reaction requires PLP as cofactor and occurs through the usual PLP–amino acid imine. Propose a mechanism.



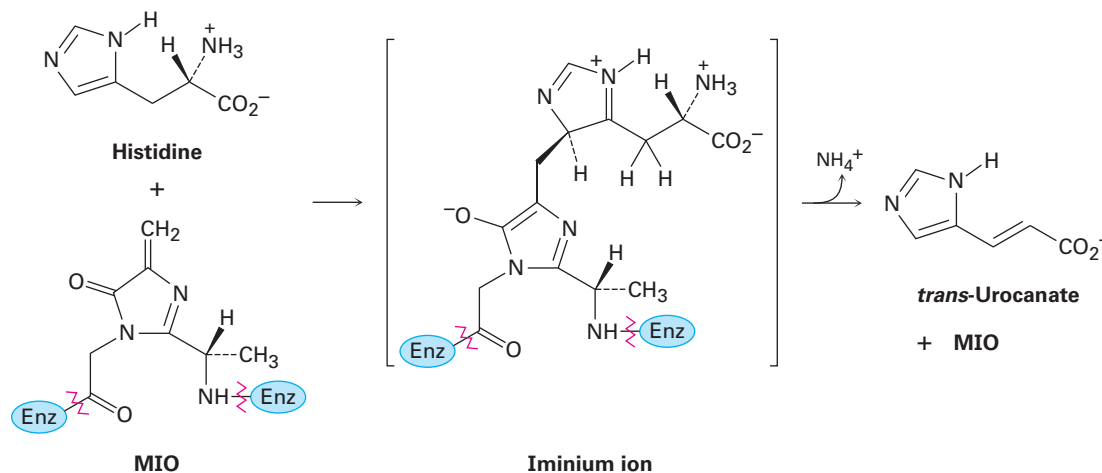
- 20.23** Histidine catabolism begins with elimination of ammonia to give *trans*-urocanate in a step catalyzed by histidine ammonia lyase.



The process is more complex than it appears and involves initial formation of a 4-methylideneimidazol-5-one (MIO) ring that arises by cyclization and dehydration of an –Ala–Ser–Gly– segment within the histidine ammonia lyase enzyme. Propose a mechanism for the formation of the MIO ring.



- 20.24** After the MIO ring is formed (Problem 20.23), histidine adds to the MIO in a conjugate nucleophilic addition reaction, producing an iminium ion on histidine that makes the neighboring –CH₂– hydrogens acidic and allows a subsequent E1cB reaction. Show the mechanism.

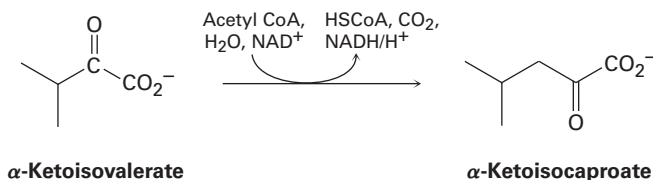


Following the E1cB reaction, expulsion of *trans*-urocanate by a mechanism that is the opposite of the conjugate addition step regenerates the MIO. Show the mechanism.

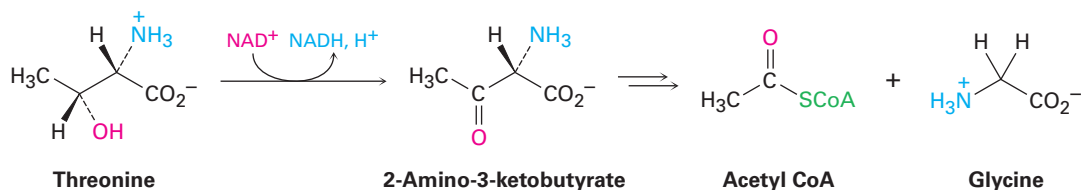
20.25 Leucine is biosynthesized from α -ketoisocaproate, which is itself formed from α -ketoisovalerate by a multistep route that involves:

- (1) reaction of α -ketoisocaproate with acetyl CoA in an aldol-like reaction
- (2) hydrolysis of the thioester
- (3) dehydration by an E1cB mechanism
- (4) hydration by a conjugate addition reaction
- (5) oxidation of an alcohol to a ketone
- (6) decarboxylation of a β -keto acid

Show the steps in the biosynthesis, and propose a mechanism for each.



20.26 Threonine is catabolized by several different pathways. Most commonly, it is oxidized by NAD^+ to 2-amino-3-ketobutyrate, which is then converted by a PLP-dependent reaction into acetyl CoA and glycine.

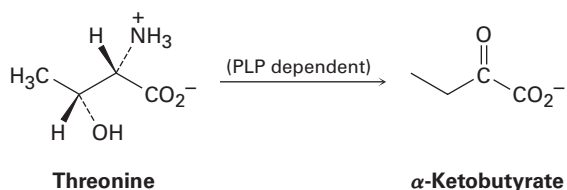


- (a) The first step in the pathway is formation of a 2-amino-3-ketobutyrate imine with PLP. Draw the structure of this imine.
- (b) The second step is a nucleophilic addition of coenzyme A to the PLP imine to give a tetrahedral intermediate, which is then cleaved in a retro-Claisen-like reaction to yield acetyl CoA plus the PLP imine of glycine. Show the mechanism of the cleavage reaction (the pyridinium ring of PLP acts as the electron acceptor), and draw the structure of the PLP-glycine imine.
- (c) The third step is hydrolysis of the PLP-glycine imine to give glycine and PMP. Show the mechanism of the hydrolysis.

20.27 An alternative pathway for threonine catabolism is a PLP-dependent sequence to yield glycine plus acetaldehyde, which is oxidized to acetate and converted into acetyl CoA.

- The first step is formation of a PLP–threonine imine. Draw the structure.
- The second step is a retro-aldol-like cleavage of the PLP–threonine imine to give acetaldehyde plus a PLP–glycine imine. Show the mechanism of the reaction.

20.28 Yet a third pathway for threonine catabolism converts threonine into α -ketobutyrate through a multistep mechanism that involves a PLP-dependent dehydration reaction analogous to what occurs in serine catabolism (Figure 20.8).



- The PLP–threonine imine formed by reaction of threonine with a PLP–enzyme imine undergoes an E1cB dehydration reaction to give an unsaturated PLP imine. Show the mechanism of the reaction and the product.
- The unsaturated PLP imine reacts with enzyme to give an enamine plus regenerated PLP–enzyme imine. Show the mechanism of the reaction and the product.
- The enamine is hydrolyzed to give α -ketobutyrate. Show the mechanism of the reaction.

21

Biomolecules: Carbohydrates

CONTENTS

- 21-1 Classifying Carbohydrates
- 21-2 Representing Carbohydrate Stereochemistry: Fischer Projections
- 21-3 D,L Sugars
- 21-4 Configurations of the Aldoses
- 21-5 Cyclic Structures of Monosaccharides: Anomers
- 21-6 Reactions of Monosaccharides
- 21-7 The Eight Essential Monosaccharides
- 21-8 Disaccharides
- 21-9 Polysaccharides and Their Synthesis
- 21-10 Some Other Important Carbohydrates

SOMETHING EXTRA
Sweetness



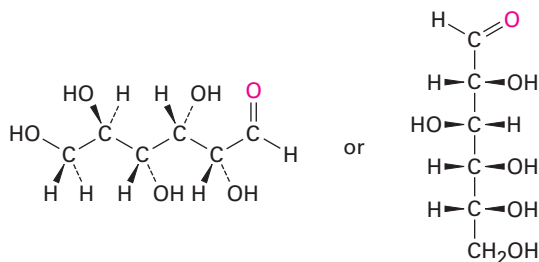
Hexokinase catalyzes the phosphorylation of glucose, the first step in carbohydrate metabolism.

WHY THIS CHAPTER?

Continuing our coverage of the major kinds of biomolecules, carbohydrates are the second class to be discussed. We'll see in this chapter what the structures and primary biological functions of carbohydrates are, and we'll look in the following chapter at how carbohydrates are biosynthesized and degraded in organisms.

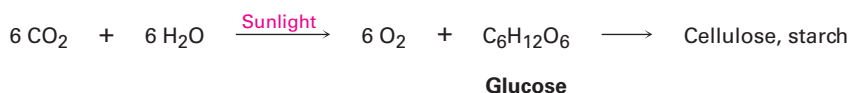
Carbohydrates occur in every living organism. The sugar and starch in food, and the cellulose in wood, paper, and cotton are nearly pure carbohydrate. Modified carbohydrates form part of the coating around living cells, other carbohydrates are part of the nucleic acids that carry our genetic information, and still others are used as medicines.

The word **carbohydrate** derives historically from the fact that glucose, the first simple carbohydrate to be obtained pure, has the molecular formula $C_6H_{12}O_6$ and was originally thought to be a “hydrate of carbon, $C_6(H_2O)_6$.” This view was soon abandoned, but the name survived. Today, the term *carbohydrate* is used to refer loosely to the broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Glucose, also known as dextrose in medical work, is the most familiar example.



**Glucose (dextrose),
a pentahydroxyhexanal**

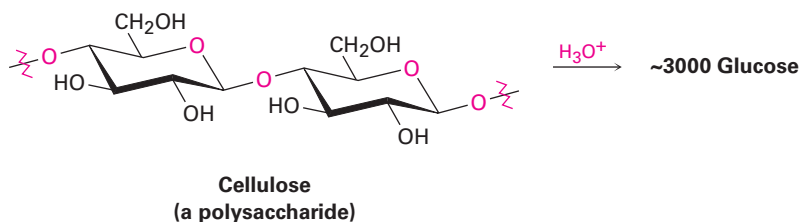
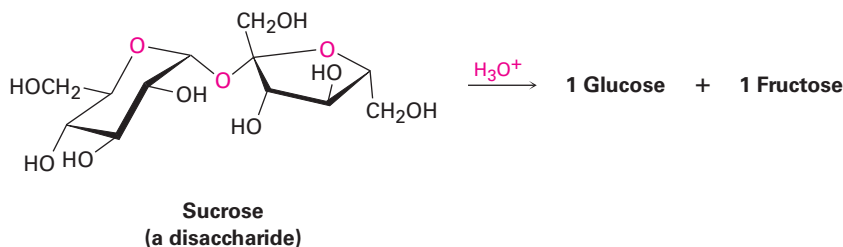
Carbohydrates are synthesized by green plants during photosynthesis, a complex process in which sunlight provides the energy to convert CO_2 and H_2O into glucose plus oxygen. Many molecules of glucose are then chemically linked for storage by the plant in the form of either cellulose or starch. It has been estimated that more than 50% of the dry weight of the earth's biomass—all plants and animals—consists of glucose polymers. When eaten and metabolized, carbohydrates then provide animals with a source of readily available energy. Thus, carbohydrates act as the chemical intermediaries by which solar energy is stored and used to support life.



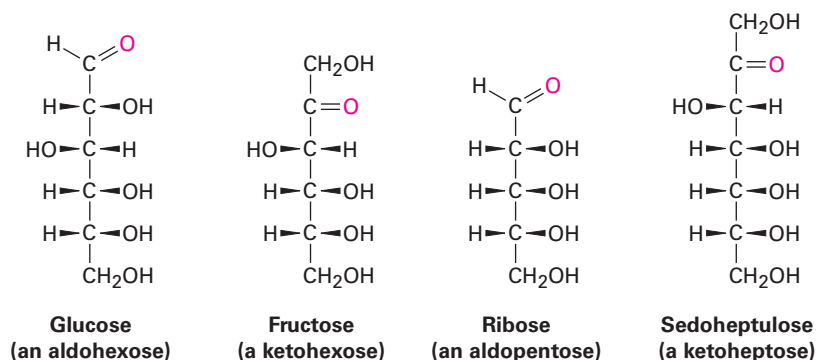
Because humans and most other mammals lack the enzymes needed for digestion of cellulose, they require starch as their dietary source of carbohydrates. Grazing animals such as cows, however, have microorganisms in their first stomach that are able to digest cellulose. The energy stored in cellulose is thus moved along the biological food chain when these ruminants eat grass and are themselves used for food.

21-1 Classifying Carbohydrates

Carbohydrates are generally classed as either simple or complex. **Simple sugars**, or **monosaccharides**, are carbohydrates like glucose and fructose that can't be converted into smaller sugars by hydrolysis. **Complex carbohydrates** are made of two or more simple sugars linked together by acetal bonds (Section 14-8). Sucrose (table sugar), for instance, is made up of one glucose linked to one fructose. Similarly, cellulose is made up of several thousand glucose units linked together. Enzyme-catalyzed hydrolysis of a complex carbohydrate breaks it down into its constituent monosaccharides.

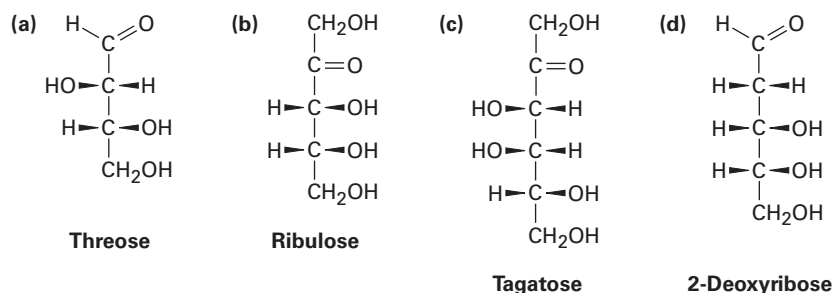


Monosaccharides are further classified as either **aldoses** or **ketoses**. The *-ose* suffix designates a carbohydrate, and the *aldo-* and *keto-* prefixes identify the kind of carbonyl group in the molecule, whether aldehyde or ketone. The number of carbon atoms in the monosaccharide is indicated by the appropriate numerical prefix *tri-*, *tetr-*, *pent-*, *hex-*, and so forth, in the name. Thus, glucose is an aldohexose, a six-carbon aldehyde sugar; fructose is a ketohexose, a six-carbon keto sugar; ribose is an aldopentose, a five-carbon aldehyde sugar; and sedoheptulose is a ketoheptose, a seven-carbon keto sugar. Most of the common simple sugars are either pentoses or hexoses.



PROBLEM 21.1

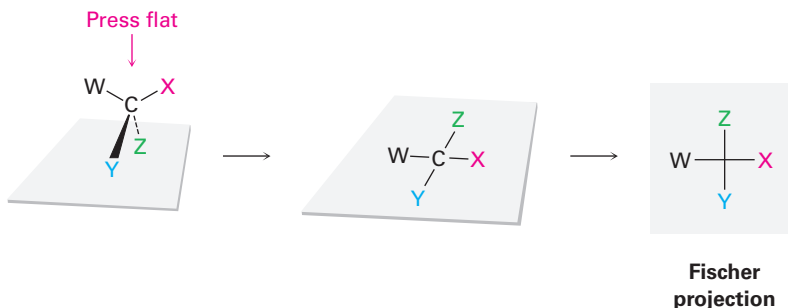
Classify each of the following monosaccharides:



21-2 Representing Carbohydrate Stereochemistry: Fischer Projections

Because carbohydrates usually have numerous chirality centers, it was recognized long ago that a quick method for representing their stereochemistry is needed. In 1891, the German chemist Emil Fischer suggested a method based on the projection of a tetrahedral carbon atom onto a flat surface. These **Fischer projections** were soon adopted and are now a common means of representing stereochemistry at chirality centers, particularly in carbohydrate chemistry.

A tetrahedral carbon atom is represented in a Fischer projection by two crossed lines. The horizontal lines represent bonds coming out of the page, and the vertical lines represent bonds going into the page:



For example, (*R*)-glyceraldehyde, the simplest monosaccharide, can be drawn as in **FIGURE 21.1**.

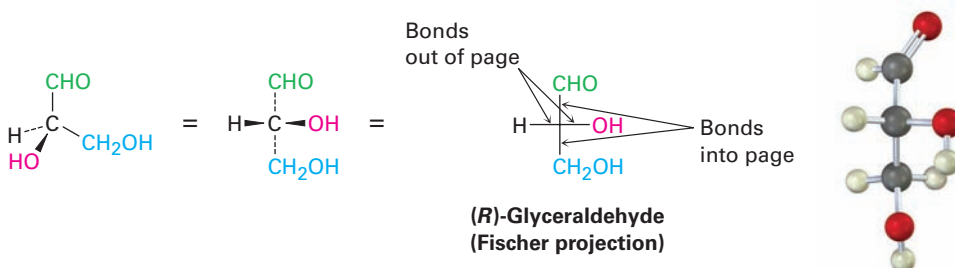
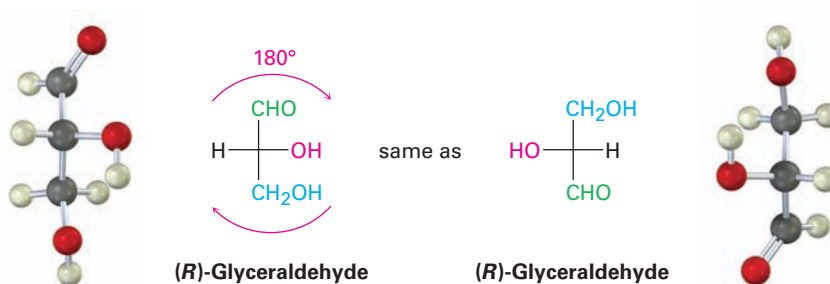


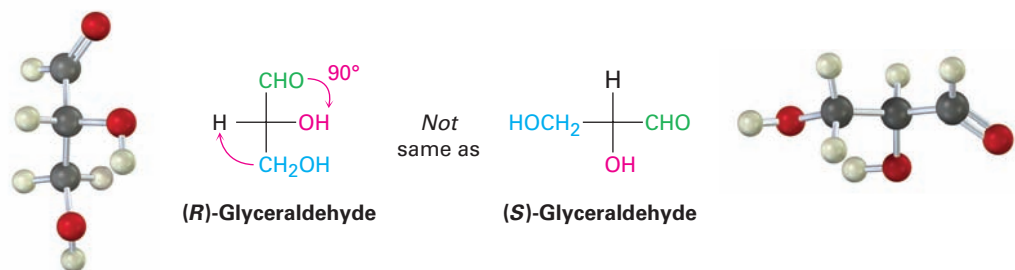
FIGURE 21.1
A Fischer projection of (*R*)-glyceraldehyde.

Because a given chiral molecule can be drawn in many ways, it's sometimes necessary to compare two projections to see if they represent the same or different enantiomers. To test for identity, Fischer projections can be moved around on the paper, but only two kinds of motions are allowed; moving a Fischer projection in any other way inverts its meaning.

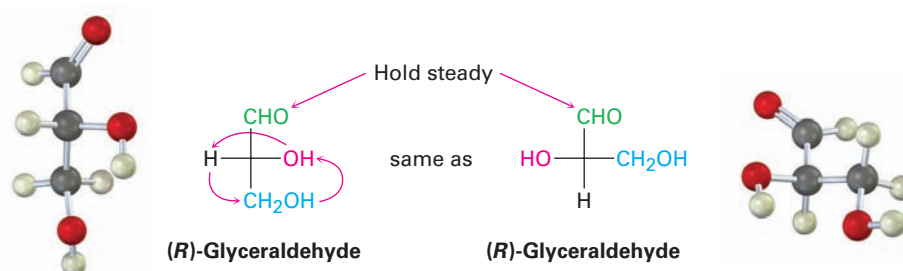
- A Fischer projection can be rotated on the page by 180° , but not by 90° or 270° . Only a 180° rotation maintains the Fischer convention by keeping the same substituent groups going into and coming out of the plane. In the following Fischer projection of (*R*)-glyceraldehyde, for example, the $-H$ and $-OH$ groups come out of the plane both before and after a 180° rotation:



A 90° rotation breaks the Fischer convention by exchanging the groups that go into the plane and those that come out. In the following Fischer projections of (*R*)-glyceraldehyde, the $-H$ and $-OH$ groups come out of the plane before rotation but go into the plane after a 90° rotation. As a result, the rotated projection represents (*S*)-glyceraldehyde:



- A Fischer projection can have one group held steady while the other three rotate in either a clockwise or a counterclockwise direction. The effect is simply to rotate around a single bond, which does not change the stereochemistry.

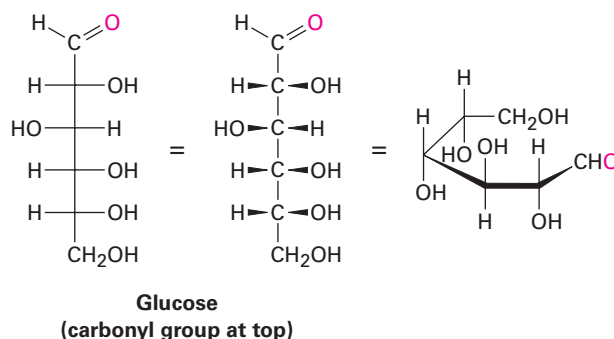


R,S stereochemical designations (Section 5-5) can be assigned to the chirality center in a Fischer projection by following three steps, as shown in Worked Example 21.1.

- Step 1** Rank the four substituents in the usual way (Section 5-5).
- Step 2** Place the group of lowest ranking, usually H, at the top of the Fischer projection by using one of the allowed motions. This means that the lowest-ranked group is oriented back, away from the viewer, as required for assigning configuration.
- Step 3** Determine the direction of rotation $1 \rightarrow 2 \rightarrow 3$ of the remaining three groups, and assign *R* or *S* configuration.

Carbohydrates with more than one chirality center are shown in Fischer projections by stacking the centers on top of one another, with the carbonyl carbon at or near the top. Glucose, for example, has four chirality centers

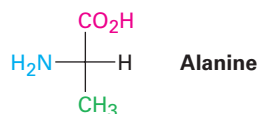
stacked on top of one another in a Fischer projection. Such representations don't, however, give an accurate picture of a molecule's true three-dimensional conformation, which is curled around on itself like a bracelet.



Assigning *R* or *S* Configuration to a Fischer Projection

WORKED EXAMPLE 21.1

Assign *R* or *S* configuration to the following Fischer projection of alanine:



Strategy

Follow the steps listed in the text. (1) Rank the four substituents on the chiral carbon. (2) Manipulate the Fischer projection to place the group of lowest ranking at the top by carrying out one of the allowed motions. (3) Determine the direction 1 → 2 → 3 of the remaining three groups.

Solution

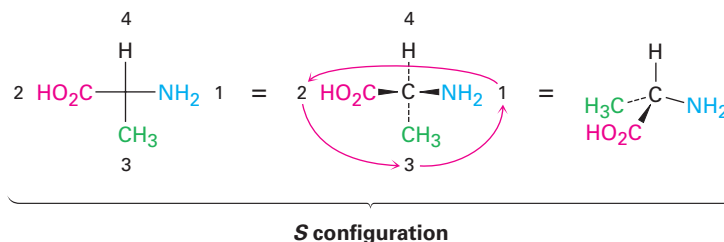
The rankings of the groups are (1) $-\text{NH}_2$, (2) $-\text{CO}_2\text{H}$, (3) $-\text{CH}_3$, and (4) $-\text{H}$. To bring the group of lowest ranking ($-\text{H}$) to the top, we might want to hold the $-\text{CH}_3$ group steady while rotating the other three groups counterclockwise:

Rotate 3 groups
counterclockwise



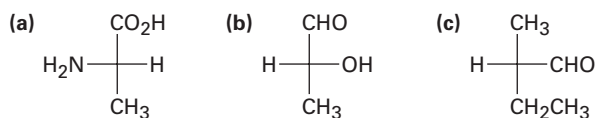
Hold CH_3
steady

Going from first- to second- to third-highest ranking requires a counter-clockwise turn, corresponding to *S* stereochemistry.



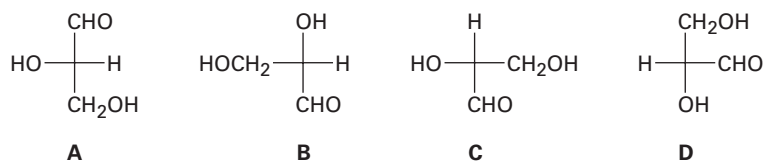
PROBLEM 21.2

Convert the following Fischer projections into tetrahedral representations, and assign *R* or *S* stereochemistry to each:



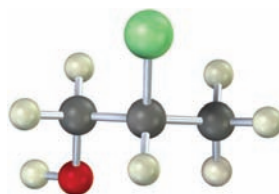
PROBLEM 21.3

Which of the following Fischer projections of glyceraldehyde represent the same enantiomer?



PROBLEM 21.4

Redraw the following molecule as a Fischer projection, and assign *R* or *S* configuration to the chirality center (green = Cl):



21-3 D,L Sugars

Glyceraldehyde, the simplest aldose, has only one chirality center and thus has two enantiomeric (nonidentical mirror-image) forms. Only the dextrorotatory enantiomer occurs naturally, however. That is, a sample of naturally occurring glyceraldehyde placed in a polarimeter rotates plane-polarized light in a clockwise direction, denoted (+). Since (+)-glyceraldehyde has been found to have an *R* configuration at C2, it can be represented in a Fischer projection as shown previously in Figure 21.1. For historical reasons dating back long before the adoption of the *R,S* system, (*R*)-(+)-glyceraldehyde is also referred to as D-glyceraldehyde (D for dextrorotatory). The other enantiomer, (*S*)-(–)-glyceraldehyde, is known as L-glyceraldehyde (L for levorotatory).

Because of the way that monosaccharides are biosynthesized in nature, glucose, fructose, and most other naturally occurring monosaccharides have the same *R* stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the hydroxyl group at the bottom chirality center pointing to the right (FIGURE 21.2). Such compounds are referred to as **D sugars**.

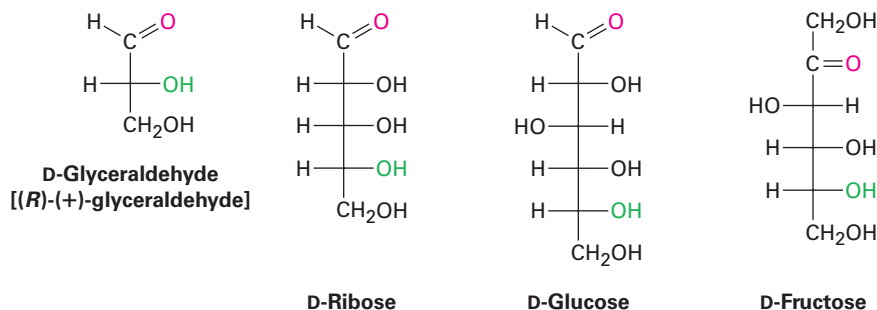
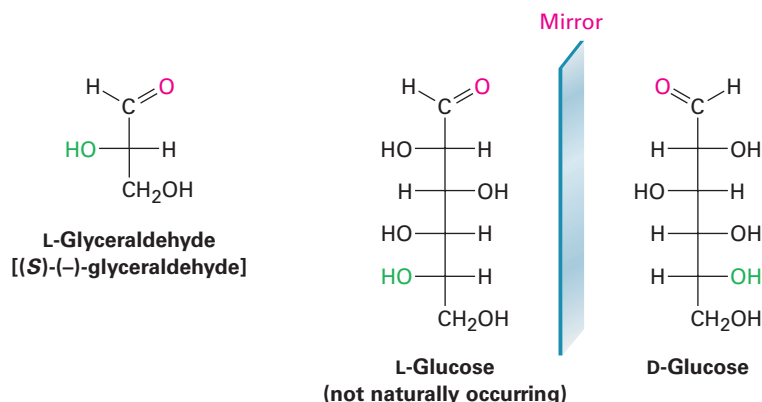


FIGURE 21.2 Some naturally occurring **D sugars**. The –OH group at the chirality center farthest from the carbonyl group has the same configuration as (*R*)-(+)-glyceraldehyde and points toward the right in Fischer projections.

In contrast with **D sugars**, **L sugars** have an *S* configuration at the lowest chirality center, with the bottom –OH group pointing to the left in Fischer projections. Thus, an L sugar is the mirror-image (enantiomer) of the corresponding D sugar and has the opposite configuration at all chirality centers.

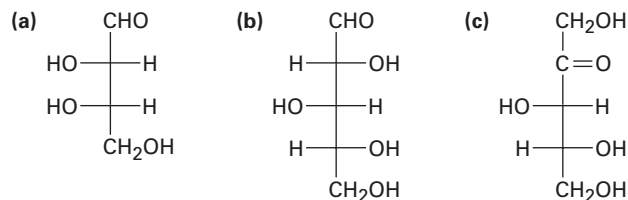


Note that the **D** and **L** notations have no relation to the direction in which a given sugar rotates plane-polarized light. A **D** sugar can be either dextrorotatory or levorotatory. The prefix **D** indicates only that the –OH group at the lowest chirality center has *R* stereochemistry and points to the right when the

molecule is drawn in the standard way in a Fischer projection. Note also that the D,L system of carbohydrate nomenclature describes the configuration at only one chirality center and says nothing about the configuration of other chirality centers that may be present.

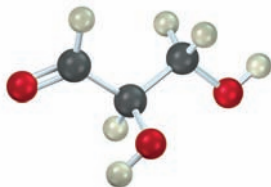
PROBLEM 21.5

Assign *R* or *S* configuration to each chirality center in the following monosaccharides, and tell whether each is a D sugar or an L sugar:



PROBLEM 21.6

(+)-Arabinose, an aldopentose that is widely distributed in plants, is systematically named (2*R*,3*S*,4*S*)-2,3,4,5-tetrahydroxypentanal. Draw a Fischer projection of (+)-arabinose, and identify it as a D sugar or an L sugar.



PROBLEM 21.7

Draw the adjacent molecular model as a Fischer projection. Does it represent D-glyceraldehyde or L-glyceraldehyde?

21-4 Configurations of the Aldoses

Aldotetroses are four-carbon sugars with two chirality centers. Thus, there are $2^2 = 4$ possible stereoisomeric aldotetroses, or two D,L pairs of enantiomers, named erythrose and threose.

Aldopentoses have three chirality centers and a total of $2^3 = 8$ possible stereoisomers, or four D,L pairs of enantiomers. These four pairs are called ribose, arabinose, xylose, and lyxose. All except lyxose occur widely. D-Ribose is an important constituent of RNA (ribonucleic acid), L-arabinose is found in many plants, and D-xylose is found in both plants and animals.

Aldohexoses have four chirality centers and a total of $2^4 = 16$ possible stereoisomers, or eight D,L pairs of enantiomers. The names of the eight are allose, altrose, glucose, mannose, gulose, idose, galactose, and talose. Only D-glucose, from starch and cellulose, and D-galactose, from gums and fruit pectins, are widely distributed in nature. D-Mannose and D-talose also occur naturally but in lesser abundance.

Fischer projections of the four-, five-, and six-carbon D aldoses are shown in **FIGURE 21.3**. Starting with D-glyceraldehyde, we can imagine constructing the two D aldotetroses by inserting a new chirality center just below the aldehyde carbon. Each of the two D aldotetroses then leads to two D aldopentoses (four total), and each of the four D aldopentoses leads to two D aldohexoses (eight total). In addition, each of the D aldoses in Figure 21.3 has a mirror-image L enantiomer, which is not shown.

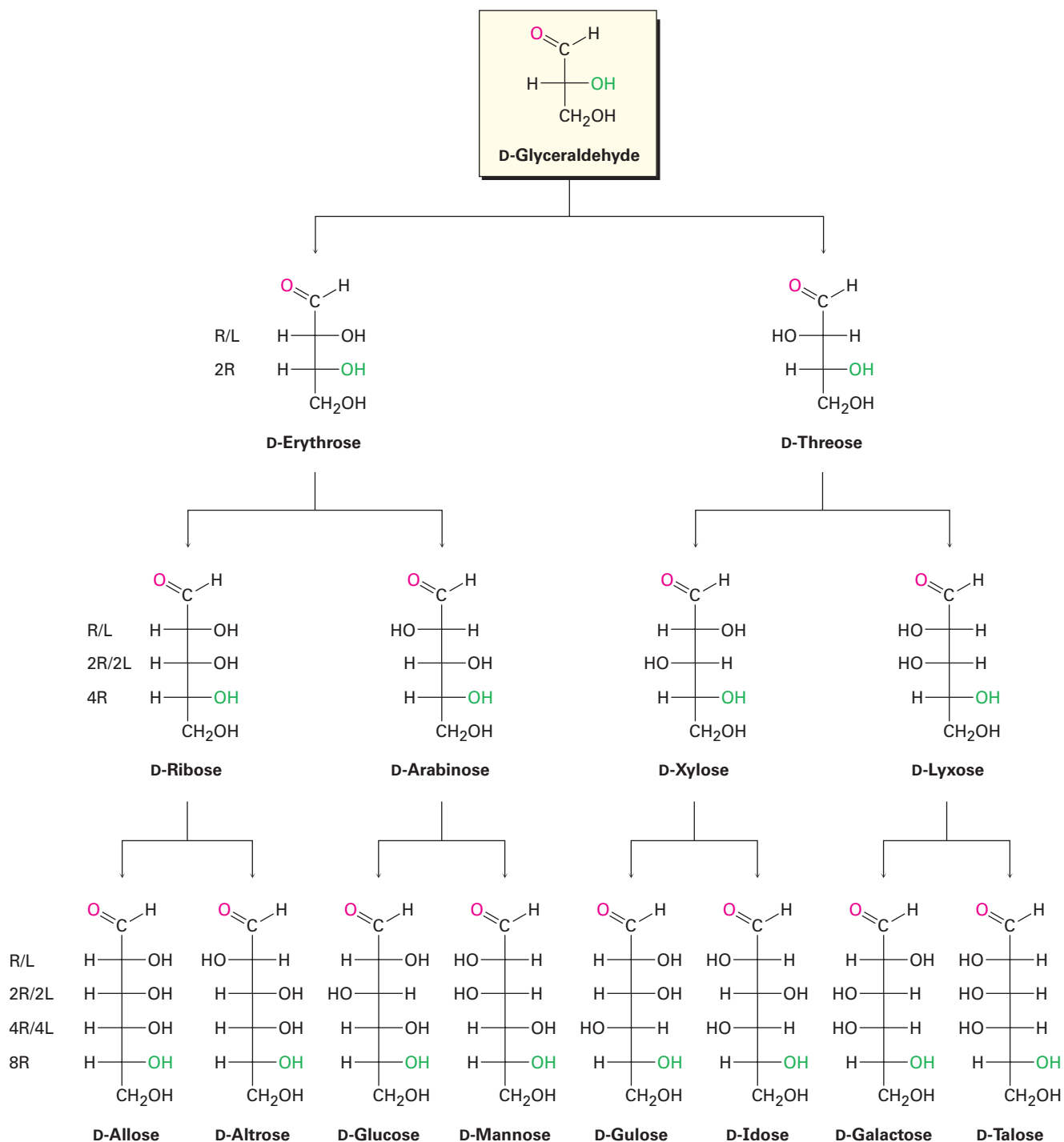


FIGURE 21.3 Configurations of D-aldoses. The structures are arranged from left to right so that the $-\text{OH}$ groups on C2 alternate right/left (R/L) in going across a series. Similarly, the $-\text{OH}$ groups at C3 alternate two right/two left (2R/2L), the $-\text{OH}$ groups at C4 alternate 4R/4L, and the $-\text{OH}$ groups at C5 are to the right in all eight (8R). Each D-aldose has a mirror-image L-enantiomer that is not shown.

The following procedure might help if you need to remember the names and structures of the eight D aldohexoses:

- Step 1** Set up eight Fischer projections with the $-\text{CHO}$ group on top and the $-\text{CH}_2\text{OH}$ group at the bottom.
- Step 2** At C5, place all eight $-\text{OH}$ groups to the right (D series).
- Step 3** At C4, alternate four $-\text{OH}$ groups to the right and four to the left.
- Step 4** At C3, alternate two $-\text{OH}$ groups to the right, two to the left.
- Step 5** At C2, alternate $-\text{OH}$ groups right, left, right, left.
- Step 6** Name the eight isomers using the mnemonic “**All alchemists gladly make gum in gallon tanks.**”

The structures of the four D aldopentoses can be generated in a similar way and named by the mnemonic suggested by a Cornell University undergraduate: “**Ribs are extra lean.**”

WORKED EXAMPLE 21.2

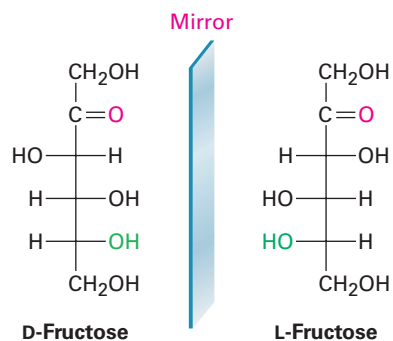
Drawing a Fischer Projection

Draw a Fischer projection of L-fructose.

Strategy

Because L-fructose is the enantiomer of D-fructose, look at the structure of D-fructose and reverse the configuration at each chirality center.

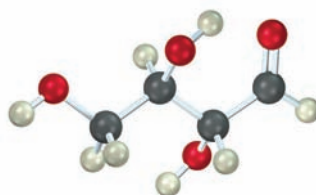
Solution



WORKED EXAMPLE 21.3

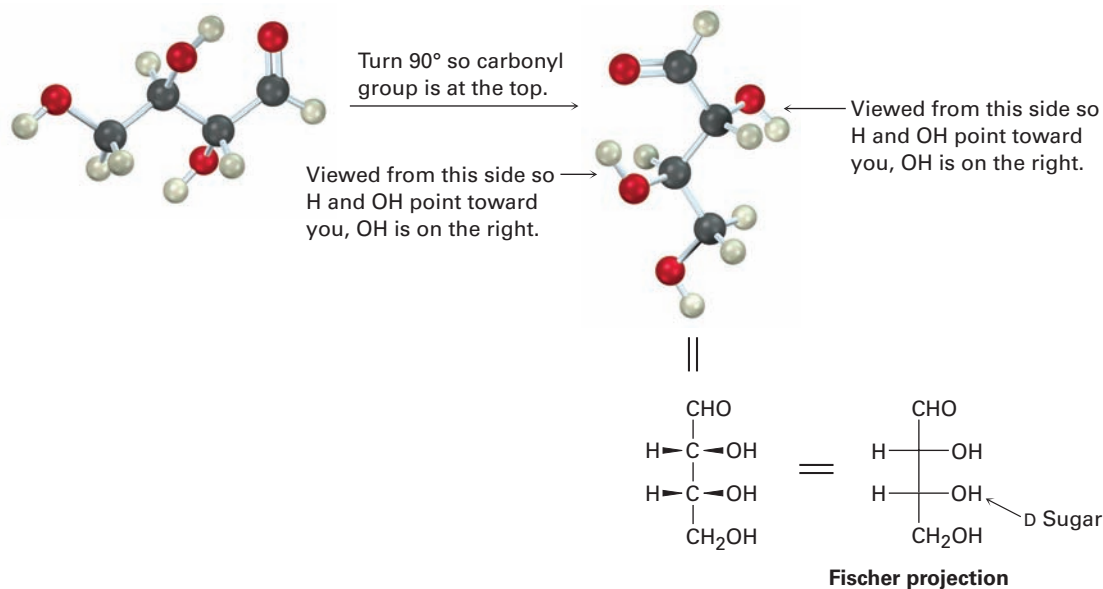
Drawing a Fischer Projection of a Molecular Model

Draw the following aldotetrose as a Fischer projection, and identify it as a D sugar or an L sugar:



Strategy

The Fischer projection of a monosaccharide is drawn vertically, with the carbonyl group at or near the top and the $-\text{CH}_2\text{OH}$ group at the bottom. The interior $-\text{H}$ and $-\text{OH}$ are drawn to the sides, pointing up out of the page toward the viewer.

Solution**PROBLEM 21.8**

Only the D sugars are shown in Figure 21.3. Draw Fischer projections for the following L sugars:

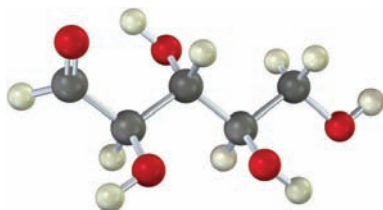
- (a) L-Xylose (b) L-Galactose (c) L-Allose

PROBLEM 21.9

How many aldoheptoses are there? How many are D sugars, and how many are L sugars?

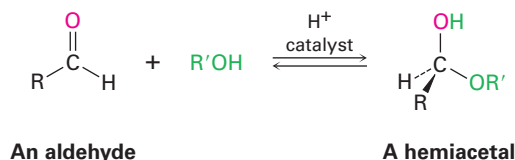
PROBLEM 21.10

The following model is that of an aldopentose. Draw a Fischer projection of the sugar, name it, and identify it as a D sugar or an L sugar.



21-5 Cyclic Structures of Monosaccharides: Anomers

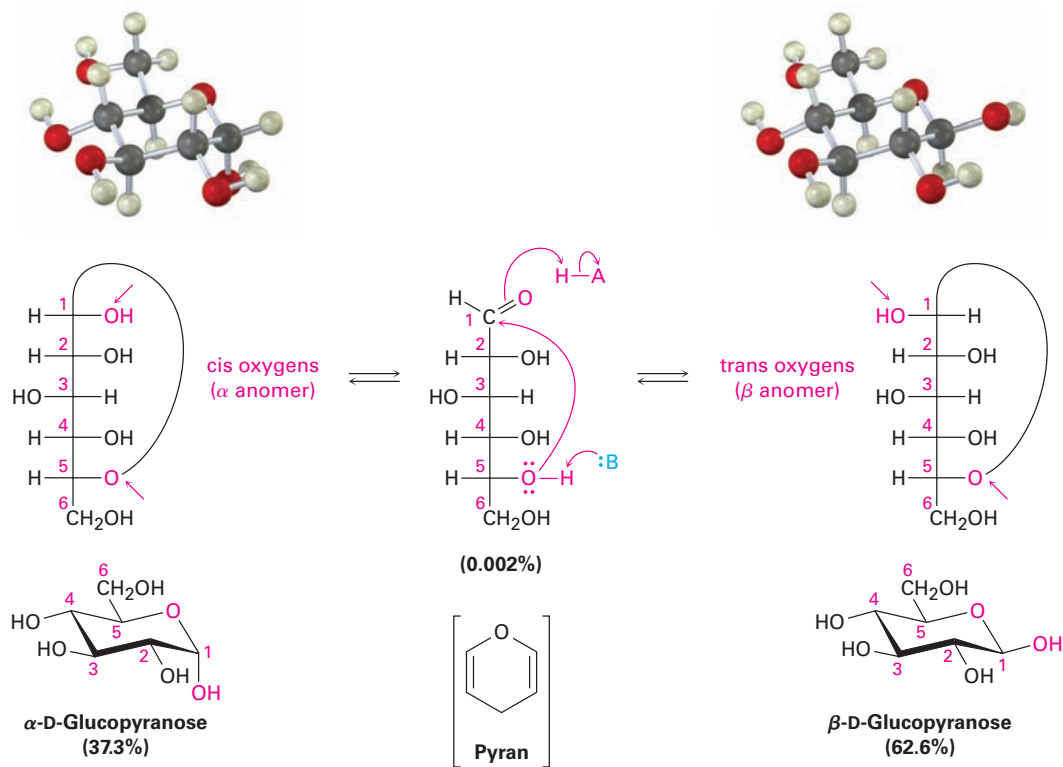
We said in Section 14-8 that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals:



If the carbonyl and the hydroxyl group are in the same molecule, an intramolecular nucleophilic addition can take place, leading to the formation of a cyclic hemiacetal. Five- and six-membered cyclic hemiacetals are relatively strain-free and particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms. Glucose, for instance, exists in aqueous solution primarily in the 6-membered, **pyranose** form resulting from intramolecular nucleophilic addition of the –OH group at C5 to the C1 carbonyl group (FIGURE 21.4). The word *pyranose* is derived from *pyran*, the name of the unsaturated six-membered cyclic ether.

Like cyclohexane rings (Section 4-6), pyranose rings have a chairlike geometry with axial and equatorial substituents. By convention, the rings are usually drawn by placing the hemiacetal oxygen atom at the right rear, as shown in Figure 21.4. Note that an –OH group on the right in a Fischer projection is on the bottom face of the pyranose ring, and an –OH group on the left in a Fischer projection is on the top face of the ring. For D sugars, the terminal –CH₂OH group is on the top of the ring, whereas for L sugars, the –CH₂OH group is on the bottom.

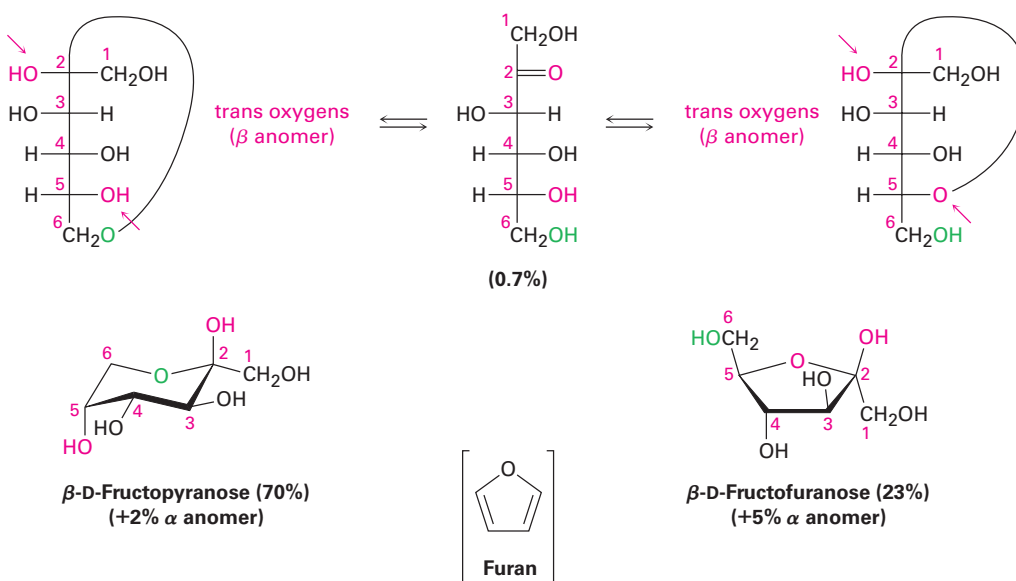
FIGURE 21.4 Glucose in its cyclic pyranose forms. As explained in the text, two anomers are formed by cyclization of glucose. The molecule whose newly formed –OH group at C1 is cis to the oxygen atom on the lowest chirality center (C5) in a Fischer projection is the α anomer. The molecule whose newly formed –OH group is trans to the oxygen atom on the lowest chirality center in a Fischer projection is the β anomer.



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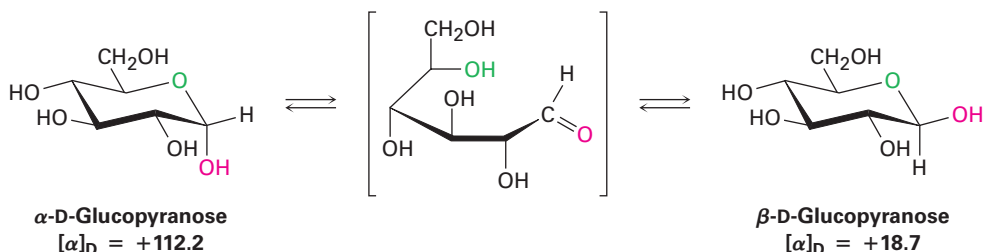
When an open-chain monosaccharide cyclizes to a pyranose form, a new chirality center is generated at the former carbonyl carbon and two diastereomers, called **anomers**, are produced. The hemiacetal carbon atom is referred to as the **anomeric center**. For example, glucose cyclizes reversibly in aqueous solution to a 37:63 mixture of two anomers (Figure 21.4). The compound with its newly generated -OH group at C1 cis to the -OH at the lowest chirality center in a Fischer projection is called the **α anomer** and has the full name α -D-glucopyranose. The compound with its newly generated -OH group trans to the -OH at the lowest chirality center in a Fischer projection is called the **β anomer** and has the full name β -D-glucopyranose. Note that in β -D-glucopyranose, all the substituents on the ring are equatorial. Thus, β -D-glucopyranose is the least sterically crowded and most stable of the eight D aldohexoses.

Some monosaccharides also exist in a 5-membered cyclic hemiacetal form called a **furanose**. D-Fructose, for instance, exists in water solution as 70% β -pyranose, 2% α -pyranose, 0.7% open-chain, 23% β -furanose, and 5% α -furanose. The pyranose form results from addition of the -OH at C6 to the carbonyl group, while the furanose form results from addition of the -OH at C5 to the carbonyl group (**FIGURE 21.5**).



Both anomers of D-glucopyranose can be crystallized and purified. Pure α -D-glucopyranose has a melting point of 146 °C and a specific rotation $[\alpha]_D = +112.2$; pure β -D-glucopyranose has a melting point of 148–155 °C and a specific rotation $[\alpha]_D = +18.7$. When a sample of either pure anomer is dissolved in water, however, its optical rotation slowly changes until it reaches a constant value of +52.6. That is, the specific rotation of the α -anomer solution decreases from +112.2 to +52.6, and the specific rotation of the β -anomer solution increases from +18.7 to +52.6. Called **mutarotation**, this change in optical rotation is due to the slow interconversion of the pure anomers to give a 37:63 equilibrium mixture.

Mutarotation occurs by a reversible ring-opening of each anomer to the open-chain aldehyde, followed by reclosure. Although the equilibration is slow at neutral pH, it is catalyzed by both acid and base.



WORKED EXAMPLE 21.4

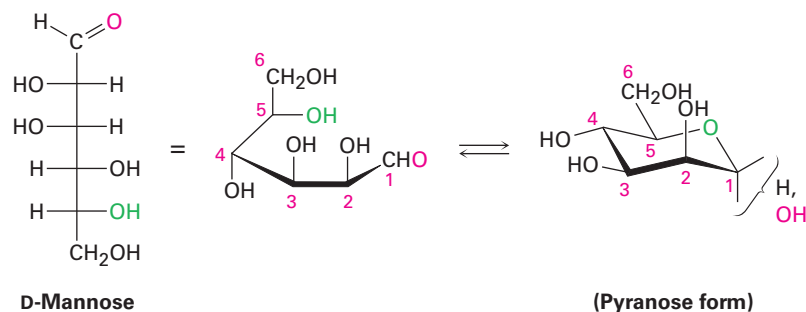
Drawing the Chair Conformation of an Aldohexose

D-Mannose differs from D-glucose in its stereochemistry at C2. Draw D-mannose in its chairlike pyranose form.

Strategy

First draw a Fischer projection of D-mannose. Then, lay it on its side and curl it around so that the $-\text{CHO}$ group (C1) is toward the right front and the $-\text{CH}_2\text{OH}$ group (C6) is toward the left rear. Now, connect the $-\text{OH}$ at C5 to the C1 carbonyl group to form the pyranose ring. In drawing the chair form, raise the leftmost carbon (C4) up and drop the rightmost carbon (C1) down.

Solution



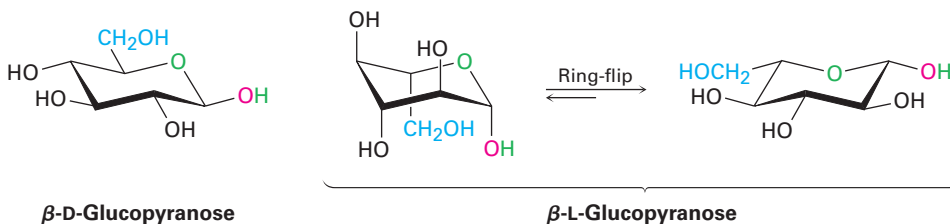
WORKED EXAMPLE 21.5

Drawing the Chair Conformation of a Pyranose

Draw β -L-glucopyranose in its more stable chair conformation.

Strategy

It's probably easiest to begin by drawing the chair conformation of β -D-glucopyranose. Then draw its mirror-image L enantiomer by changing the stereochemistry at every position on the ring, and carry out a ring-flip to give the more stable chair conformation. Note that the $-\text{CH}_2\text{OH}$ group is on the bottom face of the ring in the L enantiomer as is the anomeric $-\text{OH}$.

Solution**PROBLEM 21.11**

Ribose exists largely in a furanose form, produced by addition of the C4 –OH group to the C1 aldehyde. Draw D-ribose in its furanose form.

PROBLEM 21.12

Figure 21.5 shows only the β -pyranose and β -furanose anomers of D-fructose. Draw the α -pyranose and α -furanose anomers.

PROBLEM 21.13

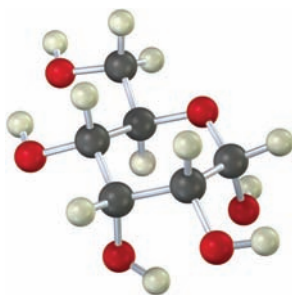
Draw β -D-galactopyranose and β -D-mannopyranose in their more stable chair conformations. Label each ring substituent as either axial or equatorial. Which would you expect to be more stable, galactose or mannose?

PROBLEM 21.14

Draw β -L-galactopyranose in its more stable chair conformation, and label the substituents as either axial or equatorial.

PROBLEM 21.15

Identify the following monosaccharide, write its full name, and draw its open-chain form in Fischer projection:



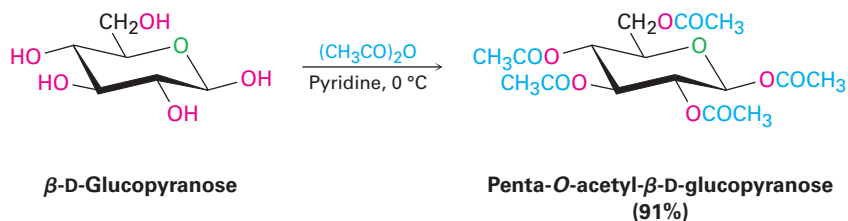
21-6 Reactions of Monosaccharides

Because monosaccharides contain only two kinds of functional groups, hydroxyls and carbonyls, most of the chemistry of monosaccharides is the familiar chemistry of these two groups. As we've seen, alcohols can be converted to esters and ethers and can be oxidized; carbonyl compounds can react with nucleophiles and can be reduced.

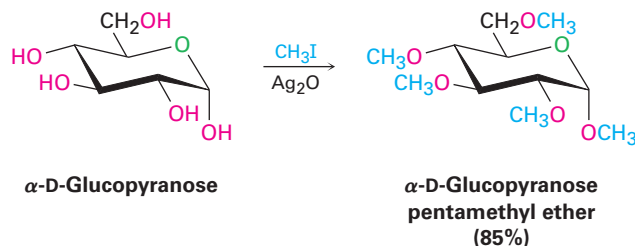
Ester and Ether Formation

Monosaccharides behave as simple alcohols in much of their chemistry. For example, carbohydrate -OH groups can be converted into esters and ethers, which are often easier to work with than the free sugars. Because of their many hydroxyl groups, monosaccharides are usually soluble in water but insoluble in organic solvents such as ether. They are also difficult to purify and have a tendency to form syrups rather than crystals when water is removed. Ester and ether derivatives, however, are soluble in organic solvents and are easily purified and crystallized.

Esterification is normally carried out by treating the carbohydrate with an acid chloride or acid anhydride in the presence of a base (Sections 16-4 and 16-5). All the -OH groups react, including the anomeric one. For example, β -D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.

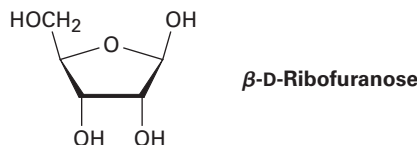


Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base—the Williamson ether synthesis (Section 13-9). Standard Williamson conditions using a strong base tend to degrade sensitive sugar molecules, but silver oxide works well as a mild base and gives high yields of ethers. For example, α -D-glucopyranose is converted into its penta-methyl ether in 85% yield on reaction with iodomethane and Ag_2O .



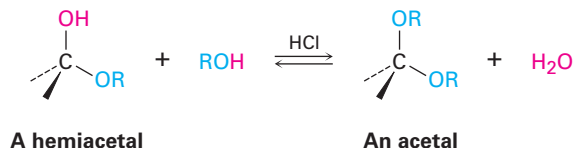
PROBLEM 21.16

Draw the products you would obtain by reaction of β -D-ribofuranose with:
(a) CH_3I , Ag_2O (b) $(\text{CH}_3\text{CO})_2\text{O}$, pyridine

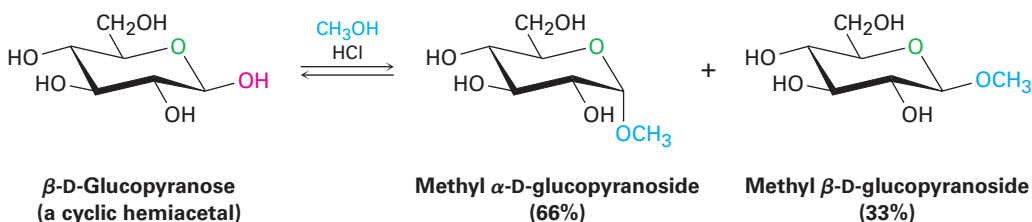


Glycoside Formation

We saw in Section 14-8 that treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal:

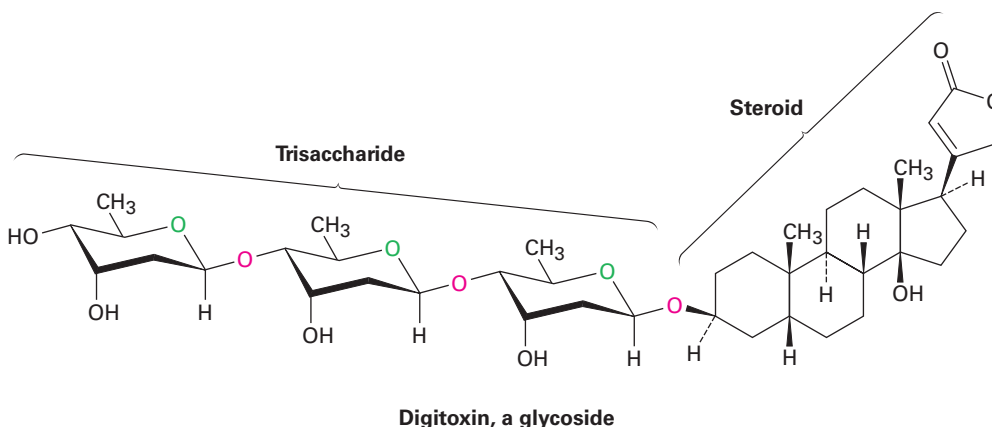


In the same way, treatment of a monosaccharide hemiacetal with an alcohol and an acid catalyst yields an acetal called a **glycoside**, in which the anomeric -OH has been replaced by an -OR group. For example, reaction of β -D-glucopyranose with methanol gives a mixture of α and β methyl D-glucopyranosides. (Note that a *glycoside* is the functional-group name for any sugar, whereas a *glucoside* is a glycoside formed specifically from glucose.)



Glycosides are named by first citing the alkyl group and then replacing the *-ose* ending of the sugar with *-oside*. Like all acetals, glycosides are stable to neutral water. They aren't in equilibrium with an open-chain form, and they don't show mutarotation. They can, however, be hydrolyzed to give back the free monosaccharide plus alcohol on treatment with aqueous acid (Section 14-8).

Glycosides are abundant in nature, and many biologically important molecules contain glycosidic linkages. For example, digitoxin, the active component of the digitalis preparations used for treatment of heart disease, is a glycoside consisting of a steroid alcohol linked to a trisaccharide. Note also that the three sugars are linked to one another by glycoside bonds.

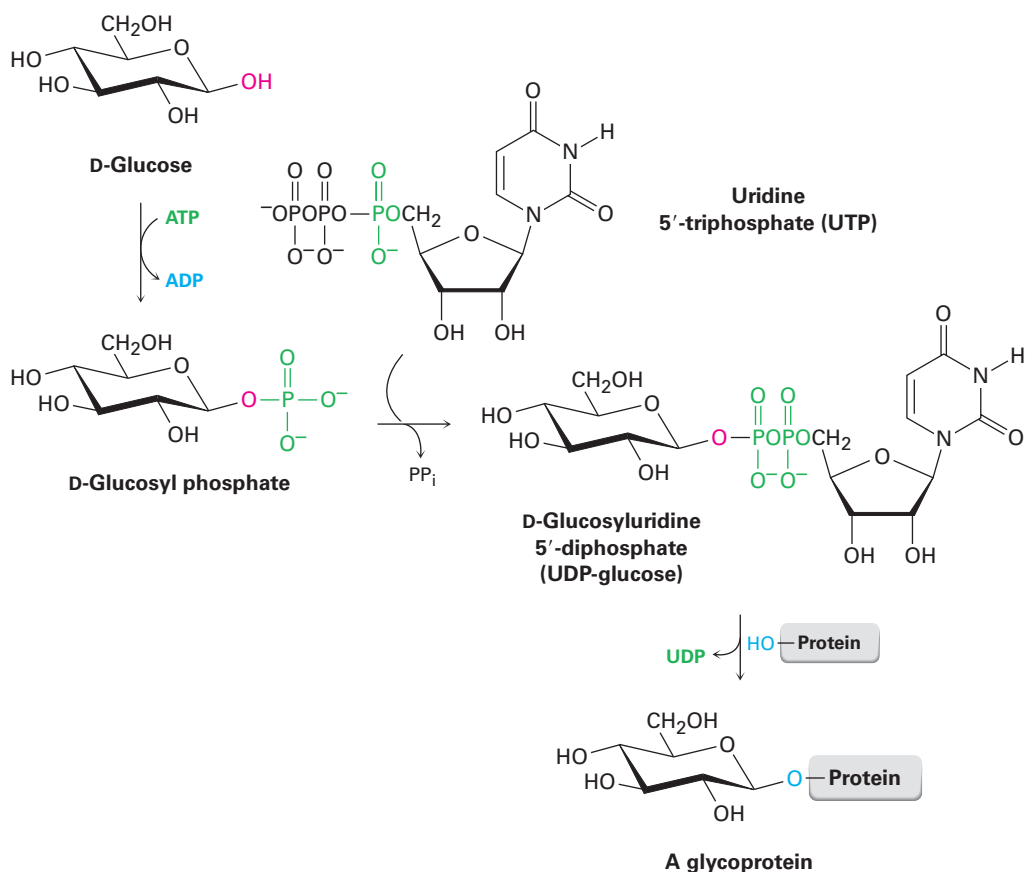


Biological Ester Formation: Phosphorylation

In living organisms, carbohydrates occur not only in the free form but also linked through their anomeric center to other molecules such as lipids (glycolipids) or proteins (glycoproteins). Collectively called *glycoconjugates*, these sugar-linked molecules are components of cell walls and are crucial to the mechanism by which different cell types recognize one another.

Glycoconjugate formation occurs by reaction of the lipid or protein with a glycosyl nucleoside diphosphate. This diphosphate is itself formed by initial reaction of a monosaccharide with adenosine triphosphate (ATP) to give a glycosyl monophosphate, followed by reaction with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. (We'll see the structures of nucleoside phosphates in Section 24-1.) The purpose of the phosphorylation is to activate the anomeric $-OH$ group of the sugar and make it a better leaving group in a nucleophilic substitution reaction with a protein or lipid (FIGURE 21.6).

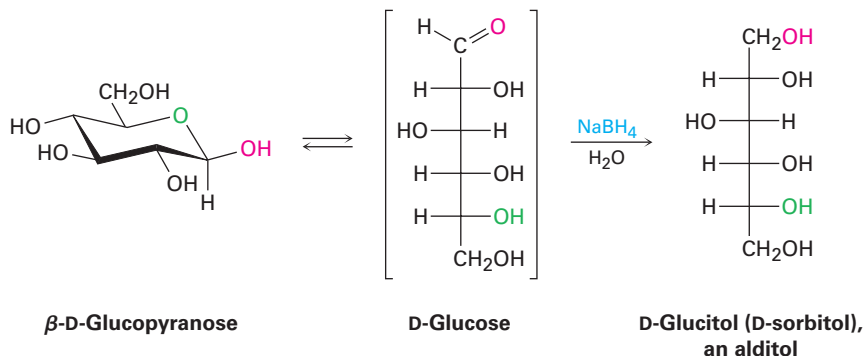
FIGURE 21.6 Glyco-protein formation. The reaction sequence occurs by initial phosphorylation of the starting carbohydrate with ATP to a glycosyl monophosphate followed by reaction with UTP to form a glycosyl uridine 5'-diphosphate. Nucleophilic substitution by an $-OH$ (or $-NH_2$) group on a protein then gives the glycoprotein.



Reduction of Monosaccharides

Treatment of an aldose or ketose with $NaBH_4$ reduces it to a polyalcohol called an **alditol**. The reduction occurs by reaction of the open-chain form present in the aldehyde/ketone \rightleftharpoons hemiacetal equilibrium. Although only a small amount of the open-chain form is present at any given time, that small

amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction.



D-Glucitol, the alditol produced by reduction of D-glucose, is itself a naturally occurring substance found in many fruits and berries. It is used under the name D-sorbitol as a sweetener and sugar substitute in many foods.

PROBLEM 21.17

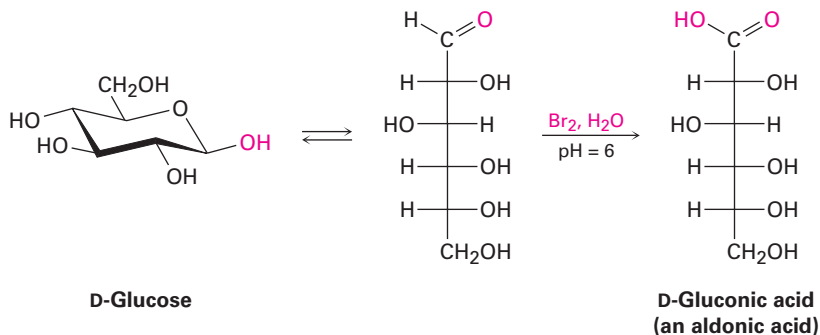
Reduction of D-glucose leads to an optically active alditol (D-glucitol), whereas reduction of D-galactose leads to an optically inactive alditol. Explain.

PROBLEM 21.18

Reduction of L-gulose with NaBH_4 leads to the same alditol (D-glucitol) as reduction of D-glucose. Explain.

Oxidation of Monosaccharides

Like other aldehydes, aldoses are easily oxidized to yield the corresponding carboxylic acids, called **aldonic acids**. A buffered solution of aqueous Br_2 is often used for the purpose.



Historically, the oxidation of an aldose with either Ag^+ in aqueous ammonia (Tollens' reagent) or Cu^{2+} with aqueous sodium citrate (Benedict's reagent) formed the basis of simple tests for what are called **reducing sugars**. (*Reducing* because the aldose reduces the metal oxidizing agent.) Some simple diabetes self-test kits sold in drugstores still use Benedict's reagent to detect glucose in urine, although more modern methods have largely replaced the chemical test.

All aldoses are reducing sugars because they contain an aldehyde group, but some ketoses are reducing sugars as well. Fructose reduces Tollens' reagent, for example, even though it contains no aldehyde group. Reduction occurs because fructose is readily isomerized to a mixture of aldoses (glucose and mannose) in basic solution by a series of keto–enol tautomeric shifts (Section 17-1), as shown in **FIGURE 21.7**. Glycosides, however, are nonreducing because the acetal group is not hydrolyzed to an aldehyde under basic conditions.

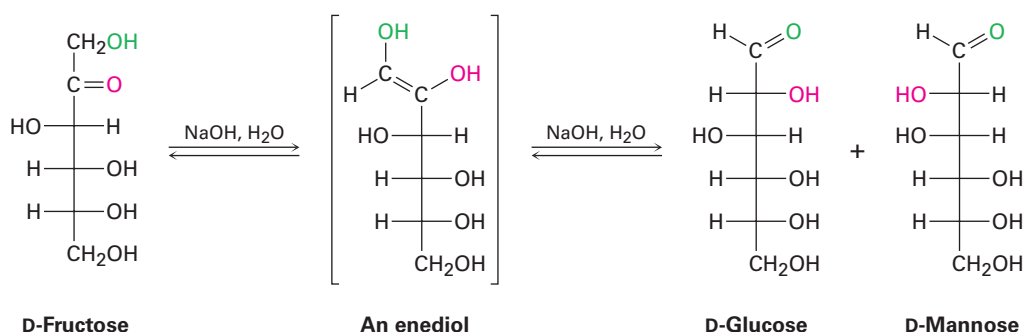
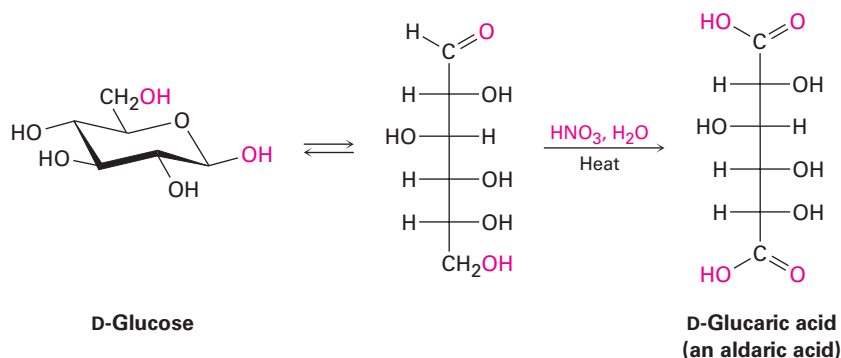


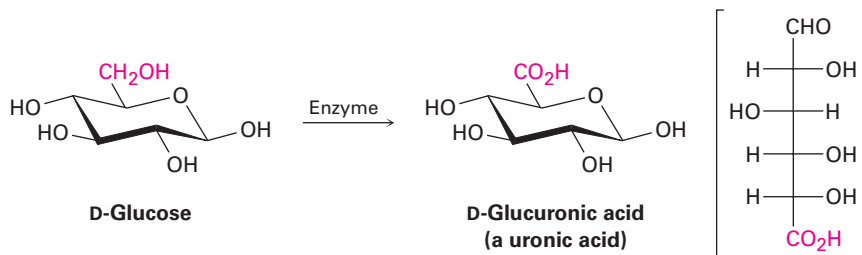
FIGURE 21.7 Fructose, a ketose, is a reducing sugar. It undergoes two base-catalyzed keto–enol tautomerizations that result in conversion to a mixture of aldoses.

If warm dilute HNO_3 (nitric acid) is used as the oxidizing agent, an aldose is oxidized to a dicarboxylic acid called an **aldaric acid**. Both the aldehyde carbonyl and the terminal $-\text{CH}_2\text{OH}$ group are oxidized in this reaction.



Finally, if only the $-\text{CH}_2\text{OH}$ end of the aldose is oxidized without affecting the $-\text{CHO}$ group, the product is a monocarboxylic acid called a **uronic acid**.

The reaction can only be done enzymatically; no chemical reagent is known that can accomplish this selective oxidation in the laboratory.



PROBLEM 21.19

D-Glucose yields an optically active aldaric acid on treatment with HNO_3 , but D-allose yields an optically inactive aldaric acid. Explain.

PROBLEM 21.20

Which of the other six D aldohexoses yield optically active aldaric acids on oxidation, and which yield optically inactive (meso) aldaric acids? (See Problem 21.19.)

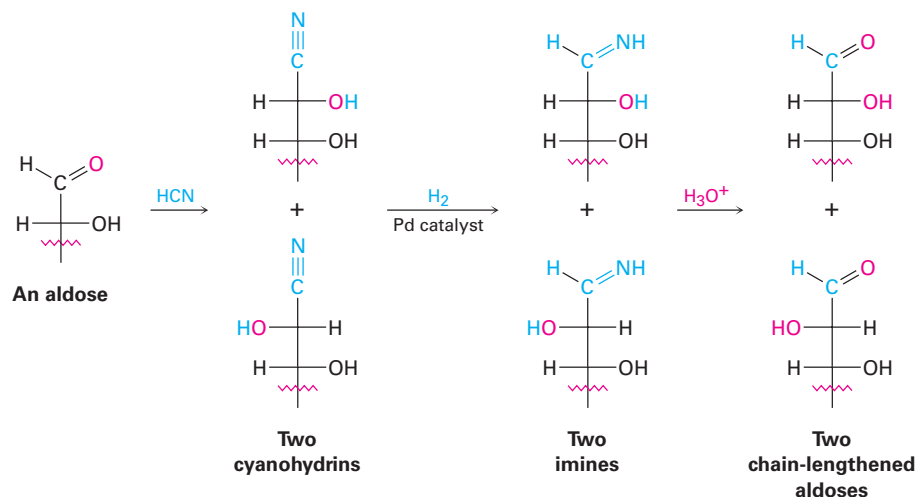
Chain Lengthening: The Kiliani–Fischer Synthesis

Much early activity in carbohydrate chemistry was devoted to unraveling the stereochemical relationships among monosaccharides. One of the most important methods used was the *Kiliani–Fischer synthesis*, which results in the lengthening of an aldose chain by one carbon atom. The C1 aldehyde group of the starting sugar becomes C2 of the chain-lengthened sugar, and a new C1 carbon is added. For example, an aldopentose is converted by the Kiliani–Fischer synthesis into two aldohexoses.

Discovery of the chain-lengthening sequence was initiated by the observation of Heinrich Kiliani in 1886 that an aldose undergoes a nucleophilic addition reaction with HCN to form a *cyanohydrin*—a compound with an $-\text{OH}$ and a $-\text{C}\equiv\text{N}$ attached to the same carbon, $\text{R}_2\text{C}(\text{OH})\text{CN}$. Emil Fischer immediately realized the importance of Kiliani's discovery and devised a method for converting the cyanohydrin nitrile group into an aldehyde.

Fischer's original method for conversion of the nitrile into an aldehyde involved hydrolysis to a carboxylic acid, ring closure to a cyclic ester (lactone), and subsequent reduction. A modern improvement is to reduce the nitrile over a palladium catalyst, yielding an imine intermediate that is hydrolyzed to an aldehyde. Note that the cyanohydrin is formed as a mixture of stereoisomers at the new chirality center, so two new aldoses, differing only in their stereochemistry at C2, result from Kiliani–Fischer synthesis.

Chain extension of D-arabinose, for instance, yields a mixture of D-glucose and D-mannose.



PROBLEM 21.21

What product(s) would you expect from Kiliani–Fischer reaction of D-ribose?

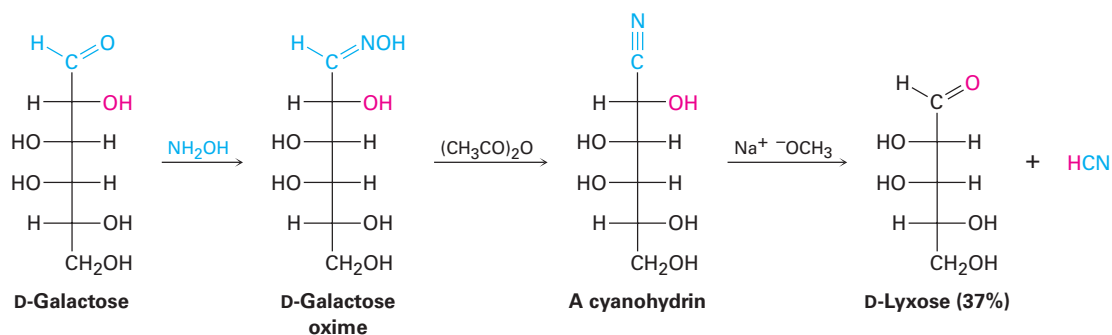
PROBLEM 21.22

What aldopentose would give a mixture of L-gulose and L-idose on Kiliani–Fischer chain extension?

Chain Shortening: The Wohl Degradation

Just as the Kiliani–Fischer synthesis lengthens an aldose chain by one carbon, the *Wohl degradation* shortens an aldose chain by one carbon. The Wohl degradation is almost the exact opposite of the Kiliani–Fischer sequence. That is, the aldose aldehyde carbonyl group is converted into a nitrile and the resulting cyanohydrin loses HCN under basic conditions—the reverse of a nucleophilic addition reaction.

Conversion of the aldehyde into a nitrile is accomplished by treatment of an aldose with hydroxylamine to give a hydroxy imine called an *oxime*, followed by dehydration of the oxime with acetic anhydride. The Wohl degradation does not give particularly high yields of chain-shortened aldoses, but the reaction is general for all aldopentoses and aldohexoses. For example, D-galactose is converted by Wohl degradation into D-lyxose.



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PROBLEM 21.23

Two of the four D aldopentoses yield D-threose on Wohl degradation. What are their structures?

21-7 The Eight Essential Monosaccharides

Humans need to obtain eight monosaccharides for proper functioning. Although all eight can be biosynthesized from simpler precursors if necessary, it's more energetically efficient to obtain them from the diet. The eight are L-fucose (6-deoxy-L-galactose), D-galactose, D-glucose, D-mannose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, D-xylose, and *N*-acetyl-D-neuraminic acid (FIGURE 21.8). All eight are used for the synthesis of the glycoconjugate components of cell walls, and glucose is also the body's primary source of energy.

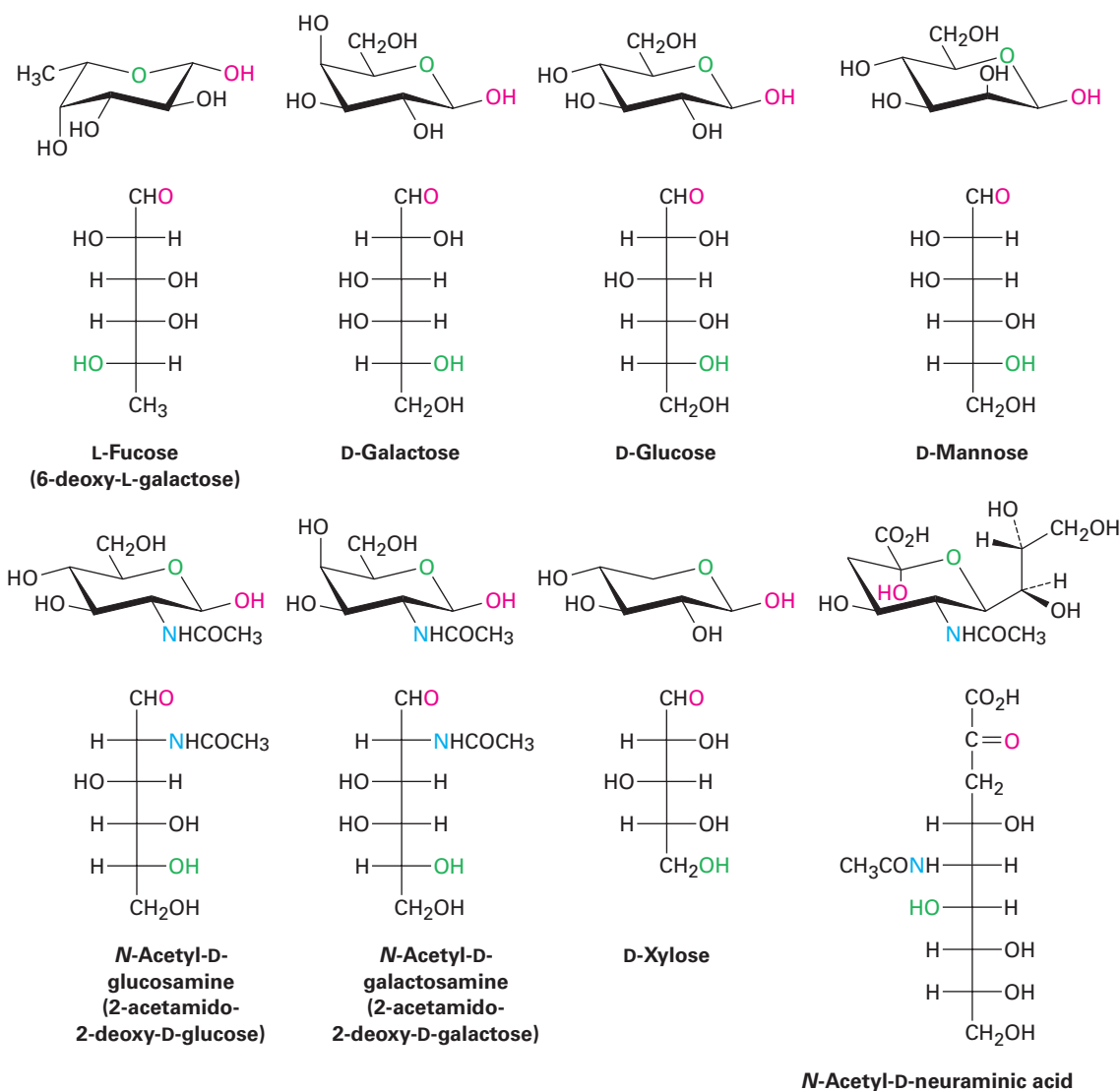


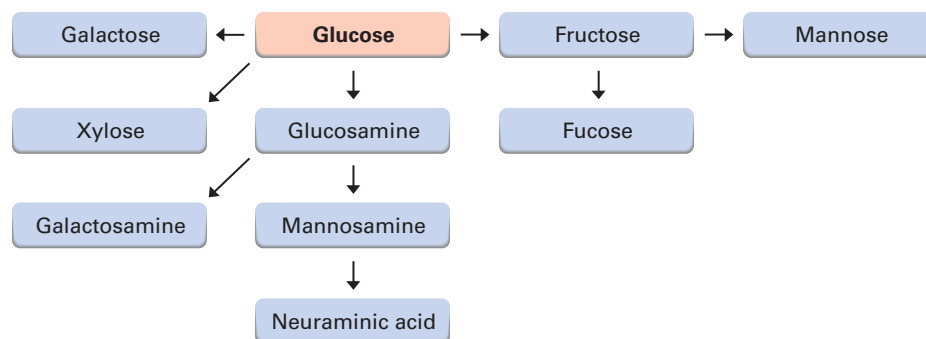
FIGURE 21.8 Structures of the eight monosaccharides essential to humans.

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Of the eight essential monosaccharides, galactose, glucose, and mannose are simple aldohexoses, while xylose is an aldopentose. Fucose is a **deoxy sugar**, meaning that it has an oxygen atom “missing.” That is, an $-OH$ group (the one at C6) is replaced by an $-H$. *N*-Acetylglucosamine and *N*-acetylgalactosamine are amide derivatives of **amino sugars** in which an $-OH$ (the one at C2) is replaced by an $-NH_2$ group. *N*-Acetylneuraminic acid is the parent compound of the sialic acids, a group of more than 30 substances with different modifications, including various oxidations, acetylations, sulfations, and methylations. Note that neuraminic acid has nine carbons and is an aldol reaction product of *N*-acetylmannosamine with pyruvate ($CH_3COCO_2^-$). We'll see in the Chapter 22 *Something Extra* that neuraminic acid is crucially important to the mechanism by which an influenza virus spreads.

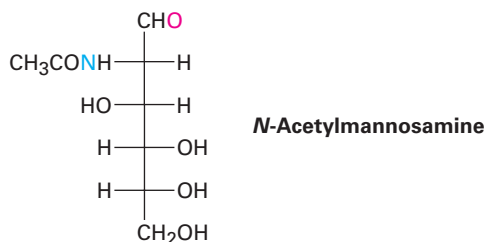
All the essential monosaccharides arise from glucose, by the conversions summarized in **FIGURE 21.9**. We'll not look specifically at these conversions, but might note that Problems 22.19, 22.20, 22.21, and 22.27 at the end of the next chapter lead you through several of the biosynthetic pathways.

FIGURE 21.9 An overview of biosynthetic pathways for the eight essential monosaccharides.



PROBLEM 21.24

Show how *N*-acetylneuraminic acid can arise by an aldol reaction of *N*-acetylmannosamine with pyruvate, $CH_3COCO_2^-$.



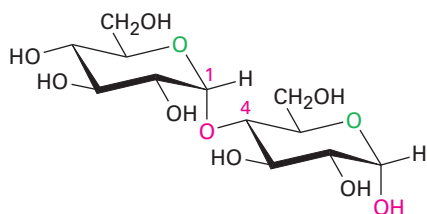
21-8 Disaccharides

We saw in Section 21-6 that reaction of a monosaccharide with an alcohol yields a glycoside, in which the anomeric $-OH$ is replaced by an $-OR$ group. If the alcohol is itself a sugar, the glycosidic product is a **disaccharide**.

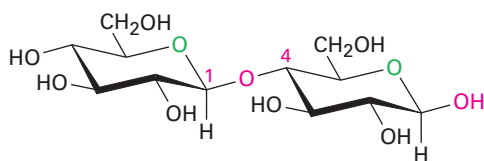
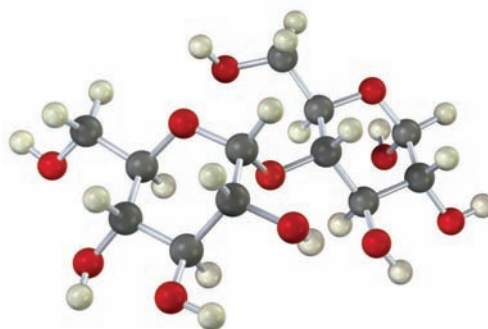
Maltose and Cellobiose

Disaccharides contain a glycosidic acetal bond between the anomeric carbon of one sugar and an $-OH$ group at any position on the other sugar. A glycosidic bond between C1 of the first sugar and the $-OH$ at C4 of the second sugar is particularly common. Such a bond is called a $1 \rightarrow 4$ link.

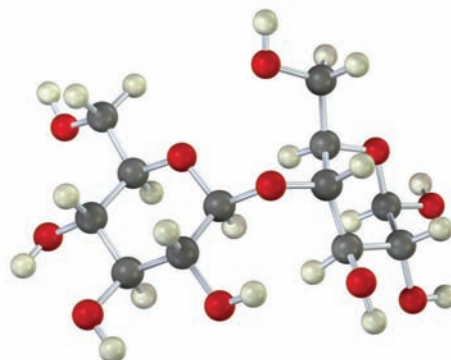
The glycosidic bond to an anomeric carbon can be either α or β . Maltose, the disaccharide obtained by enzyme-catalyzed hydrolysis of starch, consists of two α -D-glucopyranose units joined by an α -(1 \rightarrow 4) glycoside bond. Cellobiose, the disaccharide obtained by partial hydrolysis of cellulose, consists of two β -D-glucopyranose units joined by a β -(1 \rightarrow 4) glycoside bond.



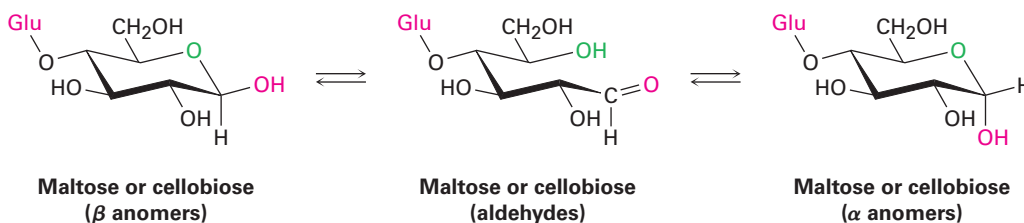
Maltose, an α -(1 \rightarrow 4) glycoside
[α -D-Glucopyranosyl-(1 \rightarrow 4)- α -D-glucopyranose]



Cellobiose, a β -(1 \rightarrow 4) glycoside
[β -D-Glucopyranosyl-(1 \rightarrow 4)- β -D-glucopyranose]



Maltose and cellobiose are both reducing sugars because the anomeric carbons on the right-hand glucopyranose units have hemiacetal groups and are in equilibrium with aldehyde forms. For a similar reason, both maltose and cellobiose show mutarotation of α and β anomers of the glucopyranose unit on the right.



Despite the similarities of their structures, cellobiose and maltose have dramatically different biological properties. Cellobiose can't be digested by humans and can't be fermented by yeast. Maltose, however, is digested without difficulty and is fermented readily.

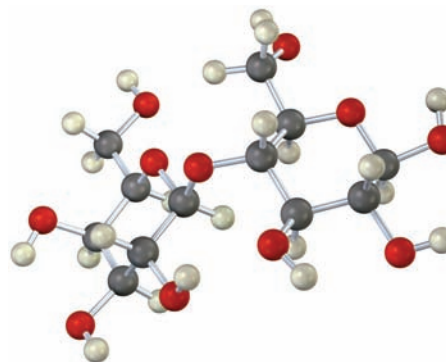
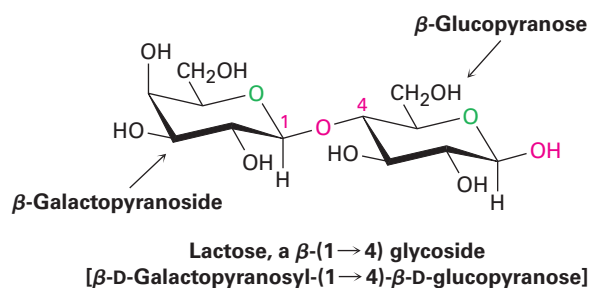
PROBLEM 21.25

Show the product you would obtain from the reaction of cellobiose with the following reagents:

(a) NaBH_4 (b) $\text{Br}_2, \text{H}_2\text{O}$ (c) CH_3COCl , pyridine

Lactose

Lactose is a disaccharide that occurs naturally in both human and cow's milk. It is widely used in baking and in commercial milk formulas for infants. Like maltose and cellobiose, lactose is a reducing sugar. It exhibits mutarotation and is a β -(1 \rightarrow 4) linked glycoside. Unlike maltose and cellobiose, however, lactose contains two different monosaccharides—D-glucose and D-galactose—joined by a β -glycosidic bond between C1 of galactose and C4 of glucose.



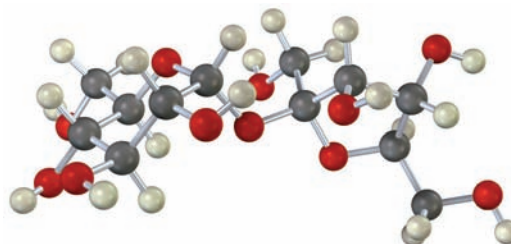
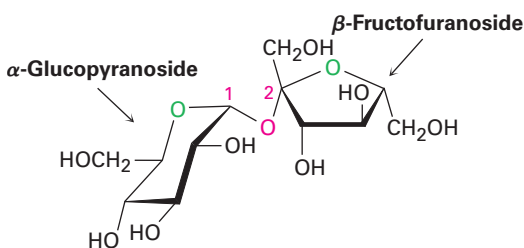
Sucrose

Sucrose, or ordinary table sugar, is probably the most abundant pure organic chemical in the world. Whether from sugar cane (20% sucrose by weight) or sugar beets (15% by weight), and whether raw or refined, all table sugar is sucrose.

Sucrose is a disaccharide that yields 1 equivalent of glucose and 1 equivalent of fructose on hydrolysis. This 1:1 mixture of glucose and fructose is often referred to as *invert sugar* because the sign of optical rotation changes, or inverts, during the hydrolysis of sucrose ($[\alpha]_{\text{D}} = +66.5$) to a glucose/fructose mixture ($[\alpha]_{\text{D}} = -22.0$). Some insects, such as honeybees, have enzymes called invertases that catalyze the sucrose hydrolysis. Honey, in fact, is primarily a mixture of glucose, fructose, and sucrose.

Unlike most other disaccharides, sucrose is not a reducing sugar and does not undergo mutarotation. These observations imply that sucrose is not

a hemiacetal and suggest that glucose and fructose must both be glycosides. This can happen only if the two sugars are joined by a glycoside link between the anomeric carbons of both sugars: C1 of glucose and C2 of fructose.



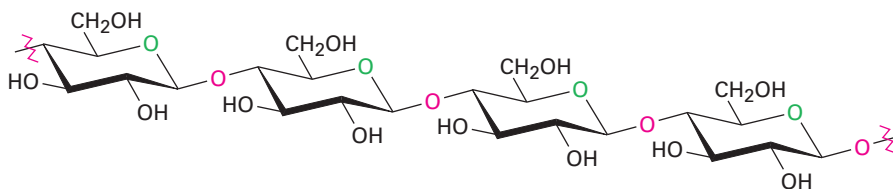
Sucrose, a (1 → 2) glycoside
[α -D-Glucopyranosyl-(1 → 2)- β -D-fructofuranoside]

21-9 Polysaccharides and Their Synthesis

Polysaccharides are complex carbohydrates in which tens, hundreds, or even thousands of simple sugars are linked together through glycoside bonds. Because they have only the one free anomeric –OH group at the end of a very long chain, polysaccharides are not reducing sugars and don't show noticeable mutarotation. Cellulose and starch are the two most widely occurring polysaccharides.

Cellulose

Cellulose consists of several thousand D-glucose units linked by β -(1 → 4) glycoside bonds like those in cellobiose. Different cellulose molecules then interact to form a large aggregate structure held together by hydrogen bonds.

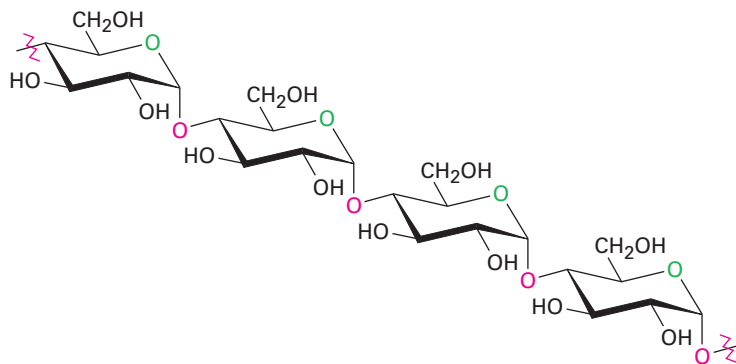


Cellulose, a β -(1 → 4)-D-Glucopyranoside polymer

Nature uses cellulose primarily as a structural material to impart strength and rigidity to plants. Leaves, grasses, and cotton, for instance, are primarily cellulose. Cellulose also serves as raw material for the manufacture of cellulose acetate, known commercially as acetate rayon, and cellulose nitrate, known as guncotton. Guncotton is the major ingredient in smokeless powder, the explosive propellant used in artillery shells and ammunition for firearms.

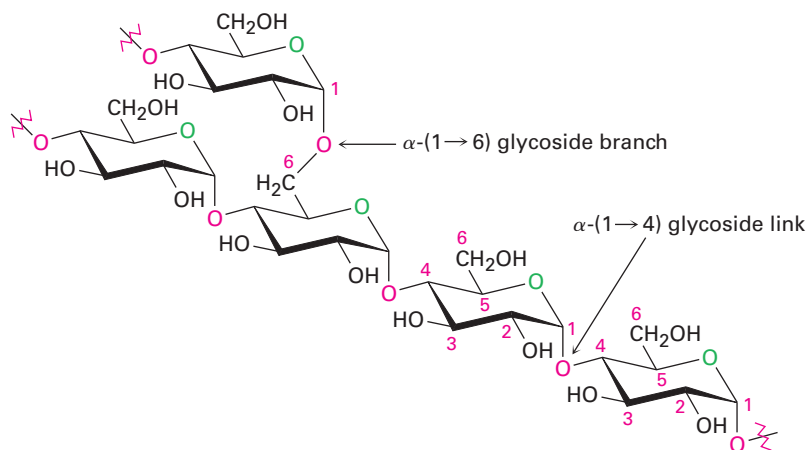
Starch and Glycogen

Potatoes, corn, and cereal grains contain large amounts of *starch*, a polymer of glucose in which the monosaccharide units are linked by α -(1 \rightarrow 4) glycoside bonds like those in maltose. Starch can be separated into two fractions: amylose and amylopectin. Amylose accounts for about 20% by weight of starch and consists of several hundred glucose molecules linked together by α -(1 \rightarrow 4) bonds.



Amylose, an α -(1 \rightarrow 4)-D-Glucopyranoside polymer

Amylopectin accounts for the remaining 80% of starch and is more complex in structure than amylose. Unlike cellulose and amylose, which are linear polymers, amylopectin contains α -(1 \rightarrow 6) glycoside branches approximately every 25 glucose units.



**Amylopectin: α -(1 \rightarrow 4) links
with α -(1 \rightarrow 6) branches**

Starch is digested in the mouth and stomach by α -glycosidases, which catalyze the hydrolysis of glycoside bonds and release individual molecules of glucose. Like most enzymes, α -glycosidases are highly selective in their

action. They hydrolyze only the α -glycoside links in starch and leave the β -glycoside links in cellulose untouched. Thus, humans can digest potatoes and grains but not grass and leaves.

Glycogen is a polysaccharide that serves the same energy storage function in animals that starch serves in plants. Dietary carbohydrates not needed for immediate energy are converted by the body to glycogen for long-term storage. Like the amylopectin found in starch, glycogen contains a complex branching structure with both 1 \rightarrow 4 and 1 \rightarrow 6 links (FIGURE 21.10). Glycogen molecules are larger than those of amylopectin—up to 100,000 glucose units—and contain even more branches.

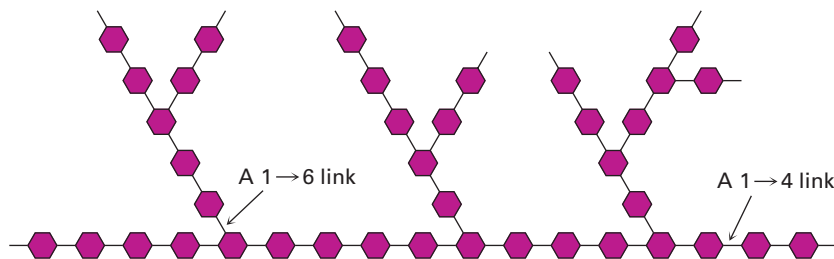
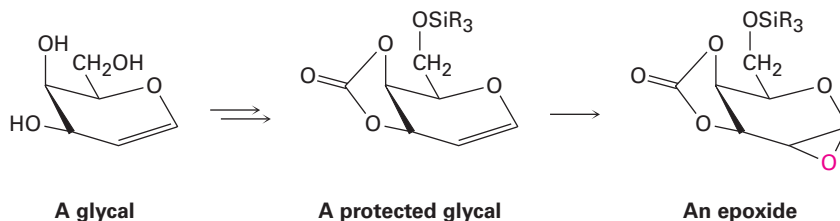


FIGURE 21.10 A representation of the structure of glycogen. The hexagons represent glucose units linked by 1 \rightarrow 4 and 1 \rightarrow 6 glycoside bonds.

Polysaccharide Synthesis

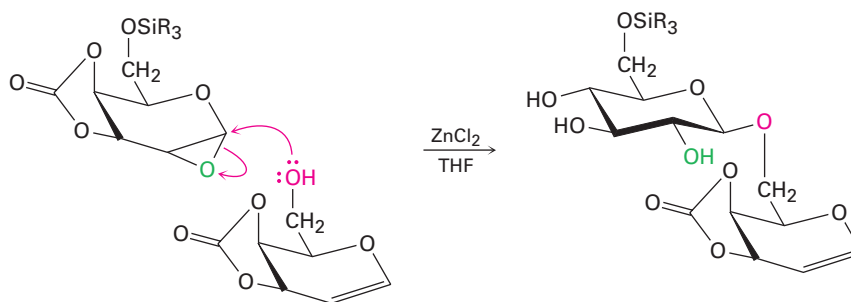
With numerous -OH groups of similar reactivity, polysaccharides are so structurally complex that their laboratory synthesis has been a particularly difficult problem. Several methods have recently been devised, however, that have greatly simplified the problem. Among these approaches is the *glycal assembly method*.

Easily prepared from the appropriate monosaccharide, a glycal is an unsaturated sugar with a C1–C2 double bond. To ready it for use in polysaccharide synthesis, the glycal is first protected at its primary -OH group by formation of a silyl ether ($\text{R}_3\text{Si-O-R}'$; Section 13-6) and at its two adjacent secondary -OH groups by formation of a cyclic carbonate ester. Then, the protected glycal is epoxidized.



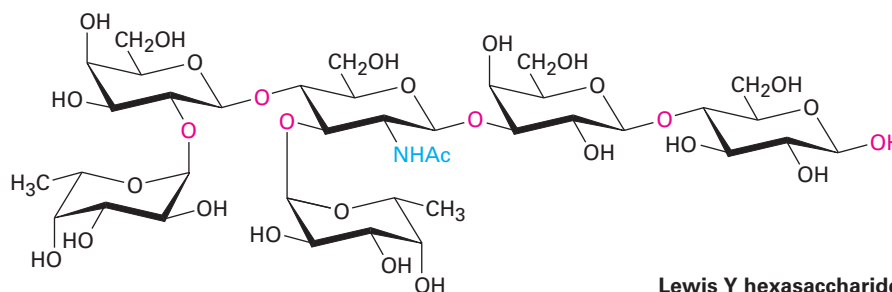
Treatment of the protected glycal epoxide in the presence of ZnCl_2 as a Lewis acid with a second glycal having a free -OH group causes acid-catalyzed opening of the epoxide ring by $\text{S}_{\text{N}}2$ backside attack and yields a disaccharide. The disaccharide is itself a glycal, so it can be epoxidized and coupled again to yield a trisaccharide, and so on. Using the appropriate sugars at each step, a great variety of polysaccharides can be prepared. After the

appropriate sugars are linked, the silyl ethers and cyclic carbonate protecting groups are removed by hydrolysis.



A disaccharide glycal

Among the numerous complex polysaccharides that have been synthesized in the laboratory is the Lewis Y hexasaccharide, a tumor marker in colon–rectal adenocarcinoma that is being explored as a potential cancer vaccine.



Lewis Y hexasaccharide

21-10 Some Other Important Carbohydrates

TABLE 21.1 Human Blood-Group Compatibilities

Donor blood type	Acceptor blood type			
	A	B	AB	O
A	○	×	○	×
B	×	○	○	×
AB	×	×	○	×
O	○	○	○	○

It was once thought that carbohydrates were useful in nature only as structural materials and energy sources. Although carbohydrates do indeed serve these purposes, they have many other important biochemical functions as well. As noted in Section 21-6, for instance, glycoconjugates are centrally involved in cell–cell recognition, the critical process by which one type of cell distinguishes another. Small polysaccharide chains, covalently bound by glycosidic links to –OH or –NH₂ groups on proteins, act as biochemical markers on cell surfaces, as illustrated by the human blood-group antigens.

It has been known for more than a century that human blood can be classified into four blood-group types (A, B, AB, and O) and that blood from a donor of one type can't be transfused into a recipient with another type unless the two types are compatible (TABLE 21.1). Should an incompatible mix be made, the red blood cells clump together, or *agglutinate*.

The agglutination of incompatible red blood cells, which indicates that the body's immune system has recognized the presence of foreign cells in the body and has formed antibodies against them, results from the presence of

polysaccharide markers on the surface of the cells. Types A, B, and O red blood cells each have their own unique markers, called *antigenic determinants*. Type AB cells have both type A and type B markers. The structures of all three blood-group determinants are shown in **FIGURE 21.11**. Note that the monosaccharide constituents of each marker are among the eight essential sugars shown previously in Figure 21.8.

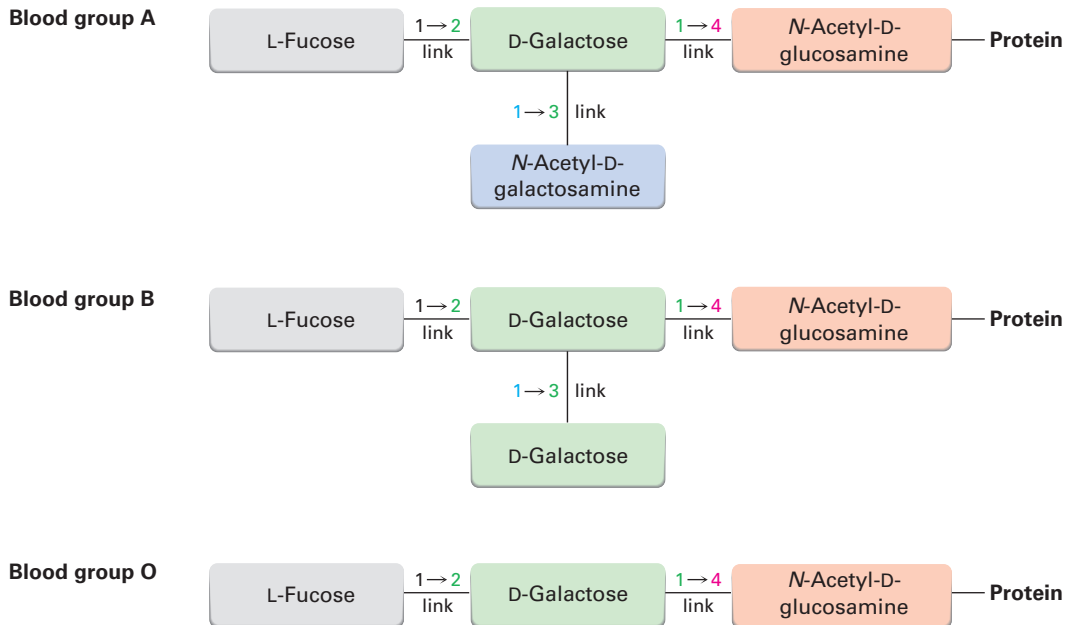
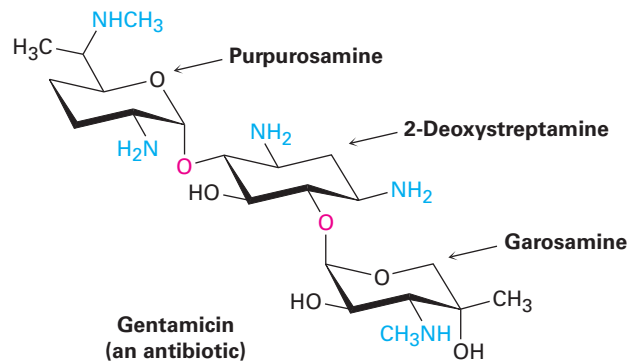
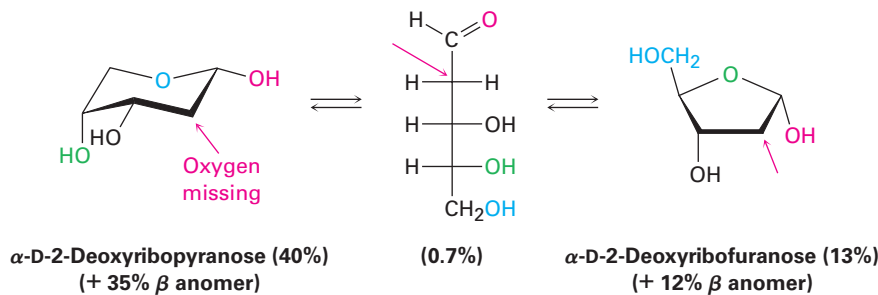


FIGURE 21.11 Structures of the A, B, and O blood-group antigenic determinants.

Other important carbohydrates include 2-deoxyribose, a deoxysugar found in DNA (deoxyribonucleic acid), and various amino sugars found in antibiotics such as streptomycin and gentamicin.



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SOMETHING EXTRA

Sweetness

Say the word *sugar* and most people immediately think of sweet-tasting candies, desserts, and such. In fact, most simple carbohydrates do taste sweet but the degree of sweetness varies greatly from one sugar to another. With sucrose (table sugar) as a reference point, fructose is nearly twice as sweet, but lactose is only about one-sixth as sweet. Comparisons are difficult, though, because perceived sweetness varies depending on the concentration of the solution being tasted and on personal opinion. Nevertheless, the ordering in **TABLE 21.2** is generally accepted.

TABLE 21.2 Sweetness of Some Sugars and Sugar Substitutes

Name	Type	Sweetness
Lactose	Disaccharide	0.16
Glucose	Monosaccharide	0.75
Sucrose	Disaccharide	1.00
Fructose	Monosaccharide	1.75
Aspartame	Synthetic	180
Acesulfame-K	Synthetic	200
Saccharin	Synthetic	350
Sucralose	Semisynthetic	600
Alitame	Semisynthetic	2000

The desire of many people to cut their caloric intake has led to the development of synthetic sweeteners such as saccharin, aspartame, acesulfame, and sucralose. All are far sweeter than natural sugars, so the choice of one or another depends on personal taste, government regulations, and (for baked goods) heat stability.

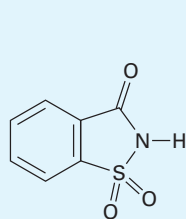
The real thing comes from cane fields like this one.



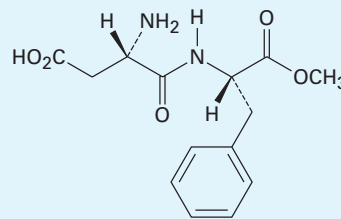
Warren Jacobi/Corbis

Saccharin, the oldest synthetic sweetener, has been used for more than a century, although it has a somewhat metallic aftertaste. Doubts about its safety and potential carcinogenicity were raised in the early 1970s, but it has now been cleared of suspicion.

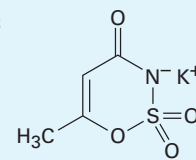
Acesulfame potassium, approved for general use in the U.S. in 2003, has proved to be extremely popular in soft drinks because it has little aftertaste. Sucralose, another recently approved sweetener, is particularly useful in baked goods because of its stability at high temperatures. Alitame, marketed in some countries under the name Aclame, is not approved for sale in the United States. It is some 2000 times as sweet as sucrose and, like acesulfame-K, has no aftertaste. Of the five synthetic sweeteners listed in Table 21.2, only sucralose has clear structural resemblance to a carbohydrate, although it differs dramatically in containing three chlorine atoms. Aspartame and alitame are both dipeptides.



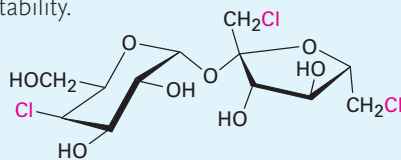
Saccharin



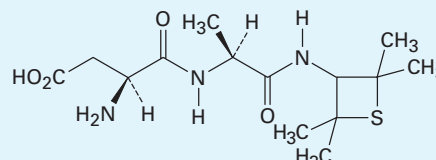
Aspartame



Acesulfame potassium



Sucralose



Alitame

SUMMARY

Carbohydrates are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehyde sugar. **Monosaccharides** are further classified as either **D sugars** or **L sugars**, depending on the stereochemistry of the chirality center farthest from the carbonyl group. Carbohydrate stereochemistry is frequently shown using **Fischer projections**, which represent a chirality center as the intersection of two crossed lines.

Monosaccharides normally exist as cyclic hemiacetals rather than as open-chain aldehydes or ketones. The hemiacetal linkage results from reaction of the carbonyl group with an $-OH$ group three or four carbon atoms away. A five-membered cyclic hemiacetal is called a **furanose**, and a six-membered cyclic hemiacetal is called a **pyranose**. Cyclization leads to the formation of a new chirality center called the **anomeric center** and the production of two diastereomeric hemiacetals called **alpha (α)** and **beta (β) anomers**.

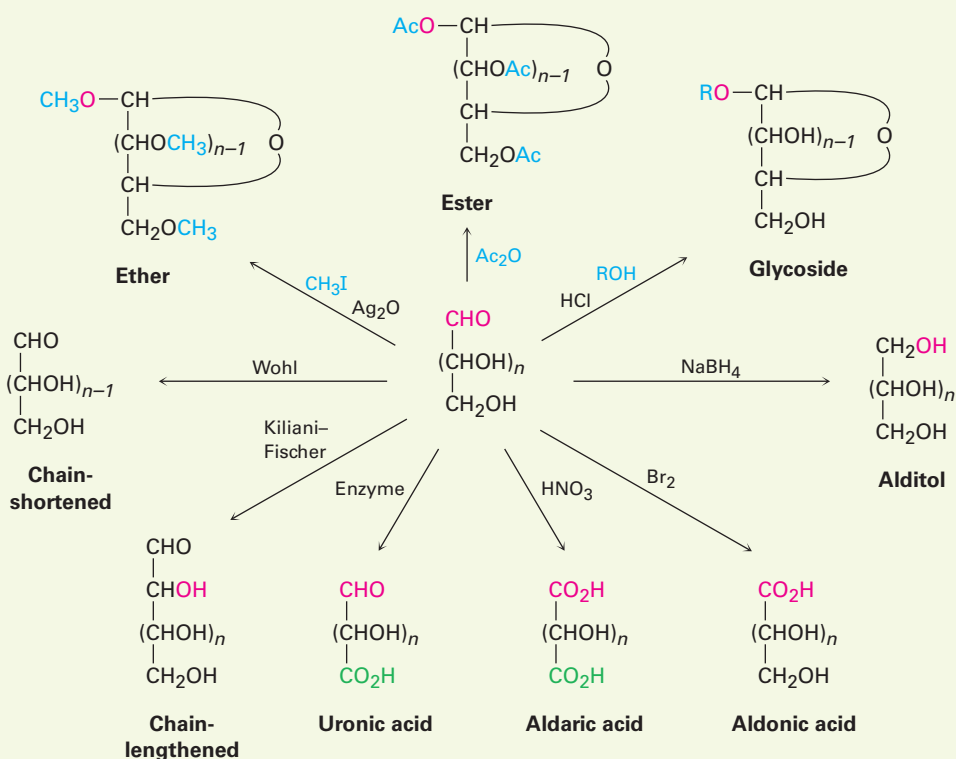
Much of the chemistry of monosaccharides is the familiar chemistry of alcohols and aldehydes/ketones. Thus, the hydroxyl groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with $NaBH_4$ to form an **alditol**, oxidized with aqueous Br_2 to form an **aldonic acid**, oxidized with HNO_3 to form an **aldaric acid**, oxidized enzymatically to form a **uronic acid**, or treated with an alcohol in the presence of acid to form a **glycoside**. Monosaccharides can also be chain-lengthened by the multistep Kiliani–Fischer synthesis and can be chain-shortened by the Wohl degradation.

Disaccharides are complex carbohydrates in which simple sugars are linked by a glycoside bond between the anomeric center of one unit and a hydroxyl of the second unit. The sugars can be the same, as in maltose and cellobiose, or different, as in lactose and sucrose. The glycosidic bond can be either α (maltose) or β (cellobiose, lactose) and can involve any hydroxyl of the second sugar. A 1 \rightarrow 4 link is most common (cellobiose, maltose), but others such as 1 \rightarrow 2 (sucrose) are also known. **Polysaccharides**, such as cellulose, starch, and glycogen, are used in nature as structural materials, as a means of long-term energy storage, and as cell-surface markers.

KEY WORDS

aldaric acid,	758
alditol,	756
aldonic acid,	757
aldose,	740
amino sugar,	762
α anomer, β anomer,	751
anomeric center,	751
carbohydrate,	738
complex carbohydrate,	739
D sugar,	745
deoxy sugar,	762
disaccharide,	762
Fischer projection,	740
furanose,	751
glycoside,	755
ketose,	740
L sugar,	745
monosaccharide,	739
mutarotation,	751
polysaccharide,	765
pyranose,	750
reducing sugar,	758
simple sugar,	739
uronic acid,	758

SUMMARY OF REACTIONS

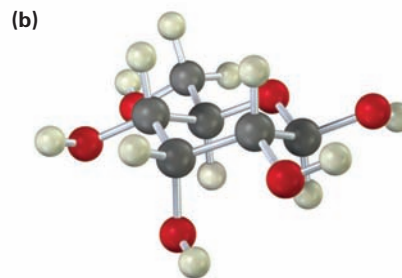
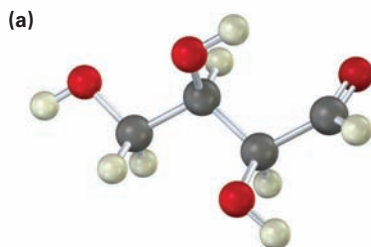


EXERCISES

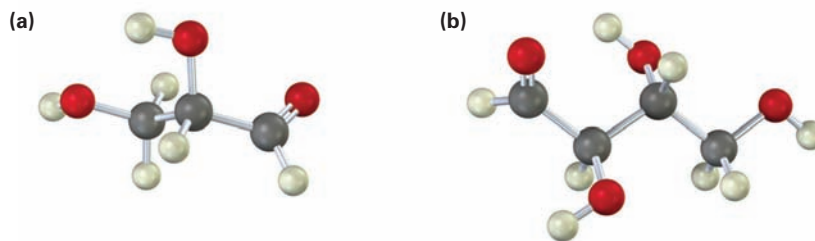
VISUALIZING CHEMISTRY

(Problems 21.1–21.25 appear within the chapter.)

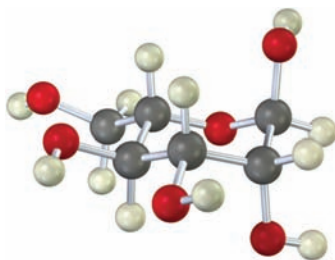
21.26 Identify the following aldoses, and tell whether each is a D or L sugar:



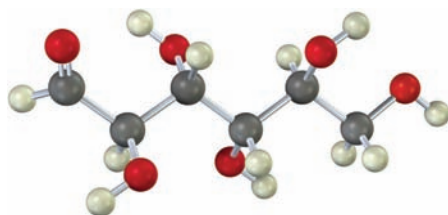
21.27 Draw Fischer projections of the following molecules, placing the carbonyl group at the top in the usual way, and identify each as a D or L sugar:



21.28 The following structure is that of an L aldohexose in its pyranose form. Identify it, and tell whether it is an α or β anomer.



21.29 The following model is that of an aldohexose:

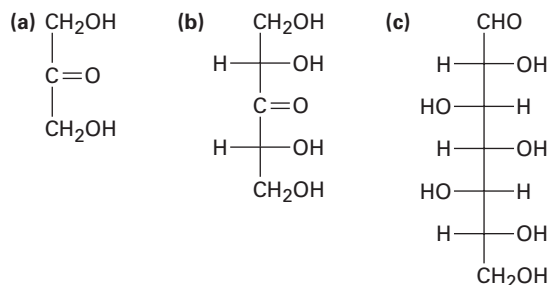


- (a) Draw Fischer projections of the sugar, its enantiomer, and a diastereomer.
- (b) Is this a D sugar or an L sugar? Explain.
- (c) Draw the β anomer of the sugar in its furanose form.

ADDITIONAL PROBLEMS

Carbohydrate Structures

21.30 Classify each of the following sugars. (For example, glucose is an aldohexose.)



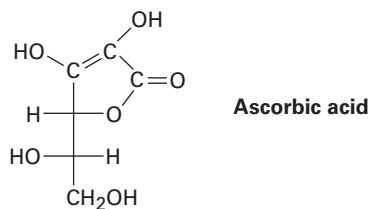
21.31 Write open-chain structures for the following:

- (a)** A ketotetrose **(b)** A ketopentose
(c) A deoxyaldohexose **(d)** A five-carbon amino sugar

21.32 What is the stereochemical relationship of D-ribose to L-xylose? What generalizations can you make about the following properties of the two sugars?

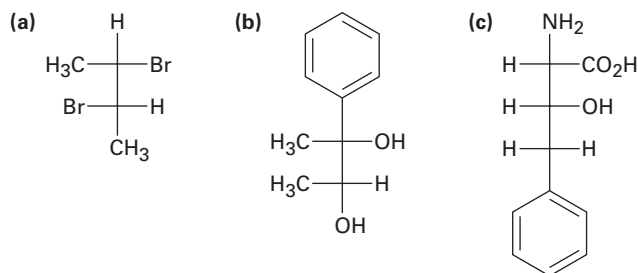
- (a)** Melting point **(b)** Solubility in water
(c) Specific rotation **(d)** Density

21.33 Does ascorbic acid (vitamin C) have a D or L configuration?

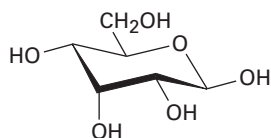


21.34 Draw the three-dimensional furanose form of ascorbic acid (Problem 21.33), and assign *R* or *S* stereochemistry to each chirality center.

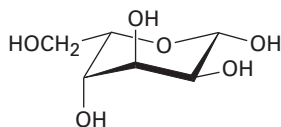
21.35 Assign *R* or *S* configuration to each chirality center in the following molecules:



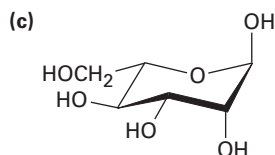
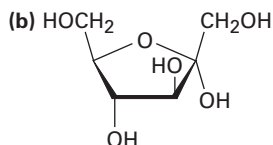
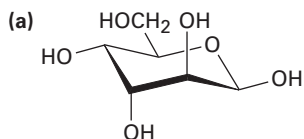
- 21.36** Draw Fischer projections of the following molecules:
- The *S* enantiomer of 2-bromobutane
 - The *R* enantiomer of alanine, $\text{CH}_3\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$
 - The *R* enantiomer of 2-hydroxypropanoic acid
 - The *S* enantiomer of 3-methylhexane
- 21.37** Draw Fischer projections for the two D aldoheptoses whose stereochemistry at C3, C4, C5, and C6 is the same as that of D-glucose at C2, C3, C4, and C5.
- 21.38** The following cyclic structure is that of allose. Is this a furanose or pyranose form? Is it an α or β anomer? Is it a D or L sugar?



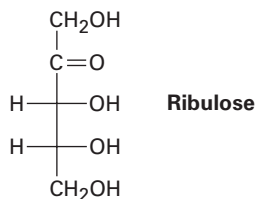
- 21.39** What is the complete name of the following sugar?



- 21.40** Write the following sugars in their open-chain forms:



- 21.41** Draw D-ribulose in its five-membered cyclic β -hemiacetal form.



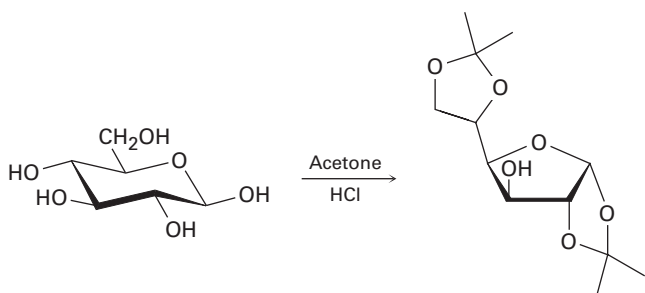
- 21.42** Look up the structure of D-talose in Figure 21.3, and draw the β anomer in its pyranose form. Identify the ring substituents as axial or equatorial.

Carbohydrate Reactions

- 21.43** Draw structures for the products you would expect to obtain from reaction of β -D-talopyranose with each of the following reagents:
- (a) NaBH_4 in H_2O (b) Warm dilute HNO_3
(c) Br_2 , H_2O (d) $\text{CH}_3\text{CH}_2\text{OH}$, HCl
(e) CH_3I , Ag_2O (f) $(\text{CH}_3\text{CO})_2\text{O}$, pyridine
- 21.44** All aldoses exhibit mutarotation. For example, α -D-galactopyranose has $[\alpha]_{\text{D}} = +150.7$, and β -D-galactopyranose has $[\alpha]_{\text{D}} = +52.8$. If either anomer is dissolved in water and allowed to reach equilibrium, the specific rotation of the solution is $+80.2$. What are the percentages of each anomer at equilibrium? Draw the pyranose forms of both anomers.
- 21.45** How many D-2-ketohexoses are possible? Draw them.
- 21.46** One of the D-2-ketohexoses is called *sorbose*. On treatment with NaBH_4 , sorbose yields a mixture of gulitol and iditol. What is the structure of sorbose?
- 21.47** Another D-2-ketohexose, *psicose*, yields a mixture of allitol and altritol when reduced with NaBH_4 . What is the structure of psicose?
- 21.48** L-Gulose can be prepared from D-glucose by a route that begins with oxidation to D-glucaric acid, which cyclizes to form two six-membered-ring lactones. Separating the lactones and treating them with sodium amalgam, $\text{Na}(\text{Hg})$, reduces the $-\text{CO}_2\text{H}$ group to a primary alcohol and the lactone to an aldehyde, giving D-glucose and L-gulose. What are the structures of the two lactones, and which one is reduced to L-gulose?
- 21.49** What other D aldohexose gives the same alditol as D-talose?
- 21.50** Which of the eight D aldohexoses give the same aldaric acids as their L enantiomers?
- 21.51** Which of the other three D aldopentoses gives the same aldaric acid as D-lyxose?
- 21.52** Draw the structure of L-galactose, and then answer the following questions:
- (a) Which other aldohexose gives the same aldaric acid as L-galactose on oxidation with warm HNO_3 ?
(b) Is this other aldohexose a D sugar or an L sugar?
(c) Draw this other aldohexose in its most stable pyranose conformation.
- 21.53** Gentiobiose, a rare disaccharide found in saffron and gentian, is a reducing sugar and forms only D-glucose on hydrolysis with aqueous acid. Reaction of gentiobiose with iodomethane and Ag_2O yields an octamethyl derivative, which can be hydrolyzed with aqueous acid to give 1 equivalent of 2,3,4,6-tetra-O-methyl-D-glucopyranose and 1 equivalent of 2,3,4-tri-O-methyl-D-glucopyranose. If gentiobiose contains a β -glycoside link, what is its structure?

General Problems

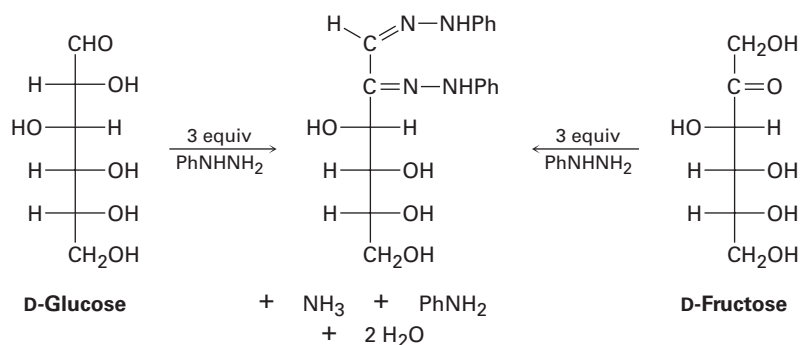
- 21.54** Amygdalin, or laetrile, is a cyanogenic glycoside isolated in 1830 from almond and apricot seeds. Acidic hydrolysis of amygdalin liberates HCN, along with benzaldehyde and 2 equivalents of D-glucose. If amygdalin is a β -glycoside of benzaldehyde cyanohydrin with gentiobiose (Problem 21.53), what is its structure? [A cyanohydrin has the structure $R_2C(OH)CN$ and is formed by reversible nucleophilic addition of HCN to an aldehyde or ketone.]
- 21.55** Trehalose is a nonreducing disaccharide that is hydrolyzed by aqueous acid to yield 2 equivalents of D-glucose. Methylation followed by hydrolysis yields 2 equivalents of 2,3,4,6-tetra-*O*-methylglucose. How many structures are possible for trehalose?
- 21.56** Trehalose (Problem 21.55) is cleaved by enzymes that hydrolyze α -glycosides but not by enzymes that hydrolyze β -glycosides. What is the structure and systematic name of trehalose?
- 21.57** Trehalose-6-phosphate (T6P) has been found to trigger the onset of blooming in flowering plants. Draw the structure of T6P.
- 21.58** Isotrehalose and neotrehalose are chemically similar to trehalose (Problems 21.55 and 21.56) except that neotrehalose is hydrolyzed only by β -glycosidases, whereas isotrehalose is hydrolyzed by both α - and β -glycosidases. What are the structures of isotrehalose and neotrehalose?
- 21.59** D-Glucose reacts with acetone in the presence of acid to yield the nonreducing 1,2:5,6-diisopropylidene-D-glucofuranose. Propose a mechanism.



1,2:5,6-Diisopropylidene-D-glucofuranose

- 21.60** D-Mannose reacts with acetone to give a diisopropylidene derivative (Problem 21.59) that is still a reducing sugar. Propose a likely structure for this derivative.
- 21.61** Glucose and mannose can be interconverted (in low yield) by treatment with dilute aqueous NaOH. Propose a mechanism.
- 21.62** Raffinose, a trisaccharide found in sugar beets, is formed by a 1 \rightarrow 6 α linkage of D-galactose to the glucose unit of sucrose. Draw the structure of raffinose.

- 21.63** Is raffinose (see Problem 14.62) a reducing sugar? Explain.
- 21.64** Propose a mechanism to account for the fact that D-gluconic acid and D-mannonic acid are interconverted when either is heated in pyridine solvent.
- 21.65** The *cyclitols* are a group of carbocyclic sugar derivatives having the general formulation cyclohexane-1,2,3,4,5,6-hexol. How many stereoisomeric cyclitols are possible? Draw them in their chair forms.
- 21.66** What product(s) would you expect from Kiliani–Fischer reaction of D-ribose?
- 21.67** What aldopentose would give a mixture of L-gulose and L-idose on Kiliani–Fischer chain extension?
- 21.68** Which two of the four D aldopentoses yield D-threose on Wohl degradation?
- 21.69** Compound **A** is a D aldopentose that can be oxidized to an optically inactive aldaric acid **B**. On Kiliani–Fischer chain extension, **A** is converted into **C** and **D**; **C** can be oxidized to an optically active aldaric acid **E**, but **D** is oxidized to an optically inactive aldaric acid **F**. What are the structures of **A–F**?
- 21.70** Simple sugars undergo reaction with phenylhydrazine, PhNHNH₂, to yield crystalline derivatives called *osazones*. The reaction is a bit complex, however, as shown by the fact that glucose and fructose yield the same osazone.



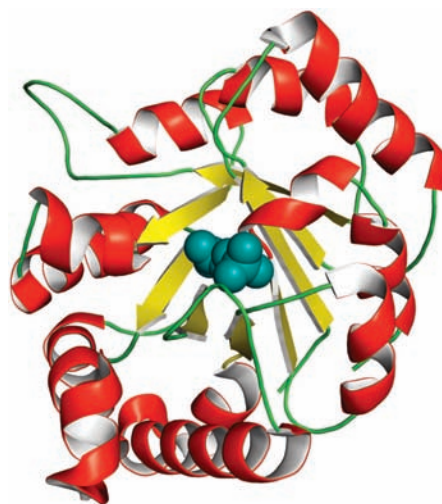
- (a) Draw the structure of a third sugar that yields the same osazone as glucose and fructose.
- (b) Using glucose as the example, the first step in osazone formation is reaction of the sugar with phenylhydrazine to yield an imine called a *phenylhydrazone*. Draw the structure of the product.
- (c) The second and third steps in osazone formation are tautomerization of the phenylhydrazone to give an enol, followed by elimination of aniline to give a keto imine. Draw the structures of both the enol tautomer and the keto imine.
- (d) The final step is reaction of the keto imine with 2 equivalents of phenylhydrazine to yield the osazone plus ammonia. Propose a mechanism for this step.

CONTENTS

- 22-1** Hydrolysis of Complex Carbohydrates
- 22-2** Catabolism of Glucose: Glycolysis
- 22-3** Conversion of Pyruvate to Acetyl CoA
- 22-4** The Citric Acid Cycle
- 22-5** Biosynthesis of Glucose: Gluconeogenesis

SOMETHING EXTRA

Influenza Pandemics



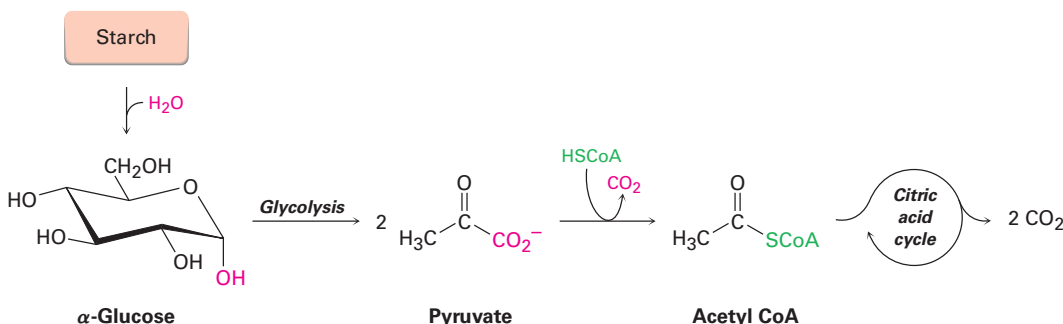
Triose-phosphate isomerase catalyzes the interconversion of dihydroxyacetone phosphate and glyceraldehyde 3-phosphate during glycolysis.

WHY THIS CHAPTER?

Glucose metabolism is at the center of biological chemistry. Fortunately, it's also relatively straightforward because the molecules are small and contain only carbon, hydrogen, and oxygen. The reactions involved are almost entirely the carbonyl-group processes discussed in Chapters 14–17: alcohol oxidations, carbonyl reductions, imine formations, aldol reactions, keto–enol tautomerizations, nucleophilic acyl substitutions, conjugate nucleophilic additions, and so forth. Thus, all the hard work you did in learning that material now pays off.

Carbohydrates are the chemical intermediaries by which carbon atoms from CO_2 are incorporated into growing organisms and by which solar energy is stored and used to support life. Thus, carbohydrates are the biological starting point, and their metabolism is intimately interconnected with the metabolism of all other biomolecules. The catabolism of glucose, in fact, has been called the backbone of all metabolic pathways.

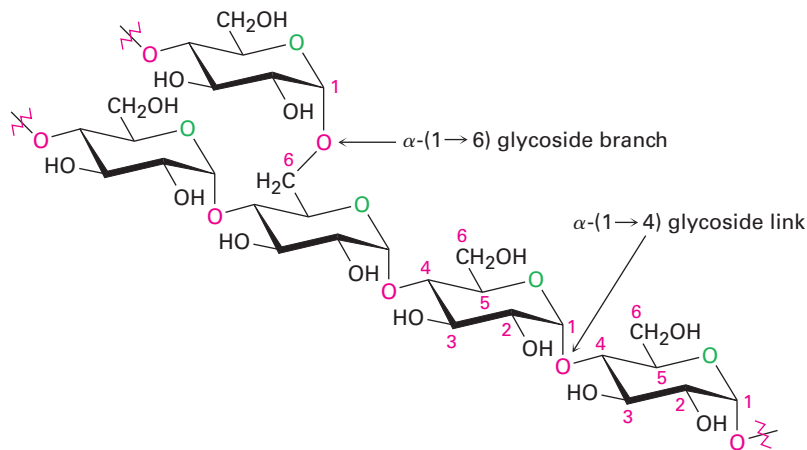
We'll look at that metabolic backbone in this chapter, beginning with the hydrolysis of dietary starch to give glucose, which is then catabolized to pyruvate in the *glycolysis* pathway. We'll then see how pyruvate is decarboxylated to yield acetyl CoA and how acetyl CoA is degraded to CO_2 in the *citric acid cycle*. Following this look at catabolism, we'll finish the chapter by seeing how glucose is biosynthesized from pyruvate in the *gluconeogenesis* pathway.



22-1 Hydrolysis of Complex Carbohydrates

The carbohydrate in our food is largely starch, a glucose polymer in which the monosaccharide units are linked by α -(1 \rightarrow 4) glycoside bonds. As discussed in Section 21-9, starch consists of two main fractions—amylose and amylopectin. Amylose makes up about 20% of starch by mass and is a linear polymer of several hundred α -(1 \rightarrow 4)-linked glucose units. Amylopectin makes up the remaining 80% of starch by mass and is a branched polymer of up to 5000 glucose units with α -(1 \rightarrow 6) branches every 25 or so units (**FIGURE 22.1**).

FIGURE 22.1 The structure of amylopectin, the major carbohydrate in starch.



**Amylopectin: α -(1 \rightarrow 4) links
with α -(1 \rightarrow 6) branches**

Digestion of starch begins in the mouth where many of the internal (1 \rightarrow 4) glycoside links, but not the (1 \rightarrow 6) links or terminal (1 \rightarrow 4) links, are randomly hydrolyzed by α -amylase, a glycosidase. Further digestion continues in the small intestine to give a mixture of the disaccharide maltose (Section 21-8), the trisaccharide maltotriose, and small oligosaccharides called *limit dextrins*, which contain the (1 \rightarrow 6) branches. Final processing in the intestinal mucosa by additional glycosidases hydrolyzes the remaining glycoside bonds and yields glucose, which is absorbed by the intestine and transported through the bloodstream.

Glycosidase-catalyzed hydrolysis of a glycoside bond in a polysaccharide can occur with either inversion or retention of stereochemistry at the anomeric center. Both mechanisms probably proceed through a short-lived oxonium ion (R_3O^+) intermediate in which one face of the carbohydrate is effectively shielded by the leaving group, leaving the other face open to nucleophilic attack (**FIGURE 22.2a**). Inverting glycosidases operate through a single S_N2 -like inversion in which a carboxylate residue in the enzyme, either aspartate or glutamate, acts as a base to deprotonate water, which then adds to the oxonium ion from the side opposite the leaving group (**FIGURE 22.2b**). Retaining glycosidases operate through two inversions. In the first, a carboxylate group in the enzyme adds to the oxonium ion from the side opposite the leaving group, giving a covalently bonded, glycosylated enzyme. In the second, water displaces the carboxylate through a second oxonium ion (**FIGURE 22.2c**).

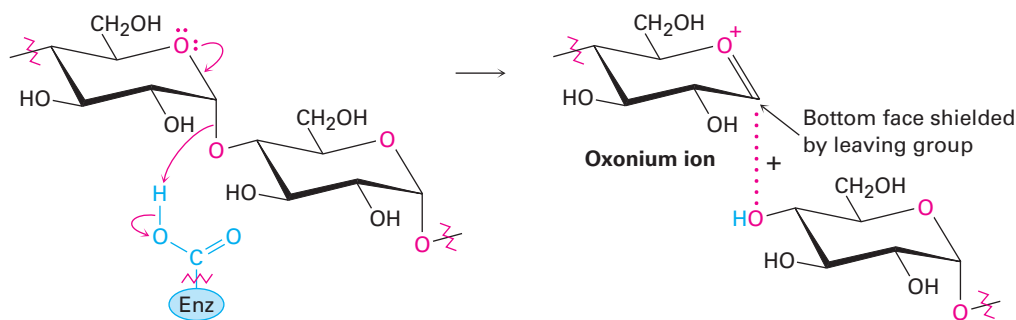
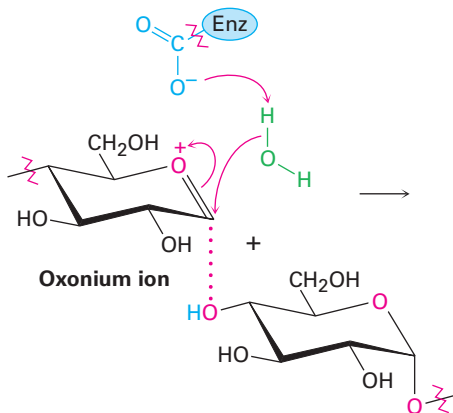
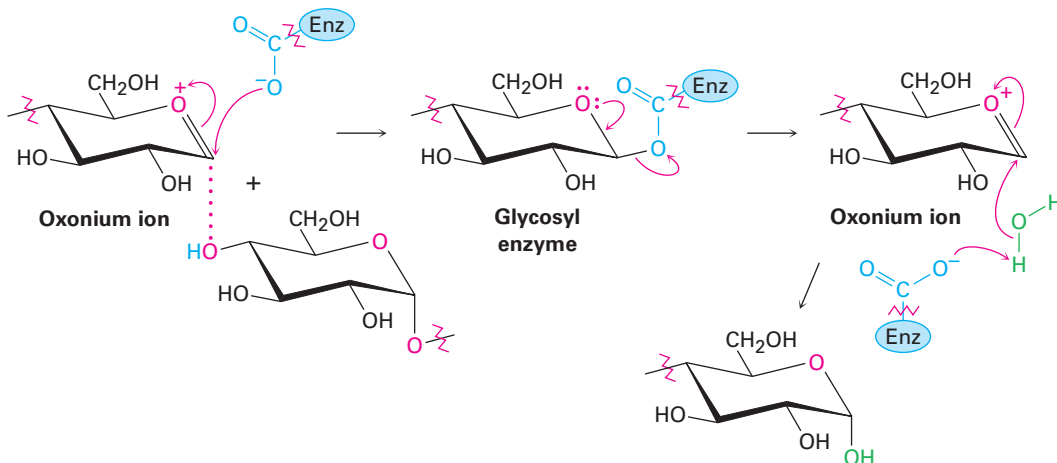
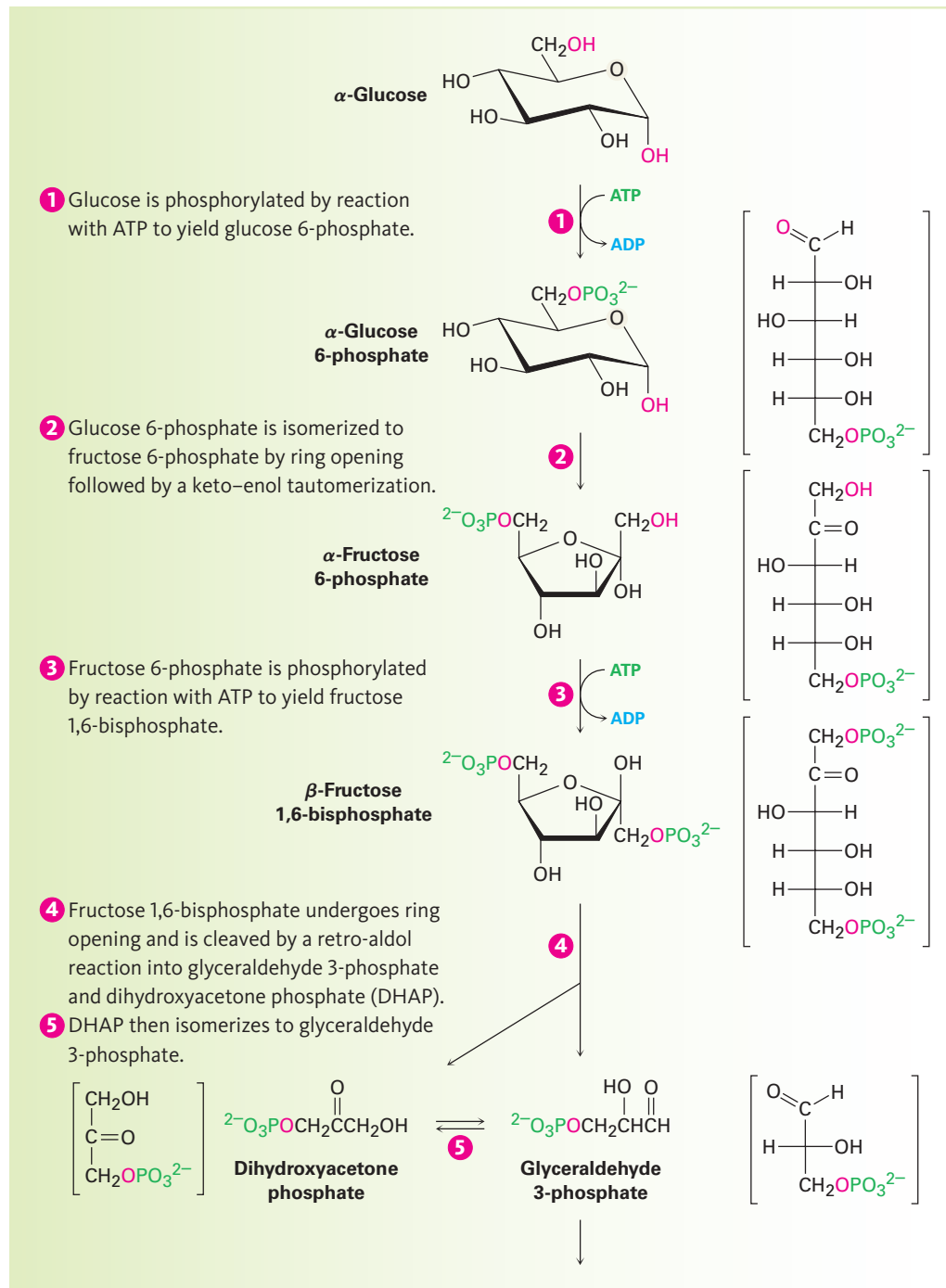
(a) Initial oxonium ion formation**(b) Inverting glycosidase****(c) Retaining glycosidase**

FIGURE 22.2 Mechanism of polysaccharide hydrolysis by glycosidases. (a) Initial formation of an oxonium ion is followed by either one inversion or two. (b) Inverting glycosidases use a single inversion by nucleophilic attack of water. (c) Retaining glycosidases use two inversions, the first by a carboxylate ion to give a glycosylated enzyme intermediate and the second by nucleophilic attack of water.

22-2 Catabolism of Glucose: Glycolysis

Glucose is the body's primary source of short-term energy. Its catabolism begins with **glycolysis**, a series of ten enzyme-catalyzed steps that break down glucose into 2 equivalents of pyruvate, $\text{CH}_3\text{COCO}_2^-$. The steps of glycolysis, also called the *Embden–Meyerhoff pathway* after its discoverers, are summarized in **FIGURE 22.3**.

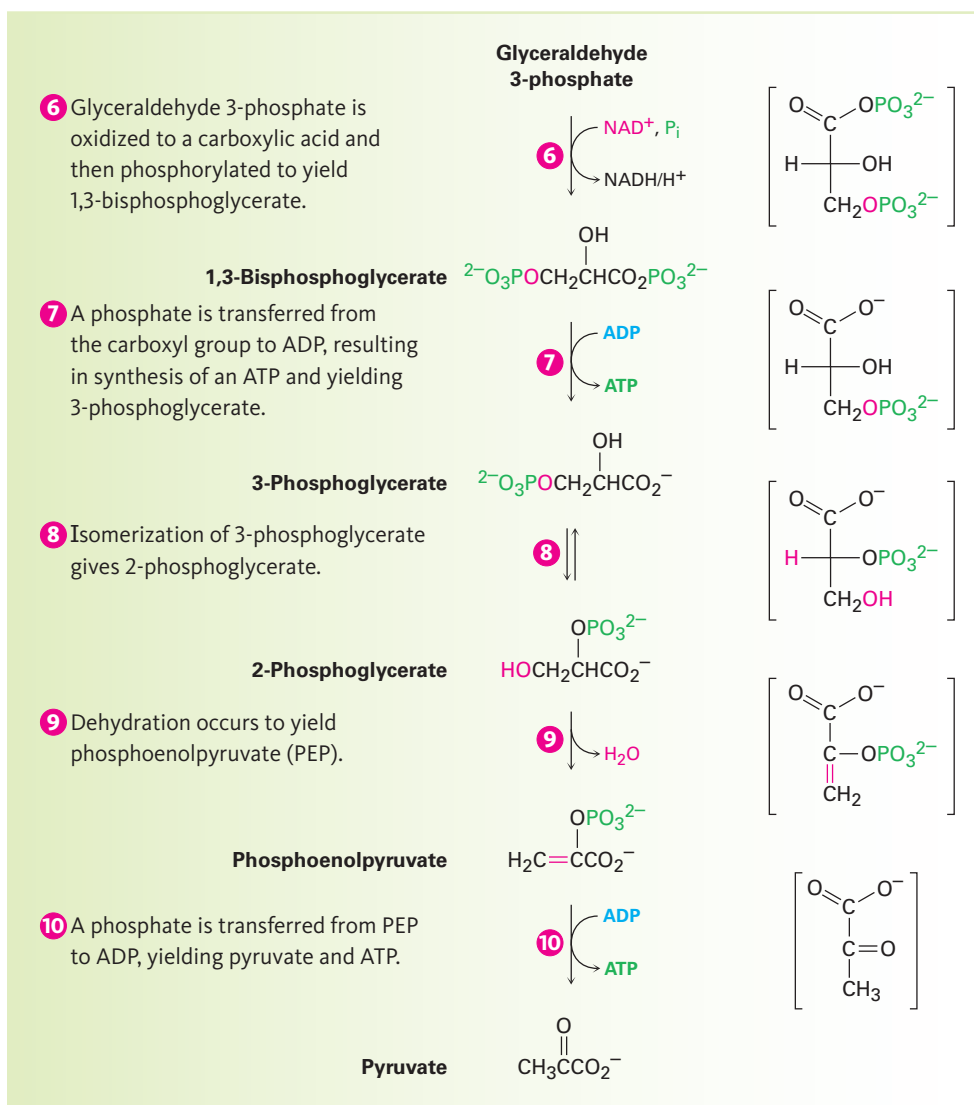
FIGURE 22.3 The ten-step glycolysis pathway that converts glucose into two molecules of pyruvate. Individual steps are explained in the text.



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FIGURE 22.3 (continued)

**STEPS 1–2 OF FIGURE 22.3: PHOSPHORYLATION AND ISOMERIZATION**

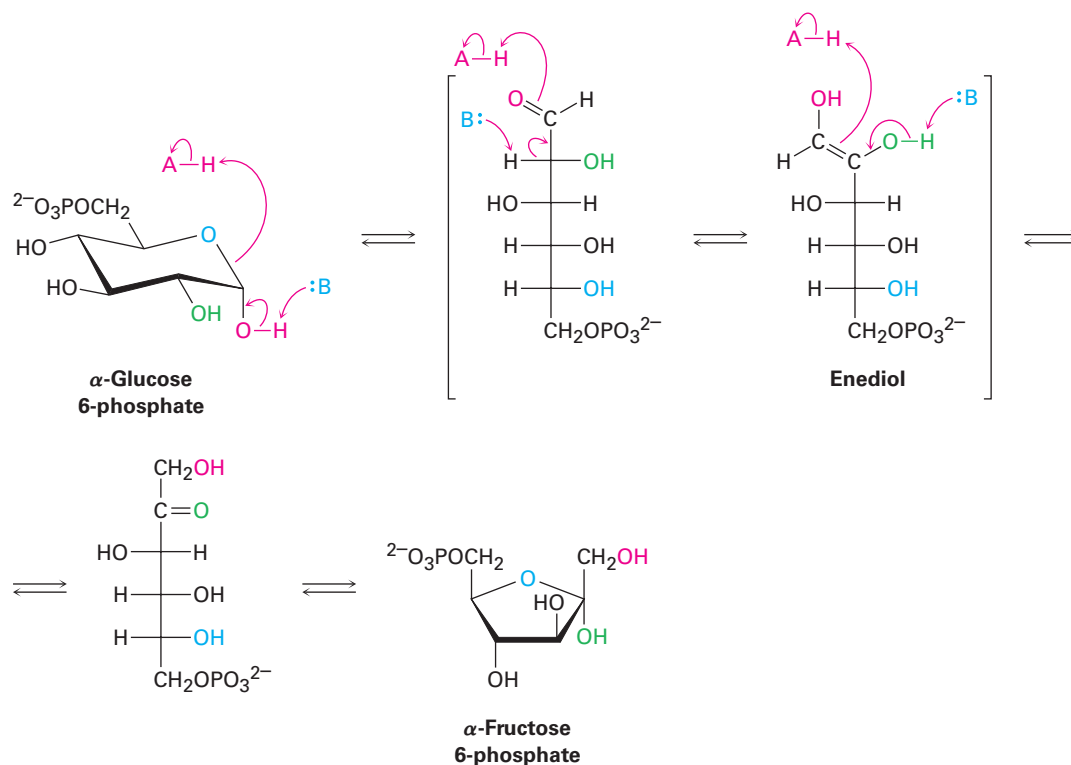
The glycolysis pathway begins with the phosphorylation of glucose at its C6 hydroxyl group by reaction with ATP in a process catalyzed by hexokinase. As noted in Section 20-1, the reaction requires Mg^{2+} as a cofactor to complex with the negatively charged phosphate oxygens.

The glucose 6-phosphate that results is isomerized in step 2 by glucose-6-phosphate isomerase to give fructose 6-phosphate (FIGURE 22.4). The isomerization takes place by initial opening of the glucose hemiacetal ring to the open-chain form, followed by keto–enol tautomerization (Section 17-1) to a cis enediol, $\text{HO}-\text{C}=\text{C}-\text{OH}$. But because glucose and fructose share a common enediol, further tautomerization to a different keto form produces open-chain fructose. Cyclization to a hemiacetal completes the process.

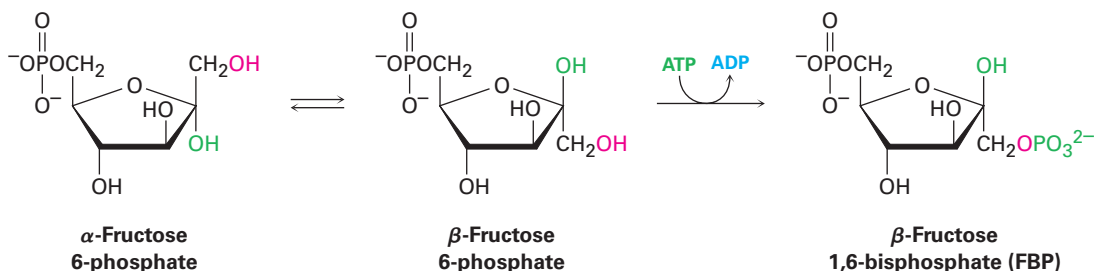
STEP 3 OF FIGURE 22.3: PHOSPHORYLATION Fructose 6-phosphate is converted in step 3 to fructose 1,6-bisphosphate, abbreviated FBP, by a phosphofruktokinase-catalyzed reaction with ATP (recall that the prefix *bis-* means

FIGURE 22.4

Mechanism of step 2 in glycolysis. The isomerization of glucose 6-phosphate to fructose 6-phosphate occurs by keto–enol tautomerization.



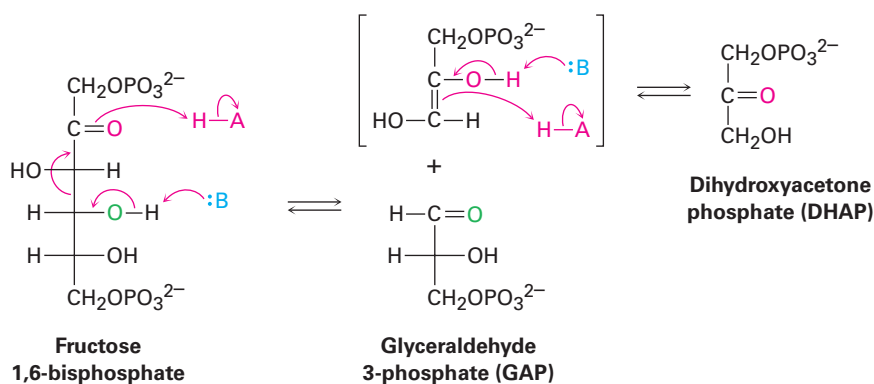
two). The mechanism of the phosphorylation is similar to that in step 1, with Mg^{2+} ion again required as cofactor. Interestingly, the product of step 2 is the α anomer of fructose 6-phosphate but it is the β anomer that is phosphorylated in step 3, implying that the two anomers equilibrate rapidly through the open-chain form prior to reaction. The result of step 3 is a molecule ready to be split into the two 3-carbon intermediates that will ultimately become two molecules of pyruvate.



STEP 4 OF FIGURE 22.3: CLEAVAGE OF FRUCTOSE 1,6-BISPHOSPHATE

Fructose 1,6-bisphosphate is cleaved in step 4 into two 3-carbon pieces, dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GAP). The bond between C3 and C4 of fructose 1,6-bisphosphate breaks, and a C=O group is formed at C4 (FIGURE 22.5). Mechanistically, the cleavage is the reverse of an aldol reaction (Section 17-6) and is catalyzed by an aldolase. A *forward* aldol reaction joins two aldehydes or ketones to give a β -hydroxy

carbonyl compound, while a *retro* aldol reaction such as that occurring here cleaves a β -hydroxy carbonyl compound into two aldehydes or ketones.



As mentioned previously in Section 17-13, two classes of aldolases are used by organisms to catalyze the retro-aldol reaction. In fungi, algae, and some bacteria, the retro-aldol reaction is catalyzed by class II aldolases, which function by coordination of the fructose carbonyl group with Zn^{2+} as Lewis acid. In plants and animals, the reaction is catalyzed by class I aldolases and does not take place on the free ketone. Instead, fructose 1,6-bisphosphate undergoes reaction with the side-chain $-\text{NH}_2$ group of a lysine residue on the aldolase to yield a protonated, enzyme-bound imine. As noted in Section 14-7, an imine is often called a Schiff base in biochemistry.

Because of its positive charge, the iminium ion is a better electron acceptor than a ketone carbonyl group. Retro-aldol reaction ensues, giving glyceraldehyde 3-phosphate and an enamine, which is protonated to give another iminium ion that is hydrolyzed to yield dihydroxyacetone phosphate.

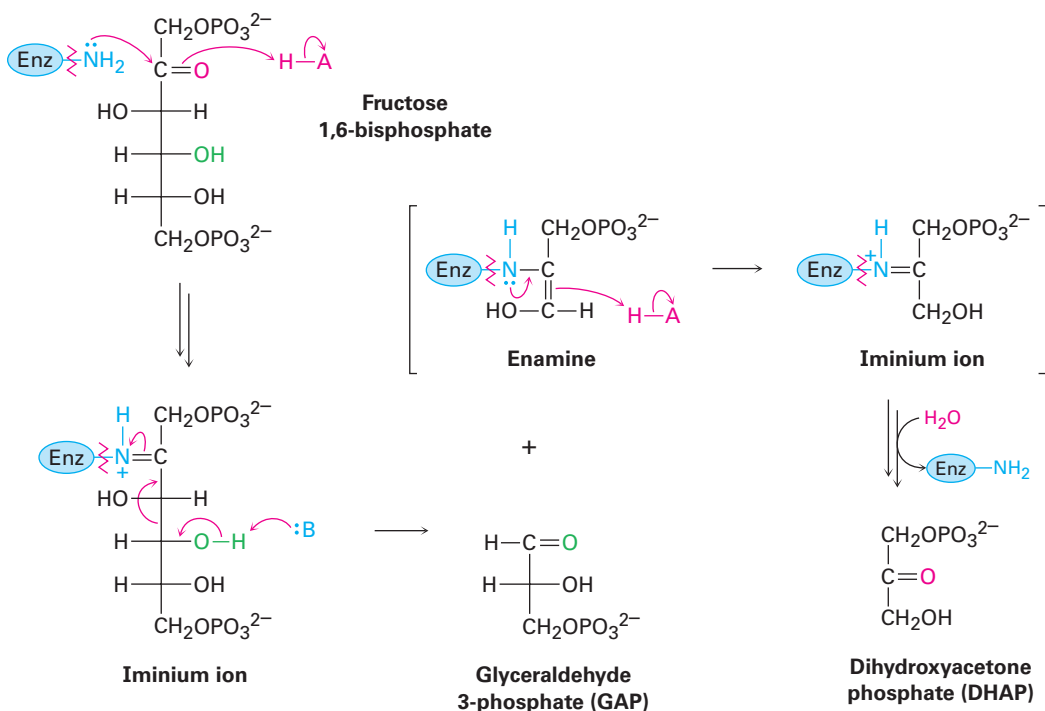
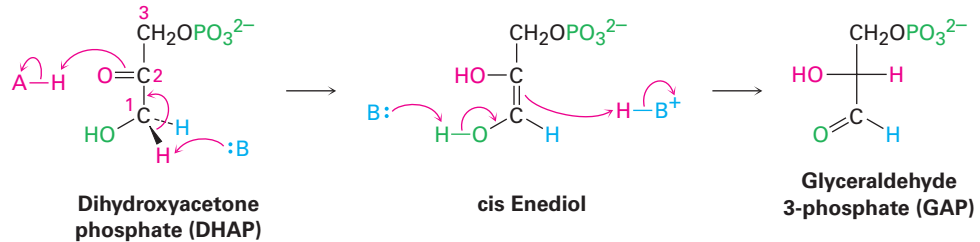


FIGURE 22.5
Mechanism of step 4
in Figure 22.3. Fructose 1,6-bisphosphate is cleaved by a retro-aldol reaction to yield glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. The reaction occurs through an iminium ion formed by reaction with a lysine residue in the enzyme.

STEP 5 OF FIGURE 22.3: ISOMERIZATION Dihydroxyacetone phosphate is isomerized in step 5 by triose phosphate isomerase to produce a second equivalent of glyceraldehyde 3-phosphate. As in the conversion of glucose 6-phosphate to fructose 6-phosphate in step 2, the isomerization takes place by keto–enol tautomerization through a common enediol intermediate. A base deprotonates at C1 and then reprotonates at C2 using the same hydrogen. The net result of steps 4 and 5 together is the production of two glyceraldehyde 3-phosphate molecules, both of which pass down the rest of the pathway. Thus, each of the remaining five steps of glycolysis takes place twice for every glucose molecule that enters at step 1.



STEPS 6–7 OF FIGURE 22.3: OXIDATION, PHOSPHORYLATION, AND DEPHOSPHORYLATION Glyceraldehyde 3-phosphate is oxidized and phosphorylated in step 6 to give 1,3-bisphosphoglycerate (**FIGURE 22.6**). The reaction is catalyzed by glyceraldehyde 3-phosphate dehydrogenase and begins by nucleophilic addition of the –SH group of a cysteine residue in the enzyme to the aldehyde carbonyl group to yield a *hemithioacetal* (RS–C–OH), the sulfur analog of a hemiacetal. Oxidation of the hemithioacetal –OH group by NAD⁺ then yields a thioester, which reacts with phosphate ion in a nucleophilic acyl substitution step to give the acyl phosphate 1,3-bisphosphoglycerate, a mixed anhydride between a carboxylic acid and phosphoric acid.

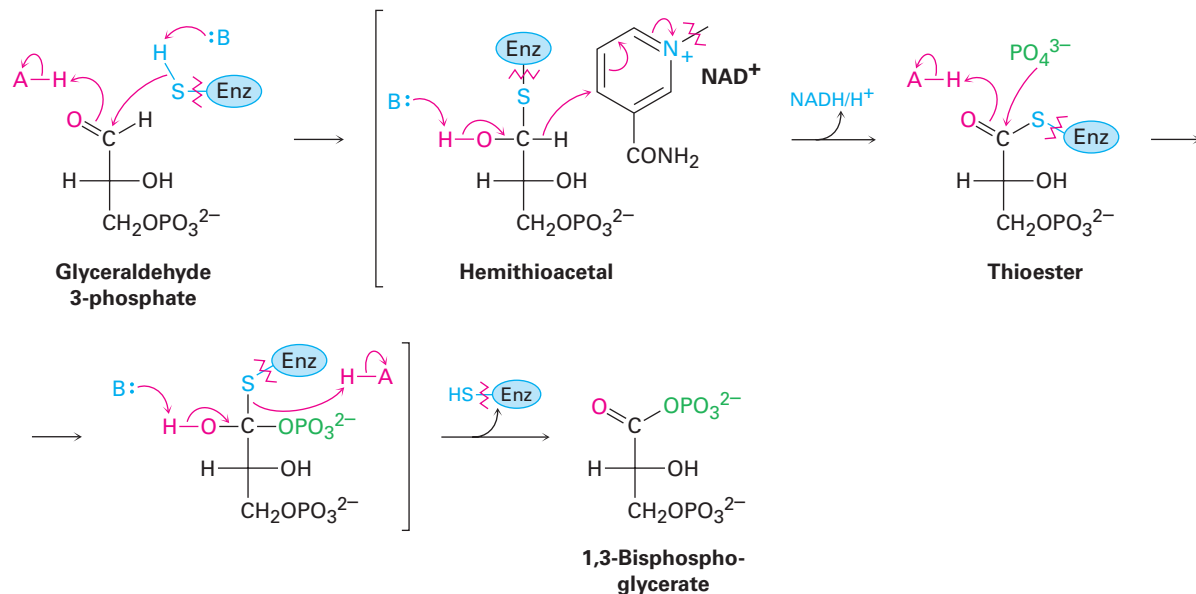
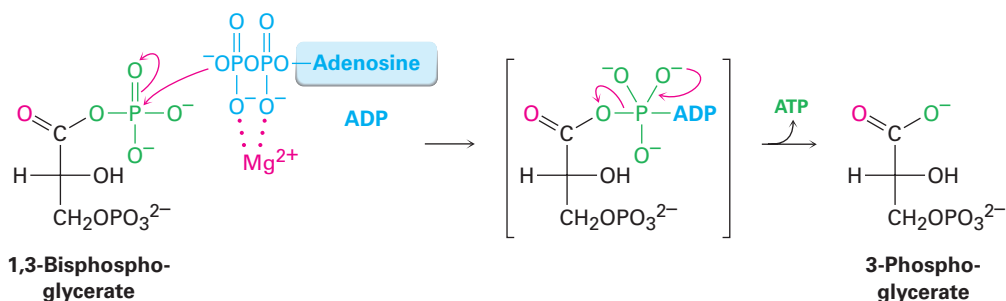
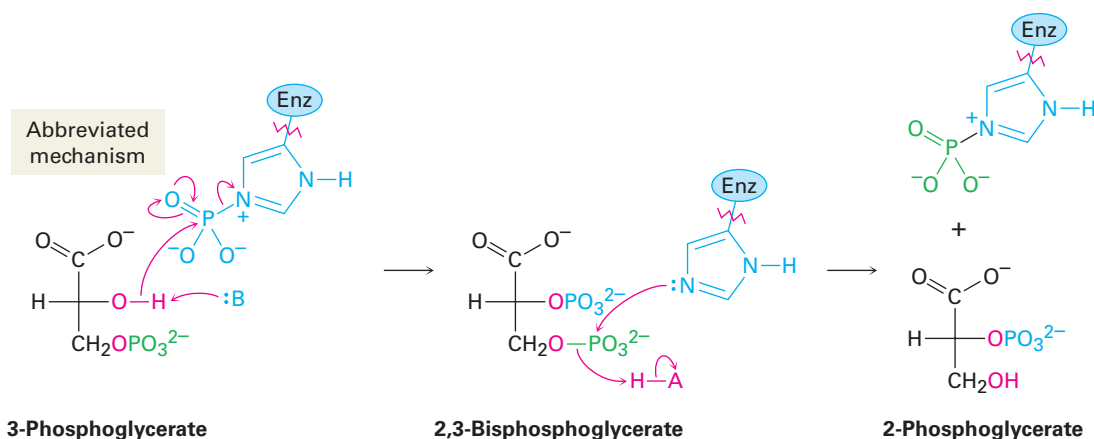


FIGURE 22.6 Mechanism of step 6 in Figure 22.3. Oxidation and phosphorylation of glyceraldehyde 3-phosphate gives 1,3-bisphosphoglycerate. The process occurs through initial formation of a hemiacetal that is oxidized to a thioester and converted into an acyl phosphate.

Like all anhydrides (Section 16-5), the mixed carboxylic–phosphoric anhydride is a reactive substrate in nucleophilic acyl (or phosphoryl) substitution reactions. Reaction of 1,3-bisphosphoglycerate with ADP occurs in step 7 by substitution on phosphorus, resulting in transfer of a phosphate group to ADP and giving ATP plus 3-phosphoglycerate. The process is catalyzed by phosphoglycerate kinase and requires Mg^{2+} as cofactor. Together, steps 6 and 7 accomplish the oxidation of an aldehyde to a carboxylic acid.

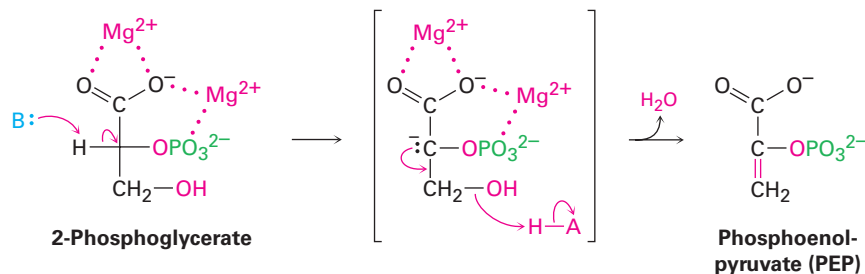


STEP 8 OF FIGURE 22.3: ISOMERIZATION 3-Phosphoglycerate isomerizes to 2-phosphoglycerate in step 8, a reaction catalyzed by phosphoglycerate mutase. In plants, 3-phosphoglycerate transfers its phosphoryl group from its C3 oxygen to a histidine residue on the enzyme in one step and then accepts the same phosphoryl group back onto the C2 oxygen in a second step. In animals and yeast, however, the enzyme contains a phosphorylated histidine, which transfers its phosphoryl group to the C2 oxygen of 3-phosphoglycerate and forms 2,3-bisphosphoglycerate as intermediate. The same histidine then accepts a phosphoryl group from the C3 oxygen to yield the isomerized product plus regenerated enzyme. As explained in Section 20-5, we'll occasionally use an abbreviated mechanism for nucleophilic acyl substitution reactions to save space.

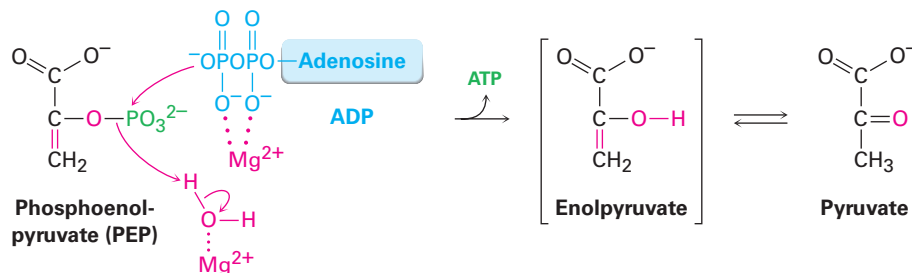


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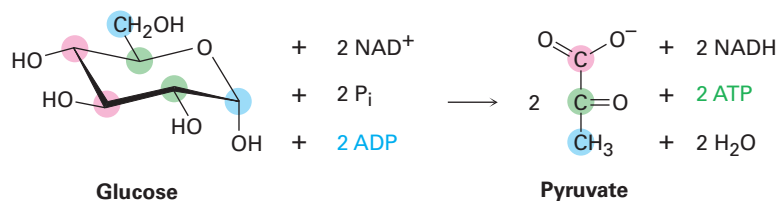
STEPS 9–10 OF FIGURE 22.3: DEHYDRATION AND DEPHOSPHORYLATION 2-Phosphoglycerate, a β -hydroxy carbonyl compound, undergoes a ready dehydration in step 9 by an E1cB mechanism (Section 17-7). The process is catalyzed by enolase, and the product is phosphoenolpyruvate, abbreviated PEP. Two Mg^{2+} ions are associated with the 2-phosphoglycerate to neutralize the negative charges.



Transfer of the phosphoryl group to ADP in step 10 then generates ATP and gives enolpyruvate, which tautomerizes to pyruvate. The reaction is catalyzed by pyruvate kinase and requires that a molecule of fructose 1,6-bisphosphate also be present, as well as 2 equivalents of Mg^{2+} . One Mg^{2+} ion coordinates to ADP, and the other increases the acidity of a water molecule necessary for protonation of the enolate ion. The requirement for a molecule of fructose 1,6-bisphosphate is not fully understood.



The overall result of glycolysis is summarized by the following equation:



PROBLEM 22.1

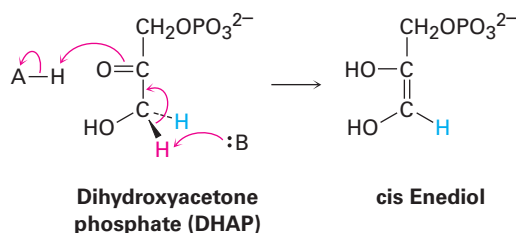
Identify the two steps in glycolysis in which ATP is produced.

PROBLEM 22.2

Look at the entire glycolysis pathway and make a list of the kinds of organic reactions that take place—nucleophilic acyl substitutions, aldol reactions, imine formations, E1cB reactions, and so forth.

PROBLEM 22.3

Is it the *pro-R* or *pro-S* hydrogen that is removed in step 5 of glycolysis, the isomerization of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate? You might want to review Section 5-11 on prochirality.

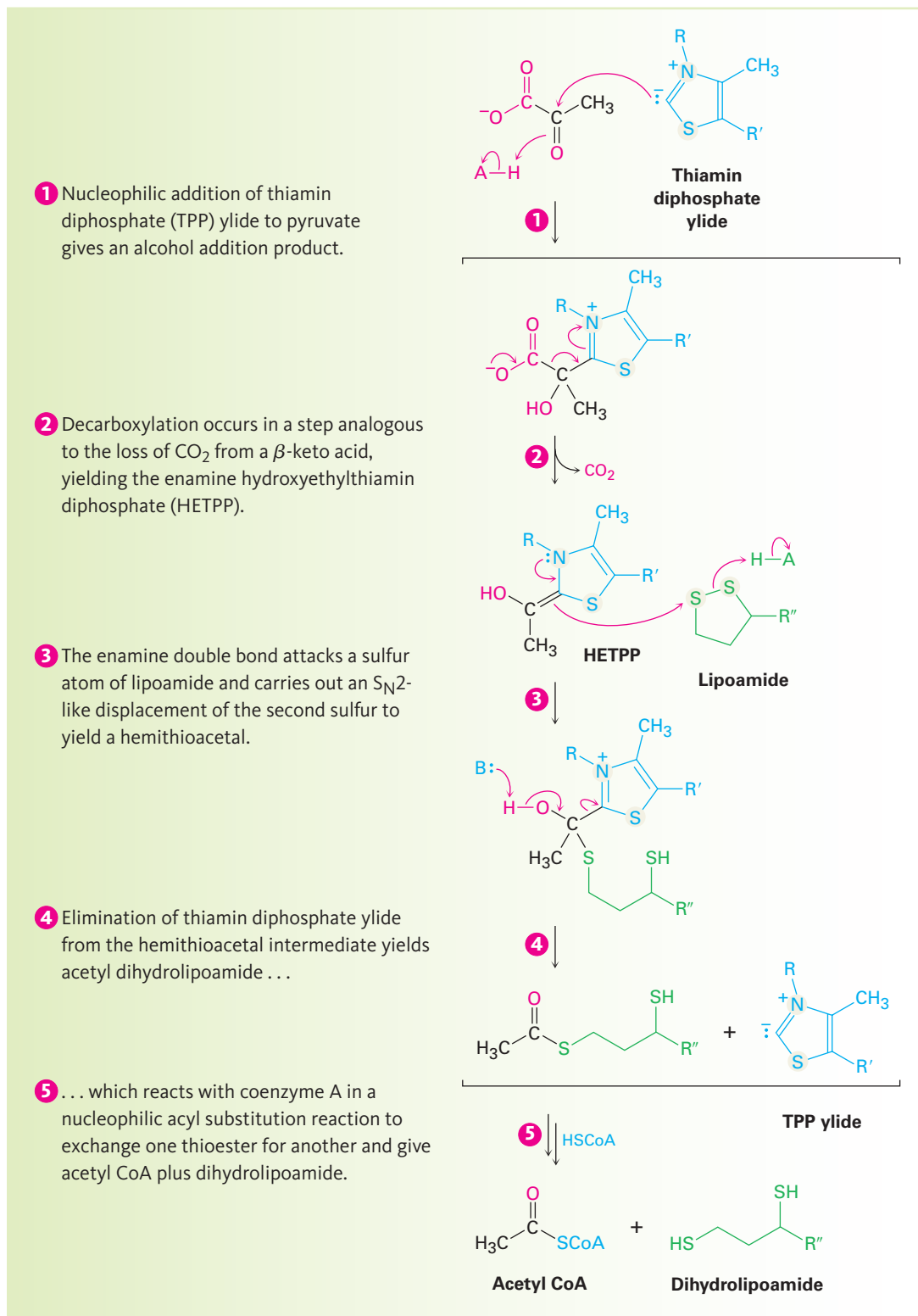
**PROBLEM 22.4**

In step 6 of glycolysis (Figure 22.6) the hydride ion from glyceraldehyde 3-phosphate adds to the *Si* face of NAD^+ . Draw the structure of the NADH that results, and indicate which hydrogen in NADH is the one added.

22-3 Conversion of Pyruvate to Acetyl CoA

Pyruvate, which is produced both by catabolism of glucose and by degradation of several amino acids (Section 20-4), can undergo several further transformations depending on the conditions and on the organism. In the absence of oxygen, pyruvate can be either reduced by NADH to yield lactate $[\text{CH}_3\text{CH}(\text{OH})\text{CO}_2^-]$ or, in yeast, fermented to give ethanol. Under typical aerobic conditions in mammals, however, pyruvate is converted by a process called *oxidative decarboxylation* to give acetyl CoA plus CO_2 . (*Oxidative* because the oxidation state of the carbonyl carbon rises from that of a ketone to that of a thioester.)

The conversion occurs through a multistep sequence of reactions catalyzed by a complex of enzymes and cofactors called the *pyruvate dehydrogenase complex*. The process occurs in three stages, each catalyzed by one of the enzymes in the complex, as outlined in **FIGURE 22.7**. Acetyl CoA, the ultimate product, then acts as fuel for the final stage of catabolism, the citric acid cycle.

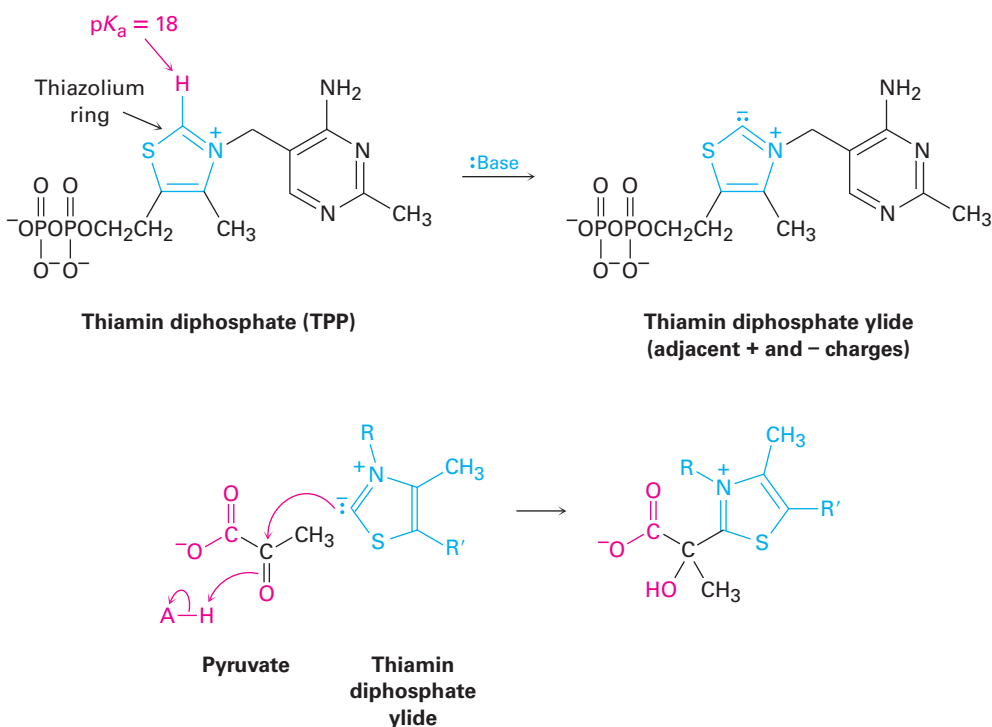


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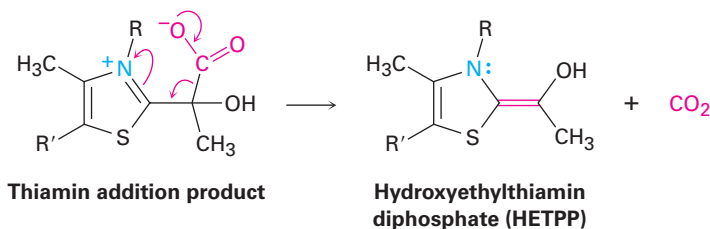
FIGURE 22.7 Mechanism of the conversion of pyruvate to acetyl CoA. Three different enzymes and five different coenzymes are required for this multistep series of reactions. Individual steps are explained in the text.

STEP 1 OF FIGURE 22.7: ADDITION OF THIAMIN DIPHOSPHATE The conversion of pyruvate to acetyl CoA begins by reaction of pyruvate with thiamin diphosphate, a derivative of vitamin B₁. Because it was originally called thiamin *pyrophosphate*, thiamin diphosphate is usually abbreviated as TPP. The spelling *thiamine* is also correct and frequently used.

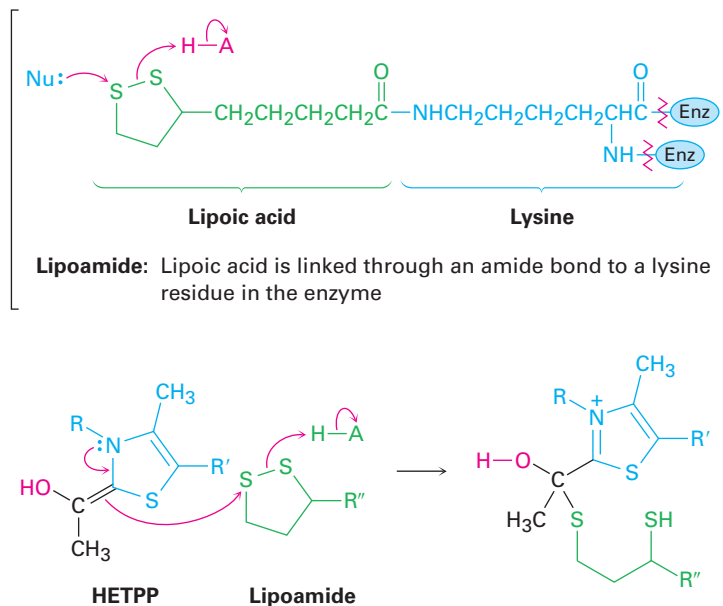
The key structural element in thiamin diphosphate is the presence of a thiazolium ring—a five-membered, unsaturated heterocycle containing a sulfur atom and a positively charged nitrogen atom. The thiazolium ring is weakly acidic, with a pK_a of approximately 18 for the C–H ring hydrogen between N and S. Bases can therefore deprotonate thiamin diphosphate, leading to formation of an *ylide*—a neutral species with adjacent + and – charges, such as the phosphonium ylides used in the Wittig reaction (Section 14-9). The TPP ylide is a nucleophile and adds to the ketone carbonyl group of pyruvate to yield an alcohol addition product.



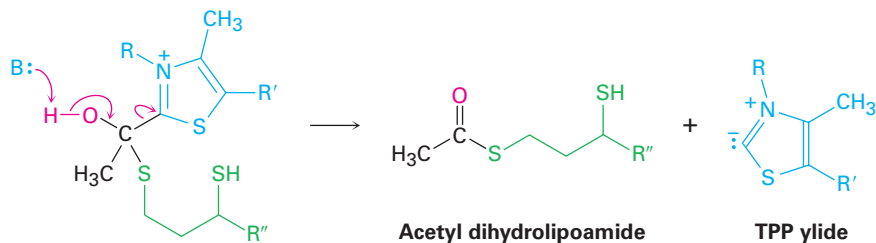
STEP 2 OF FIGURE 22.7: DECARBOXYLATION The TPP addition product, which contains an iminium ion β to a carboxylate anion, undergoes decarboxylation in step 2 in much the same way that a β -keto acid decarboxylates in the acetoacetic ester synthesis (Section 17-5). The $C=N^+$ bond of the pyruvate addition product acts like the $C=O$ bond of a β -keto acid to accept electrons as CO_2 leaves, giving hydroxyethylthiamin diphosphate (HETPP).



STEP 3 OF FIGURE 22.7: REACTION WITH LIPOAMIDE Hydroxyethylthiamin diphosphate is an enamine ($R_2N-C=C$), which, like all enamines, is nucleophilic (Section 17-12). It therefore reacts in step 3 with the enzyme-bound disulfide lipoamide by nucleophilic attack on a sulfur atom, displacing the second sulfur in an S_N2 -like substitution process.

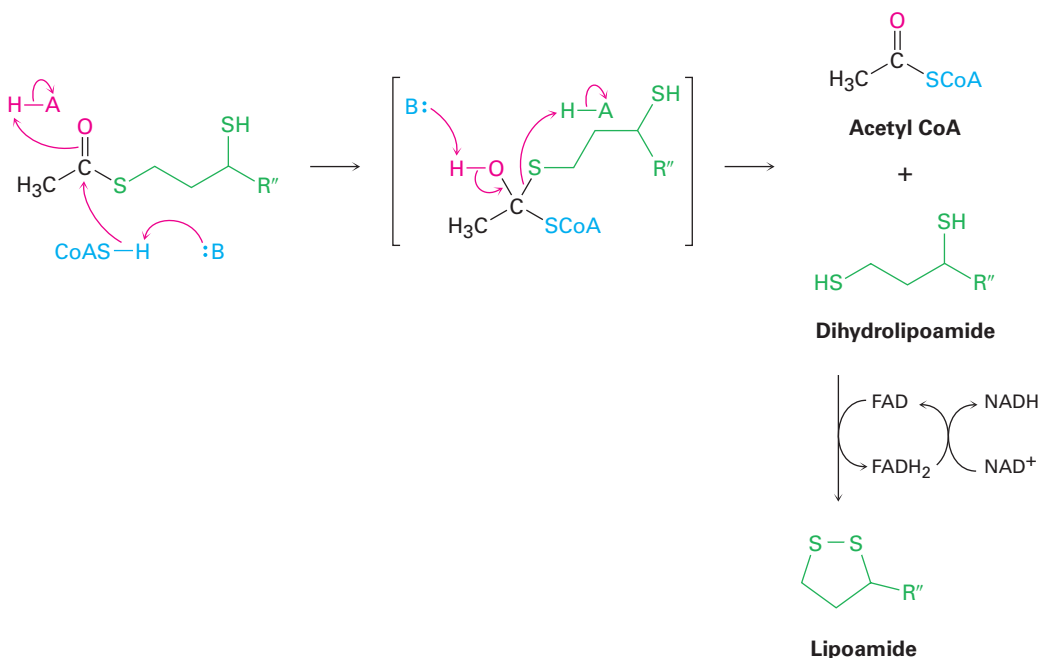


STEP 4 OF FIGURE 22.7: ELIMINATION OF THIAMIN DIPHOSPHATE The product of the HETPP reaction with lipoamide is a hemithioacetal, which eliminates thiamin diphosphate ylide in step 4. This elimination generates acetyl dihydrolipoamide by a mechanism that is the reverse of the ketone addition in step 1.



STEP 5 OF FIGURE 22.7: ACYL TRANSFER Acetyl dihydrolipoamide, a thioester, undergoes a nucleophilic acyl substitution reaction with coenzyme A in step 5 to yield acetyl CoA plus dihydrolipoamide. The dihydrolipoamide is then oxidized back to lipoamide by flavin adenine dinucleotide (FAD; Section 8-6), and the $FADH_2$ that results is in turn oxidized back to FAD by

NAD^+ , completing the catalytic cycle. We'll look in more detail at some reactions catalyzed by FAD in Section 23-5.



PROBLEM 22.5

Which carbon atoms in glucose end up as $-\text{CH}_3$ carbons in acetyl CoA, and which carbons end up as CO_2 ?

22-4 The Citric Acid Cycle

The initial stages of catabolism just discussed result in the conversion of carbohydrates into acetyl groups that are bonded through a thioester link to coenzyme A. Acetyl CoA then enters the next stage of catabolism—the **citric acid cycle**, also called the *tricarboxylic acid (TCA) cycle*, or *Krebs cycle*, after Hans Krebs, who unraveled its complexities in 1937. The overall result of the cycle is the conversion of an acetyl group into two molecules of CO_2 plus reduced coenzymes by the eight-step sequence of reactions shown in **FIGURE 22.8**.

As its name implies, the citric acid *cycle* is a closed loop of reactions in which the product of the final step (oxaloacetate) is a reactant in the first step. The intermediates are constantly regenerated and flow continuously through the cycle, which operates as long as the oxidizing coenzymes NAD^+ and FAD are available. To meet this condition, the reduced coenzymes NADH and FADH_2 must be reoxidized via the electron-transport chain, which in turn relies on oxygen as the ultimate electron acceptor. Thus, the cycle is

dependent on the availability of oxygen and on the operation of the electron-transport chain.

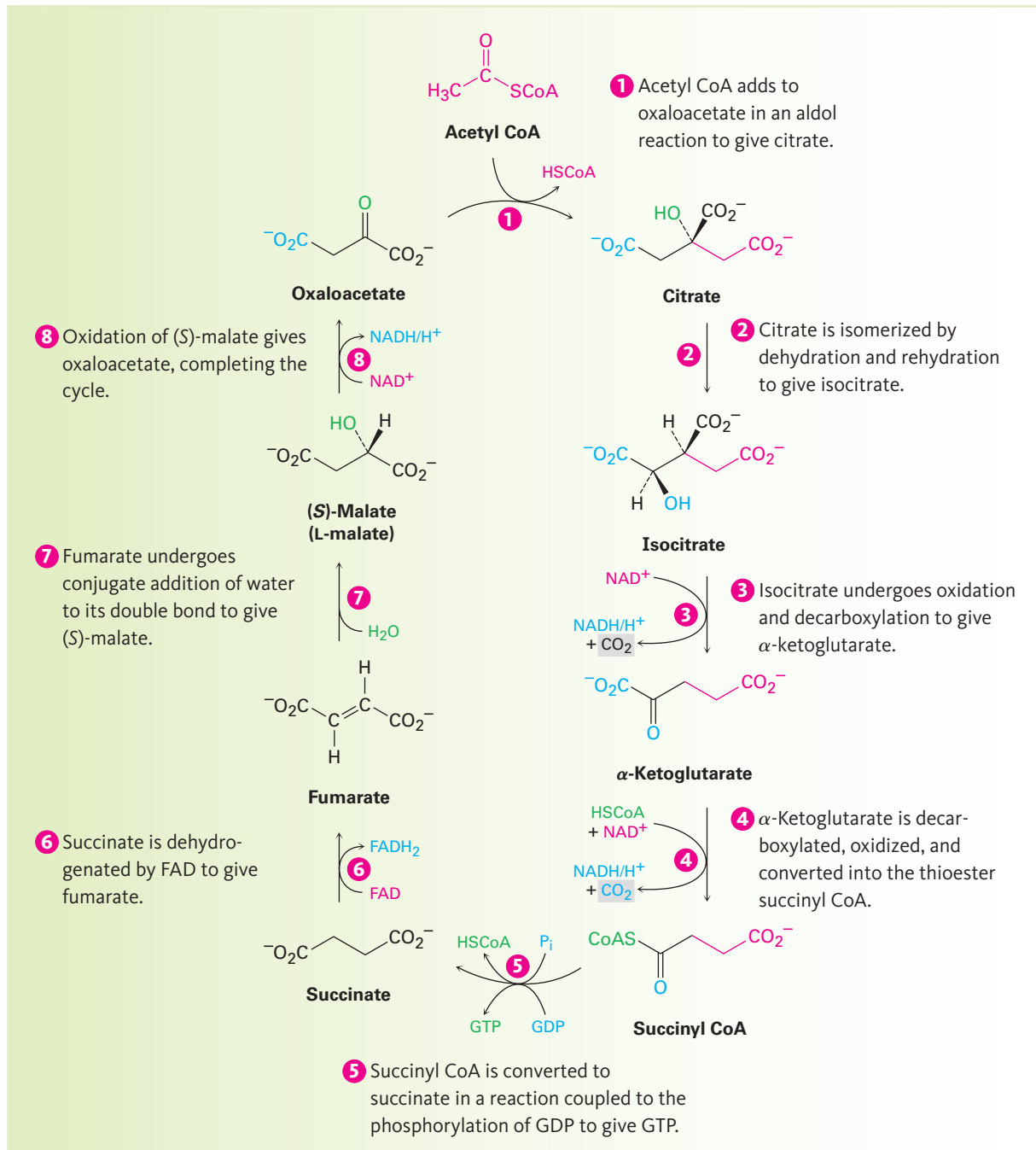
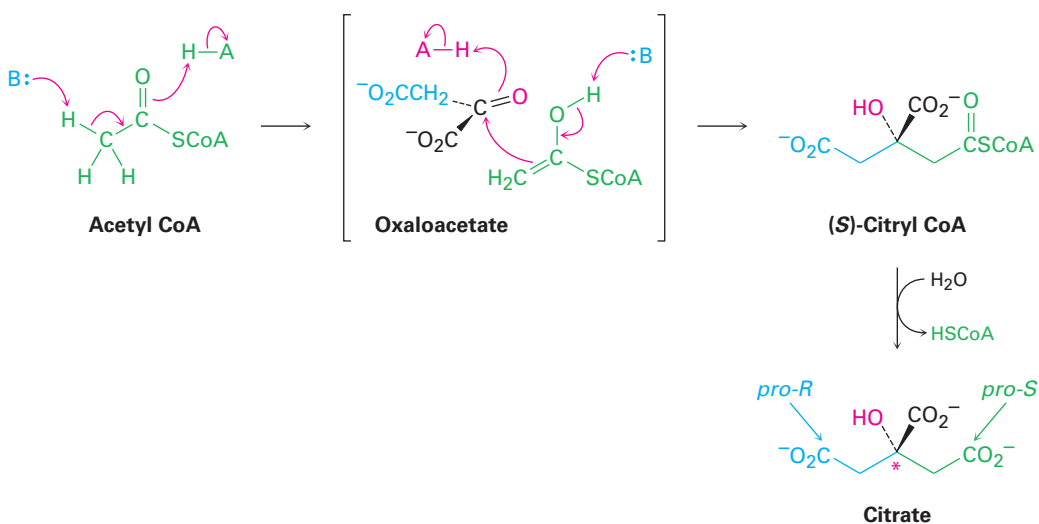


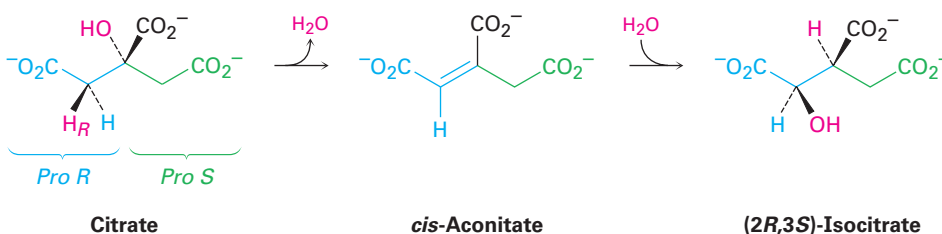
FIGURE 22.8 The citric acid cycle for metabolism of acetyl CoA. The cycle is an eight-step series of reactions that results in the conversion of an acetyl group into two molecules of CO_2 plus reduced coenzymes. Individual steps are explained in the text.

STEP 1 OF FIGURE 22.8: ADDITION TO OXALOACETATE Acetyl CoA enters the citric acid cycle in step 1 by nucleophilic addition to the oxaloacetate carbonyl group to give (*S*)-citryl CoA. The addition is an aldol reaction and is catalyzed by citrate synthase, as discussed in Section 19-10. (*S*)-Citryl CoA is then hydrolyzed to citrate by a typical nucleophilic acyl substitution reaction with water, catalyzed by the same citrate synthase enzyme.

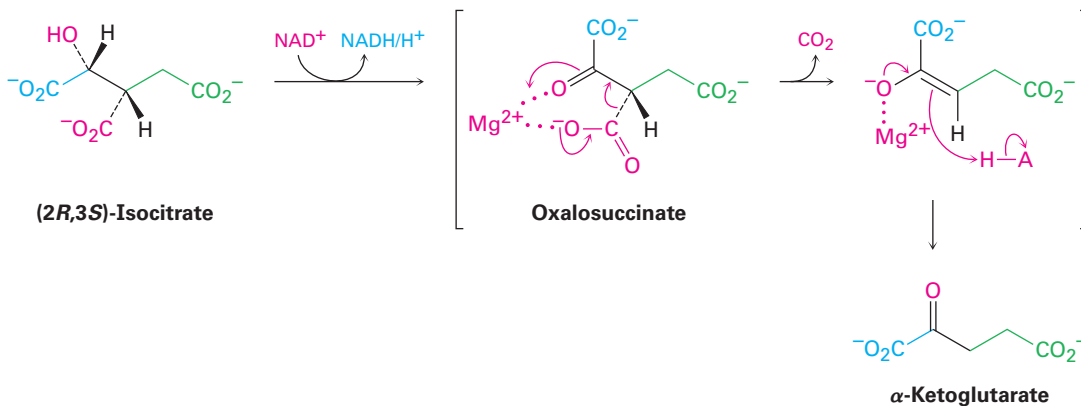
Note that the hydroxyl-bearing carbon of citrate is a prochirality center that contains two identical arms. Because the initial aldol reaction of acetyl CoA to oxaloacetate occurs specifically from the *Si* face of the ketone carbonyl group, the *pro-S* arm of citrate is derived from acetyl CoA and the *pro-R* arm is derived from oxaloacetate. You might want to review Section 5-11 on prochirality to brush up on the meanings of the various terms *pro-R*, *pro-S*, *Si*, and *Re*.



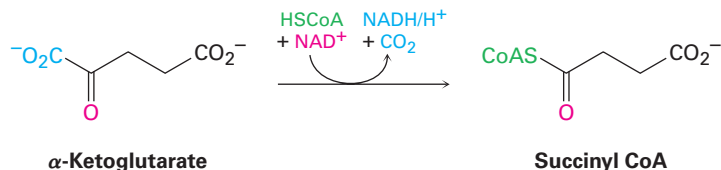
STEP 2 OF FIGURE 22.8: ISOMERIZATION Citrate, a prochiral tertiary alcohol, is converted in step 2 into its isomer, (*2R,3S*)-isocitrate, a chiral secondary alcohol. The isomerization occurs in two steps, both of which are catalyzed by the same aconitase enzyme. The initial step is an E1cB dehydration of a β -hydroxy acid to give *cis*-aconitate, the same sort of reaction that occurs in step 9 of glycolysis (Figure 22.3). The second step is a conjugate nucleophilic addition of water to the C=C bond (Section 14-11). The dehydration of citrate takes place specifically on the *pro-R* arm—the one derived from oxaloacetate—rather than on the *pro-S* arm derived from acetyl CoA.



STEP 3 OF FIGURE 22.8: OXIDATION AND DECARBOXYLATION (2*R*,3*S*)-Isocitrate, a secondary alcohol, is oxidized by NAD^+ in step 3 to give the ketone oxalosuccinate, which loses CO_2 to give α -ketoglutarate. Catalyzed by isocitrate dehydrogenase, the decarboxylation is a typical reaction of a β -keto acid, just like that in the acetoacetic ester synthesis (Section 17-5). The enzyme requires a divalent cation as cofactor to polarize the ketone carbonyl group and make it a better electron acceptor.

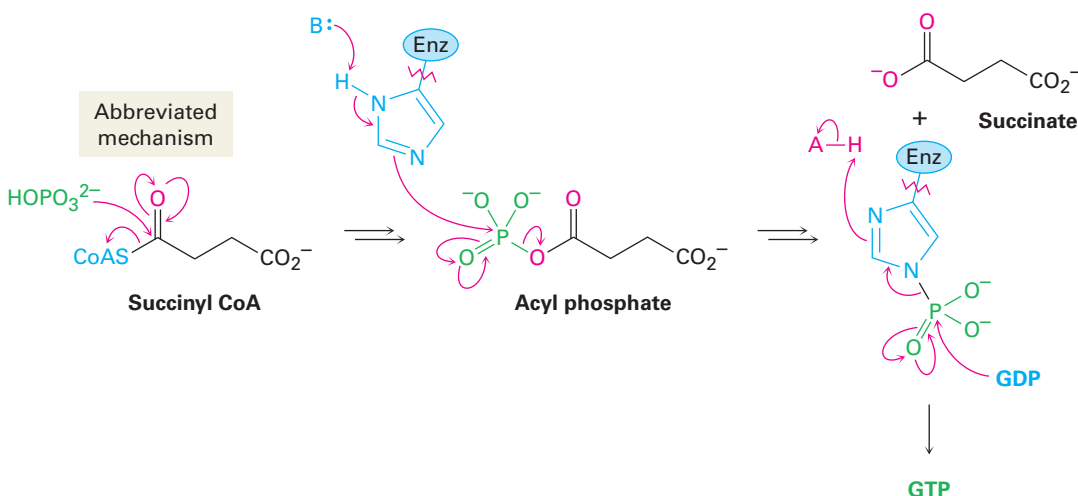


STEP 4 OF FIGURE 22.8: OXIDATIVE DECARBOXYLATION The transformation of α -ketoglutarate to succinyl CoA in step 4 is a multistep process just like the transformation of pyruvate to acetyl CoA that we saw in Figure 22-7. In both cases, an α -keto acid loses CO_2 and is oxidized to a thioester in a series of steps catalyzed by a multienzyme dehydrogenase complex. As in the conversion of pyruvate to acetyl CoA, the reaction involves an initial nucleophilic addition reaction of thiamin diphosphate ylide to α -ketoglutarate, followed by decarboxylation. Reaction with lipoamide, elimination of TPP ylide, and finally a transesterification of the dihydrolipoamide thioester with coenzyme A yields succinyl CoA.

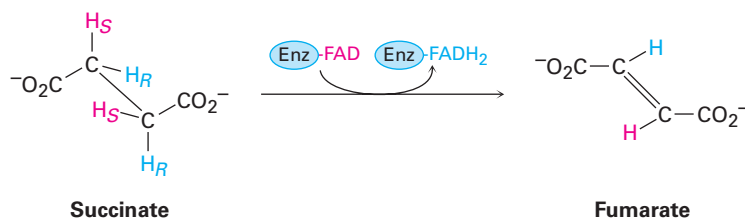


STEP 5 OF FIGURE 22.8: ACYL CoA CLEAVAGE Succinyl CoA is converted to succinate in step 5. The reaction is catalyzed by succinyl CoA synthetase and is coupled with phosphorylation of guanosine diphosphate (GDP) to give guanosine triphosphate (GTP). The overall transformation is similar to that of steps 6 to 8 in glycolysis (Figure 22.3), in which a thioester is converted into an acyl phosphate and a phosphate is then transferred to ADP.

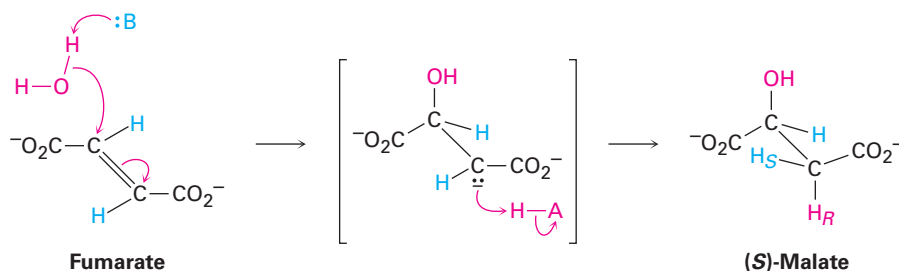
The overall result is a “hydrolysis” of the thioester group, but without involving water.



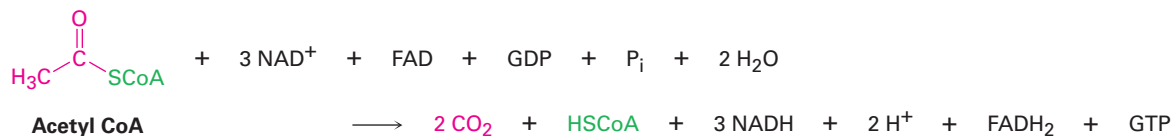
STEP 6 OF FIGURE 22.8: DEHYDROGENATION Succinate is dehydrogenated in step 6 by the FAD-dependent succinate dehydrogenase to give fumarate. The process is analogous to what occurs in fatty-acid catabolism, but the mechanism is a bit complex so we'll defer comments about it until Section 23-5. The reaction is stereospecific, removing the *pro-S* hydrogen from one carbon and the *pro-R* hydrogen from the other.



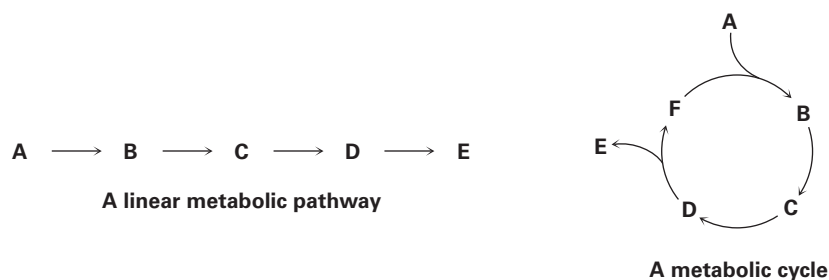
STEPS 7–8 OF FIGURE 22.8: HYDRATION AND OXIDATION The final two steps in the citric acid cycle are the conjugate nucleophilic addition of water to fumarate to yield (*S*)-malate and the oxidation of (*S*)-malate by NAD⁺ to give oxaloacetate. The addition is catalyzed by fumarase and is mechanistically similar to the addition of water to *cis*-aconitate in step 2. The reaction occurs through an enolate-ion intermediate, which is protonated on the side opposite the OH, leading to a net anti addition.



The final step is the oxidation of (*S*)-malate by NAD^+ to give oxaloacetate, a reaction catalyzed by malate dehydrogenase. The citric acid cycle has now returned to its starting point, ready to revolve again. The overall result of the cycle is



One further point before leaving this discussion of the citric acid cycle: most metabolic pathways—glycolysis, for example—are *linear*, starting with one substance and ending some number of steps later with the final product. The citric acid cycle, however, is a *cycle*—a closed loop of reactions that starts and ends with the same substance, while throwing off the products at some intermediate point. Why is a cyclic pathway needed for acetyl CoA metabolism?

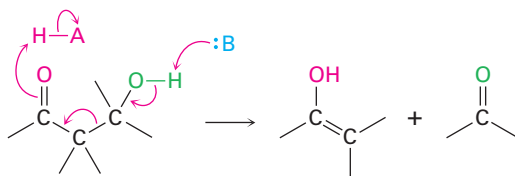


Cyclic metabolic pathways are less common than linear pathways, and those that occur all have one thing in common: all involve very small molecules with few functional groups. The urea cycle, for instance, begins with NH_3 (Section 20-3); the citric acid cycle begins with acetyl CoA; the photosynthetic Calvin cycle used by green plants to synthesize carbohydrates begins with CO_2 ; and so forth. When starting with a relatively large multifunctional molecule like glucose, the number of potential reaction choices is also large, so an efficient linear pathway is energetically feasible, but when starting with a small monofunctional molecule like NH_3 , CO_2 , or acetyl CoA, limited reaction choices are available and a linear pathway may not be possible.

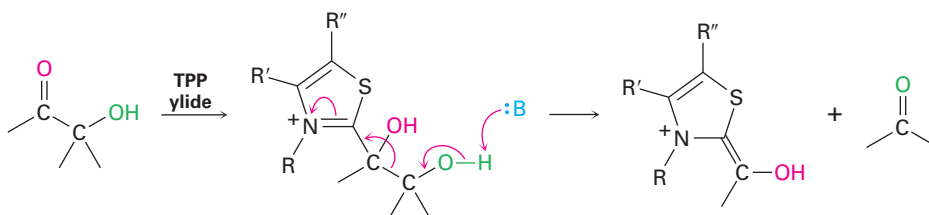
Take the citric acid cycle for example. The metabolic purpose of the cycle is to convert the two-carbon molecule acetyl CoA into two molecules of CO_2 , which means that a C–C bond must be broken. But there are very few organic reaction mechanisms for breaking C–C bonds, and only two are common in biochemistry. One is the retro-aldol cleavage of a β -hydroxy (or β -carboxy) ketone, as occurs in step 4 of glycolysis (Figure 22.3); the other is the thiamin diphosphate (TPP) dependent cleavage of an α -hydroxy (or α -carboxy) ketone,

as occurs in step 1 of pyruvate catabolism (Figure 22.7). Neither of these mechanisms is applicable to acetyl CoA, however, because both require two functional groups. As a result, acetyl CoA can't be degraded in a simple, linear pathway, leaving a more complex cycle as the only option.

Retro-aldol β cleavage



TPP-dependent α cleavage



PROBLEM 22.6

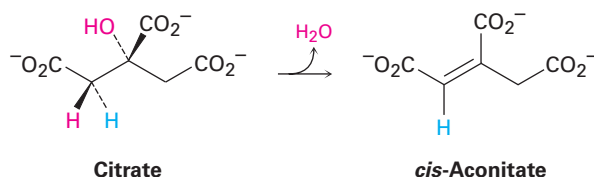
Which of the substances in the citric acid cycle are tricarboxylic acids, thus giving the cycle its alternative name?

PROBLEM 22.7

Write mechanisms for step 2 of the citric acid cycle, the dehydration of citrate and the addition of water to *cis*-aconitate.

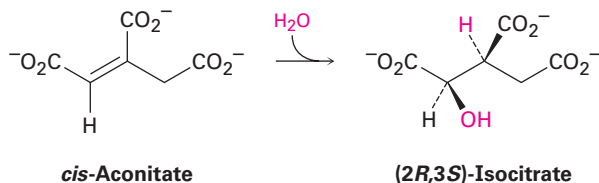
PROBLEM 22.8

Is the *pro-R* or *pro-S* hydrogen removed from citrate during the dehydration in step 2 of the citric acid cycle? Does the elimination reaction occur with syn or anti geometry?



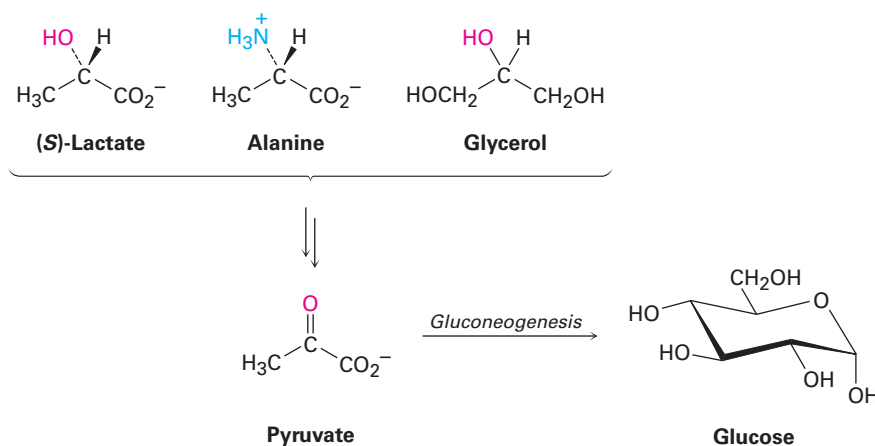
PROBLEM 22.9

Does -OH add to the *Si* face or the *Re* face of *cis*-aconitate in step 2 of the citric acid cycle? Does the addition of water occur with syn or anti geometry?

**22-5 Biosynthesis of Glucose: Gluconeogenesis**

Now that we've seen how glucose is catabolized, let's finish this chapter by seeing how it is biosynthesized. Glucose is the body's primary fuel when food is plentiful, but in times of fasting or prolonged exercise, glucose stores can become depleted. Most tissues then begin metabolizing fats as their source of acetyl CoA, but the brain is different. The brain relies almost entirely on glucose for fuel and is dependent on receiving a continuous supply in the blood. When the supply of glucose fails, even for a brief time, irreversible damage can occur. Thus, a pathway for synthesizing glucose from simple precursors is crucial.

Higher organisms are not able to synthesize glucose from acetyl CoA but must instead use one of the three-carbon precursors (*S*)-lactate, alanine, or glycerol, all of which are readily converted into pyruvate.



Pyruvate then becomes the starting point for **gluconeogenesis**, the 11-step biosynthetic pathway by which organisms make glucose (FIGURE 22.9). The gluconeogenesis pathway by which glucose is made, however, is not the reverse of the glycolysis pathway by which it is degraded. The catabolic and anabolic pathways *must* differ in at least some details for both to be energetically favorable and for independent regulatory mechanisms to operate.

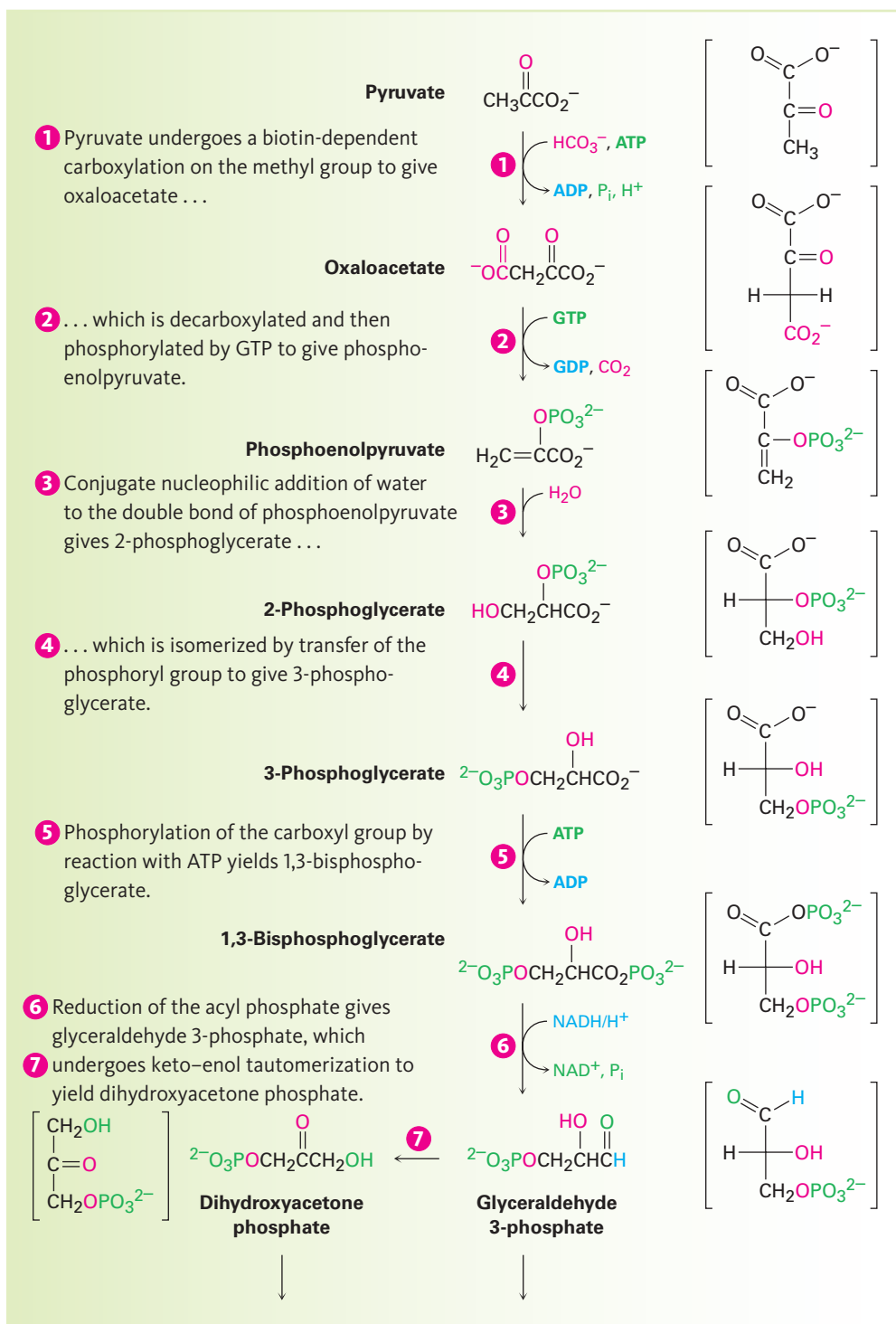


FIGURE 22.9 The 11-step gluconeogenesis pathway for the biosynthesis of glucose from pyruvate. Individual steps are explained in the text.

continued

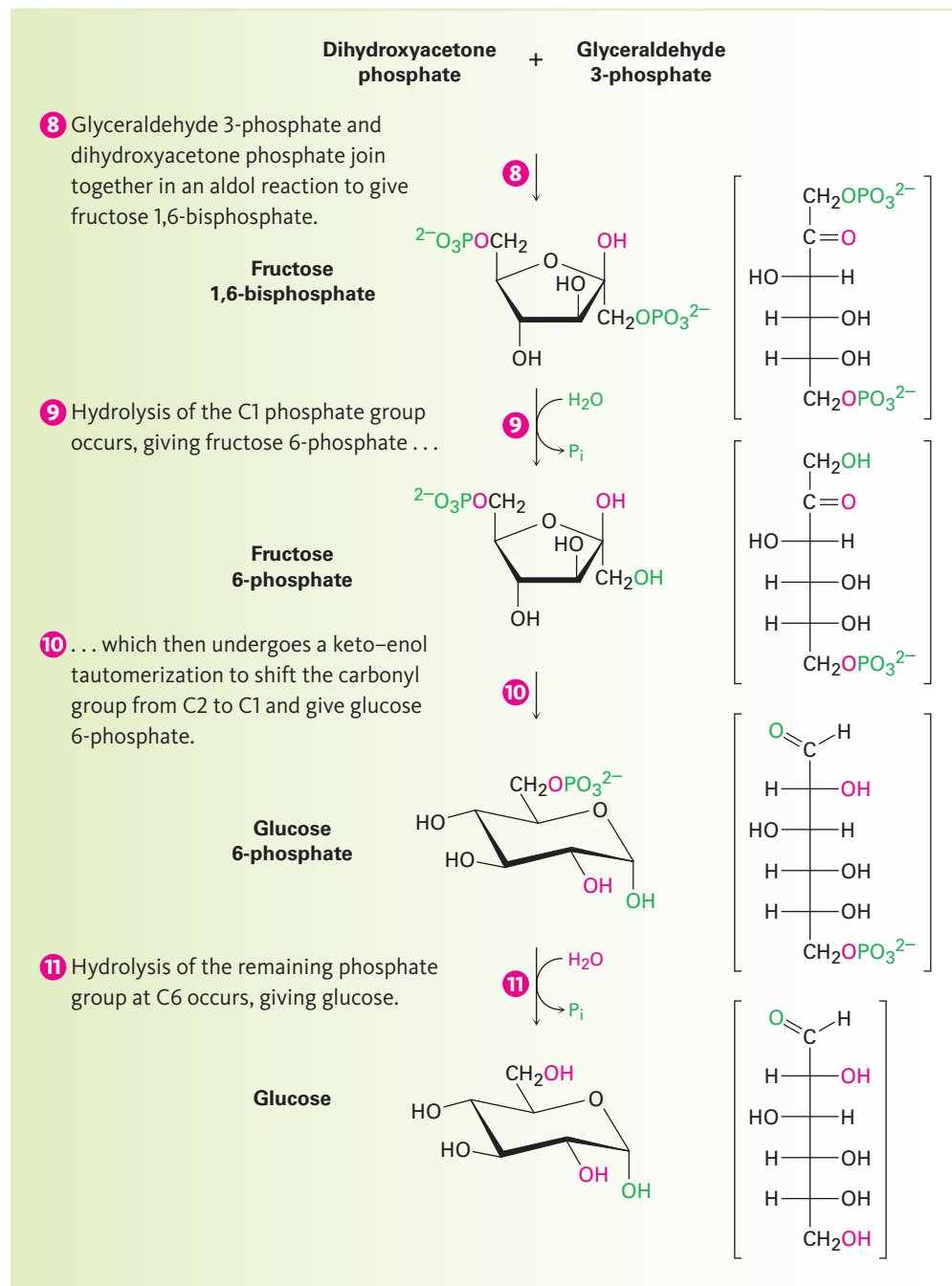
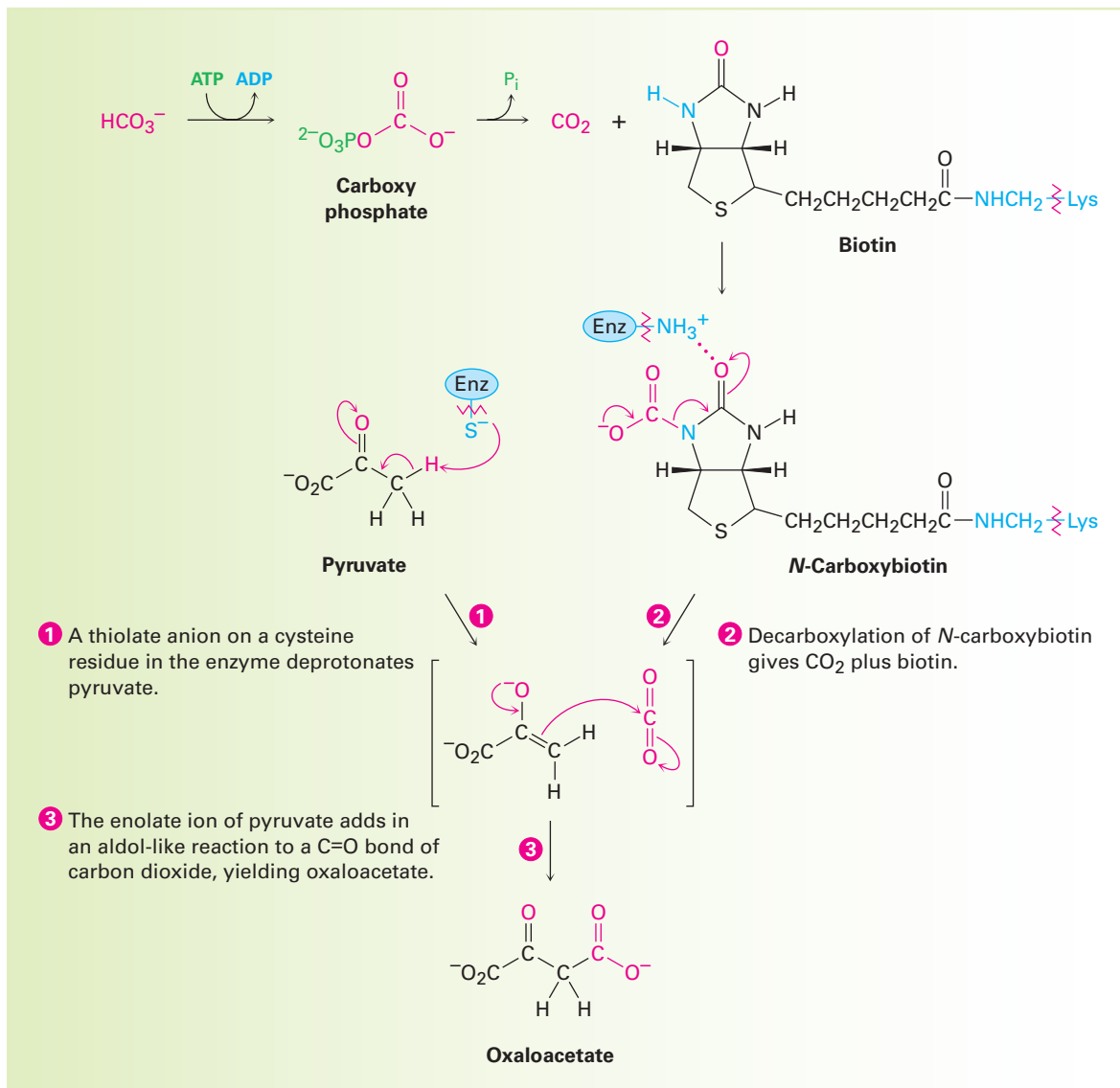


FIGURE 22.9 (continued)

STEP 1 OF FIGURE 22.9: CARBOXYLATION Gluconeogenesis begins with the carboxylation of pyruvate to yield oxaloacetate. The reaction is catalyzed by pyruvate carboxylase and requires ATP, bicarbonate ion, and the coenzyme biotin, which acts as a carrier to transport CO_2 to the enzyme active site. ATP first reacts with bicarbonate to give carboxy phosphate, as in the urea cycle

(Figure 20.4, page 724), and carboxy phosphate then undergoes decarboxylation. Biotin reacts with the released CO_2 to give *N*-carboxybiotin, which itself then decarboxylates. Simultaneously, and in close proximity on the enzyme, pyruvate is deprotonated to give an anion that immediately adds to the CO_2 , yielding oxaloacetate. The mechanism of this carboxylation step is shown in **FIGURE 22.10**.



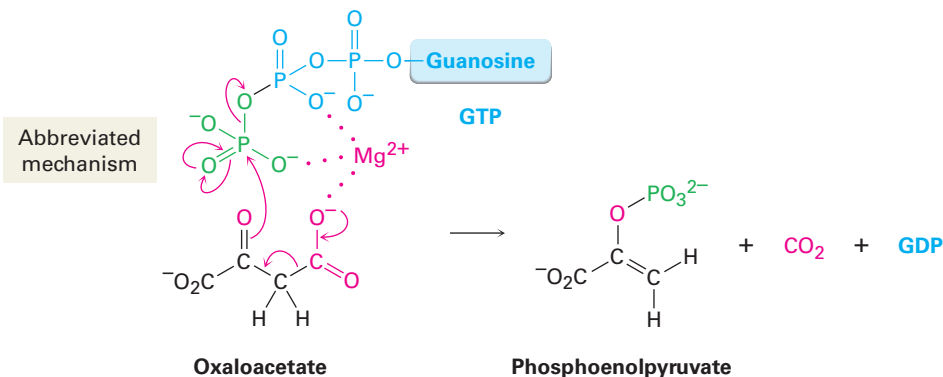
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FIGURE 22.10 Mechanism of step 1 in Figure 22.9, carboxylation of pyruvate to give oxaloacetate. Biotin acts as a carrier of CO_2 , moving it to the appropriate position in the enzyme so that it can react with pyruvate.

STEP 2 OF FIGURE 22.9: DECARBOXYLATION AND PHOSPHORYLATION

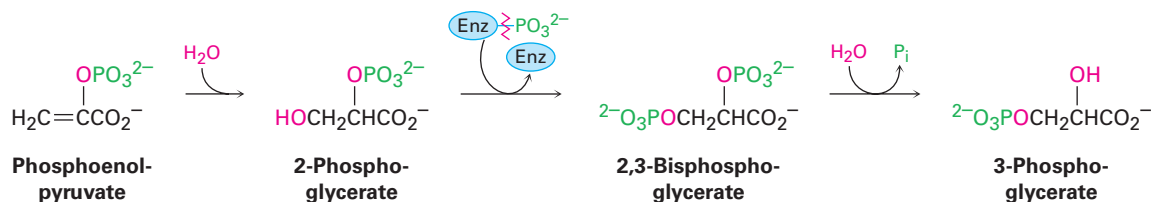
Decarboxylation of oxaloacetate, a β -keto acid, occurs in step 2 by a typical retro-aldol mechanism like that in step 3 in the citric acid cycle (Figure 22.8). Phosphorylation of the resultant pyruvate enolate ion by GTP

occurs concurrently to give phosphoenolpyruvate in a reaction catalyzed by phosphoenolpyruvate carboxykinase.



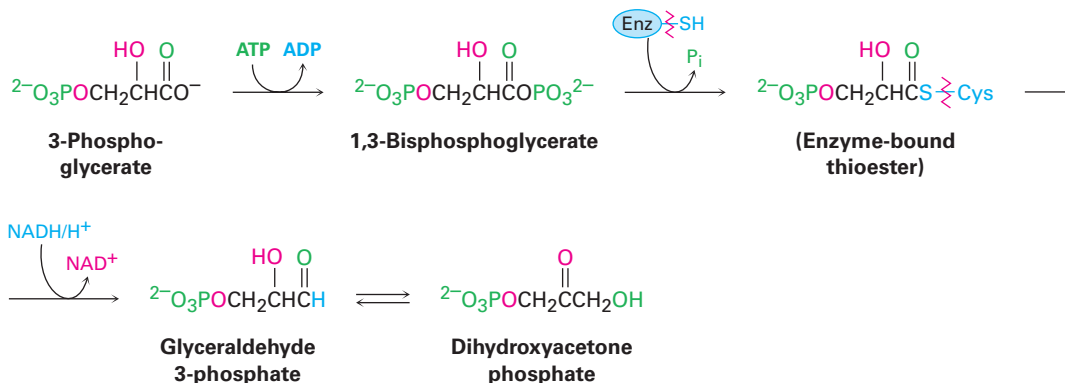
Why is carbon dioxide added in step 1 and then immediately removed in step 2? Why doesn't the conversion of pyruvate to phosphoenolpyruvate proceed directly in a single step by reaction of pyruvate enolate ion with GTP rather than indirectly in two steps? The likely answer lies in the energetics of the process. Phosphoenolpyruvate is sufficiently high in energy that its direct synthesis from pyruvate is unfavorable even though it consumes a molecule of GTP. In the two-step process involving oxaloacetate, however, *two* molecules of nucleoside triphosphate are consumed (one ATP and one GTP), releasing sufficient energy to make the overall process favorable.

STEPS 3–4 OF FIGURE 22.9: HYDRATION AND ISOMERIZATION Conjugate nucleophilic addition of water to the double bond of phosphoenolpyruvate gives 2-phosphoglycerate in step 3 by a process similar to that of step 7 in the citric acid cycle (Figure 22.8). Phosphorylation of C3 and dephosphorylation of C2 then yields 3-phosphoglycerate in step 4. Mechanistically, these steps are the reverse of steps 9 and 8 in glycolysis (Figure 22.3), both of which have equilibrium constants near 1.

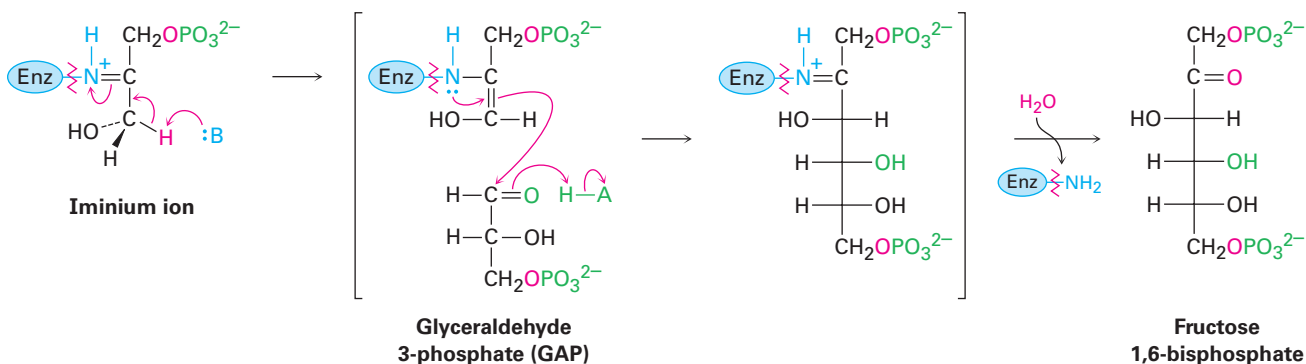


STEPS 5–7 OF FIGURE 22.9: PHOSPHORYLATION, REDUCTION, AND TAUTOMERIZATION Reaction of 3-phosphoglycerate with ATP in step 5 generates the corresponding acyl phosphate, 1,3-bisphosphoglycerate, which binds to the glyceraldehyde 3-phosphate dehydrogenase by a thioester bond to a cysteine residue. Reduction of the thioester by NADH/H⁺ in step 6 then yields the corresponding aldehyde, and keto–enol tautomerization of the

aldehyde in step 7 gives dihydroxyacetone phosphate. All three steps are mechanistically the reverse of the corresponding steps 7, 6, and 5 of glycolysis and have equilibrium constants near 1.



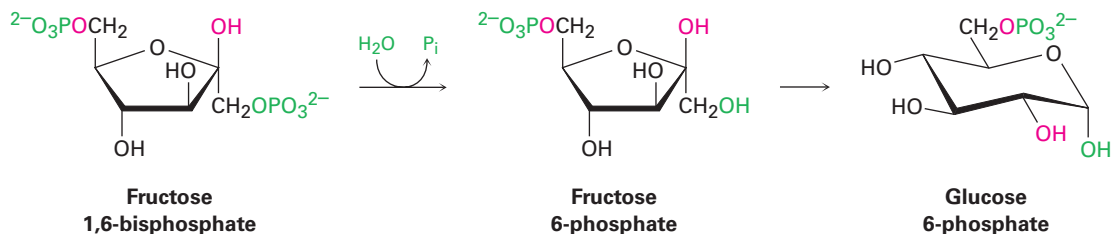
STEP 8 OF FIGURE 22.9: ALDOL REACTION Dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, the two 3-carbon units produced in step 7, join by an aldol reaction in step 8 to give fructose 1,6-bisphosphate, the reverse of step 4 in glycolysis. As in glycolysis (Figure 22.3), the reaction is catalyzed in plants and animals by a class I aldolase and takes place on an iminium ion formed by reaction of dihydroxyacetone phosphate with a side-chain lysine -NH_2 group on the enzyme. Loss of a proton from the neighboring carbon then generates an enamine, an aldol-like reaction ensues, and the product is hydrolyzed.



STEPS 9–10 OF FIGURE 22.9: HYDROLYSIS AND ISOMERIZATION

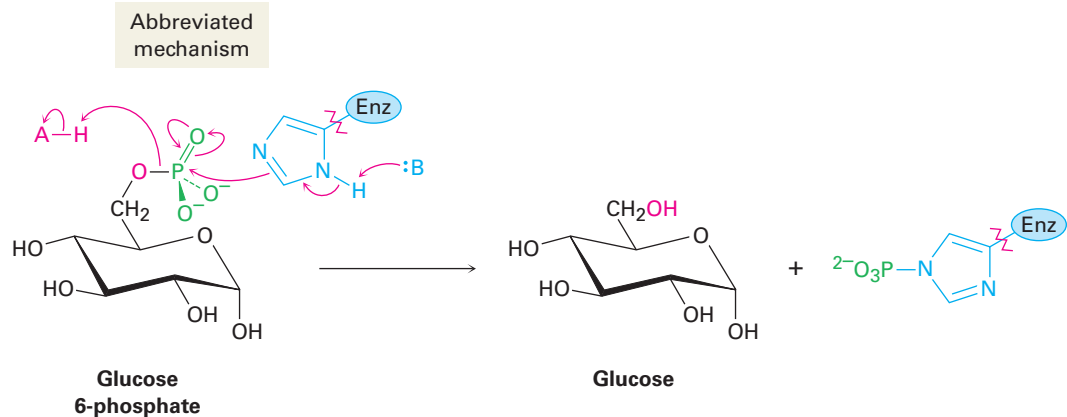
Hydrolysis of the phosphate group at C1 of fructose 1,6-bisphosphate gives fructose 6-phosphate in step 9. Although the *result* of the reaction is the opposite of step 3 in glycolysis, the mechanism is not. In glycolysis, the phosphorylation is accomplished by reaction of fructose with ATP, with formation of ADP as by-product. The reverse of that process, however—the reaction of fructose 1,6-bisphosphate with ADP to give fructose 6-phosphate and ATP—is energetically unfavorable because ATP is too high in energy. Thus, an alternative pathway is used in which the C1 phosphate group is removed by a direct hydrolysis reaction, catalyzed by fructose 1,6-bisphosphatase.

Following hydrolysis, keto–enol tautomerization of the carbonyl group from C2 to C1 in step 10 gives glucose 6-phosphate. The isomerization is the reverse of step 2 in glycolysis (Figure 22.3).

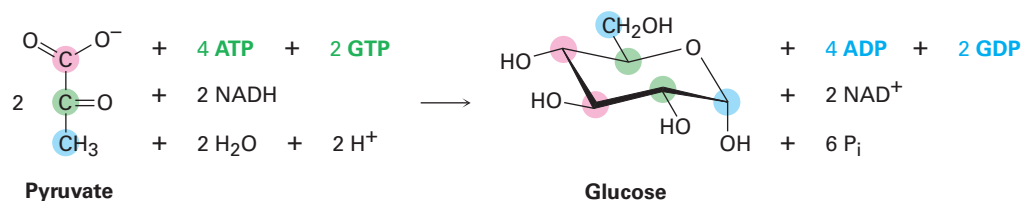


STEP 11 OF FIGURE 22.9: HYDROLYSIS The final step in gluconeogenesis is the conversion of glucose 6-phosphate to glucose by a second phosphatase-catalyzed hydrolysis reaction. As just discussed for the hydrolysis of fructose 1,6-bisphosphate in step 9, and for the same energetic reasons, the mechanism of the glucose 6-phosphate hydrolysis is not the reverse of the corresponding step 1 in glycolysis.

Interestingly, however, the mechanisms of the two phosphate hydrolysis reactions in steps 9 and 11 are not the same. In step 9, water is the nucleophile, but in the glucose 6-phosphate reaction of step 11, a histidine residue on the enzyme attacks phosphorus, giving a phosphoryl enzyme intermediate that subsequently reacts with water.



The overall result of gluconeogenesis is summarized by the following equation, and a comparison of the gluconeogenesis and glycolysis pathways is given in **FIGURE 22.11**. The pathways differ at the three steps indicated by red reaction arrows.



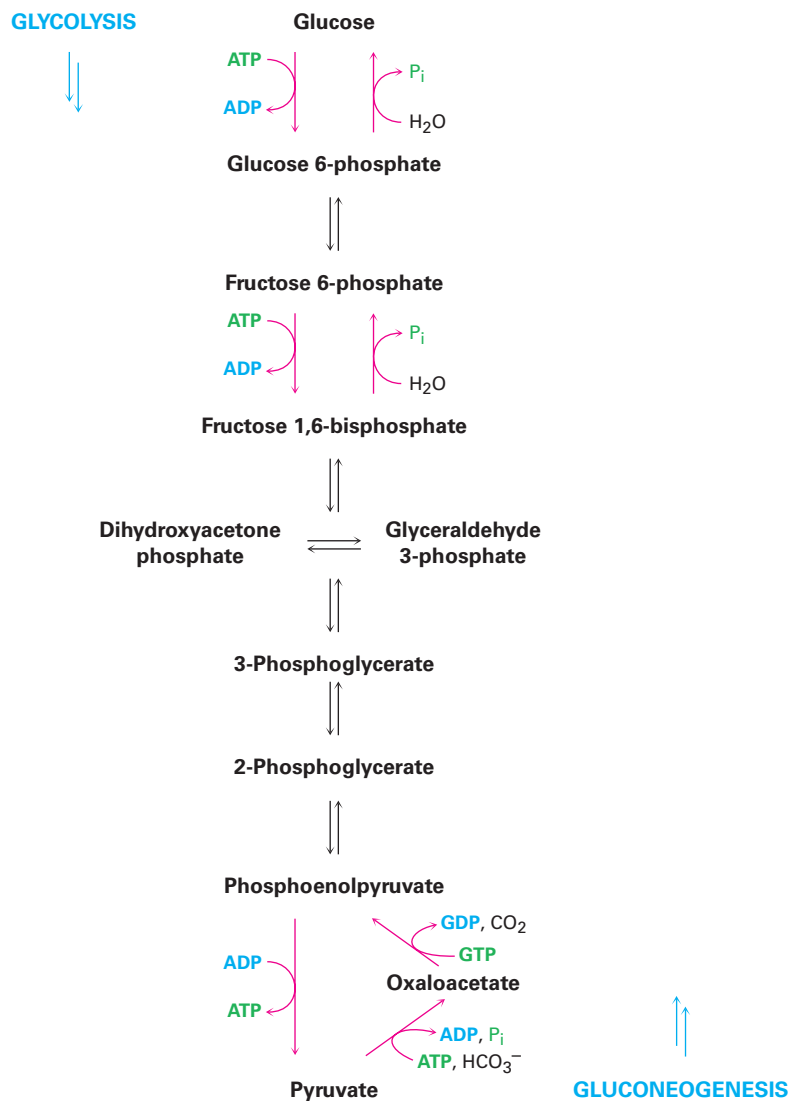


FIGURE 22.11 Comparison of glycolysis and gluconeogenesis pathways. The pathways differ at the three steps indicated by red reaction arrows.

PROBLEM 22.10

Write a mechanism for step 6 of gluconeogenesis, the reduction of 1,3-bisphosphoglycerate with NADH/H^+ to yield glyceraldehyde 3-phosphate.

SOMETHING EXTRA

Influenza Pandemics

Each year, seasonal outbreaks of influenza occur throughout the world, usually without particular notice. These outbreaks are caused by subtypes of known flu viruses that are already present in the population, and they can usually be controlled or prevented by vaccination. Every 10 to 40 years, however, a new and virulent subtype never before seen in humans appears. The result can be a worldwide pandemic, capable of causing great disruption and killing millions.

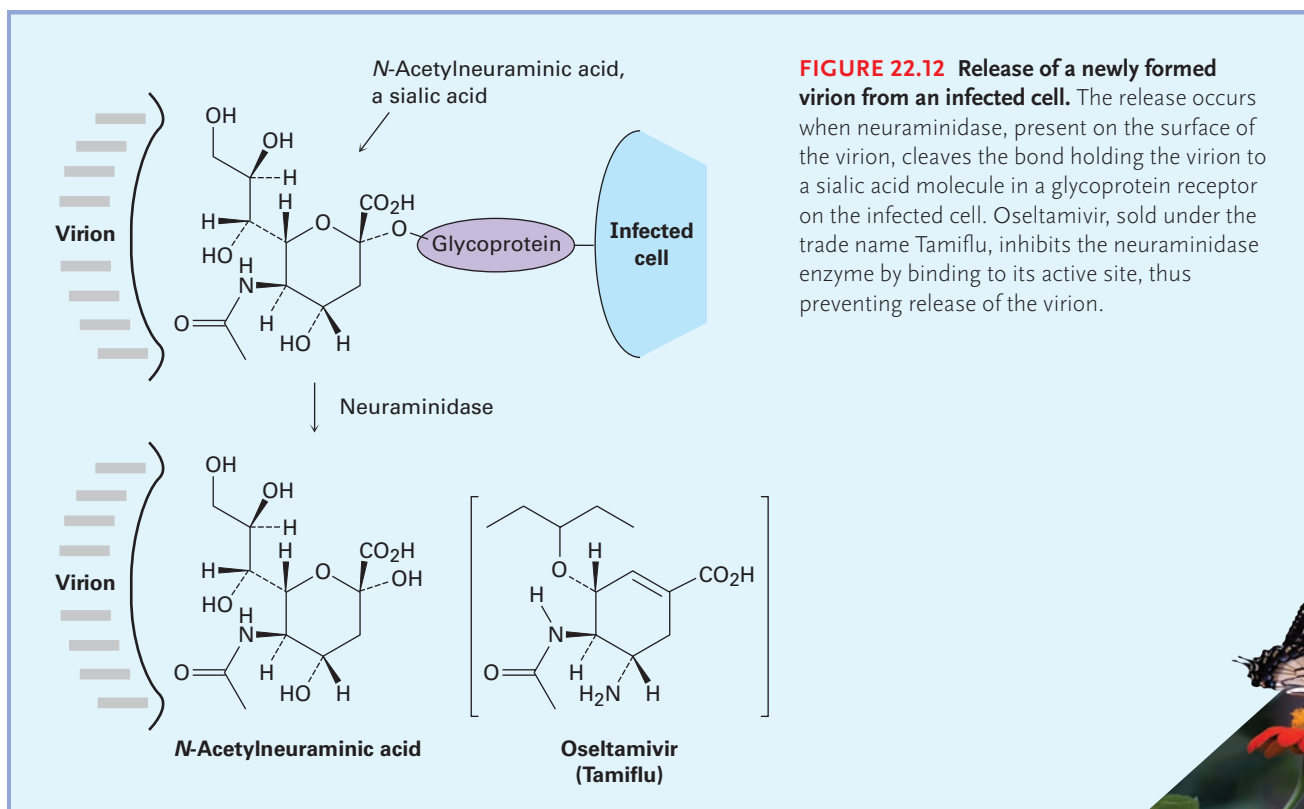
Three such pandemics struck in the 20th century, the most serious of which was the 1918–1919 “Spanish flu” that killed an estimated 50 million people worldwide, including many healthy young adults. It has now been more than 40 years since the last pandemic, an outbreak of “Hong Kong flu” in 1968–1969, and many public health officials fear that another may occur soon. The Hong Kong flu was relatively mild compared to the Spanish flu—worldwide casualties were only 750,000—but there is no way of knowing how deadly the next outbreak will be.

Several potentially serious influenza outbreaks have occurred in recent years. The first, discovered in 1997, is commonly called “bird flu.” The second, found in early 2009 is “swine flu.” Bird flu is caused by the transfer to humans of an avian H5N1 virus that has killed tens of millions of birds, primarily in Southeast Asia. Human infection by this virus was first noted in Hong Kong in 1997, and by mid-2013, 622 cases and 371 deaths had been confirmed in 15 countries. The virus is transmitted primarily from poultry to humans rather than between humans, but the H5N1 strain is highly pathogenic, mutates rapidly, and is able to acquire genes from viruses that infect other animal species. Thus, there is a fear that the capability for human-to-human transmission may increase rapidly. More recently an avian H7N9 virus has been found in humans. Sixty cases and 24 deaths had been confirmed in China as of May, 2013.

Swine flu is caused by an H1N1 virus related to those found in pigs, although the exact origin of the virus is not yet known. The virus appears to spread rapidly in humans—more than 3000 cases were found in the first 2 months after it was identified. Until it was brought under control in mid-2010, 18,449 deaths in 214 countries had been reported.

The classifications H5N1 and H1N1 for the two viral strains are based on the behavior of two kinds of glycoproteins that coat the viral surface—hemagglutinin (H, type 5 or type 1) and neuraminidase (N, type 1) which, as its name implies, is an enzyme. Infection occurs when a viral particle, or *virion*, binds to the sialic acid part (Section 21-7) of a receptor glycoprotein on the target cell and is then engulfed by the cell. New viral particles are produced inside the infected cell, pass back out, and are again held by sialic acid bonded to glycoproteins in cell-surface receptors. Finally, the neuraminidase present on the viral surface cleaves the bond between receptor glycoprotein and sialic acid, thereby releasing the virion and allowing it to invade a new cell (FIGURE 22.12).

So what can be done to limit the severity of an influenza pandemic? Development of a vaccine is the only means to limit the spread of the virus, but work can't begin until the contagious strain of virus has appeared. Until that time, the only hope is that an antiviral drug might limit the severity of infection. Oseltamivir, sold as Tamiflu, and zanamivir, sold as Relenza, are two of only a handful of known substances able to inhibit the neuraminidase enzyme. With the enzyme blocked, newly formed virions are not released, and spread of the infection within the body is thus limited. You might notice in Figure 22.12 the similarity in shape between *N*-acetylneuraminic acid and both oseltamivir and zanamivir, which allows the drugs to bind to and block the action of neuraminidase. Unfortunately, the H1N1 swine flu virus developed almost complete resistance to oseltamivir within a year of appearing, so chemists will have to work hard to keep ahead.



SUMMARY

Glucose metabolism is at the center of biological chemistry. Fortunately, it's also relatively straightforward because the molecules are small and the reactions involved are almost entirely the carbonyl-group processes discussed previously in Chapters 14 to 17.

Carbohydrates are the chemical intermediaries by which carbon atoms from CO_2 are incorporated into growing organisms. Thus, carbohydrates are the biological starting point. In humans, carbohydrate metabolism begins with glycosidase-catalyzed digestion of starch to give glucose. Glucose catabolism then begins with **glycolysis**, a series of ten enzyme-catalyzed reactions that break down glucose into 2 equivalents of pyruvate, $\text{CH}_3\text{COCO}_2^-$. Depending on the organism, pyruvate is then converted either into lactate, ethanol, or (in mammals) acetyl CoA. The key step in the formation of acetyl CoA is the decarboxylation of pyruvate catalyzed by thiamin diphosphate, TPP.

Acetyl CoA next enters the **citric acid cycle**, also called the *tricarboxylic acid (TCA) cycle*, or *Krebs cycle*. The overall result of the cycle is the conversion of an acetyl group into two molecules of CO_2 plus reduced coenzymes by an eight-step sequence. The cycle is a closed loop of reactions in which the product of the final step (oxaloacetate) is a reactant in the first step. The intermediates are constantly regenerated and flow continuously through the cycle, which operates as long as the oxidizing coenzymes NAD^+ and FAD are available.

KEY WORDS

citric acid cycle, 787
 gluconeogenesis, 794
 glycolysis, 776

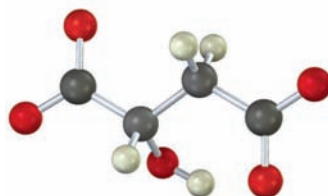
Higher organisms are not able to synthesize glucose from acetyl CoA but must instead use one of the 3-carbon precursors lactate, glycerol, or alanine, all of which are readily converted into pyruvate. Pyruvate then becomes the starting point for **gluconeogenesis**, the 11-step biosynthetic pathway by which organisms make glucose.

EXERCISES

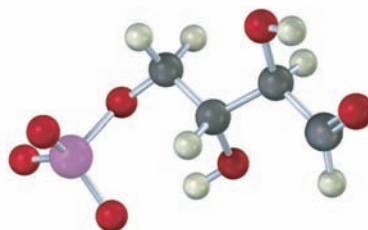
VISUALIZING CHEMISTRY

(Problems 22.1–22.10 appear within the chapter.)

- 22.11** Identify the following intermediate in the citric acid cycle, and tell whether it has *R* or *S* stereochemistry:

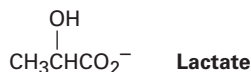


- 22.12** The following compound is an intermediate in the pentose phosphate pathway, an alternative route for glucose metabolism. Identify the sugar it is derived from.



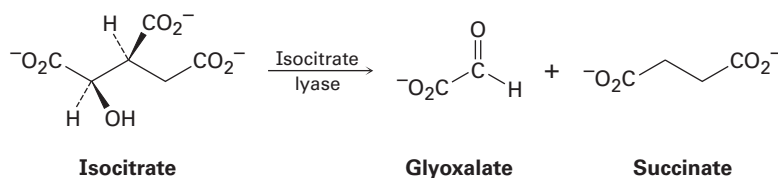
ADDITIONAL PROBLEMS

- 22.13** What coenzyme is typically associated with each of the following transformations?
- The phosphorylation of an alcohol to give a phosphate
 - The oxidative decarboxylation of an α -keto acid to give a thioester
 - The carboxylation of a ketone to give a β -keto acid
- 22.14** Lactate, a product of glucose catabolism in oxygen-starved muscles, can be converted into pyruvate by oxidation. What coenzyme do you think is needed? Write the equation in the usual biochemical format using a curved arrow.

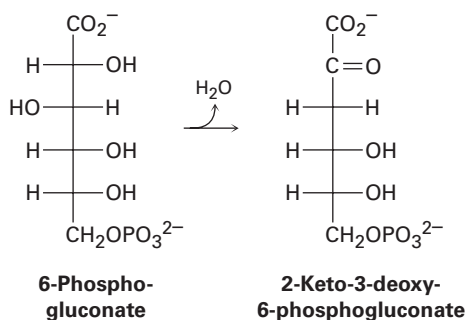


22.15 Write a mechanism for the conversion of α -ketoglutarate to succinyl CoA in step 4 of the citric acid cycle (Figure 22.8).

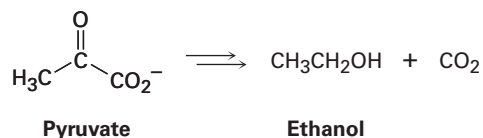
22.16 Plants, but not animals, are able to synthesize glucose from acetyl CoA by a pathway that begins with the *glyoxalate cycle*. One of the steps in the cycle is the conversion of isocitrate to glyoxalate plus succinate, a process catalyzed by isocitrate lyase. Propose a mechanism for the reaction.



22.17 Propose a mechanism for the conversion of 6-phosphogluconate to 2-keto-3-deoxy-6-phosphogluconate, a step in the Entner–Douderoff bacterial pathway for glucose catabolism.

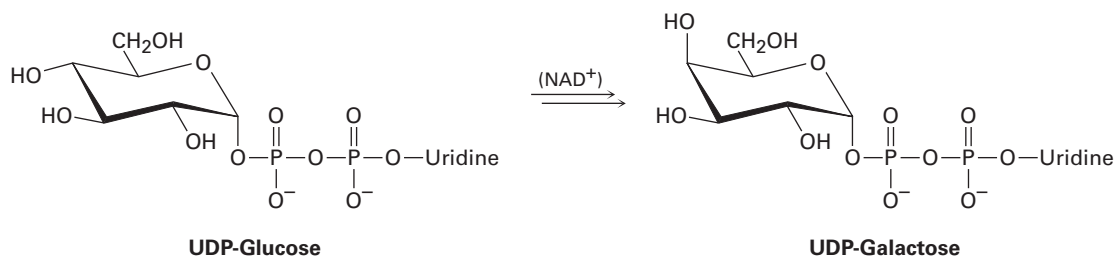


22.18 Pyruvate is converted into ethanol during fermentation in yeast.

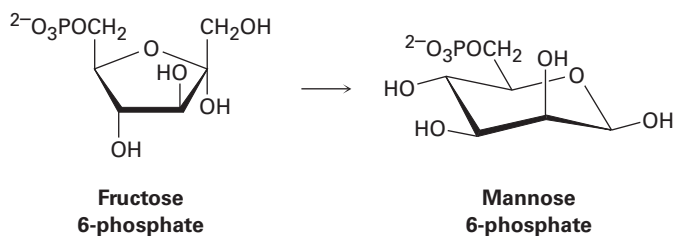


- The first step is a TPP-dependent decarboxylation of pyruvate to give HETPP. Show the mechanism.
- The second step is a protonation followed by elimination of TPP ylide to give acetaldehyde. Show the mechanism.
- The final step is a reduction with NADH. Show the mechanism.

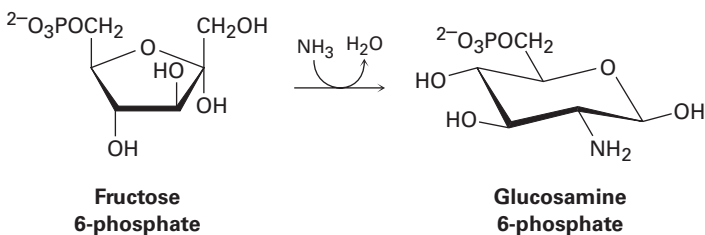
- 22.19** Galactose, one of the eight essential monosaccharides (Section 21-7), is biosynthesized from UDP-glucose by galactose 4-epimerase, where UDP = uridylyl diphosphate. The enzyme requires NAD^+ for activity, but it is not a stoichiometric reactant and NADH is not a final reaction product. Propose a mechanism.



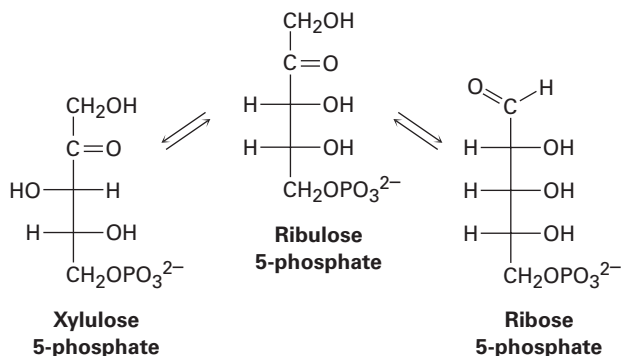
- 22.20** Mannose, one of the eight essential monosaccharides (Section 21-7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate. No cofactor is required. Propose a mechanism.



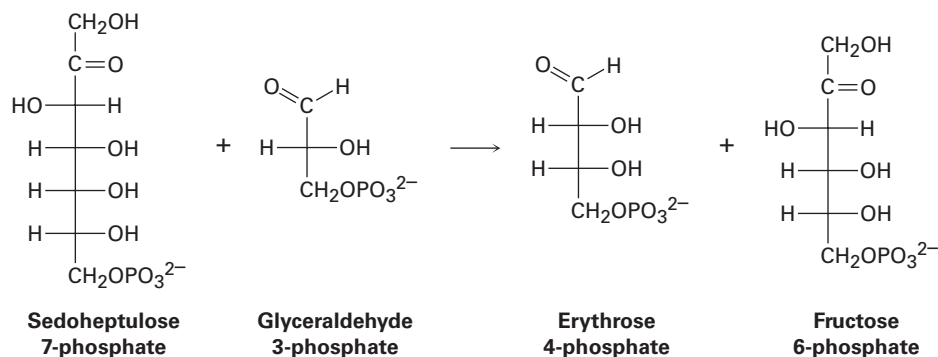
- 22.21** Glucosamine, one of the eight essential monosaccharides (Section 21-7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate by reaction with ammonia. Propose a mechanism.



- 22.22 In the pentose phosphate pathway for glucose metabolism, ribulose 5-phosphate undergoes reversible isomerizations to both ribose 5-phosphate and xylulose 5-phosphate. Show mechanisms for both.

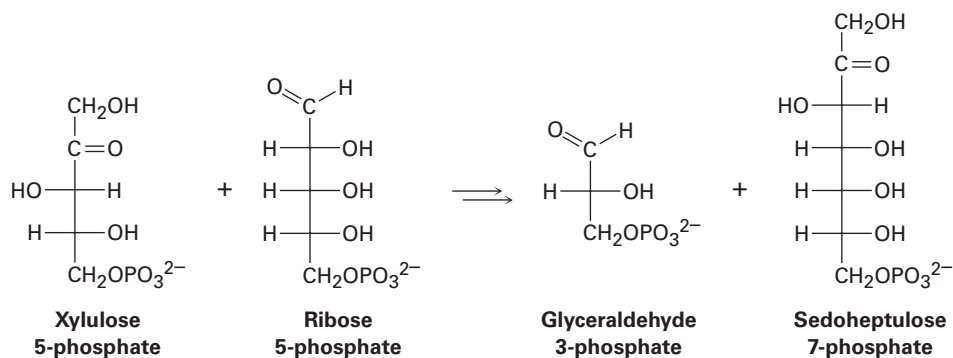


- 22.23 One of the steps in the pentose phosphate pathway for glucose catabolism is the reaction of sedoheptulose 7-phosphate with glyceraldehyde 3-phosphate in the presence of a transaldolase to yield erythrose 4-phosphate and fructose 6-phosphate.

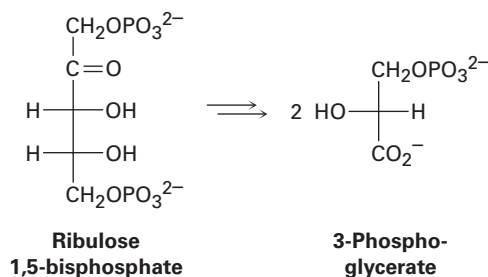


- (a) The first part of the reaction is formation of a protonated Schiff base of sedoheptulose 7-phosphate with a lysine residue in the enzyme followed by a retro-aldol cleavage to give an enamine plus erythrose 4-phosphate. Show the structure of the enamine and the mechanism by which it is formed.
- (b) The second part of the reaction is nucleophilic addition of the enamine to glyceraldehyde 3-phosphate followed by hydrolysis of the Schiff base to give fructose 6-phosphate. Show the mechanism.

22.24 One of the steps in the pentose phosphate pathway for glucose metabolism is the TPP-dependent reaction of xylulose 5-phosphate with ribose 5-phosphate to give glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate.

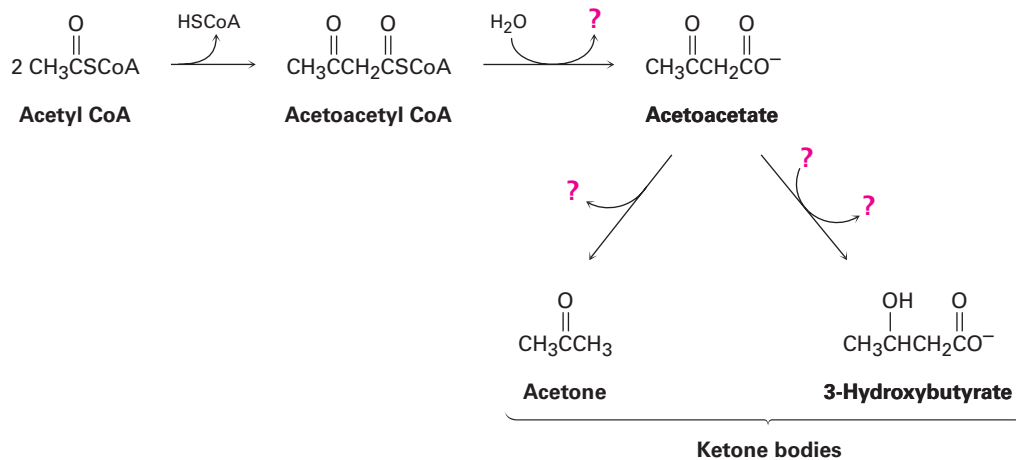


- (a) The first step is addition of TPP ylide to xylulose 5-phosphate. Show the product.
- (b) The second step is a retro-aldol cleavage of the TPP addition product to give glyceraldehyde 3-phosphate plus a TPP-containing product. Show the mechanism.
- (c) The third step is an aldol addition of the TPP-containing product from step 2 to ribose 5-phosphate. Show the product and the mechanism.
- (d) The final step is an elimination of TPP ylide to give sedoheptulose 7-phosphate. Show the mechanism.
- 22.25** One of the steps in the photosynthesis cycle is conversion of ribulose 1,5-bisphosphate to 3-phosphoglycerate.

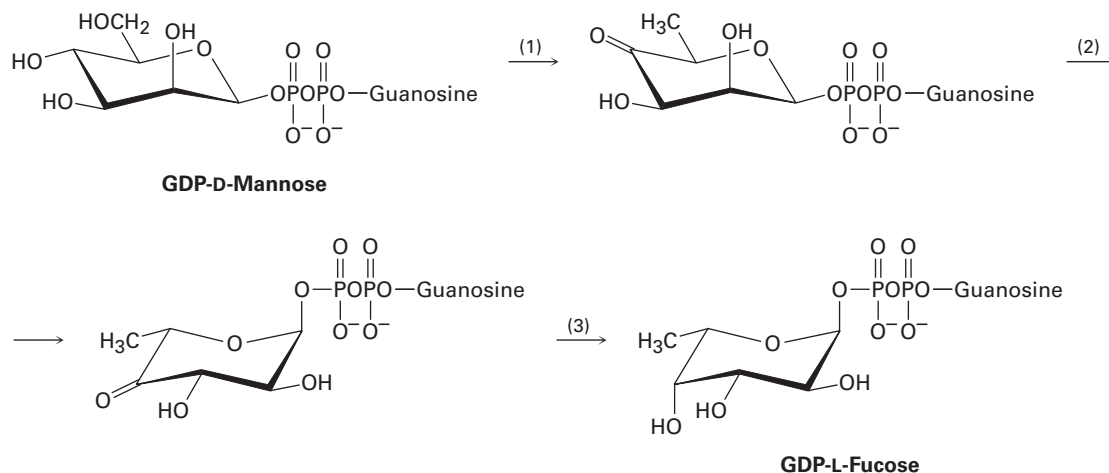


- (a) The first step is tautomerization of the carbonyl group. Show the product and the mechanism.
- (b) The second step is a biotin-dependent carboxylation to give a β -keto acid. Show the product and the mechanism.
- (c) The final step is a retro-aldol-like reaction to yield two molecules of 3-phosphoglycerate. Show the mechanism.

- 22.26** The primary fate of acetyl CoA under normal metabolic conditions is degradation in the citric acid cycle to yield CO_2 . When the body is stressed by prolonged starvation, however, acetyl CoA is converted into compounds called *ketone bodies*, which can be used by the brain as a temporary fuel. Fill in the missing information indicated by the four question marks in the following biochemical pathway for the synthesis of ketone bodies from acetyl CoA:



- 22.27** L-Fucose, one of the eight essential monosaccharides (Section 21-7), is biosynthesized from GDP-D-mannose by the following three-step reaction sequence:

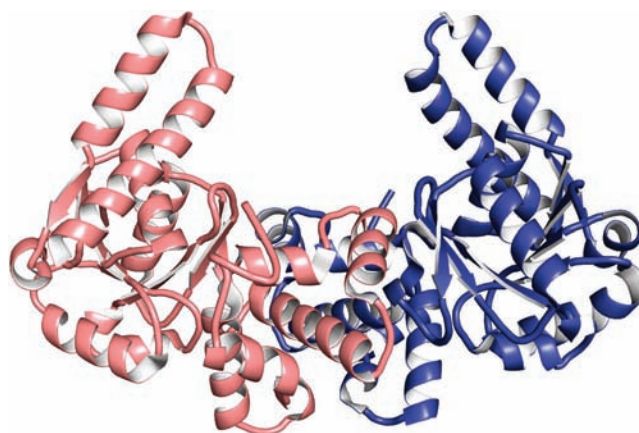


- (a) Step 1 involves an oxidation, a dehydration, and a reduction. The step requires NADP^+ , but no NADPH is formed as a final reaction product. Propose a mechanism.
- (b) Step 2 accomplishes two epimerizations and utilizes acidic and basic sites in the enzyme but does not require a coenzyme. Propose a mechanism.
- (c) Step 3 requires NADPH as coenzyme. Show the mechanism.

- 22.28** Fructose is metabolized in two ways, one that takes place in muscle tissue and another that occurs in the liver. In muscle, fructose is phosphorylated by hexokinase-catalyzed reaction with ATP to give fructose 6-phosphate, a glycolysis intermediate. In the liver, however, fructose is metabolized by a more complex pathway involving six different enzymes.
- (a) The first step is fructokinase-catalyzed phosphorylation by ATP to give fructose 1-phosphate, which undergoes a cleavage reaction to yield the glycolysis intermediate dihydroxyacetone phosphate plus glyceraldehyde. Show the mechanism of the cleavage reaction, which is catalyzed by a class I aldolase.
- (b) Glyceraldehyde is converted into a second equivalent of dihydroxyacetone phosphate in a 3-step reduction, phosphorylation, reoxidation sequence. Show the structures of the intermediates in the sequence, and suggest likely coenzymes for each step.

Biomolecules: Lipids and Their Metabolism

23



Hydroxyacyl-CoA dehydrogenase catalyzes the oxidation of a β -hydroxyacyl CoA to a β -ketoacyl CoA during fatty-acid metabolism.

WHY THIS CHAPTER?

We've now covered two of the four major classes of biomolecules—proteins and carbohydrates—and have two remaining. We'll cover lipids, the largest and most diverse class of biomolecules, in this chapter, looking both at their structure and function and at their metabolism.

CONTENTS

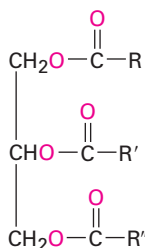
- 23-1** Waxes, Fats, and Oils
- 23-2** Soap
- 23-3** Phospholipids
- 23-4** Catabolism of Triacylglycerols: The Fate of Glycerol
- 23-5** Catabolism of Triacylglycerols: β -Oxidation
- 23-6** Biosynthesis of Fatty Acids
- 23-7** Prostaglandins and Other Eicosanoids
- 23-8** Terpenoids
- 23-9** Steroids
- 23-10** Biosynthesis of Steroids
- 23-11** Some Final Comments on Metabolism

SOMETHING EXTRA

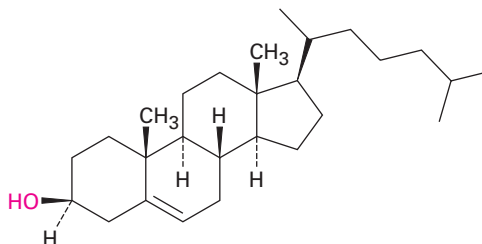
Statin Drugs

Lipids are naturally occurring organic molecules that have limited solubility in water and can be isolated from organisms by extraction with nonpolar organic solvents. Fats, oils, waxes, some vitamins and hormones, and most nonprotein cell-membrane components are examples. Note that this definition differs from the sort used for carbohydrates and proteins in that lipids are defined by a physical property (solubility) rather than by structure. Of the many kinds of lipids, we'll be concerned in this chapter only with a few: triacylglycerols, eicosanoids, terpenoids, and steroids.

Lipids are classified into two broad types: those like fats and waxes, which contain ester linkages and can be hydrolyzed, and those like cholesterol and other steroids, which don't have ester linkages and can't be hydrolyzed.



Animal fat—a triester
(R, R', R'' = C₁₁–C₁₉ chains)

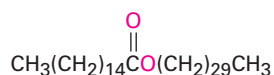
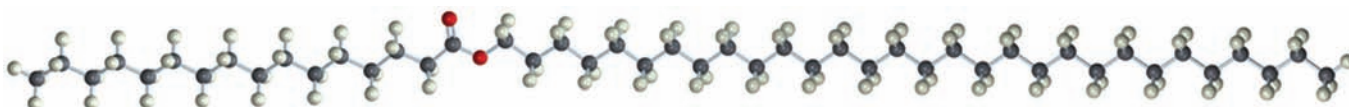


Cholesterol



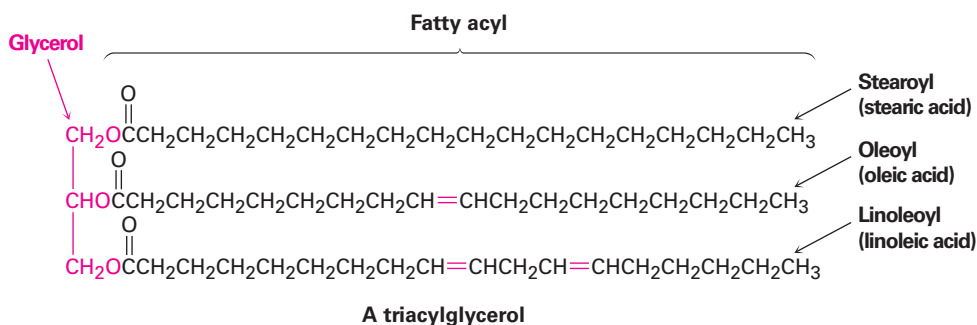
23-1 Waxes, Fats, and Oils

Waxes are mixtures of esters of long-chain carboxylic acids with long-chain alcohols. The carboxylic acid usually has an even number of carbons from 16 through 36, while the alcohol has an even number of carbons from 24 through 36. One of the major components of beeswax, for instance, is triacontyl hexadecanoate, the ester of the C₃₀ alcohol triacontan-1-ol and the C₁₆ acid hexadecanoic acid. The waxy protective coatings on most fruits, berries, leaves, and animal furs have similar structures.



Triacontyl hexadecanoate (from beeswax)

Animal fats and vegetable oils are the most widely occurring lipids. Although they appear different—animal fats like butter and lard are solids, whereas vegetable oils like corn and peanut oil are liquid—their structures are closely related. Chemically, fats and oils are *triglycerides*, or **triacylglycerols**—triesters of glycerol with three long-chain carboxylic acids called **fatty acids**. Animals use fats for long-term energy storage because they are much less highly oxidized than carbohydrates and provide about six times as much energy as an equal weight of stored, hydrated glycogen.



Hydrolysis of a fat or oil with aqueous NaOH yields glycerol and three fatty acids. The fatty acids are generally unbranched and contain an even number of carbon atoms between 12 and 20. If double bonds are present, they have largely, although not entirely, *Z*, or *cis*, geometry. The three fatty acids of a specific triacylglycerol molecule need not be the same, and the fat or oil from a given source is likely to be a complex mixture of many different triacylglycerols. **TABLE 23.1** lists some of the commonly occurring fatty acids, and **TABLE 23.2** lists the approximate composition of some fats and oils from different sources.

TABLE 23.1 Structures of Some Common Fatty Acids

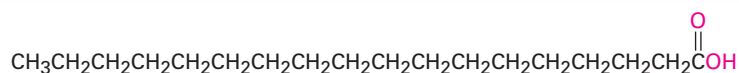
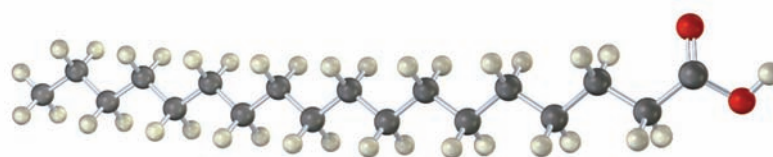
Name	No. of carbons	Melting point (°C)	Structure
Saturated			
Lauric	12	43.2	CH ₃ (CH ₂) ₁₀ CO ₂ H
Myristic	14	53.9	CH ₃ (CH ₂) ₁₂ CO ₂ H
Palmitic	16	63.1	CH ₃ (CH ₂) ₁₄ CO ₂ H
Stearic	18	68.8	CH ₃ (CH ₂) ₁₆ CO ₂ H
Arachidic	20	76.5	CH ₃ (CH ₂) ₁₈ CO ₂ H
Unsaturated			
Palmitoleic	16	-0.1	(Z)-CH ₃ (CH ₂) ₅ CH=CH(CH ₂) ₇ CO ₂ H
Oleic	18	13.4	(Z)-CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ CO ₂ H
Linoleic	18	-12	(Z,Z)-CH ₃ (CH ₂) ₄ (CH=CHCH ₂) ₂ (CH ₂) ₆ CO ₂ H
Linolenic	18	-11	(all Z)-CH ₃ CH ₂ (CH=CHCH ₂) ₃ (CH ₂) ₆ CO ₂ H
Arachidonic	20	-49.5	(all Z)-CH ₃ (CH ₂) ₄ (CH=CHCH ₂) ₄ CH ₂ CH ₂ CO ₂ H

TABLE 23.2 Composition of Some Fats and Oils

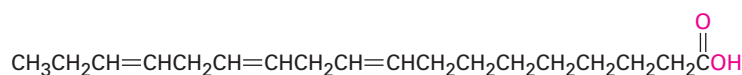
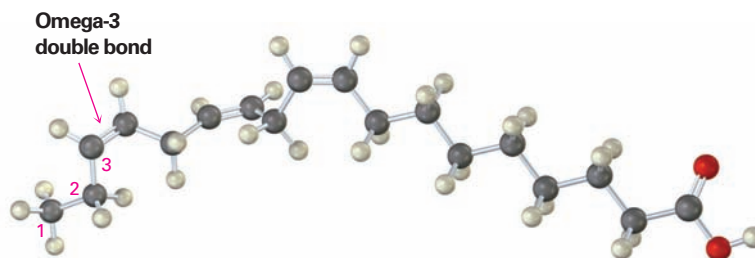
Source	Saturated fatty acids (%)				Unsaturated fatty acids (%)	
	C ₁₂ Lauric	C ₁₄ Myristic	C ₁₆ Palmitic	C ₁₈ Stearic	C ₁₈ Oleic	C ₁₈ Linoleic
Animal fat						
Lard	—	1	25	15	50	6
Butter	2	10	25	10	25	5
Human fat	1	3	25	8	46	10
Whale blubber	—	8	12	3	35	10
Vegetable oil						
Coconut	50	18	8	2	6	1
Corn	—	1	10	4	35	45
Olive	—	1	5	5	80	7
Peanut	—	—	7	5	60	20

More than 100 different fatty acids are known, and about 40 occur widely. Palmitic acid (C₁₆) and stearic acid (C₁₈) are the most abundant saturated fatty acids; oleic and linoleic acids (both C₁₈) are the most abundant unsaturated ones. Oleic acid is monounsaturated because it has only one double bond, whereas linoleic, linolenic, and arachidonic acids are **polyunsaturated fatty acids** because they have more than one double bond. Linoleic and linolenic acids occur in cream and are essential in the human diet; infants grow poorly and develop skin lesions if fed a diet of nonfat milk for prolonged periods.

Linolenic acid is an example of an *omega-3* fatty acid, which has been found to lower blood triglyceride levels and reduce the risk of heart attack. The name omega-3 means that there is a double bond three carbons in from the noncarboxyl end of the chain.



Stearic acid

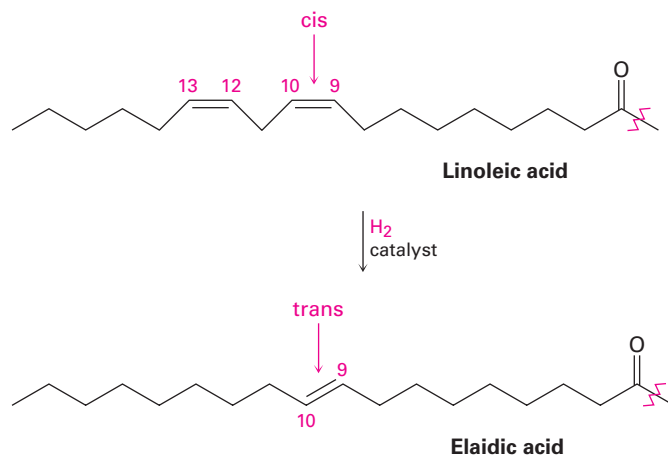


Linolenic acid, an omega-3 polyunsaturated fatty acid

The data in Table 23.1 show that unsaturated fatty acids generally have lower melting points than their saturated counterparts, a trend that is also true for triacylglycerols. Since vegetable oils generally have a higher proportion of unsaturated to saturated fatty acids than animal fats (Table 23.2), they have lower melting points. The difference is a consequence of structure. Saturated fats have a uniform shape that allows them to pack together efficiently in a crystal lattice. In unsaturated vegetable oils, however, the C=C bonds introduce bends and kinks into the hydrocarbon chains, making crystal formation more difficult and lowering the melting point of the oil.

The C=C bonds in vegetable oils can be reduced by catalytic hydrogenation, typically carried out at high temperature using a nickel catalyst, to produce saturated solid or semisolid fats. Margarine and shortening are produced by hydrogenating soybean, peanut, or cottonseed oil until the proper consistency is obtained. Unfortunately, the hydrogenation reaction is accompanied by some cis–trans isomerization of the double bonds that remain, producing fats with about 10% to 15% trans unsaturated fatty acids. Dietary intake of trans fatty acids increases cholesterol levels in the blood, thereby

increasing the risk of heart problems. The conversion of linoleic acid into elaidic acid is an example.



PROBLEM 23.1

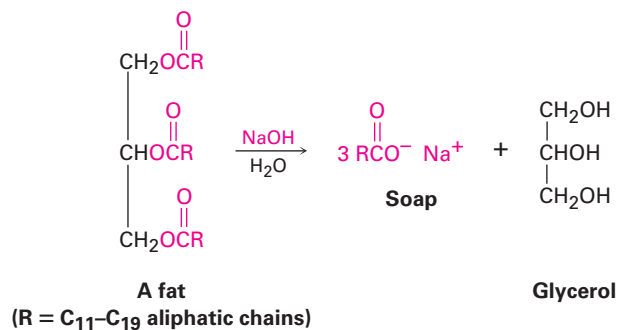
Carnauba wax, used in floor and furniture polishes, contains an ester of a C_{32} straight-chain alcohol with a C_{20} straight-chain carboxylic acid. Draw its structure.

PROBLEM 23.2

Draw structures of glyceryl tripalmitate and glyceryl trioleate. Which would you expect to have a higher melting point?

23-2 Soap

Soap has been known since at least 600 BC, when the Phoenicians living in what is now Lebanon prepared a curdy material by boiling goat fat with extracts of wood ash. The cleansing properties of soap weren't generally recognized, however, and the use of soap did not become widespread until the 18th century. Chemically, soap is a mixture of the sodium or potassium salts of the long-chain fatty acids produced by hydrolysis (*saponification*) of animal fat with alkali. Wood ash was used as a source of alkali until the early 1800s, when the development of the LeBlanc process for making Na_2CO_3 by heating sodium sulfate with limestone (CaO) became available.



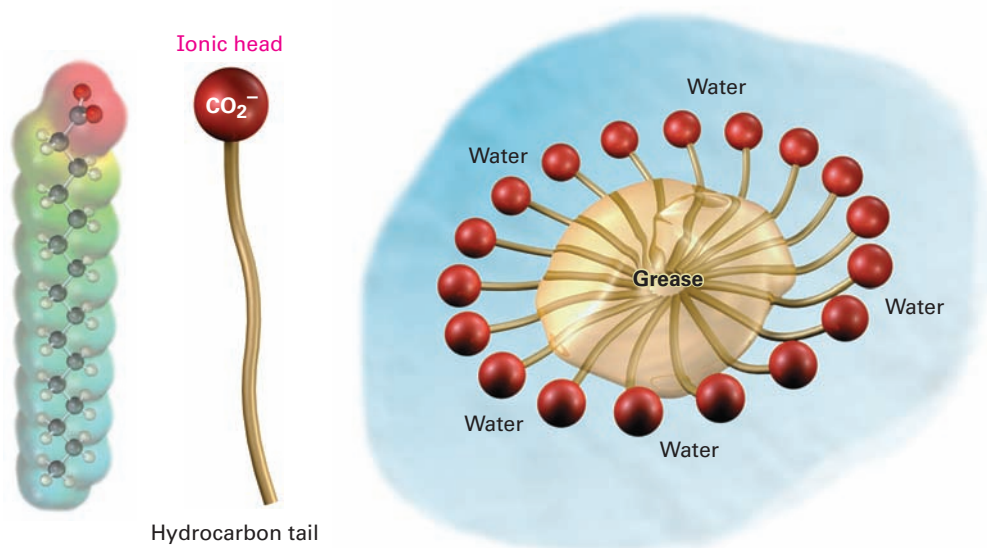
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Crude soap curds contain glycerol and excess alkali as well as soap but can be purified by boiling with water and adding NaCl or KCl to precipitate the pure carboxylate salts. The smooth soap that precipitates is dried, perfumed, and pressed into bars for household use. Dyes are added to make colored soaps, antiseptics are added for medicated soaps, pumice is added for scouring soaps, and air is blown in for soaps that float. Regardless of these extra treatments and regardless of price, though, all soaps are basically the same.

Soaps act as cleansers because the two ends of a soap molecule are so different. The carboxylate end of the long-chain molecule is ionic and therefore hydrophilic (Section 2-12), or attracted to water. The long hydrocarbon portion of the molecule, however, is nonpolar and hydrophobic, avoiding water and therefore more soluble in oils. The net effect of these two opposing tendencies is that soaps are attracted to both oils and water and are therefore useful as cleansers.

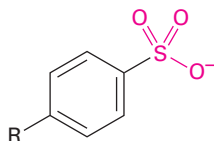
When soaps are dispersed in water, the long hydrocarbon tails cluster together on the inside of tangled, hydrophobic balls, while the ionic heads on the surface of the clusters stick out into the water layer. These spherical clusters, called **micelles**, are shown schematically in **FIGURE 23.1**. Grease and oil droplets are solubilized in water when they are coated by the nonpolar, hydrophobic tails of soap molecules in the center of micelles. Once solubilized, the grease and dirt can be rinsed away.

FIGURE 23.1 A soap micelle solubilizing a grease particle in water. An electrostatic potential map of a fatty-acid carboxylate shows how the negative charge is located in the head group.



As useful as they are, soaps also have some drawbacks. In hard water, which contains metal ions such as Mg^{2+} , Ca^{2+} , and Fe^{3+} , soluble sodium carboxylates are converted into insoluble metal salts, leaving the familiar ring of scum around bathtubs and the gray tinge on white clothes. Chemists have circumvented these problems by synthesizing a class of synthetic detergents

based on salts of long-chain alkylbenzenesulfonic acids. The principle of synthetic detergents is the same as that of soaps: the alkylbenzene end of the molecule is attracted to grease, while the anionic sulfonate end is attracted to water. Unlike soaps, though, sulfonate detergents don't form insoluble metal salts in hard water and don't leave an unpleasant scum.



A synthetic detergent
(R = a mixture of C₁₂ chains)

PROBLEM 23.3

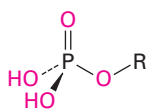
Draw the structure of magnesium oleate, a component of bathtub scum.

PROBLEM 23.4

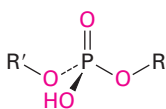
Write the saponification reaction of glyceryl dioleate monopalmitate with aqueous NaOH.

23-3 Phospholipids

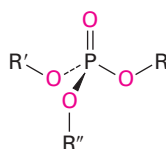
Just as waxes, fats, and oils are esters of carboxylic acids, **phospholipids** are esters of phosphoric acid, H₃PO₄:



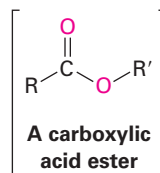
A phosphoric acid monoester



A phosphoric acid diester



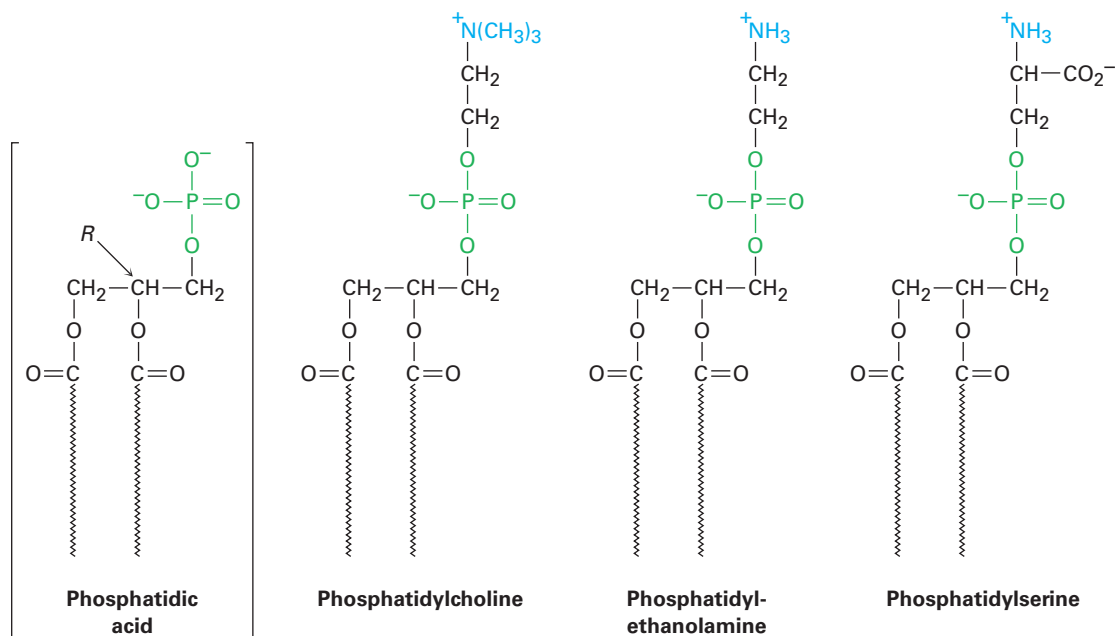
A phosphoric acid triester



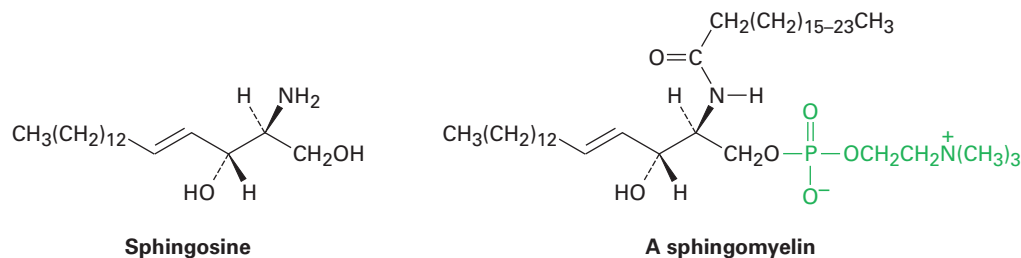
A carboxylic acid ester

Phospholipids are of two general kinds: *glycerophospholipids* and *sphingomyelins*. Glycerophospholipids are based on phosphatidic acid, which contains a glycerol backbone linked by ester bonds to two fatty acids and one phosphoric acid. Although the fatty-acid residues can be any of the C₁₂–C₂₀ units typically present in fats, the acyl group at C1 is usually saturated and the one at C2 is usually unsaturated. The phosphate group at C3 is also bonded to an amino alcohol such as choline [HOCH₂CH₂N(CH₃)₃]⁺, ethanolamine (HOCH₂CH₂NH₂), or

serine [$\text{HOCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$]. The compounds are chiral and have an L, or R, configuration at C2.

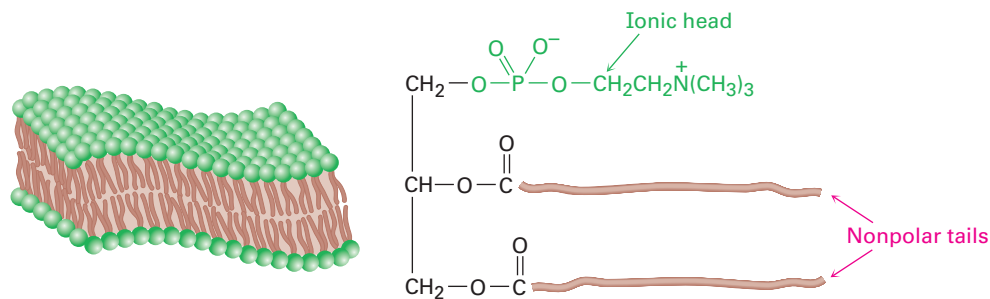


Sphingomyelins, the second major group of phospholipids, have sphingosine or a related dihydroxyamine as their backbone. They are particularly abundant in brain and nerve tissue, where they are a major constituent of the coating around nerve fibers.



Phospholipids are found widely in both plant and animal tissues and make up approximately 50% to 60% of cell membranes. Because they are like soaps in having a long, nonpolar hydrocarbon tail bound to a polar ionic head, phospholipids in the cell membrane organize into a **lipid bilayer** about 5.0 nm (50 Å) thick. As shown in **FIGURE 23.2**, the nonpolar tails aggregate in the center

FIGURE 23.2 Aggregation of glycerophospholipids into the lipid bilayer that composes cell membranes.



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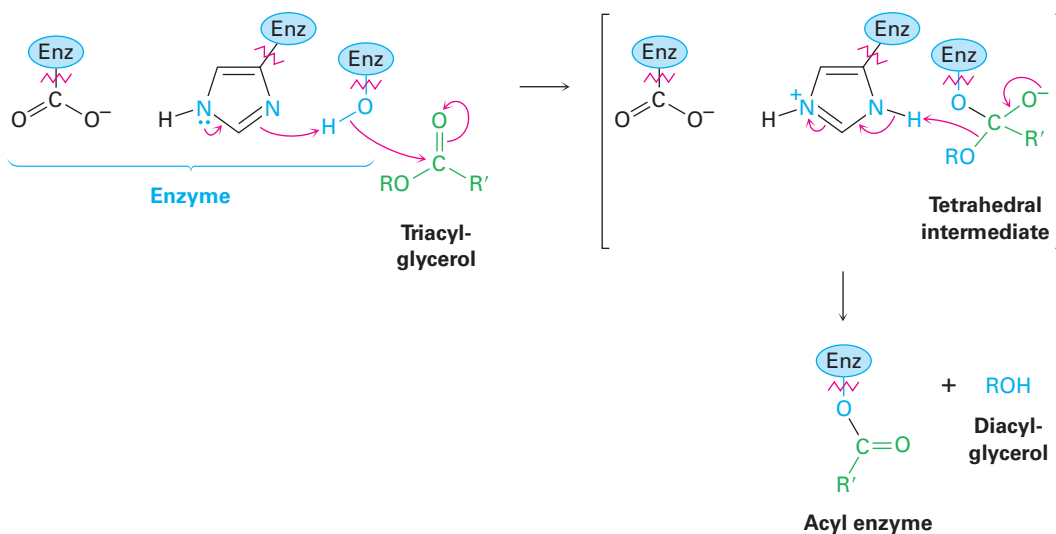
of the bilayer in much the same way that soap tails aggregate in the center of a micelle. This bilayer serves as an effective barrier to the passage of water, ions, and other components into and out of cells.

23-4 Catabolism of Triacylglycerols: The Fate of Glycerol

Triacylglycerol catabolism begins with hydrolysis in the stomach and small intestine to yield glycerol plus fatty acids. The reaction is catalyzed by a lipase, whose mechanism is shown in **FIGURE 23.3**. The active site of the enzyme contains a catalytic triad of aspartic acid, histidine, and serine residues, which act cooperatively to provide the acidic and basic catalysis for the individual steps. Hydrolysis is accomplished by two sequential nucleophilic acyl substitution reactions, one that covalently binds an acyl group to the side-chain $-OH$ of a serine residue on the enzyme and a second that frees the fatty acid from the enzyme.

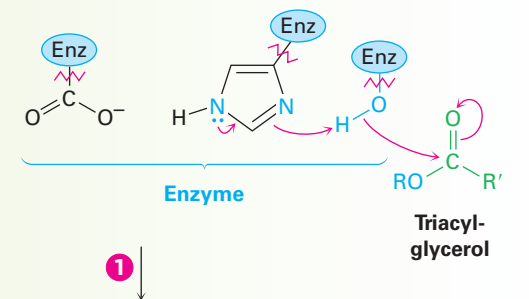
STEPS 1–2 OF FIGURE 23.3: ACYL ENZYME FORMATION The first nucleophilic acyl substitution step—reaction of the triacylglycerol with the active-site serine to give an acyl enzyme—begins with deprotonation of the serine alcohol by histidine to form the more strongly nucleophilic alkoxide ion. This proton transfer is facilitated by a nearby side-chain carboxylate anion of aspartic acid, which makes the histidine more basic and stabilizes the resultant histidine cation by electrostatic interactions. The deprotonated serine adds to a carbonyl group of a triacylglycerol to give a tetrahedral intermediate.

The tetrahedral intermediate expels a diacylglycerol as the leaving group and produces an acyl enzyme. The step is catalyzed by a proton transfer from histidine to make the leaving group a neutral alcohol.

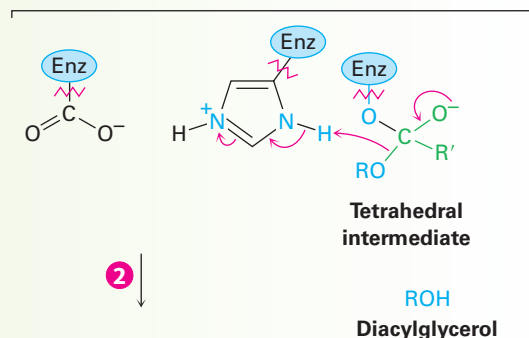


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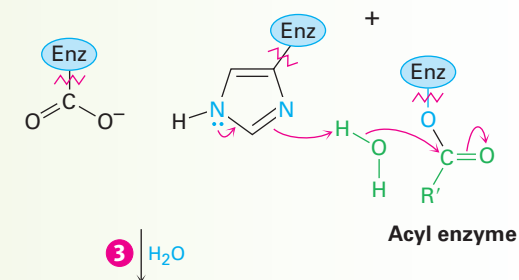
1 The enzyme active site contains an aspartic acid, a histidine, and a serine. First, histidine acts as a base to deprotonate the $-OH$ group of serine, with the negatively charged carboxylate of aspartic acid stabilizing the nearby histidine cation that results. Serine then adds to the carbonyl group of the triacylglycerol, yielding a tetrahedral intermediate.



2 This intermediate expels a diacylglycerol as leaving group in a nucleophilic acyl substitution reaction, giving an acyl enzyme. The diacylglycerol is protonated by the histidine cation.



3 Histidine deprotonates a water molecule, which adds to the acyl group. A tetrahedral intermediate is again formed, and the histidine cation is again stabilized by the nearby carboxylate.



4 The tetrahedral intermediate expels the serine as leaving group in a second nucleophilic acyl substitution reaction, yielding a free fatty acid. The serine accepts a proton from histidine, and the enzyme has now returned to its starting structure.

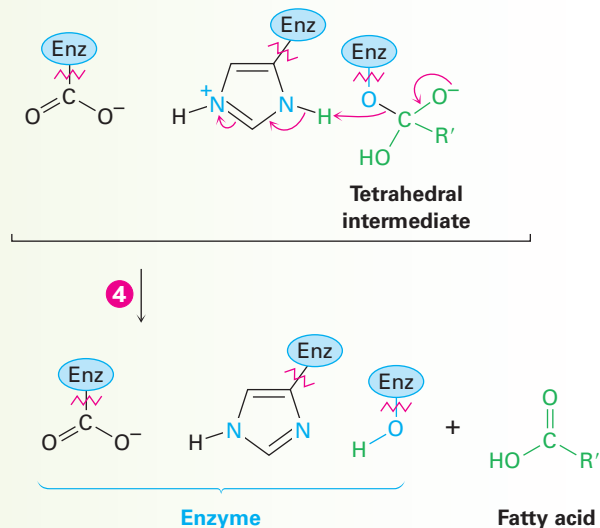
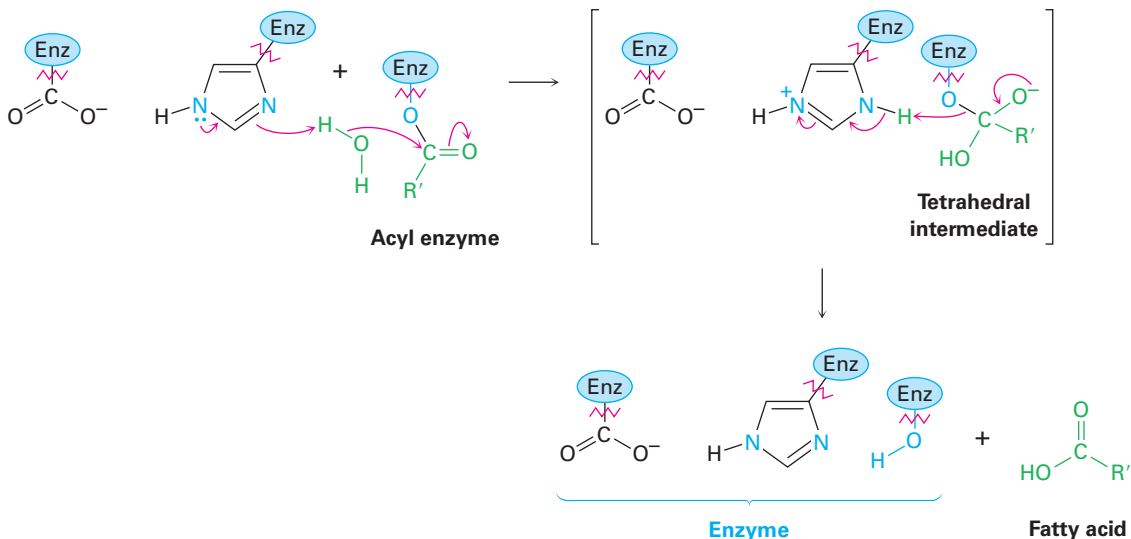
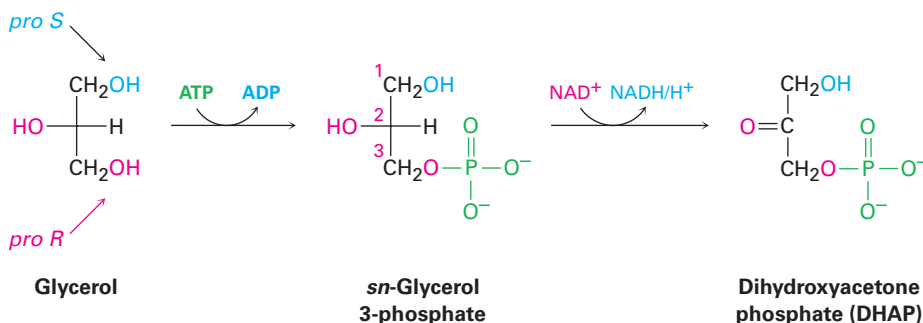


FIGURE 23.3 Mechanism of action of lipase. The active site of the enzyme contains a catalytic triad of aspartic acid, histidine, and serine, which react cooperatively to carry out two nucleophilic acyl substitution reactions. Individual steps are explained in the text.

STEPS 3–4 OF FIGURE 23.3: HYDROLYSIS The second nucleophilic acyl substitution step hydrolyzes the acyl enzyme and gives the free fatty acid by a mechanism analogous to that of the first two steps. Water is deprotonated by histidine to give hydroxide, which adds to the enzyme-bound acyl group. The tetrahedral intermediate then expels the neutral serine residue as the leaving group, freeing the fatty acid and returning the enzyme to its active form.



The fatty acids released on triacylglycerol hydrolysis are transported to mitochondria and degraded to acetyl CoA, while the glycerol is carried to the liver for further metabolism. In the liver, glycerol is first phosphorylated by reaction with ATP and then oxidized by NAD^+ . The dihydroxyacetone phosphate (DHAP) that results enters the carbohydrate glycolysis pathway that we saw in Section 22-2.



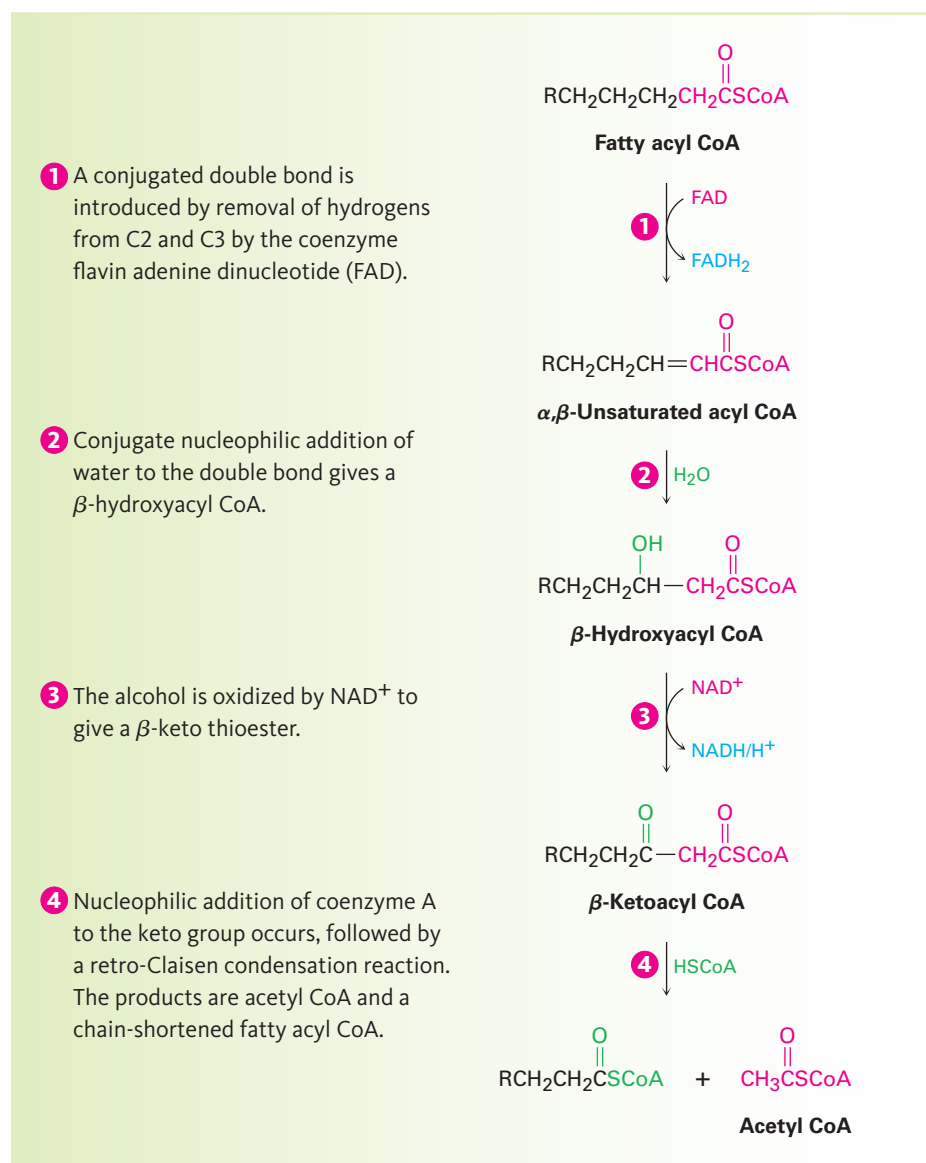
You might note that C2 of glycerol is a prochiral center with two identical arms, a situation similar to that of citrate in the citric acid cycle (Section 22-4). As is typical for enzyme-catalyzed reactions, the phosphorylation of glycerol is selective. Only the *pro-R* arm undergoes reaction, although this can't be predicted in advance.

Note also that the phosphorylation product is named *sn*-glycerol 3-phosphate, where the *sn*- prefix means “stereospecific numbering.” In this convention, the molecule is drawn in Fischer projection with the $-\text{OH}$ group at C2 pointing to the left and the glycerol carbon atoms are numbered beginning at the top.

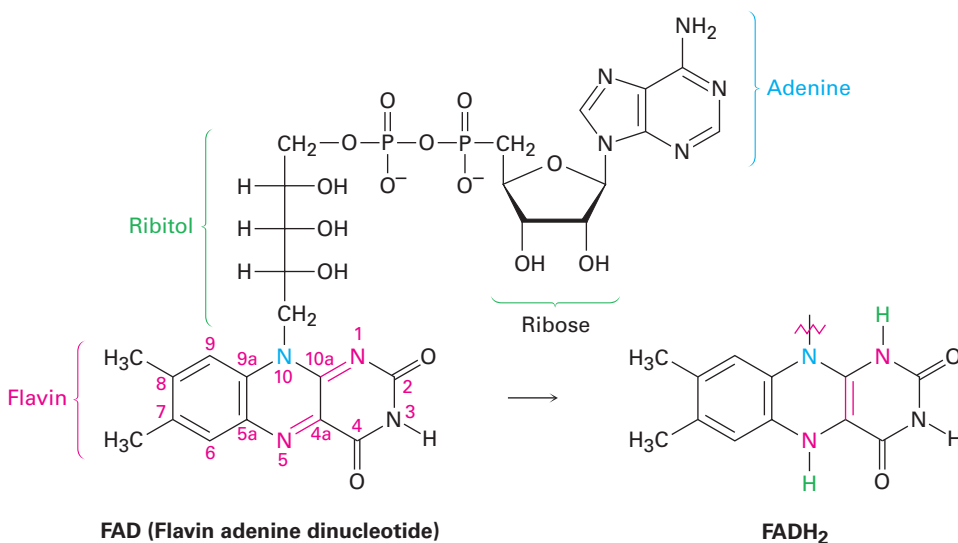
23-5 Catabolism of Triacylglycerols: β -Oxidation

The fatty acids that result from triacylglycerol hydrolysis are converted into thioesters with coenzyme A and then catabolized by a repetitive four-step sequence of reactions called the **β -oxidation pathway**, shown in **FIGURE 23.4**. Each passage along the pathway results in the cleavage of an acetyl group from the end of the fatty-acid chain, until ultimately the entire molecule is degraded. As each acetyl group is produced, it enters the citric acid cycle discussed in Section 22-4, where it is further catabolized to CO_2 .

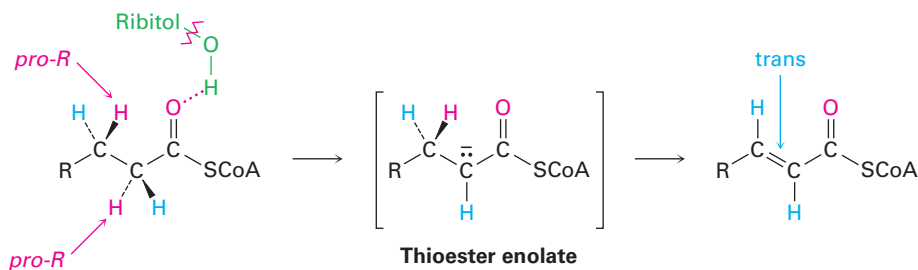
FIGURE 23.4 The four steps of the **β -oxidation pathway**. An acetyl group is cleaved from the end of the fatty-acid chain using a retro-Claisen reaction of a **β -keto thioester** as the key step. Individual steps are explained in the text.



STEP 1 OF FIGURE 23.4: INTRODUCTION OF A DOUBLE BOND The β -oxidation pathway begins when two hydrogen atoms are removed from C2 and C3 of the fatty acyl CoA by one of a family of acyl-CoA dehydrogenases to yield an α,β -unsaturated acyl CoA. This kind of oxidation—the introduction of a conjugated double bond into a carbonyl compound—occurs frequently in biochemical pathways and usually involves the coenzyme flavin adenine dinucleotide (FAD). Reduced FADH₂ is the by-product.

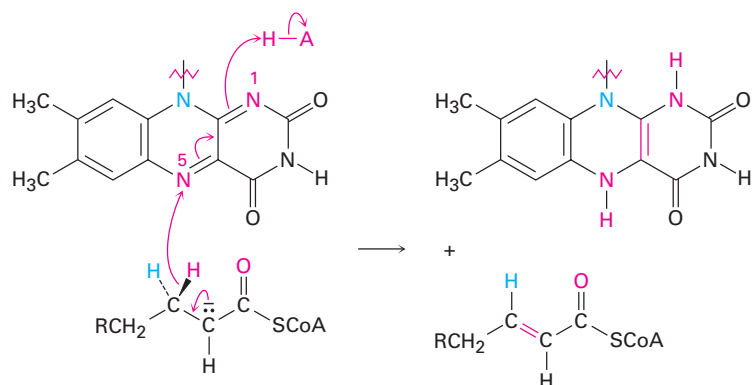


The mechanisms of FAD-catalyzed reactions are often difficult to establish because flavin coenzymes can operate by both two-electron (polar) and one-electron (radical) pathways. As a result, extensive studies of the family of acyl-CoA dehydrogenases have not yet provided a clear picture of how these enzymes function. What is known is that: (1) The first step is abstraction of the *pro-R* hydrogen from the acidic α position of the acyl CoA to give a thioester enolate ion. Hydrogen-bonding between the acyl carbonyl group and the ribitol hydroxyls of FAD increases the acidity of the acyl group. (2) The *pro-R* hydrogen at the β position is transferred to FAD. (3) The α,β -unsaturated acyl CoA that results has a *trans* double bond.

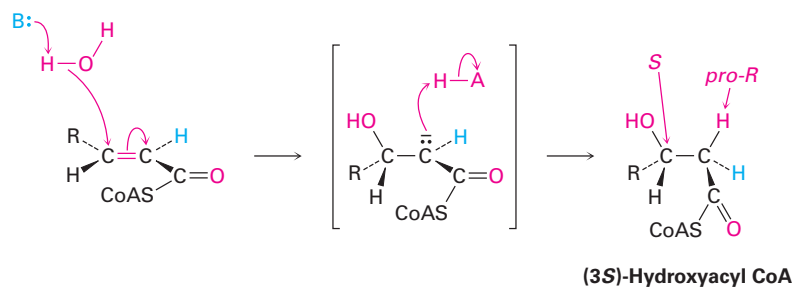


One suggested mechanism is that the reaction may take place by a conjugate nucleophilic addition of hydride, analogous to what occurs during alcohol oxidations with NAD⁺ (Section 13-5). Electrons on the enolate ion might

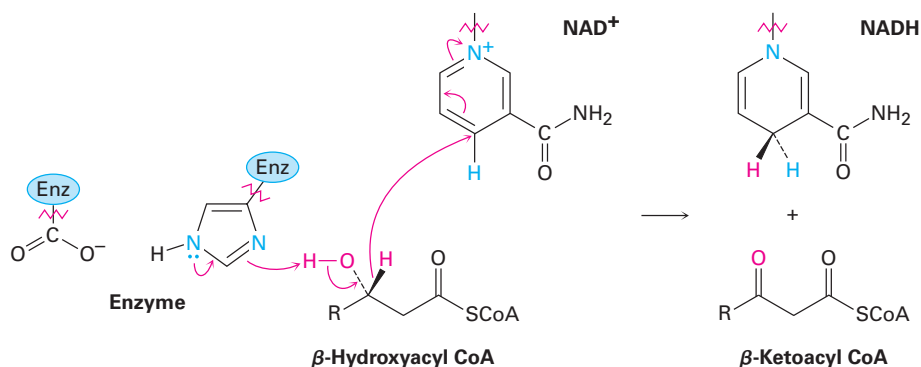
expel a β hydride ion, which could add to the doubly bonded N5 nitrogen on FAD. Protonation of the intermediate at N1 would give the product:



STEP 2 OF FIGURE 23.4: CONJUGATE ADDITION OF WATER The α,β -unsaturated acyl CoA produced in step 1 reacts with water by a conjugate nucleophilic addition pathway (Section 14-11) to yield a β -hydroxyacyl CoA in a process catalyzed by enoyl-CoA hydratase. Water as nucleophile adds to the β carbon of the double bond, yielding an intermediate thioester enolate ion that is protonated on the α position.

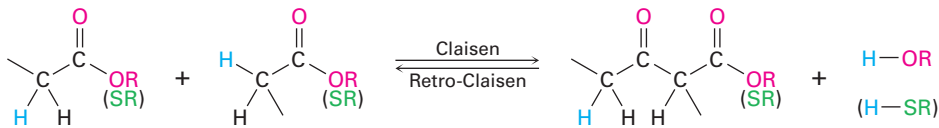


STEP 3 OF FIGURE 23.4: ALCOHOL OXIDATION The β -hydroxyacyl CoA from step 2 is oxidized to a β -ketoacyl CoA in a reaction catalyzed by one of a family of L-3-hydroxyacyl-CoA dehydrogenases, which differ in substrate specificity according to the chain length of the acyl group. As in the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate mentioned in Section 23-4, this alcohol oxidation requires NAD^+ as a coenzyme and yields reduced NADH/H^+ as by-product. The reaction is facilitated by deprotonation of the hydroxyl group by a histidine residue at the active site.

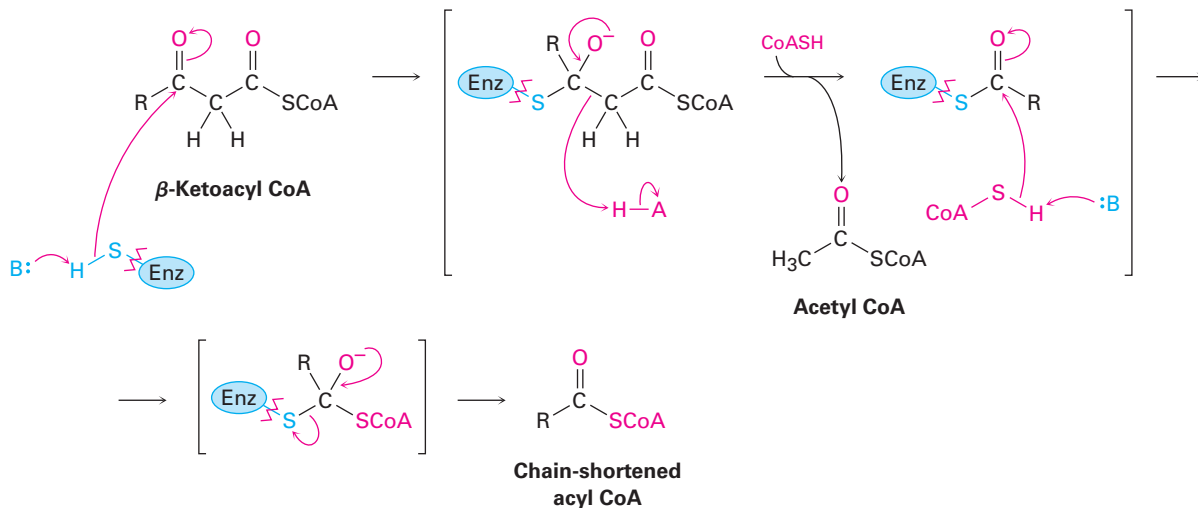


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STEP 4 OF FIGURE 23.4: CHAIN CLEAVAGE Acetyl CoA is split off from the chain in the final step of β -oxidation, leaving an acyl CoA that is two carbon atoms shorter than the original. The reaction is catalyzed by β -ketoacyl-CoA thiolase and is mechanistically the reverse of a Claisen condensation reaction (Section 17-9). In the forward direction, a Claisen condensation joins two esters together to form a β -keto ester product. In the reverse direction, a retro-Claisen reaction splits apart a β -keto ester (or β -keto thioester in this case) to form two esters (or two thioesters).



The retro-Claisen reaction occurs by nucleophilic addition of a cysteine -SH group in the enzyme to the keto group of the β -ketoacyl CoA to yield an alkoxide ion intermediate. Cleavage of the C2–C3 bond then follows, with expulsion of an acetyl CoA enolate ion that is immediately protonated. The enzyme-bound acyl group then undergoes nucleophilic acyl substitution by reaction with a molecule of coenzyme A, and the chain-shortened acyl CoA that results enters another round of the β -oxidation pathway for further degradation.

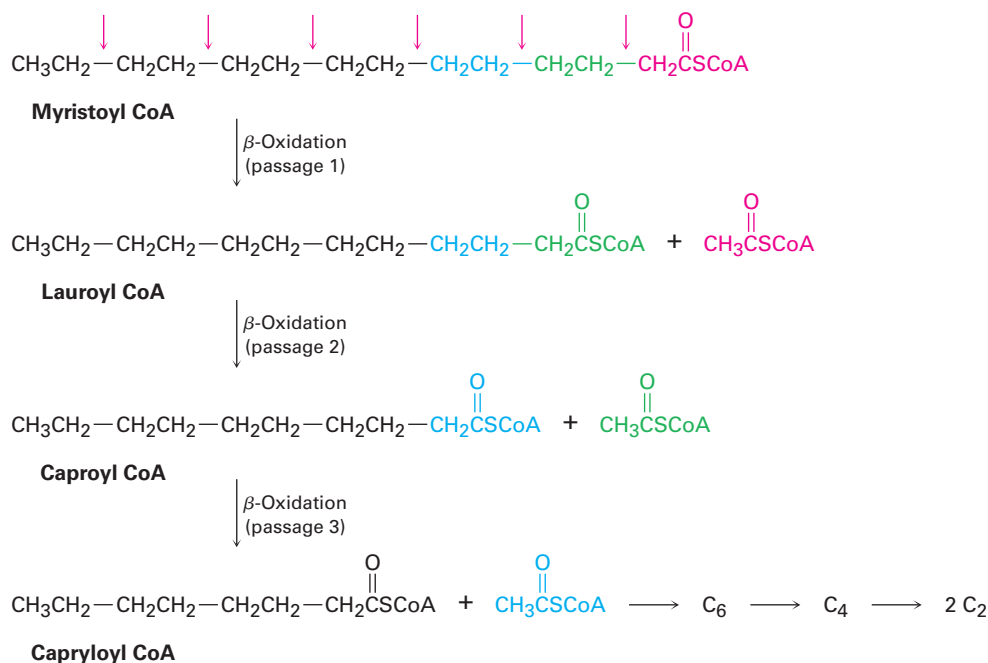


Look at the catabolism of myristic acid shown in **FIGURE 23.5** to see the overall results of the β -oxidation pathway. The first passage converts the 14-carbon myristoyl CoA into the 12-carbon lauroyl CoA plus acetyl CoA, the second passage converts lauroyl CoA into the 10-carbon caproyl CoA plus acetyl CoA, the third passage converts caproyl CoA into the 8-carbon capryloyl CoA, and so on. Note that the final passage produces two molecules of acetyl CoA because the precursor has four carbons.

Most fatty acids have an even number of carbon atoms, so none are left over after β -oxidation. Those fatty acids with an odd number of carbon atoms yield the three-carbon propionyl CoA in the final β -oxidation. Propionyl CoA is then converted to succinate by a multistep radical pathway, and succinate

FIGURE 23.5 Catabolism of the 14-carbon myristic acid by the β -oxidation pathway.

Seven molecules of acetyl CoA are produced after six passages.



enters the citric acid cycle (Section 22-4). Note that the three-carbon propionyl group should properly be called *propanoyl*, but biochemists generally use the nonsystematic name.

PROBLEM 23.5

Write the equations for the remaining passages of the β -oxidation pathway following those shown in Figure 23.5.

PROBLEM 23.6

How many molecules of acetyl CoA are produced by catabolism of the following fatty acids, and how many passages of the β -oxidation pathway are needed?

(a) Palmitic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$ (b) Arachidic acid, $\text{CH}_3(\text{CH}_2)_{18}\text{CO}_2\text{H}$

23-6 Biosynthesis of Fatty Acids

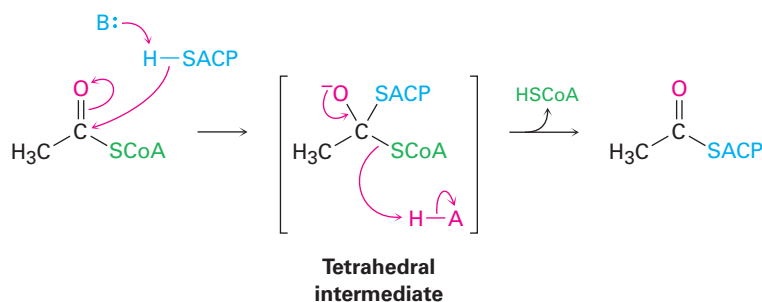
One of the most striking features of the common fatty acids is that they have an even number of carbon atoms (Table 23.1 on page 807). This even number results because all fatty acids are derived biosynthetically from acetyl CoA by sequential addition of two-carbon units to a growing chain. The acetyl CoA, in turn, arises primarily from the metabolic breakdown of carbohydrates in the glycolysis pathway (Section 22-2). Thus, dietary carbohydrates consumed in excess of immediate energy needs are turned into fats for storage.

As noted previously in Section 22-5 when discussing carbohydrate biosynthesis, the anabolic pathway by which a substance is made is not the reverse of the catabolic pathway by which it is degraded. Thus, the β -oxidation pathway that converts fatty acids into acetyl CoA and the biosynthesis pathway

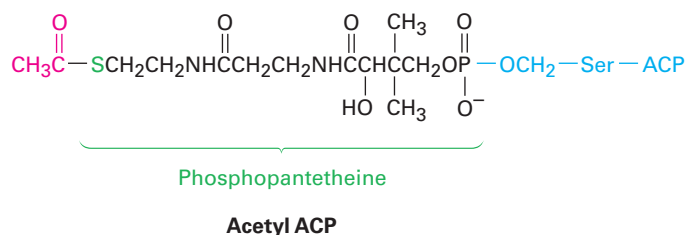
that prepares fatty acids from acetyl CoA are related but are not exact opposites. Differences include the identity of the acyl-group carrier, the stereochemistry of the β -hydroxyacyl reaction intermediate, and the identity of the redox coenzyme. FAD is used to introduce a double bond in β -oxidation, while NADPH is used to reduce the double bond in fatty-acid biosynthesis.

In bacteria, each step in fatty-acid synthesis is catalyzed by separate enzymes. In vertebrates, however, fatty-acid synthesis is catalyzed by an immense, multienzyme complex called a *synthase* that contains two identical subunits of 2505 amino acids each and catalyzes all steps in the pathway. In fact, for an 18-carbon fatty acid, the synthase catalyzes 42 separate steps! An overview of fatty-acid biosynthesis is shown in **FIGURE 23.6**.

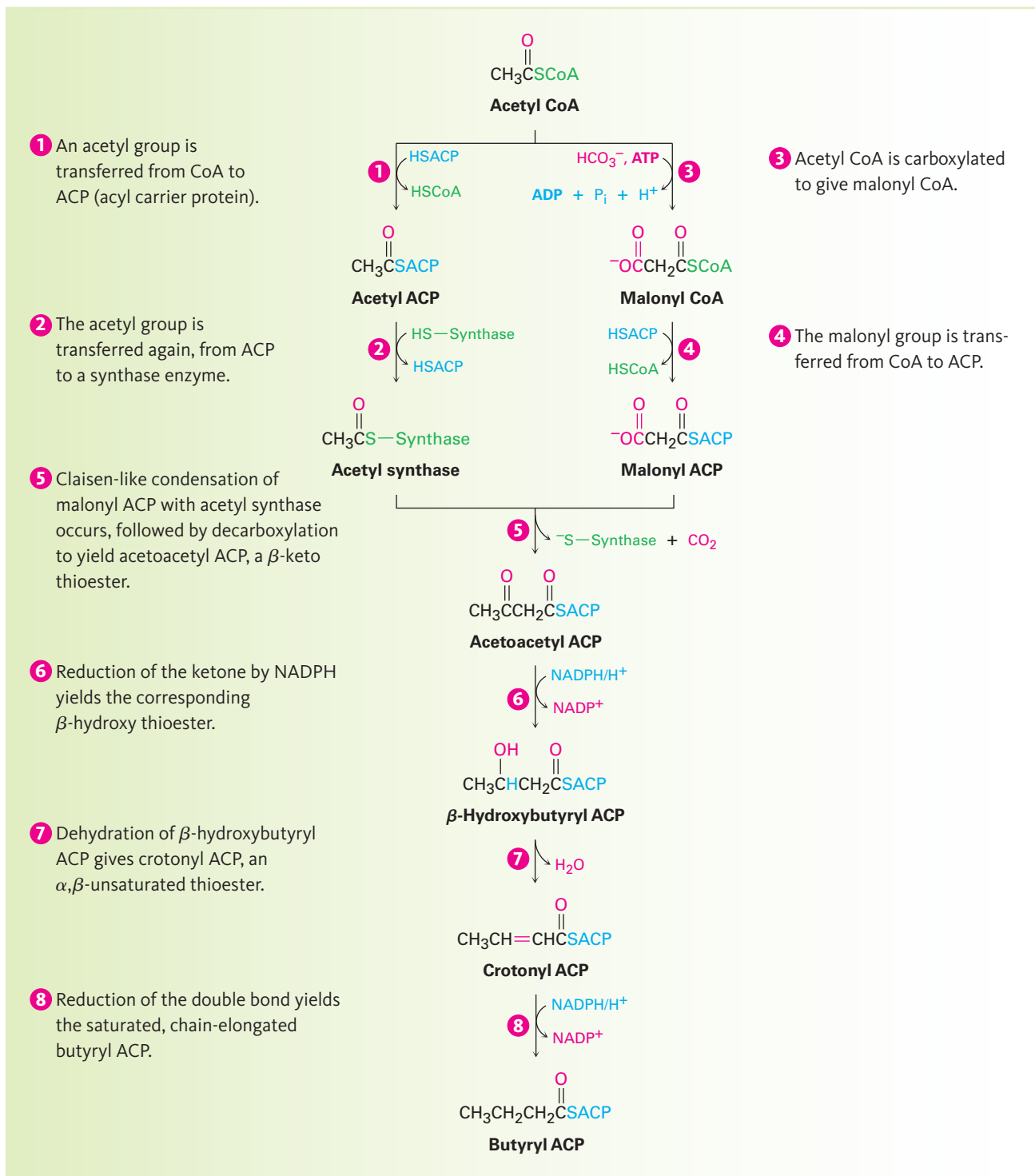
STEPS 1–2 OF FIGURE 23.6: ACYL TRANSFERS The starting material for fatty-acid biosynthesis is the thioester acetyl CoA, the final product of carbohydrate breakdown in the glycolysis pathway (Section 22-2). The pathway begins with several *priming reactions*, which transport acetyl CoA and convert it into more reactive species. The first priming reaction is a nucleophilic acyl substitution that converts acetyl CoA into acetyl ACP (acyl carrier protein). The reaction is catalyzed by ACP transacylase.



In bacteria, ACP is a small protein of 77 residues that transports an acyl group from one enzyme to another. In vertebrates, however, ACP appears to be a long arm on a multienzyme synthase complex, whose apparent function is to shepherd an acyl group from site to site within the complex. As in acetyl CoA, the acyl group in acetyl ACP is linked by a thioester bond to the sulfur atom of phosphopantetheine. The phosphopantetheine is in turn linked to ACP through the side-chain $-OH$ group of a serine residue in the enzyme.



Step 2, another priming reaction, involves a further exchange of thioester linkages by another nucleophilic acyl substitution and results in covalent bonding of the acetyl group to a cysteine residue in the synthase complex that will catalyze the upcoming condensation step.



© John McMurry

FIGURE 23.6 The pathway for fatty-acid biosynthesis from the two-carbon precursor, acetyl CoA. Individual steps are explained in the text.

STEPS 3–4 OF FIGURE 23.6: CARBOXYLATION AND ACYL TRANSFER

Step 3 is a *loading reaction* in which acetyl CoA is carboxylated by reaction with HCO_3^- and ATP to yield malonyl CoA plus ADP. As in the first step of gluconeogenesis, in which pyruvate is carboxylated to yield oxaloacetate, the coenzyme biotin acts as a carrier of CO_2 by forming *N*-carboxybiotin. The mechanism of the reaction, shown in **FIGURE 23.7**, is essentially identical to that of the pyruvate carboxylation shown in Figure 22.10 on page 797.

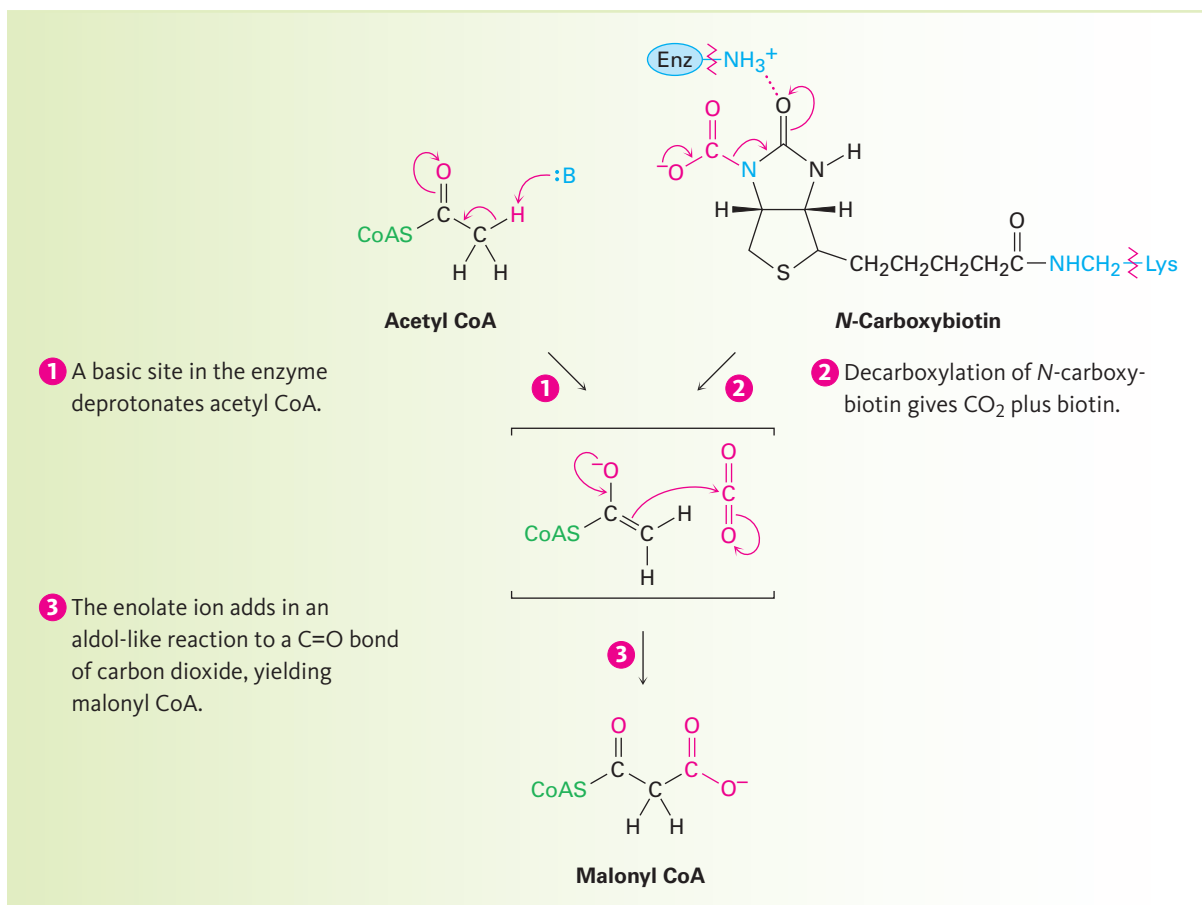
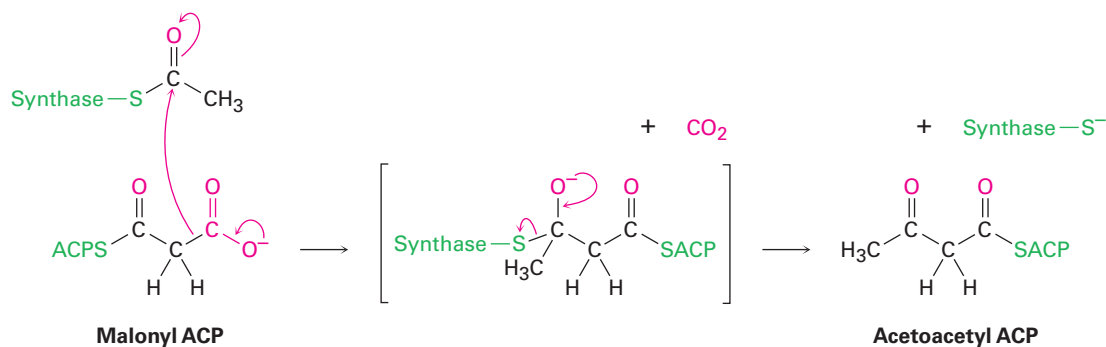


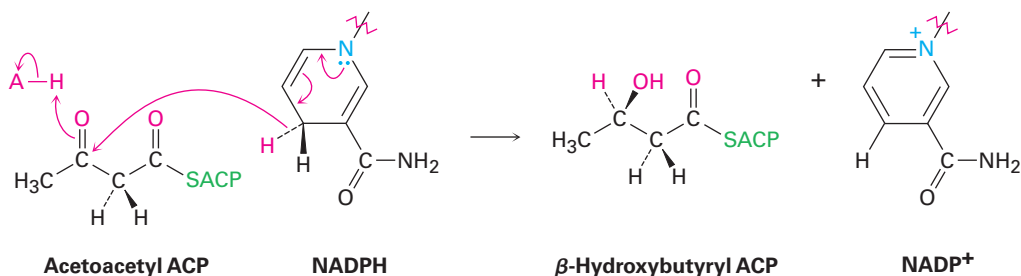
FIGURE 23.7 Mechanism of step 3 in Figure 23.6. Biotin-dependent carboxylation of acetyl CoA yields malonyl CoA by a mechanism essentially identical to that shown previously in Figure 22.10 for carboxylation of pyruvate in gluconeogenesis.

Following the formation of malonyl CoA, another nucleophilic acyl substitution reaction occurs in step 4 to form the more reactive malonyl ACP, thereby binding the malonyl group to an ACP arm of the multienzyme synthase. At this point, both acetyl and malonyl groups are bound to the enzyme and the stage is set for their condensation.

STEP 5 OF FIGURE 23.6: CONDENSATION The key carbon–carbon bond-forming reaction that builds the fatty-acid chain occurs in step 5. This step is simply a Claisen condensation between acetyl synthase as the electrophilic acceptor and malonyl ACP as the nucleophilic donor. The mechanism of the condensation is thought to involve decarboxylation of malonyl ACP to give an enolate ion, followed by immediate nucleophilic addition of the enolate ion to the carbonyl group of acetyl synthase. Breakdown of the tetrahedral intermediate then gives the four-carbon condensation product acetoacetyl ACP and frees the synthase binding site for attachment of the chain-elongated acyl group at the end of the sequence.

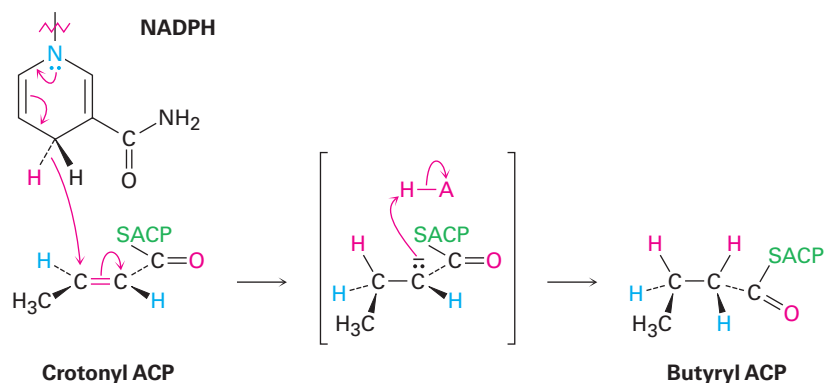


STEPS 6–8 OF FIGURE 23.6: REDUCTION AND DEHYDRATION The ketone carbonyl group in acetoacetyl ACP is reduced in step 6 to the alcohol β -hydroxybutyryl ACP by β -keto thioester reductase and NADPH. *R* Stereochemistry results at the newly formed chirality center in the β -hydroxy thioester product. (Note that the systematic name of a butyryl group is *butanoyl*.)

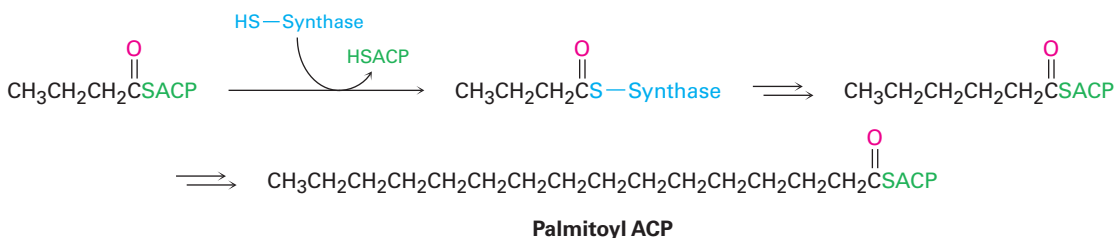


Subsequent dehydration of β -hydroxybutyryl ACP by an E1cB reaction in step 7 yields *trans*-crotonyl ACP, and the carbon–carbon double bond of crotonyl ACP is reduced by NADPH in step 8 to yield butyryl ACP. The double-bond reduction occurs by conjugate nucleophilic addition of a hydride ion from NADPH to the β carbon of *trans*-crotonyl ACP. In vertebrates, the reduction

occurs by an overall *syn* addition, but other organisms carry out a similar transformation with different stereochemistry.



The net effect of the eight steps in the fatty-acid biosynthesis pathway is to take two 2-carbon acetyl groups and combine them into a 4-carbon butyryl group. Further condensation of the butyryl group with another malonyl ACP yields a 6-carbon unit, and still further repetitions of the pathway add two more carbon atoms to the chain each time until the 16-carbon palmitoyl ACP is reached.



Further chain elongation of palmitic acid occurs by reactions similar to those just described, but CoA rather than ACP is the carrier group and separate enzymes are needed for each step rather than a multienzyme complex.

PROBLEM 23.7

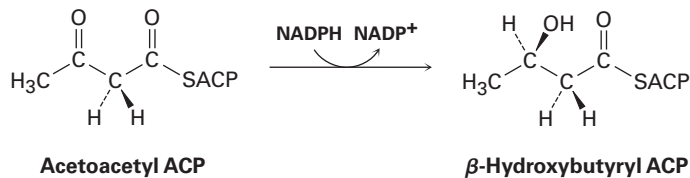
Write a mechanism for the dehydration reaction of β -hydroxybutyryl ACP to yield crotonyl ACP in step 7 of fatty-acid synthesis.

PROBLEM 23.8

Evidence for the role of acetate in fatty-acid biosynthesis comes from isotope-labeling experiments. If acetate labeled with ^{13}C in the methyl group ($^{13}\text{CH}_3\text{CO}_2\text{H}$) were incorporated into fatty acids, at what positions in the fatty-acid chain would you expect the ^{13}C label to appear?

PROBLEM 23.9

Does the reduction of acetoacetyl ACP in step 6 occur on the *Re* face or the *Si* face of the carbonyl group?

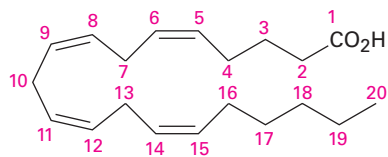


23-7 Prostaglandins and Other Eicosanoids

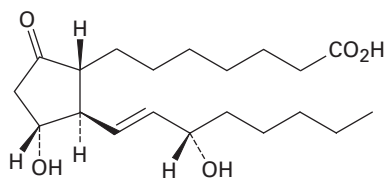
The **prostaglandins** are a group of C_{20} lipids that contain a five-membered ring with two long side chains. The name *prostaglandin* derives from the fact that the compounds were first isolated from sheep prostate glands, but they have subsequently been shown to be present in small amounts in all body tissues and fluids.

The several dozen known prostaglandins have an extraordinarily wide range of biological effects. Among their many properties, they can lower blood pressure, affect blood-platelet aggregation during clotting, lower gastric secretions, control inflammation, affect kidney function, affect reproductive systems, and stimulate uterine contractions during childbirth.

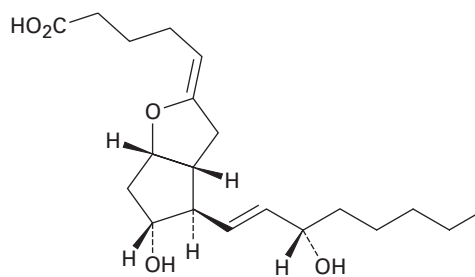
FIGURE 23.8 Structures of some representative eicosanoids. All are derived biologically from arachidonic acid.



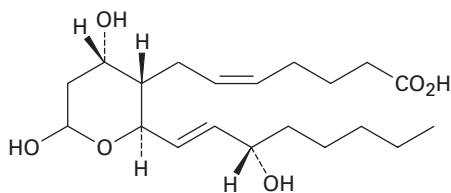
Arachidonic acid



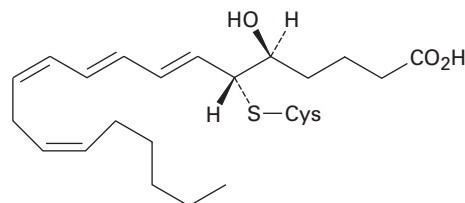
Prostaglandin E₁ (PGE₁)



Prostaglandin I₂ (PGI₂) (prostacyclin)



Thromboxane B₂ (TXB₂)



Leukotriene E₄ (LTE₄)

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Prostaglandins, together with related compounds called thromboxanes and leukotrienes, make up a class of compounds called **eicosanoids** because they are derived biologically from eicosa-5,8,11,14-tetraenoic acid, or arachidonic acid (FIGURE 23.8). Prostaglandins (PG) have a cyclopentane ring with two long side chains; thromboxanes (TX) have a six-membered, oxygen-containing ring; and leukotrienes (LT) are acyclic.

Eicosanoids are named based on their ring system (PG, TX, or LT), substitution pattern, and number of double bonds. The various substitution patterns on the ring are indicated by letter, as in FIGURE 23.9, and the number of double bonds is indicated by a subscript. Thus, PGE₁ is a prostaglandin with the “E” substitution pattern and one double bond. The numbering of the atoms in the various eicosanoids is the same as in arachidonic acid, starting with the –CO₂H carbon as C1, continuing around the ring, and ending with the –CH₃ carbon at the other end of the chain as C20.

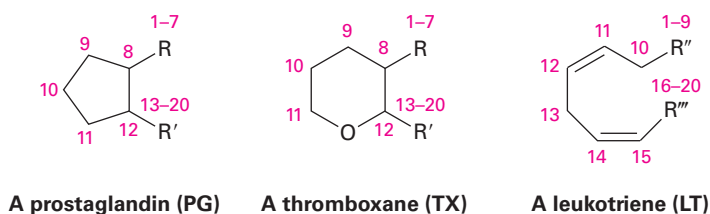
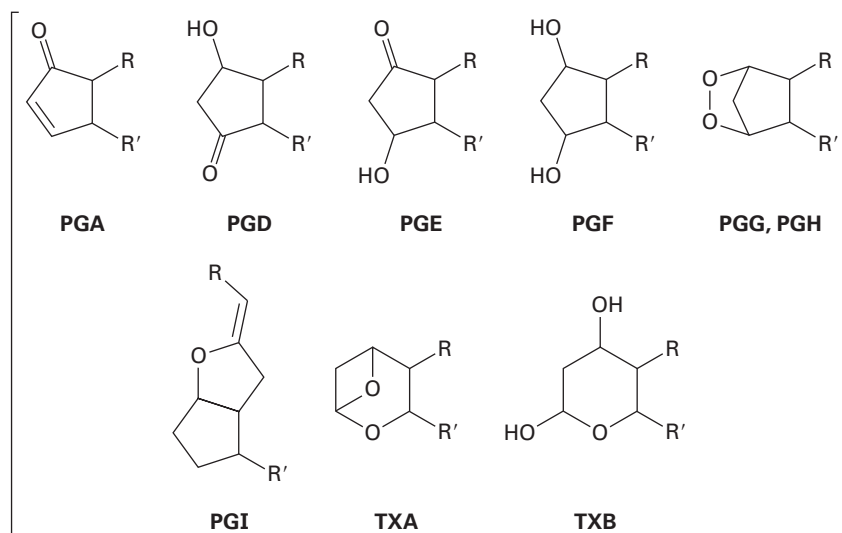


FIGURE 23.9 The naming system for eicosanoids.

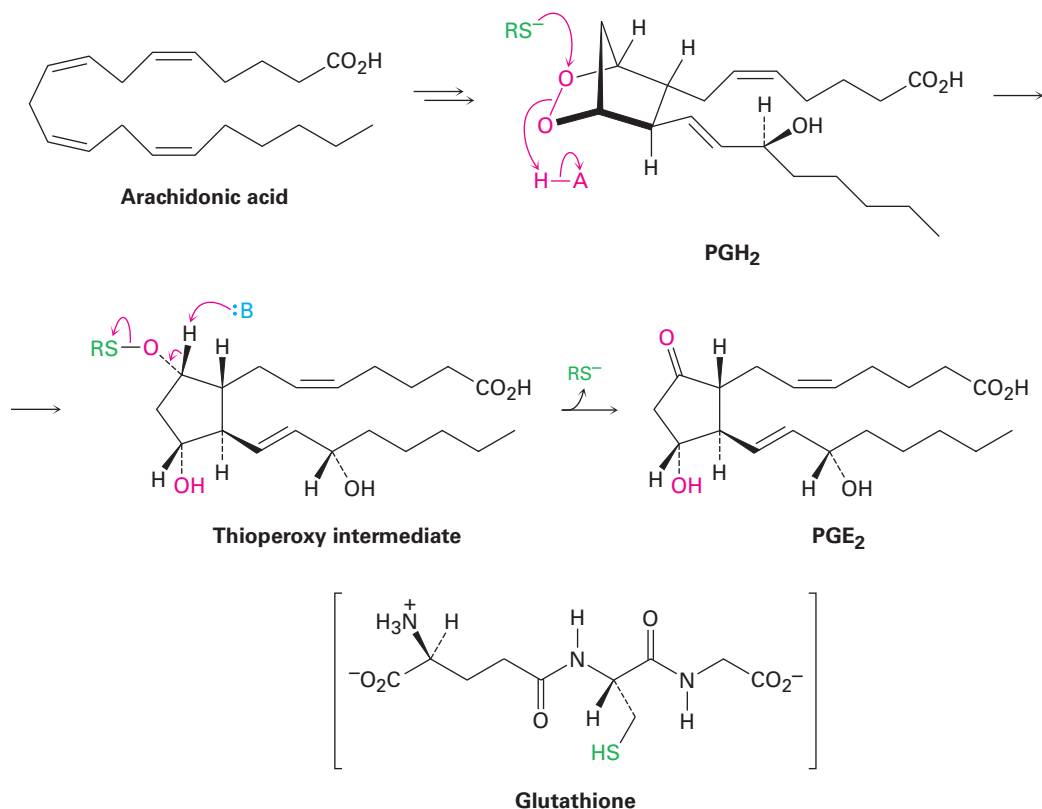


Eicosanoid biosynthesis begins with the conversion of arachidonic acid to PGH₂, catalyzed by the multifunctional PGH synthase (PGHS), also called cyclooxygenase (COX). There are two distinct enzymes, PGHS-1 and PGHS-2 (or COX-1 and COX-2), both of which accomplish the same reaction but appear to function independently. COX-1 carries out the normal physiological production of prostaglandins, and COX-2 produces additional prostaglandin in response to arthritis or other inflammatory conditions. Vioxx, Celebrex, Bextra, and several other drugs selectively inhibit the COX-2 enzyme but some also appear to cause potentially serious heart problems in weakened patients. (See the Chapter 9 *Something Extra*.)

PGHS accomplishes two transformations, an initial reaction of arachidonic acid with O_2 to yield PGG_2 and a subsequent reduction of the hydroperoxide group ($-OOH$) to the alcohol PGH_2 . The sequence of steps involved in these transformations was shown in Figure 8.10 on page 241.

Further processing of PGH_2 then leads to other eicosanoids. PGE_2 , for instance, arises by an isomerization of PGH_2 catalyzed by PGE synthase (PGES). The coenzyme glutathione is needed for enzyme activity, although it is not chemically changed during the isomerization and its role is not fully understood. One possibility is that the glutathione thiolate anion breaks the $O-O$ bond in PGH_2 by an S_N2 -like attack on one of the oxygen atoms, giving a thioperoxy intermediate ($R-S-O-R'$) that eliminates glutathione to give the ketone (FIGURE 23.10).

FIGURE 23.10
Mechanism of the conversion of PGH_2 into PGE_2 .



PROBLEM 23.10

Assign *R* or *S* configuration to each chirality center in prostaglandin E_2 (Figure 23.10), the most abundant and biologically potent of mammalian prostaglandins.

23-8 Terpenoids

In the Chapter 7 *Something Extra*, we looked briefly at **terpenoids**, a vast and diverse group of lipids found in all living organisms. Despite their apparent structural differences, all terpenoids are related. All contain a multiple of five carbons and are derived biosynthetically from the five-carbon precursor isopentenyl diphosphate (**FIGURE 23.11**). Although formally a *terpenoid* contains oxygen, while a *terpene* is a hydrocarbon, we'll use the term terpenoid to refer to both for simplicity.

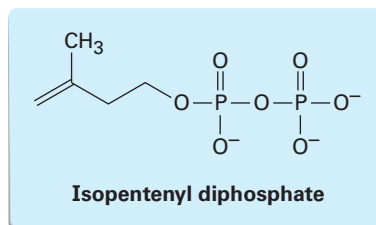
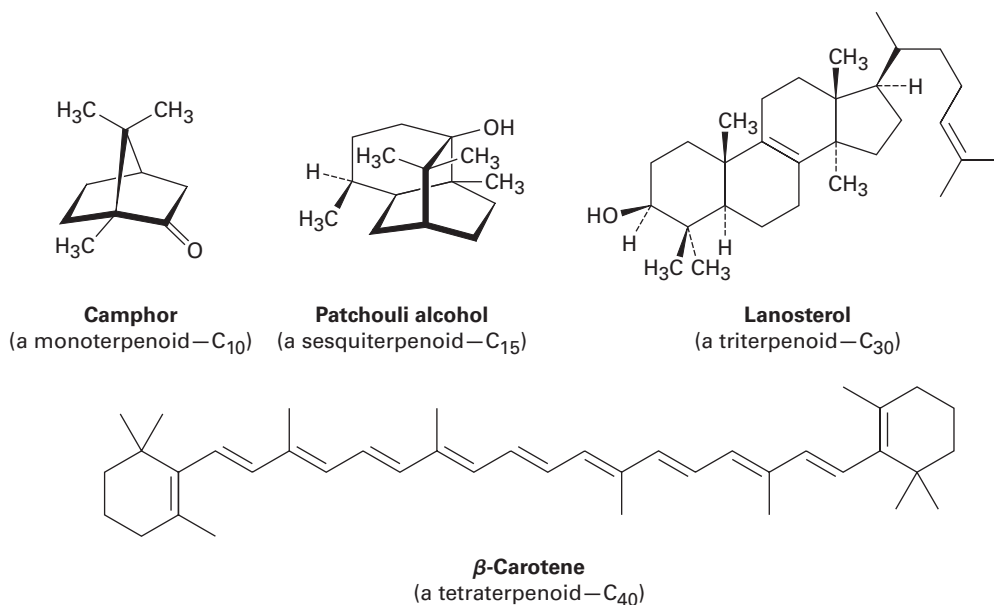
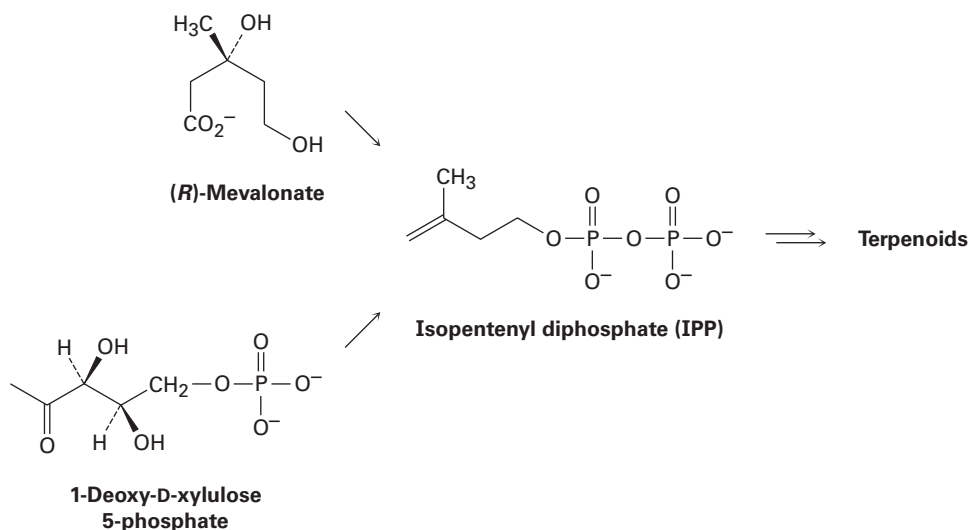


FIGURE 23.11 Structures of some representative terpenoids.



Terpenoids are classified according to the number of five-carbon multiples they contain. Monoterpenoids contain 10 carbons and are derived from two isopentenyl diphosphates, sesquiterpenoids contain 15 carbons and are derived from three isopentenyl diphosphates, diterpenoids contain 20 carbons and are derived from four isopentenyl diphosphates, and so on, up to triterpenoids (C₃₀) and tetraterpenoids (C₄₀). Monoterpenoids and sesquiterpenoids are found primarily in plants, bacteria, and fungi, but the higher terpenoids occur in both plants and animals. The triterpene lanosterol, for example, is the precursor from which steroid hormones are made, and the tetraterpene β-carotene is a dietary source of vitamin A (Figure 23.11).

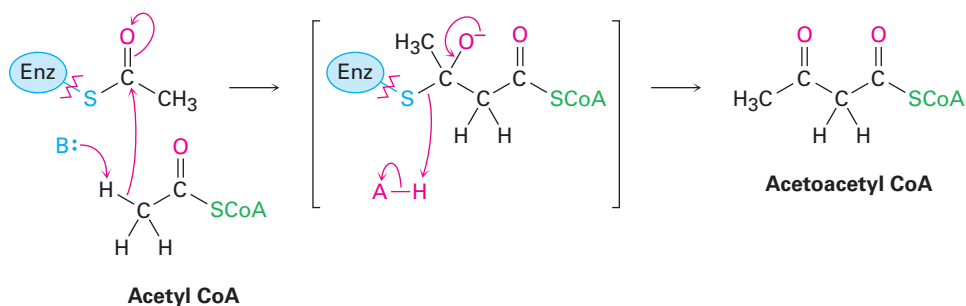
The terpenoid precursor isopentenyl diphosphate, formerly called isopentenyl pyrophosphate and thus abbreviated IPP, is biosynthesized by two different pathways, depending on the organism and the structure of the final product. In animals and higher plants, sesquiterpenoids and triterpenoids arise primarily from the *mevalonate* pathway, whereas monoterpenoids, diterpenoids, and tetraterpenoids are biosynthesized by the *1-deoxyxylulose 5-phosphate (DXP)* pathway, also called the methylerythritol phosphate, or MEP, pathway. In bacteria, both pathways are used. We'll look only at the mevalonate pathway, which is more common and better understood at present.



The Mevalonate Pathway to Isopentenyl Diphosphate

As summarized in **FIGURE 23.12**, the mevalonate pathway begins with the Claisen condensation of acetyl CoA to yield acetoacetyl CoA. A second carbonyl condensation reaction with a third molecule of acetyl CoA, this one an aldol-like process, then yields the six-carbon compound 3-hydroxy-3-methylglutaryl CoA, which is reduced to give mevalonate. Phosphorylation, followed by loss of CO₂ and phosphate ion, completes the process.

STEP 1 OF FIGURE 23.12: CLAISEN CONDENSATION The first step in mevalonate biosynthesis is a Claisen condensation to yield acetoacetyl CoA, a reaction catalyzed by acetoacetyl-CoA acetyltransferase. An acetyl group is first bound to the enzyme by a nucleophilic acyl substitution reaction with a cysteine -SH group. Formation of an enolate ion from a second molecule of acetyl CoA, followed by Claisen condensation, then yields the product.



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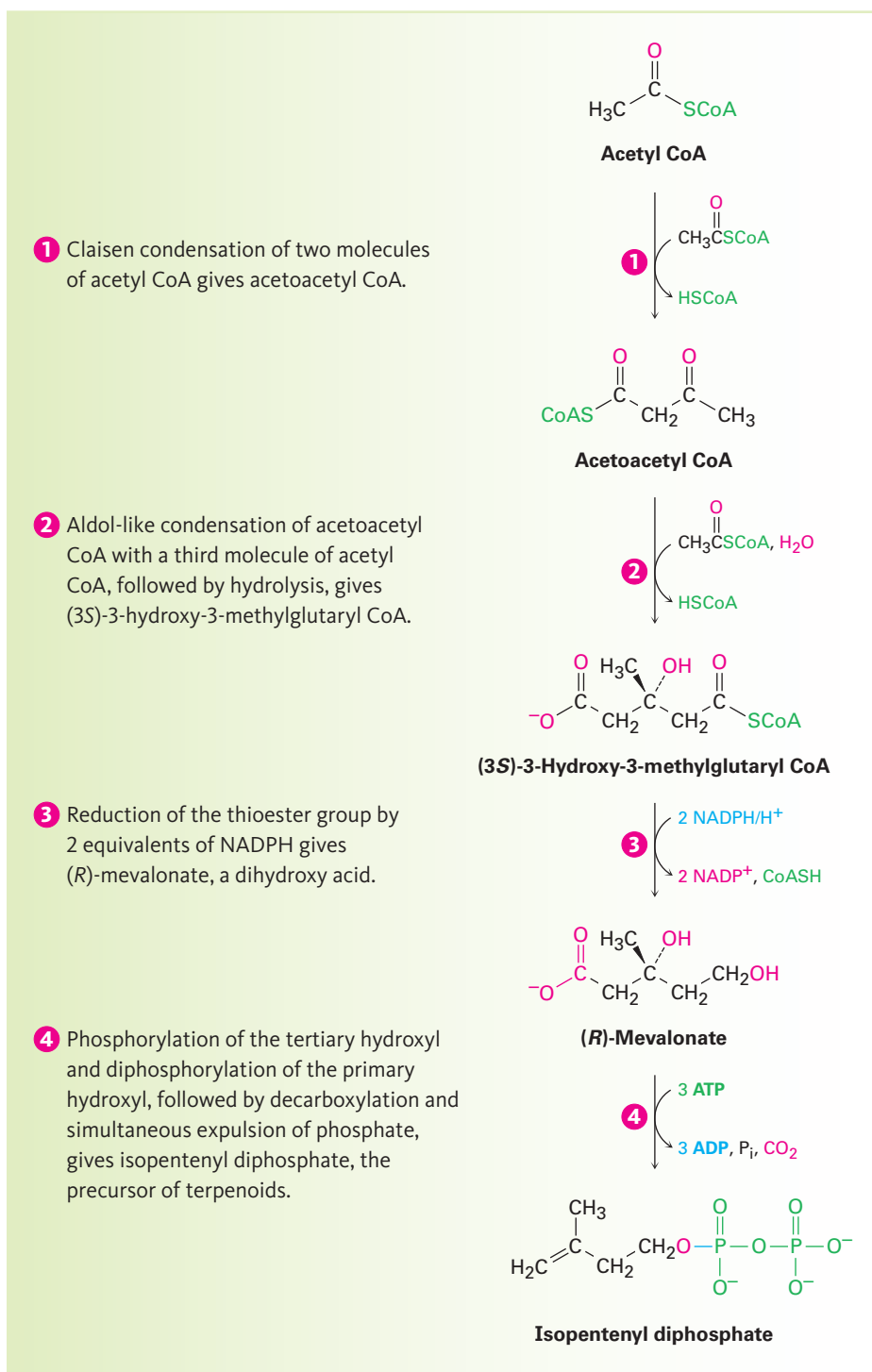
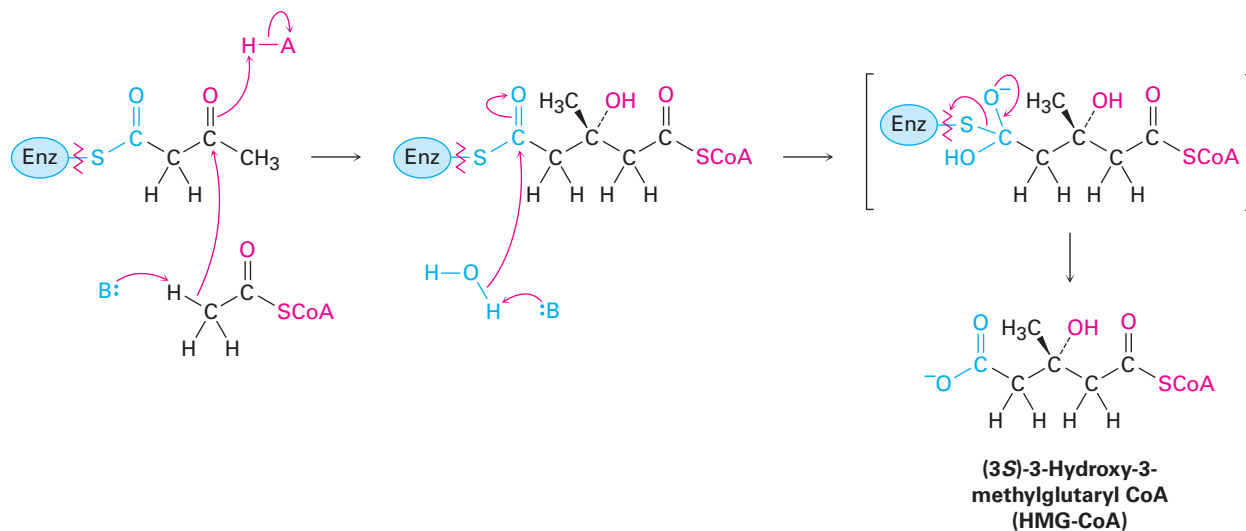


FIGURE 23.12 The mevalonate pathway for the biosynthesis of isopentenyl diphosphate from three molecules of acetyl CoA.

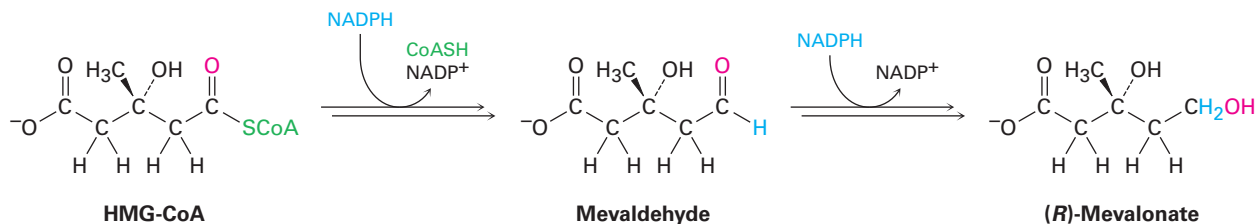
Individual steps are explained in the text.

STEP 2 OF FIGURE 23.12: ALDOL CONDENSATION Acetoacetyl CoA undergoes an aldol-like addition of an acetyl CoA enolate ion in step 2 in a reaction catalyzed by 3-hydroxy-3-methylglutaryl-CoA synthase. The reaction occurs by initial binding of the substrate to a cysteine -SH group in the

enzyme, followed by enolate-ion addition and subsequent hydrolysis to give (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).

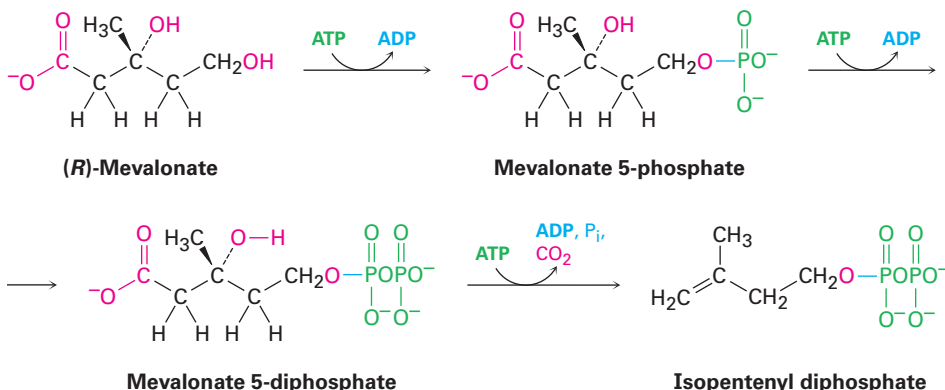


STEP 3 OF FIGURE 23.12: REDUCTION Reduction of HMG-CoA to give (*R*)-mevalonate is catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase and requires 2 equivalents of NADPH. The reaction occurs in two steps, and proceeds through an aldehyde intermediate. The first step is a nucleophilic acyl substitution reaction involving hydride transfer from NADPH to the thioester carbonyl group of HMG-CoA. Following expulsion of HSCoA as leaving group, the aldehyde intermediate undergoes a second hydride addition to give mevalonate.



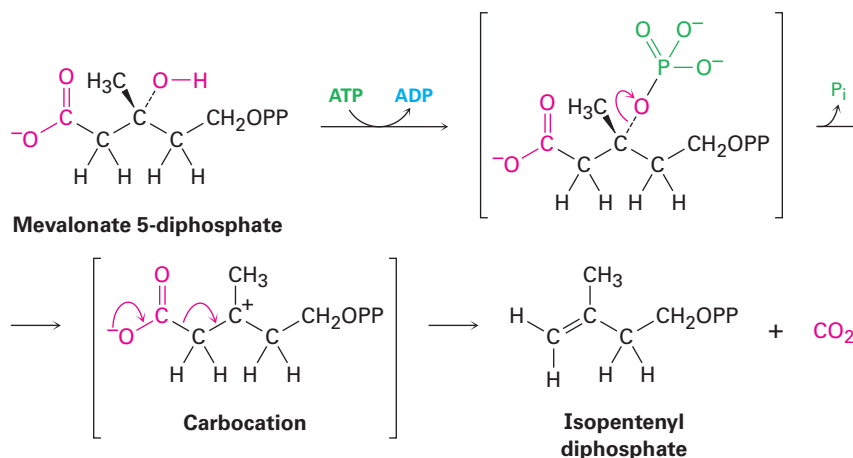
STEP 4 OF FIGURE 23.12: PHOSPHORYLATION AND DECARBOXYLATION Three additional reactions are needed to convert mevalonate to isopentenyl diphosphate. The first two are straightforward phosphorylations by ATP that occur through nucleophilic substitution reactions on the terminal phosphorus. Mevalonate is first converted to mevalonate 5-phosphate (phosphomevalonate) by reaction with ATP, and mevalonate 5-phosphate then reacts with a second ATP to give mevalonate 5-diphosphate (diphosphomevalonate).

The third reaction results in phosphorylation of the tertiary hydroxyl group, followed by decarboxylation and loss of phosphate ion.



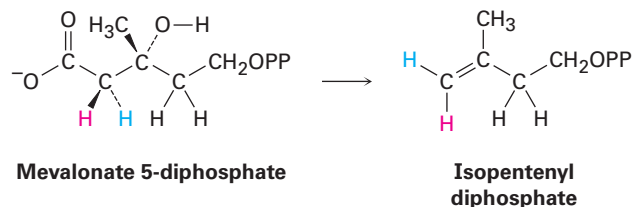
The final decarboxylation of mevalonate 5-diphosphate appears unusual because decarboxylations of acids do not typically occur except in β -keto acids and malonic acids, in which the carboxylate group is two atoms away from an additional carbonyl group. As discussed in Section 17-5, the function of this second carbonyl group is to act as an electron acceptor and stabilize the charge resulting from loss of CO_2 . In fact, though, the decarboxylation of a β -keto acid and the decarboxylation of mevalonate 5-diphosphate are closely related.

Catalyzed by mevalonate-5-diphosphate decarboxylase, the substrate is first phosphorylated on the free $-\text{OH}$ group by reaction with ATP to give a tertiary phosphate, which undergoes spontaneous $\text{S}_{\text{N}}1$ -like dissociation to give a tertiary carbocation. The positive charge then acts as an electron acceptor to facilitate decarboxylation in exactly the same way a β carbonyl group does, giving isopentenyl diphosphate. (In the following structures, the diphosphate group is abbreviated OPP.)



PROBLEM 23.11

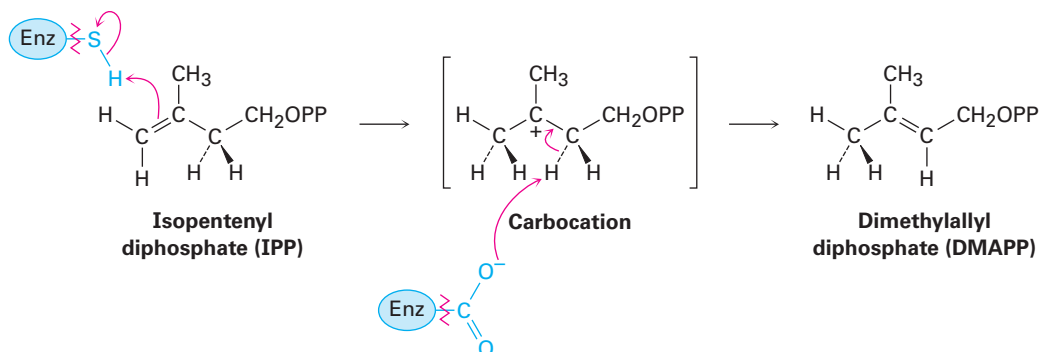
Studies of the conversion of mevalonate 5-phosphate to isopentenyl diphosphate have shown the following result. Which hydrogen, *pro-R* or *pro-S*, ends up cis to the methyl group, and which ends up trans?

**Conversion of Isopentenyl Diphosphate to Terpenoids**

The conversion of isopentenyl diphosphate (IPP) to terpenoids begins with its isomerization to dimethylallyl diphosphate, abbreviated DMAPP and formerly called dimethylallyl pyrophosphate. These two C_5 building blocks then combine to give the C_{10} unit geranyl diphosphate (GPP). The corresponding alcohol, geraniol, is itself a fragrant terpenoid that occurs in rose oil.

Further combination of GPP with another IPP gives the C_{15} unit farnesyl diphosphate (FPP), and so on, up to C_{25} . Terpenoids with more than 25 carbons—that is, triterpenoids (C_{30}) and tetraterpenoids (C_{40})—are synthesized by dimerization of C_{15} and C_{20} units, respectively. Triterpenoids and steroids, in particular, arise from dimerization of farnesyl diphosphate to give squalene (FIGURE 23.13).

The isomerization of isopentenyl diphosphate to dimethylallyl diphosphate is catalyzed by IPP isomerase and occurs through a carbocation pathway. Protonation of the IPP double bond by a hydrogen-bonded cysteine residue in the enzyme gives a tertiary carbocation intermediate, which is deprotonated by a glutamate residue as base to yield DMAPP. X-ray structural studies on the enzyme show that it holds the substrate in an unusually deep, well-protected pocket to shield the highly reactive carbocation from reaction with solvent or other external substances.



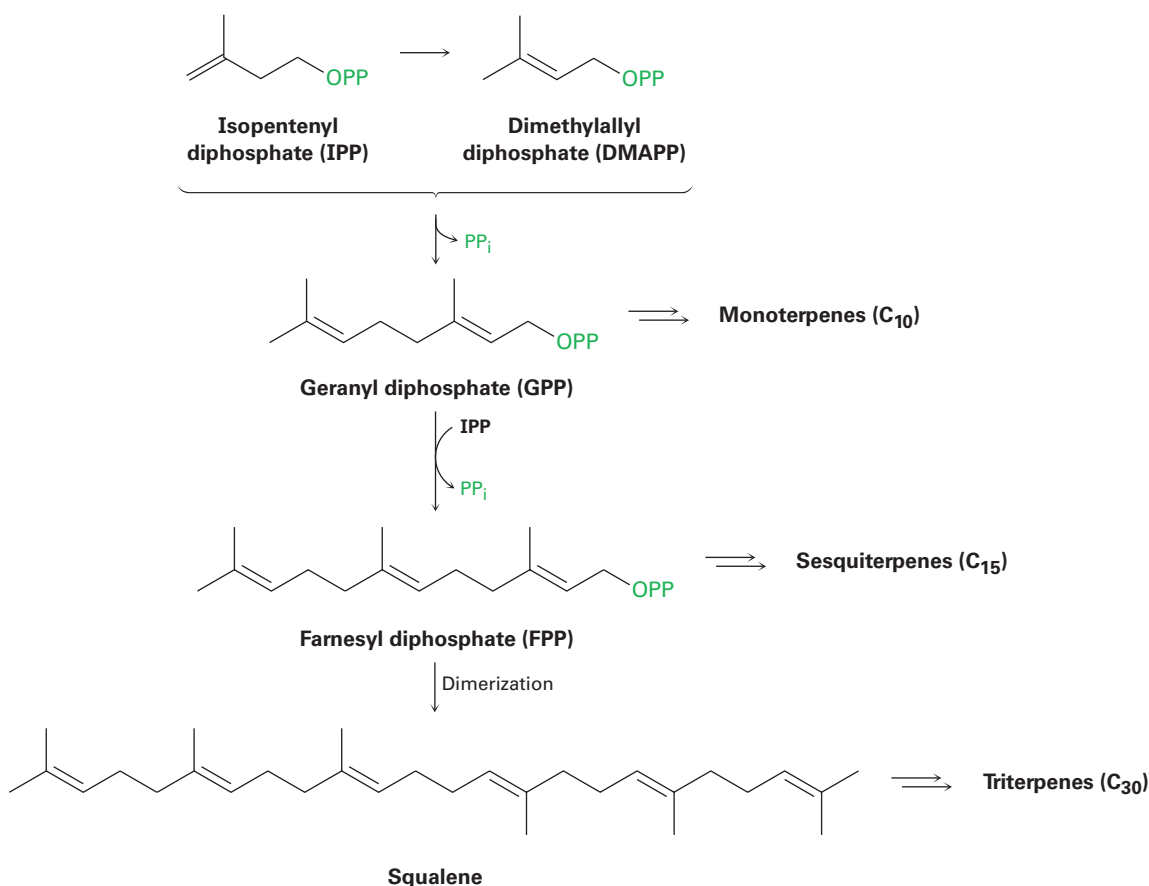
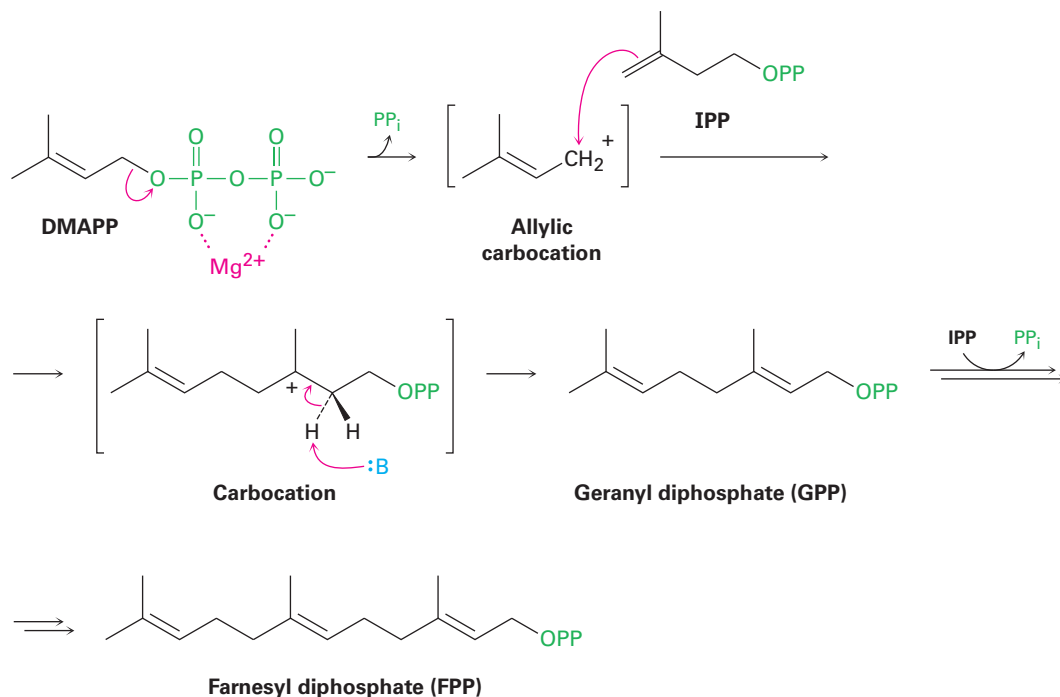


FIGURE 23.13 An overview of terpenoid biosynthesis from isopentenyl diphosphate.

Both the initial coupling of DMAPP with IPP to give geranyl diphosphate and the subsequent coupling of GPP with a second molecule of IPP to give farnesyl diphosphate are catalyzed by farnesyl diphosphate synthase. The process requires Mg^{2+} ion, and the key step is a nucleophilic substitution reaction in which the double bond of IPP behaves as a nucleophile in displacing a diphosphate ion leaving group (PP_i) on DMAPP. Evidence suggests that the DMAPP develops considerable cationic character and that spontaneous dissociation of the allylic diphosphate ion occurs in an S_N1 -like pathway (FIGURE 23.14).

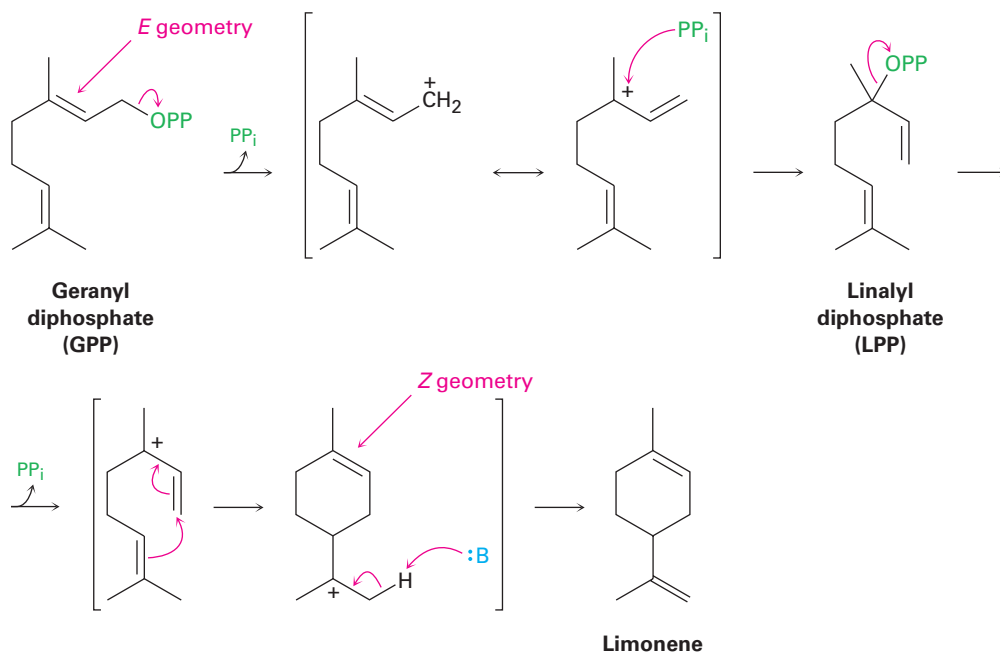
The subsequent conversion of geranyl diphosphate into monoterpenoids typically involves carbocation intermediates and multistep reaction pathways that are catalyzed by terpene cyclases. Monoterpene cyclases function by first isomerizing geranyl diphosphate to its allylic isomer linalyl diphosphate (LPP), a process that occurs by spontaneous S_N1 -like dissociation to an allylic carbocation, followed by recombination. The effect of this isomerization is to convert the C2–C3 double bond of GPP into a single bond, thereby making cyclization possible and allowing *E/Z* isomerization of the double bond.

FIGURE 23.14
Mechanism of the coupling reaction of dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) to give geranyl diphosphate (GPP). The process is an S_N1 -like reaction.



Further dissociation and cyclization by electrophilic addition of the cationic carbon to the terminal double bond then gives a cyclic cation, which might either rearrange, undergo a hydride shift, be captured by a nucleophile, or be deprotonated to give any of the several hundred known monoterpenoids. As just one example, limonene, a monoterpene found in many citrus oils, arises by the biosynthetic pathway shown in **FIGURE 23.15**.

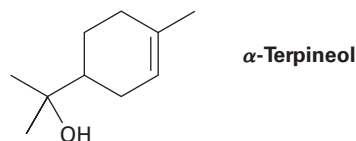
FIGURE 23.15 Mechanism of the formation of the monoterpene limonene from geranyl diphosphate.



Proposing a Terpenoid Biosynthesis Pathway

WORKED EXAMPLE 23.1

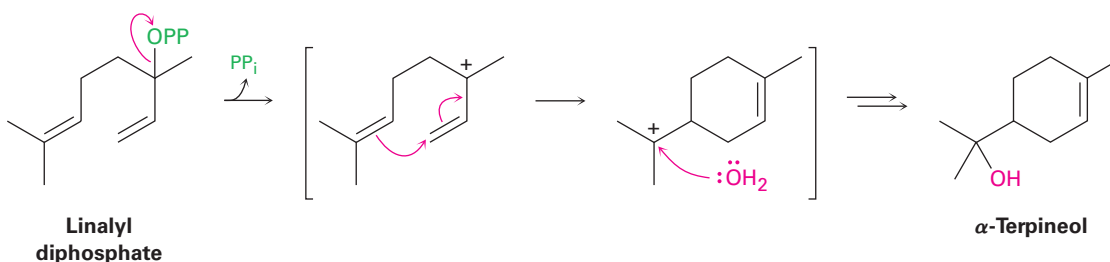
Propose a mechanistic pathway for the biosynthesis of α -terpineol from geranyl diphosphate.



Strategy

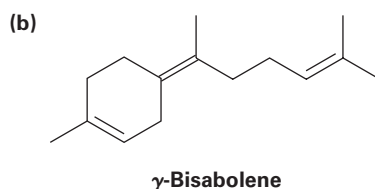
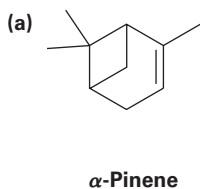
α -Terpineol, a monoterpene, is derived biologically from geranyl diphosphate through its isomer linalyl diphosphate. Draw the precursor in a conformation that approximates the structure of the target molecule, and then carry out a cationic cyclization using the appropriate double bond. Since the target is an alcohol, the carbocation resulting from cyclization evidently reacts with water.

Solution



PROBLEM 23.12

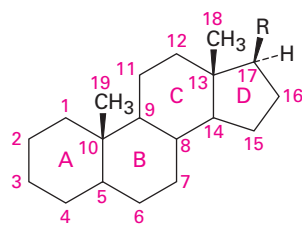
Propose mechanistic pathways for the biosynthesis of the following terpenoids:



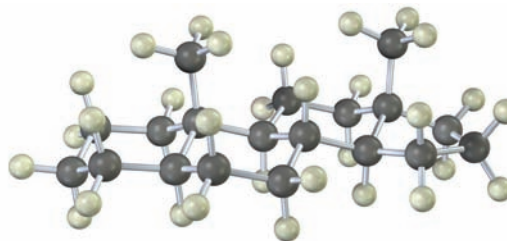
23-9 Steroids

In addition to fats, phospholipids, eicosanoids, and terpenoids, the lipid extracts of plants and animals also contain **steroids**, molecules that are derived from the triterpenoid lanosterol (Figure 23.11) and whose structures are based on a tetracyclic ring system. The four rings are designated A, B, C, and D,

beginning at the lower left, and the carbon atoms are numbered beginning in the A ring. The three 6-membered rings (A, B, and C) adopt chair conformations but are prevented by their rigid geometry from undergoing the usual cyclohexane ring-flips (Section 4-6).

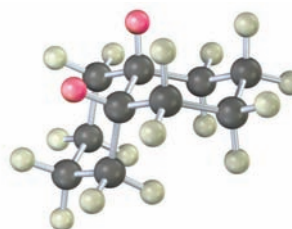
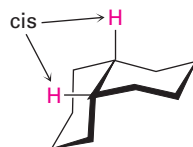


A steroid
(R = various side chains)

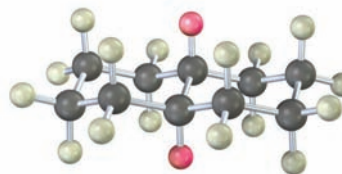
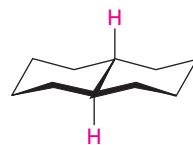


As noted in Section 4-9, two cyclohexane rings can be joined in either a *cis* or a *trans* manner. With *cis* fusion to give *cis*-decalin, both groups at the ring-junction positions (the *angular* groups) are on the same side of the two rings. With *trans* fusion to give *trans*-decalin, the groups at the ring junctions are on opposite sides.

***cis*-Decalin**

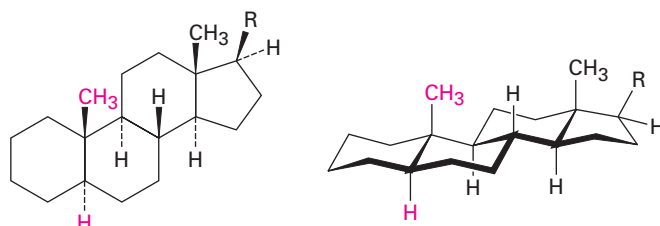


***trans*-Decalin**



Steroids can have either a *cis* or a *trans* fusion of the A and B rings, but the other ring fusions (B–C and C–D) are usually *trans* (FIGURE 23.16). An A–B *trans* steroid has the C19 angular methyl group up, denoted β , and the hydrogen atom at C5 down, denoted α , on opposite sides of the molecule. An A–B *cis* steroid, by contrast, has both the C19 angular methyl group and the C5 hydrogen atom on the same side (β) of the molecule. Both kinds of steroids are relatively long, flat molecules that have their two methyl groups protruding axially above the ring system. The A–B *trans* steroids are the more common, although A–B *cis* steroids are found in liver bile.

An A–B trans steroid



An A–B cis steroid

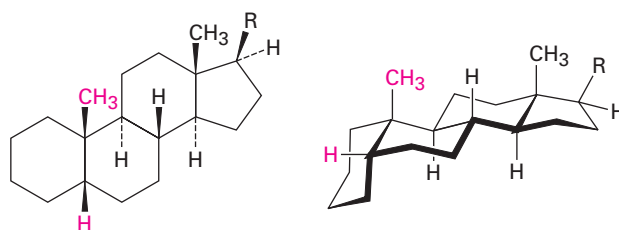
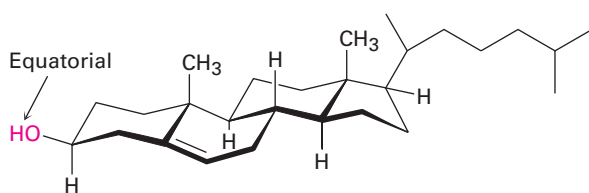
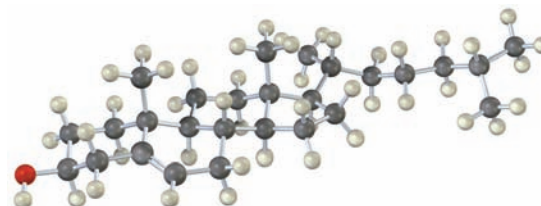


FIGURE 23.16 Steroid conformations. The three 6-membered rings have chair conformations but are unable to undergo ring-flips. The A and B rings can be either cis-fused or trans-fused.

Substituent groups on the steroid ring system can be either axial or equatorial. As with simple cyclohexanes (Section 4-7), equatorial substitution is generally more favorable than axial substitution for steric reasons. The hydroxyl group at C3 of cholesterol, for example, has the more stable equatorial orientation.

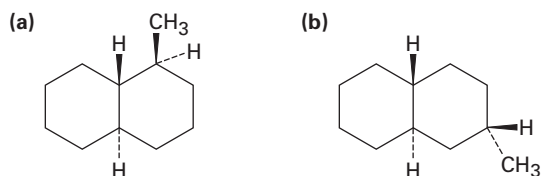


Cholesterol



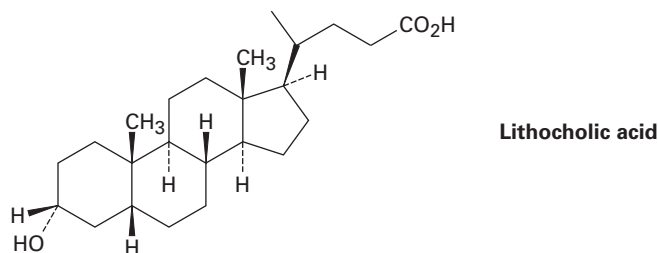
PROBLEM 23.13

Draw the following molecules in chair conformations, and tell whether the ring substituents are axial or equatorial:



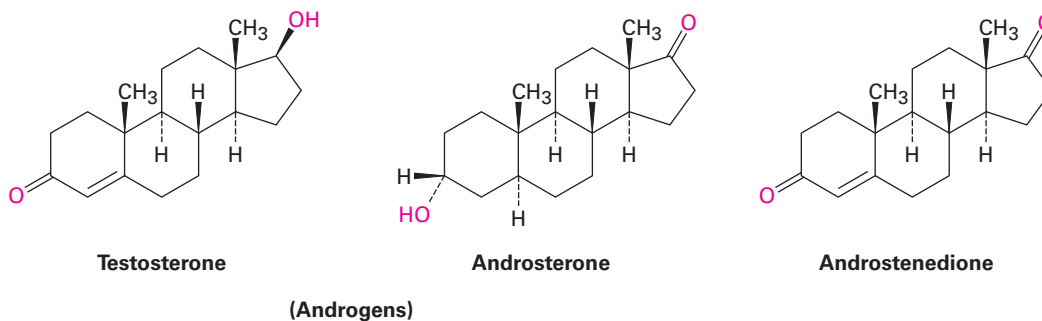
PROBLEM 23.14

Lithocholic acid is an A–B cis steroid found in human bile. Draw lithocholic acid showing chair conformations as in Figure 23.16, and tell whether the hydroxyl group at C3 is axial or equatorial.

**Steroid Hormones**

In humans, most steroids function as *hormones*, chemical messengers that are secreted by endocrine glands and carried through the bloodstream to target tissues. There are two main classes of steroid hormones: the *sex hormones*, which control maturation, tissue growth, and reproduction, and the *adrenocortical hormones*, which regulate a variety of metabolic processes.

SEX HORMONES Testosterone and androsterone are the two most important male sex hormones, or *androgens*. Androgens are responsible for the development of male secondary sex characteristics during puberty and for promoting tissue and muscle growth. Both are synthesized in the testes from cholesterol. Androstenedione is another minor hormone that has received particular attention because of its use by prominent athletes.

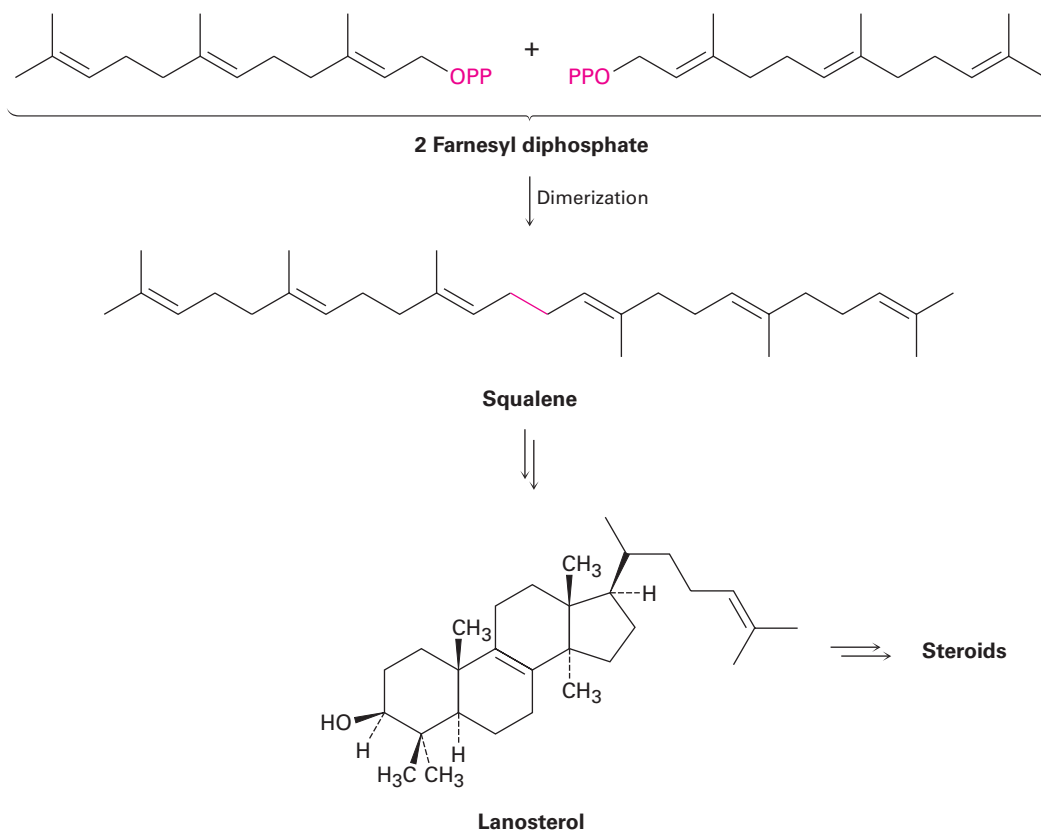


Estrone and estradiol are the two most important female sex hormones, or *estrogens*. Synthesized in the ovaries from testosterone, estrogenic hormones are responsible for the development of female secondary sex characteristics and for regulation of the menstrual cycle. Note that both have a benzene-like aromatic A ring. In addition, another kind of sex hormone called a *progestin*

23-10 Biosynthesis of Steroids

Steroids are heavily modified triterpenoids that are biosynthesized in living organisms from farnesyl diphosphate (C_{15}). A reductive dimerization first converts farnesyl diphosphate to the acyclic hydrocarbon squalene (C_{30}), which is converted into lanosterol (FIGURE 23.17). Further rearrangements and degradations then take place to yield various steroids. The conversion of squalene to lanosterol is among the most intensively studied of all biosynthetic transformations. Starting from an achiral, open-chain polyene, the entire process requires only two enzymes and results in the formation of six carbon-carbon bonds, four rings, and seven chirality centers.

FIGURE 23.17 An overview of steroid biosynthesis from farnesyl diphosphate.



Lanosterol biosynthesis begins with the selective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene, catalyzed by squalene epoxidase. Molecular O_2 provides the source of the epoxide oxygen atom, and NADPH is required, along with a flavin coenzyme. The proposed mechanism involves reaction of $FADH_2$ with O_2 to produce a flavin hydroperoxide intermediate ($ROOH$), which transfers an oxygen to squalene in a pathway initiated by nucleophilic attack of the squalene double bond on the terminal hydroperoxide oxygen (FIGURE 23.18). The flavin alcohol formed as a byproduct loses H_2O to give FAD, which is reduced back to $FADH_2$ by NADPH. As noted in Section 8-6, this biological epoxidation mechanism is closely analogous to the mechanism by which peroxyacids (RCO_3H) react with alkenes to give epoxides in the laboratory.

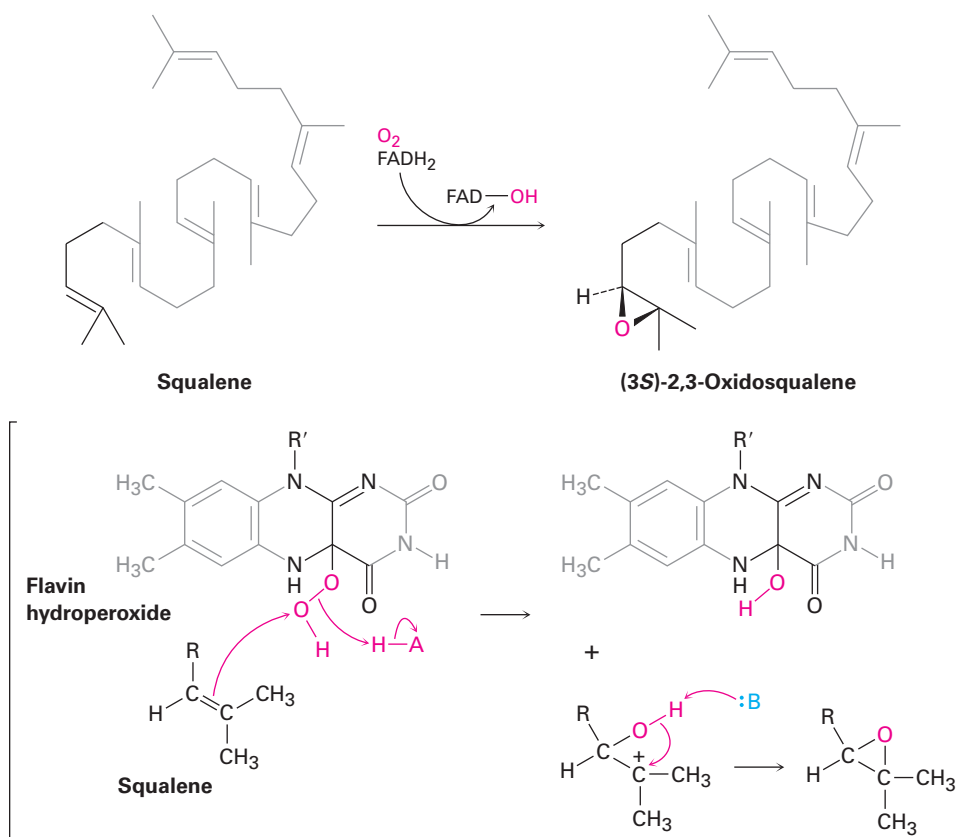
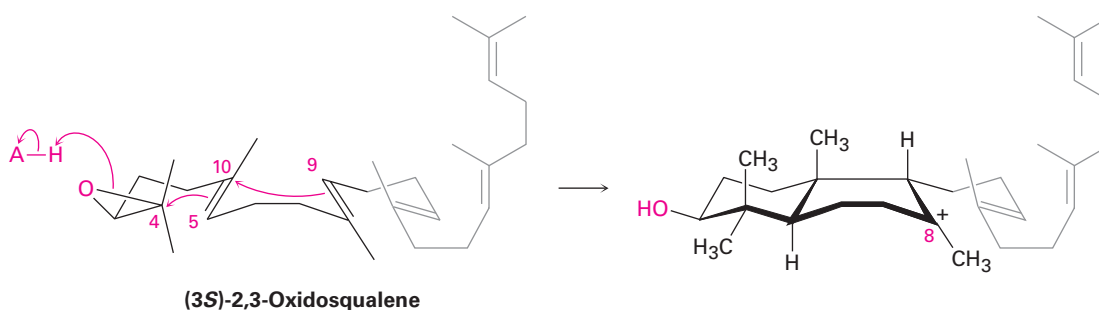


FIGURE 23.18 Proposed mechanism of the oxidation of squalene by flavin hydroperoxide.

The second part of lanosterol biosynthesis is catalyzed by oxidosqualene: lanosterol cyclase and occurs as shown in **FIGURE 23.19**. Squalene is folded by the enzyme into a conformation that aligns the various double bonds for undergoing a cascade of successive intramolecular electrophilic additions, followed by a series of hydride and methyl migrations. Except for the initial epoxide protonation–cyclization, the process is probably stepwise and appears to involve discrete carbocation intermediates that are stabilized by electrostatic interactions with electron-rich aromatic amino acids in the enzyme.

STEPS 1–2 OF FIGURE 23.19: EPOXIDE OPENING AND INITIAL CYCLIZATIONS Cyclization begins in step 1 with protonation of the epoxide ring by an aspartic acid residue in the enzyme. Nucleophilic opening of the protonated epoxide by the nearby 5,10 double bond (steroid numbering; Section 23-9) then yields a tertiary carbocation at C10. Further addition of C10 to the 8,9 double bond in step 2 next gives a bicyclic tertiary cation at C8.



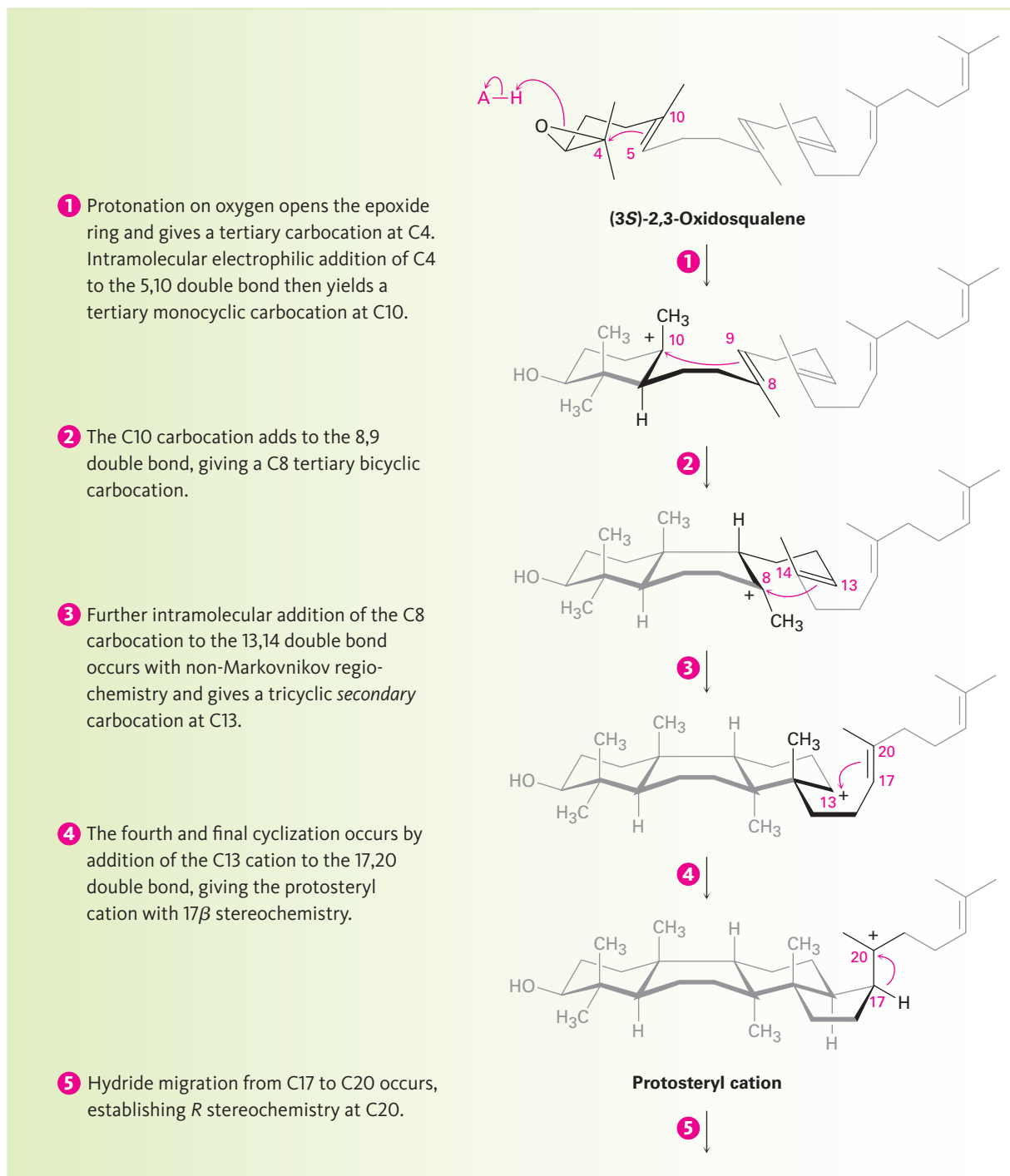


FIGURE 23.19 Mechanism of the conversion of 2,3-oxidosqualene to lanosterol. Four cationic cyclizations are followed by four rearrangements and a final loss of H^+ from C9. The steroid numbering system is used for referring to specific positions in the intermediates (Section 23-9). Individual steps are explained in the text.

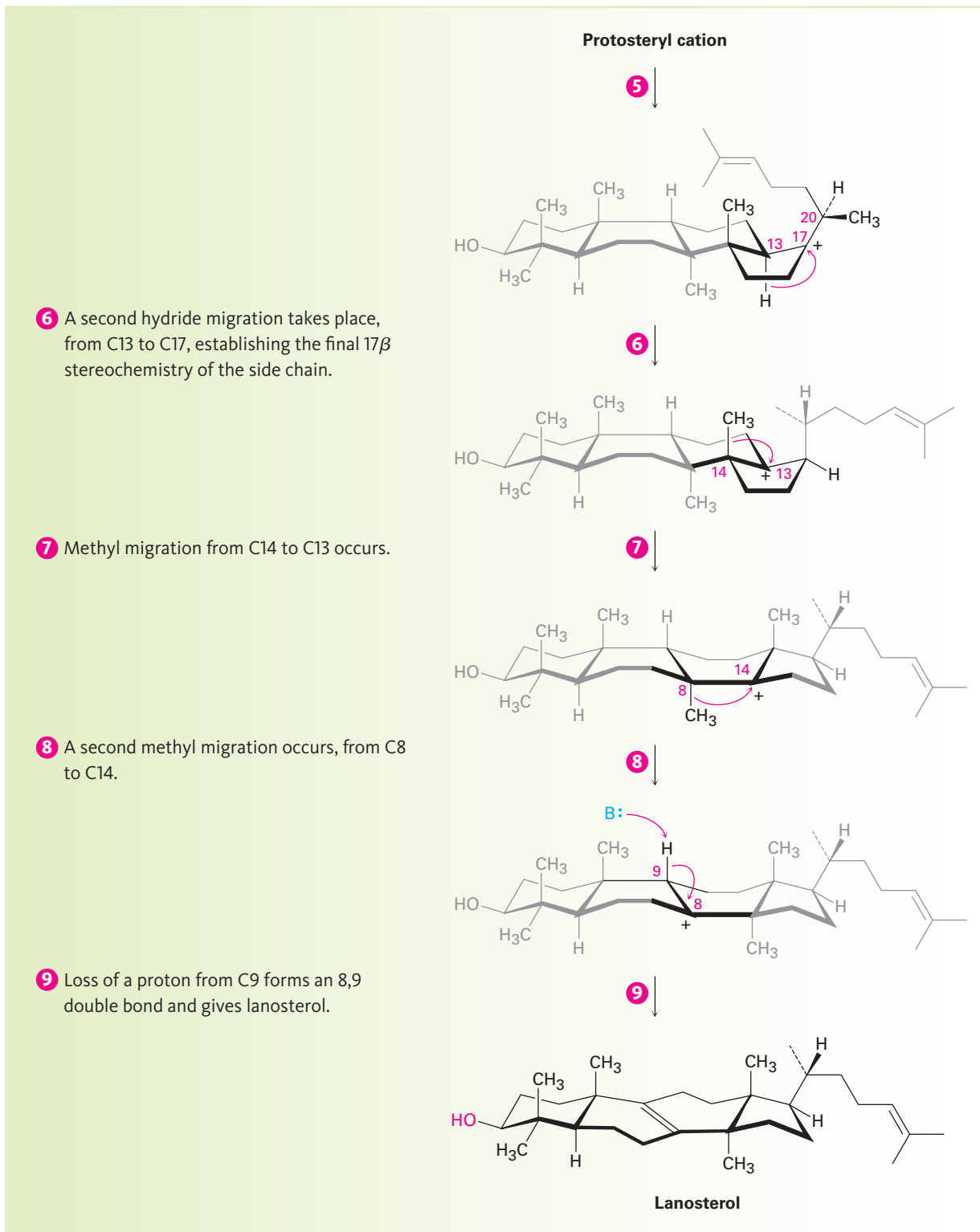
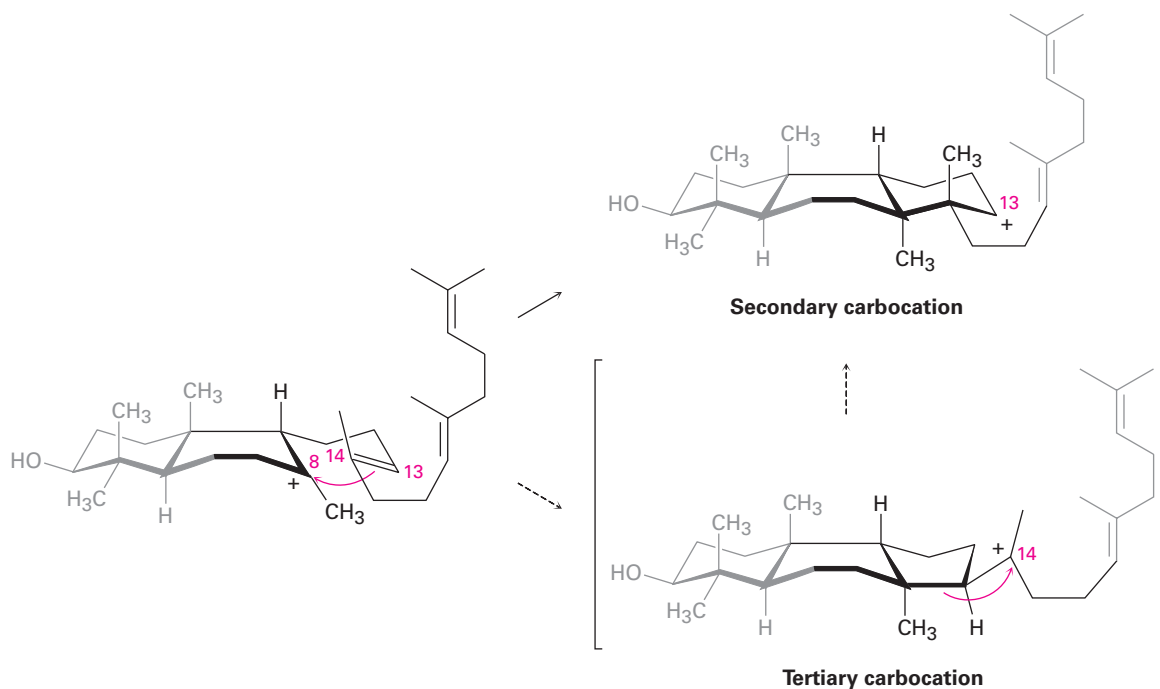
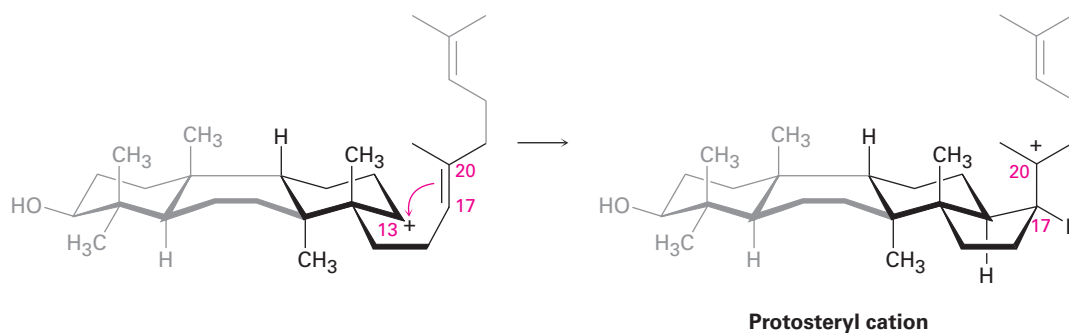


FIGURE 23.19 (continued)

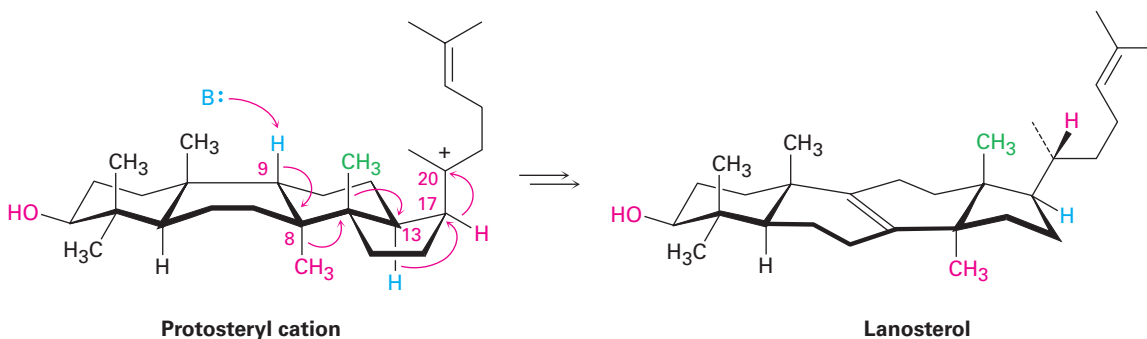
STEP 3 OF FIGURE 23.19: THIRD CYCLIZATION The third cationic cyclization is somewhat unusual because it occurs with non-Markovnikov regiochemistry and gives a secondary cation at C13 rather than the alternative tertiary cation at C14. There is growing evidence, however, that the tertiary carbocation may be formed initially and that the secondary cation arises by subsequent rearrangement. The secondary cation is probably stabilized in the enzyme pocket by the proximity of an electron-rich aromatic ring.



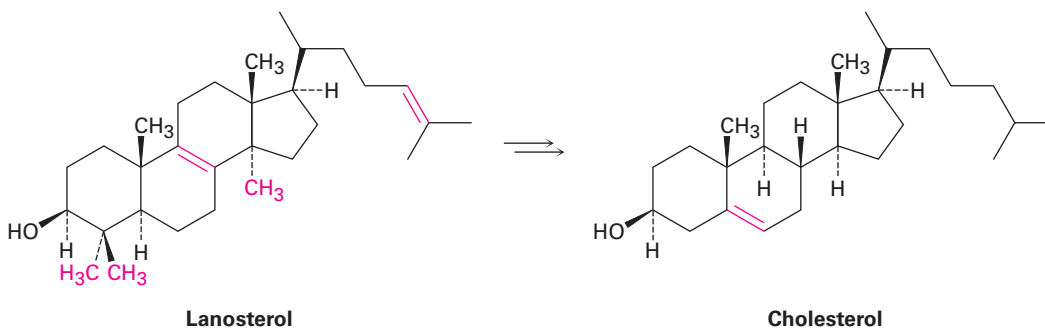
STEP 4 OF FIGURE 23.19: FINAL CYCLIZATION The fourth and last cyclization occurs in step 4 by addition of the cationic center at C13 to the 17,20 double bond, giving what is known as the *protosteryl* cation. The side-chain alkyl group at C17 has β (up) stereochemistry, although this stereochemistry is lost in step 5 and then reset in step 6.



STEPS 5–9 OF FIGURE 23.19: CARBOCATION REARRANGEMENTS Once the tetracyclic carbon skeleton of lanosterol has been formed, a series of carbocation rearrangements occur (Section 7-10). The first rearrangement, hydride migration from C17 to C20, occurs in step 5 and results in establishment of *R* stereochemistry at C20 in the side chain. A second hydride migration then occurs from C13 to C17 on the bottom (α) face of the ring in step 6 and reestablishes the 17β orientation of the side chain. Finally, two methyl migrations, the first from C14 to C13 on the top (β) face and the second from C8 to C14 on the bottom (α) face, place the positive charge at C8. A basic histidine residue in the enzyme then removes the neighboring β proton from C9 to give lanosterol.



From lanosterol, the pathway for steroid biosynthesis continues on to yield cholesterol. Cholesterol then becomes a branch point, serving as the common precursor from which all other steroids are derived.



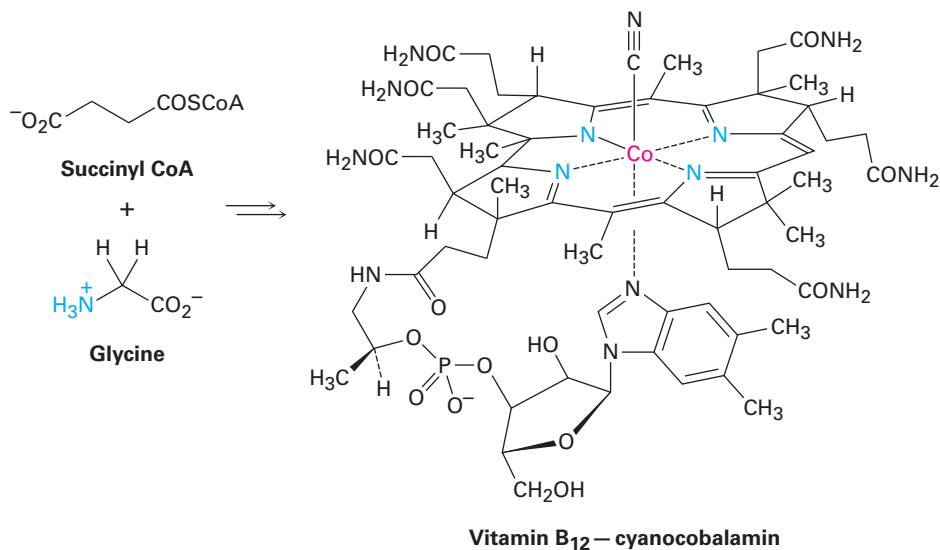
PROBLEM 23.15

Compare the structures of lanosterol and cholesterol, and catalog the changes needed for the transformation.

23-11 Some Final Comments on Metabolism

In the last several chapters, we've had a brief introduction to metabolism. There are, however, many more pathways we've not mentioned and thousands of biological molecules whose biosynthetic schemes have been explored and elucidated. Take vitamin B₁₂ (cyanocobalamin), for instance. This extraordinarily complex molecule is biosynthesized from the simple precursors glycine and succinyl CoA by a route of 60 or so steps (it depends on how you count), all of which have been worked out.

If you were to look at the steps of vitamin B₁₂ biosynthesis, you would see exactly the same kinds of reactions we've been seeing throughout the text—nucleophilic substitutions, eliminations, aldol reactions, nucleophilic acyl substitutions, and so forth. There are, of course, some complexities, but the fundamental mechanisms of organic chemistry remain the same, whether in the laboratory with smaller molecules or in organisms with larger molecules.



So, what is there to be learned from studying metabolism? One good answer is given in the following *Something Extra*, where the story is told of how knowledge of a biosynthetic pathway led to the design of new drugs that have saved many millions of lives.

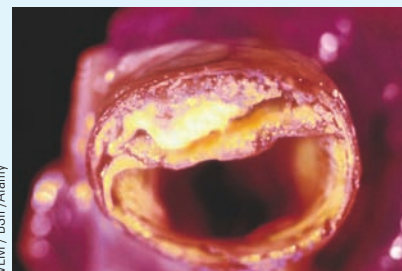
SOMETHING EXTRA

Statin Drugs

Coronary heart disease—the buildup of cholesterol-containing plaques on the walls of heart arteries—is the leading cause of death for both men and women older than age 20 in industrialized countries. It's estimated that up to one-third of women and one-half of men will develop the disease at some point in their lives.

The onset of coronary heart disease is directly correlated with blood cholesterol levels, and the first step in disease prevention is to lower those levels. It turns out that the cholesterol in your body comes from two sources: approximately 25% from your diet and the remaining 75%—about 1000 mg each day—from what you synthesize in your liver. You can change your diet to limit cholesterol intake, but what can you do to limit your own cholesterol synthesis? That's where a detailed chemical knowledge of cholesterol biosynthesis comes in.

We saw in Sections 23-9 and 23-10 that all steroids, including cholesterol, are biosynthesized from the triterpenoid lanosterol, which in turn comes from acetyl CoA through isopentenyl diphosphate. If you knew all the mechanisms for all the chemical steps in cholesterol biosynthesis, you might be able to devise a drug that would block one of those steps, thereby short-circuiting the biosynthetic process and controlling the amount of cholesterol produced. But we do know those mechanisms!

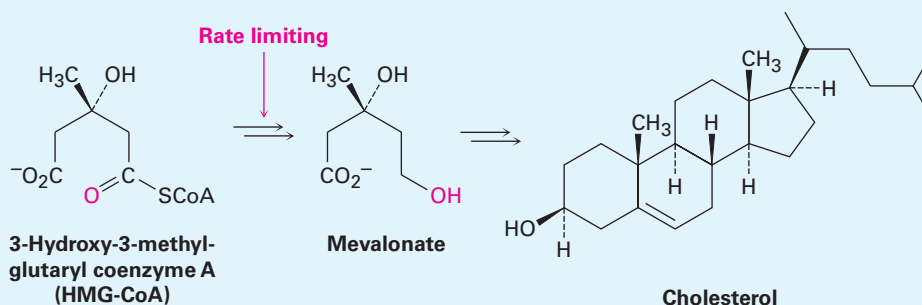


VEM / BSIP/Alamy

The buildup of cholesterol deposits inside arteries can cause coronary heart disease, a leading cause of death for both men and women.

Look back at the pathway for the biosynthesis of isopentenyl diphosphate from acetyl CoA, shown in Figure 23.12 on page 831. The rate-limiting step in the pathway is the reduction of 3-hydroxy-3-methylglutaryl CoA (abbreviated HMG-CoA) to give (*R*)-mevalonate, catalyzed by HMG-CoA reductase. If that enzyme could be stopped from functioning, cholesterol biosynthesis would also be stopped. And that is exactly what the drugs described on the very first page of this text do.

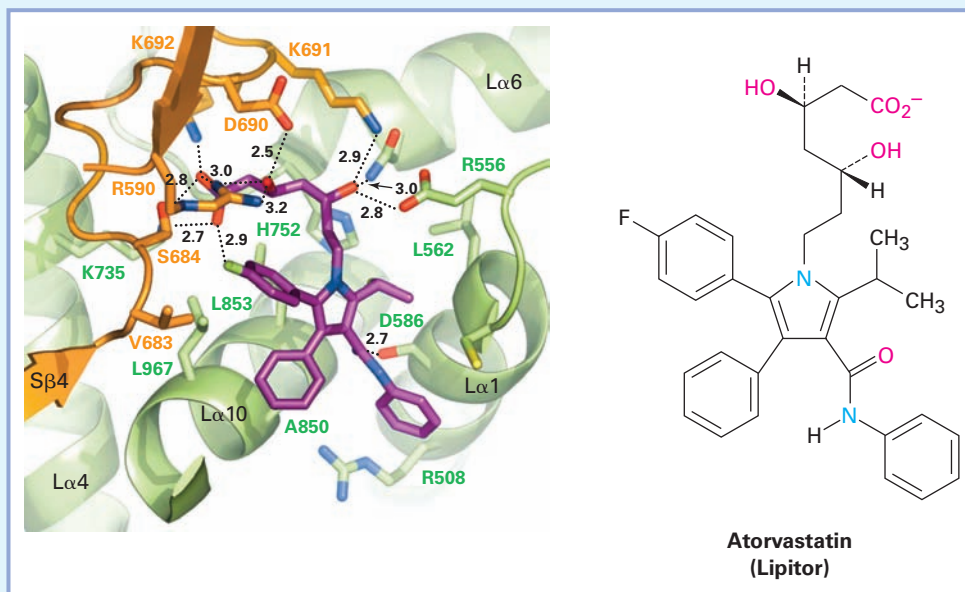
To find a drug that blocks HMG-CoA reductase, chemists did two simultaneous experiments on a large number of potential drug candidates isolated from soil microbes. In one experiment, the drug candidate and mevalonate were added to liver extract; in the second experiment, only the drug candidate was added without mevalonate. If cholesterol was produced only in the presence of added mevalonate but not in the



absence of mevalonate, the drug candidate must have blocked the enzyme for mevalonate synthesis.

The drugs that block HMG-CoA reductase, and thus control cholesterol synthesis in the body, are called *statins*. They are the most widely prescribed drugs in the world, with an estimated \$15 billion in annual sales. So effective are they that in the 10-year period following their introduction in 1994, the death rate from coronary heart disease decreased by 33% in the United States.

Atorvastatin (Lipitor), simvastatin (Zocor), rosuvastatin (Crestor), pravastatin (Pravachol), and lovastatin (Mevacor) are examples. An X-ray crystal structure of the active site in the HMG-CoA reductase enzyme is shown in the accompanying graphic, along with a molecule of atorvastatin (blue) that is tightly bound in the active site and stops the enzyme from functioning. A good understanding of organic chemistry has certainly paid off in this instance.



KEY WORDS

β -oxidation pathway, 816
 eicosanoid, 827
 fatty acid, 806
 lipid, 805
 lipid bilayer, 812
 micelle, 810
 phospholipid, 811
 polyunsaturated fatty acid, 807
 prostaglandin, 826
 steroid, 837
 terpenoid, 829
 triacylglycerol, 806
 wax, 806

SUMMARY

Lipids are the naturally occurring materials isolated from plants and animals by extraction with nonpolar organic solvents. Animal fats and vegetable oils are the most widely occurring lipids. Both are **triacylglycerols**—triesters of glycerol with long-chain **fatty acids**. Animal fats are usually saturated, whereas vegetable oils usually have unsaturated fatty-acid residues. Both are derived biosynthetically from acetyl CoA and are metabolized back to acetyl CoA in the body.

Phospholipids are important constituents of cell membranes and are of two kinds. *Glycerophospholipids*, such as phosphatidylcholine and phosphatidylethanolamine, are closely related to fats in that they have a glycerol backbone esterified to two fatty acids (one saturated and one unsaturated) and to one phosphate ester. *Sphingomyelins* have the amino alcohol sphingosine for their backbone.

Eicosanoids and **terpenoids** are still other classes of lipids. Eicosanoids, of which prostaglandins are the most abundant kind, are derived biosynthetically from arachidonic acid, are found in all body tissues, and have a wide range of physiological activity. Terpenoids are often isolated from the essential

oils of plants, have an immense diversity of structure, and are produced biosynthetically from the 5-carbon precursor isopentenyl diphosphate (IPP). Isopentenyl diphosphate is itself biosynthesized from 3 equivalents of acetate in the mevalonate pathway.

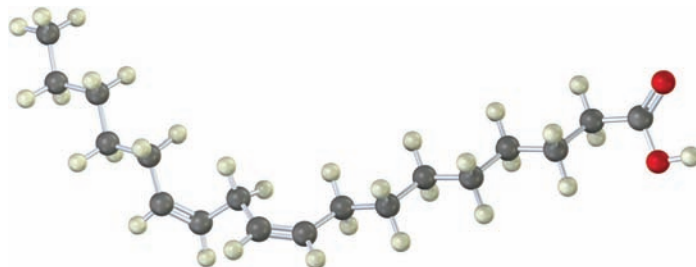
Steroids are plant and animal lipids with a characteristic tetracyclic carbon skeleton. Steroids occur widely in body tissues and have a large variety of physiological activities. They are closely related to terpenoids and arise biosynthetically from the triterpene lanosterol, which itself arises from cationic cyclization of the acyclic hydrocarbon squalene.

EXERCISES

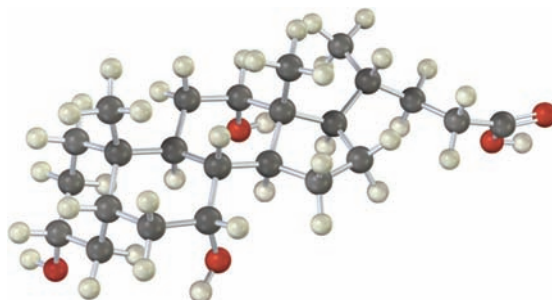
VISUALIZING CHEMISTRY

(Problems 23.1–23.15 appear within the chapter.)

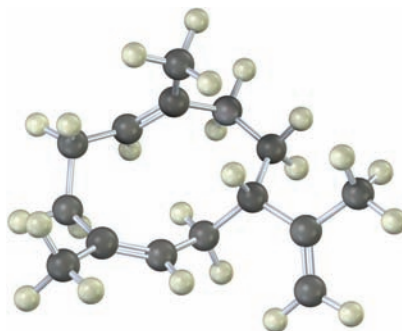
- 23.16** Identify the following fatty acid, and tell whether it is more likely to be found in peanut oil or in red meat:



- 23.17** The following model is that of cholic acid, a constituent of human bile. Locate the three hydroxyl groups, and identify each as axial or equatorial. Is cholic acid an A–B trans steroid or an A–B cis steroid?



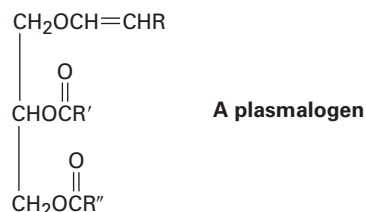
- 23.18 Propose a biosynthetic pathway for the sesquiterpene helminthogermacrene from farnesyl diphosphate:



ADDITIONAL PROBLEMS

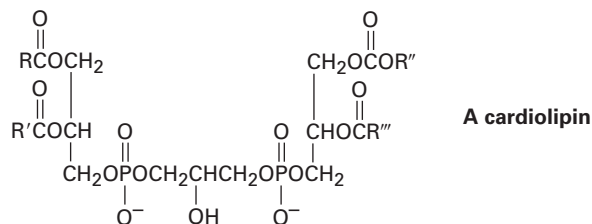
Fats, Oils, and Related Lipids

- 23.19 Cold-water fish like salmon are rich in *omega-3* fatty acids, which have a double bond three carbons in from the noncarboxyl end of the chain and have been shown to lower blood cholesterol levels. Draw the structure of eicosa-5,8,11,14,17-pentaenoic acid, a common example. (Eicosane = $C_{20}H_{42}$)
- 23.20 Fats can be either optically active or optically inactive, depending on their structure. Draw the structure of an optically active fat that yields 2 equivalents of stearic acid and 1 equivalent of oleic acid on hydrolysis. Draw the structure of an optically inactive fat that yields the same products.
- 23.21 Spermaceti, a fragrant substance from sperm whales, was much used in cosmetics until it was banned in 1976 to protect the whales from extinction. Chemically, spermaceti is cetyl palmitate, the ester of cetyl alcohol ($n-C_{16}H_{33}OH$) with palmitic acid. Draw its structure.
- 23.22 The *plasmalogens* are a group of lipids found in nerve and muscle cells. How do plasmalogens differ from fats?



- 23.23 What products would you obtain from hydrolysis of a plasmalogen (Problem 23.22) with aqueous NaOH? With H_3O^+ ?

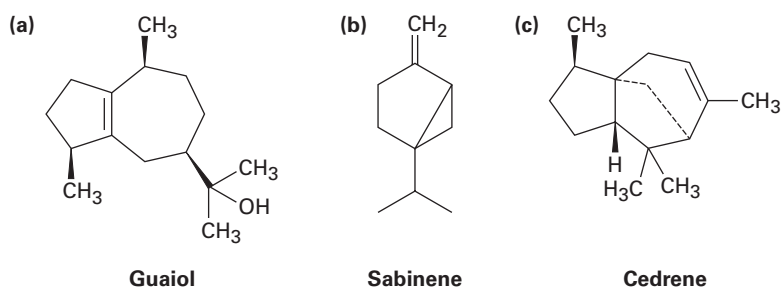
- 23.24 *Cardiolipins* are a group of lipids found in heart muscles. What products would be formed if all ester bonds, including phosphates, were saponified by treatment with aqueous NaOH?



- 23.25 Show the products you would expect to obtain from reaction of glyceryl trioleate with the following reagents:
- (a) Excess Br₂ in CH₂Cl₂ (b) H₂/Pd (c) NaOH/H₂O
 (d) LiAlH₄, then H₃O⁺ (e) CH₃MgBr, then H₃O⁺
- 23.26 How would you convert oleic acid into the following substances?
- (a) Methyl oleate (b) Methyl stearate
 (c) Pentatriacontan-18-one, CH₃(CH₂)₁₆CO(CH₂)₁₆CH₃

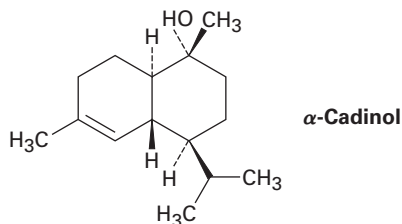
Terpenoids and Steroids

- 23.27 Without proposing an entire biosynthetic pathway, draw the appropriate precursor, either geranyl diphosphate or farnesyl diphosphate, in a conformation that shows a likeness to each of the following terpenoids:

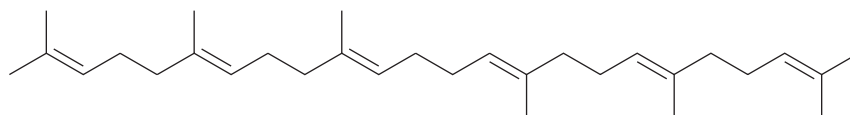


- 23.28 Indicate by asterisks the chirality centers present in each of the terpenoids shown in Problem 23.27. What is the maximum possible number of stereoisomers for each?
- 23.29 Assume that the three terpenoids in Problem 23.27 are derived biosynthetically from isopentenyl diphosphate and dimethylallyl diphosphate, each of which was isotopically labeled at the diphosphate-bearing carbon atom (C1). At what positions would the terpenoids be isotopically labeled?

- 23.30** Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material for the biosynthesis of mevalonate, as shown in Figure 23.12. At what positions in mevalonate would the isotopic label appear?
- 23.31** Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in α -cadinol where the label would appear.

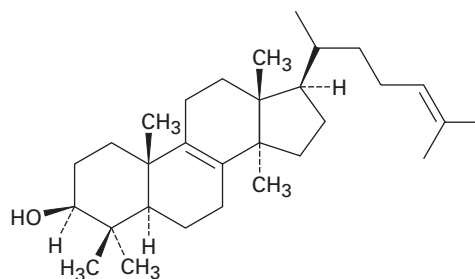


- 23.32** Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in squalene where the label would appear.



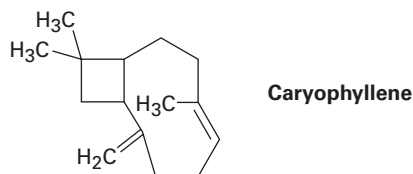
Squalene

- 23.33** Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in lanosterol where the label would appear.



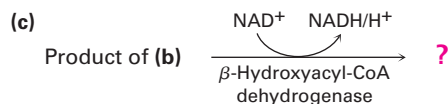
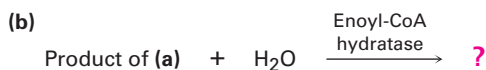
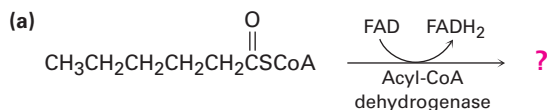
Lanosterol

- 23.34 Propose a mechanistic pathway for the biosynthesis of caryophyllene, a substance found in clove oil.

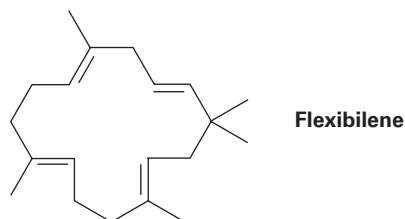


General Problems

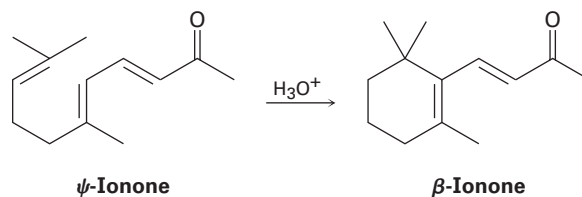
- 23.35 Stearic acid, $C_{18}H_{32}O_2$, yields stearic acid on catalytic hydrogenation and undergoes oxidative cleavage with ozone to yield nonanoic acid and nonanedioic acid. What is the structure of stearic acid?
- 23.36 How would you synthesize stearic acid (Problem 23.35) from dec-1-yne and 1-chloro-7-iodoheptane?
- 23.37 Show the product of each of the following reactions:



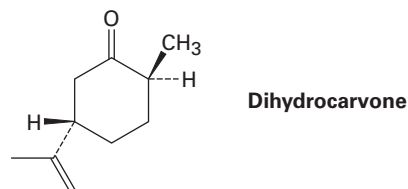
- 23.38 Draw a Fischer projection of *sn*-glycerol 1-phosphate (Section 23-4), and assign *R* or *S* configuration to the chirality center. Do the same for *sn*-glycerol 2,3-diacetate.
- 23.39 Flexibilene, a compound isolated from marine coral, is the first known terpenoid to contain a 15-membered ring. What is the structure of the acyclic biosynthetic precursor of flexibilene? Show the mechanistic pathway for the biosynthesis.



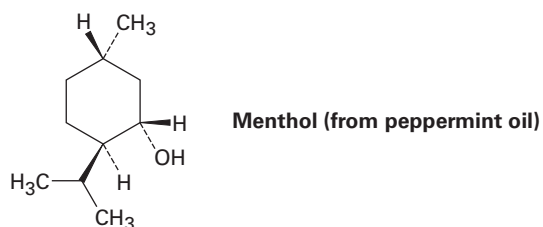
- 23.40 Suggest a mechanism by which ψ -ionone is transformed into β -ionone on treatment with acid.



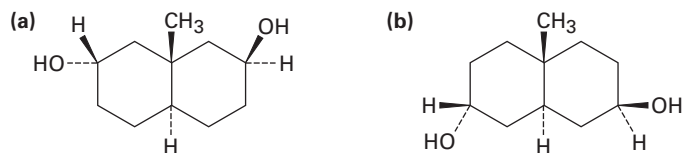
- 23.41 Draw the most stable chair conformation of dihydrocarvone.



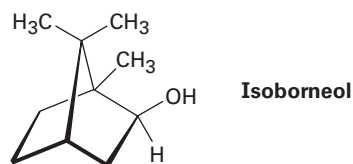
- 23.42 Draw the most stable chair conformation of menthol, and label each substituent as axial or equatorial.



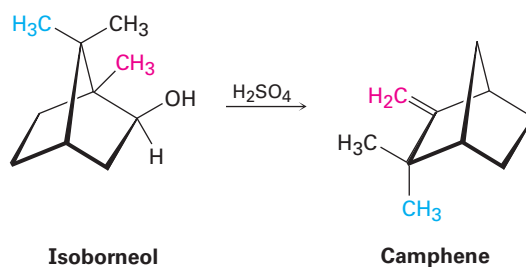
- 23.43 As a general rule, equatorial alcohols are esterified more readily than axial alcohols. What product would you expect to obtain from reaction of the following two compounds with 1 equivalent of acetic anhydride?



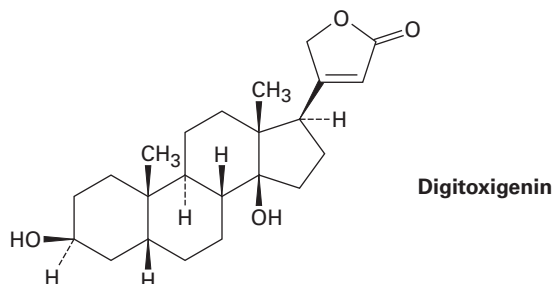
- 23.44 Propose a mechanistic pathway for the biosynthesis of isoborneol. A carbocation rearrangement is needed at one point in the scheme.



- 23.45 Isoborneol (Problem 23.44) is converted into camphene on treatment with dilute sulfuric acid. Propose a mechanism for the reaction, which involves a carbocation rearrangement.

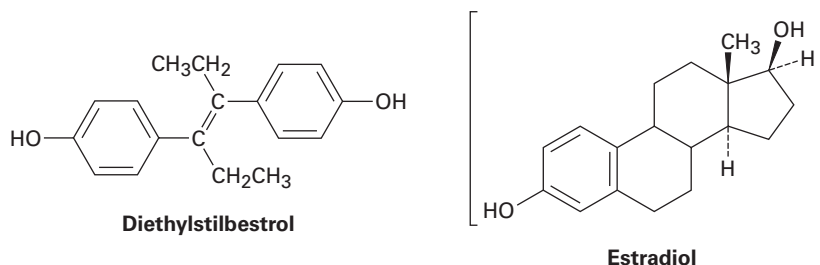


- 23.46 Digitoxigenin is a heart stimulant obtained from the purple foxglove *Digitalis purpurea* and used in the treatment of heart disease. Draw the three-dimensional conformation of digitoxigenin, and identify the two -OH groups as axial or equatorial.

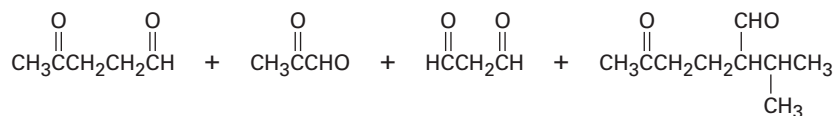


- 23.47 Eleostearic acid, $\text{C}_{18}\text{H}_{30}\text{O}_2$, is a rare fatty acid found in the tung oil used for finishing furniture. On ozonolysis followed by treatment with zinc, eleostearic acid furnishes one part pentanal, two parts glyoxal (OHC-CHO), and one part 9-oxononanoic acid [$\text{OHC}(\text{CH}_2)_7\text{CO}_2\text{H}$]. What is the structure of eleostearic acid? (Note that alkenes undergo ozonolysis followed by treatment with zinc to give carbonyl compounds in which each of the former $\text{C}=\text{C}$ carbons becomes a $\text{C}=\text{O}$ carbon.)

- 23.48** Diterpenoids are derived biosynthetically from geranylgeranyl diphosphate (GGPP), which is itself biosynthesized by reaction of farnesyl diphosphate with isopentenyl diphosphate. Show the structure of GGPP, and propose a mechanism for its biosynthesis from FPP and IPP.
- 23.49** Diethylstilbestrol (DES) has estrogenic activity even though it is structurally unrelated to steroids. Once used as an additive in animal feed, DES has been implicated as a causative agent in several types of cancer. Show how DES can be drawn so that it is sterically similar to estradiol.

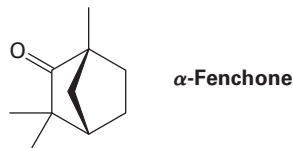


- 23.50** How many chirality centers are present in estradiol (Problem 23.49). Assign configurations to all.
- 23.51** Cembrene, $C_{20}H_{32}$, is a diterpene hydrocarbon isolated from pine resin. Cembrene has a UV absorption at 245 nm, but dihydrocembrene ($C_{20}H_{34}$), the product of hydrogenation with 1 equivalent of H_2 , has no UV absorption. On exhaustive hydrogenation, 4 equivalents of H_2 react and octahydrocembrene, $C_{20}H_{40}$, is produced. On ozonolysis of cembrene, followed by treatment of the ozonide with zinc, four carbonyl-containing products are obtained:

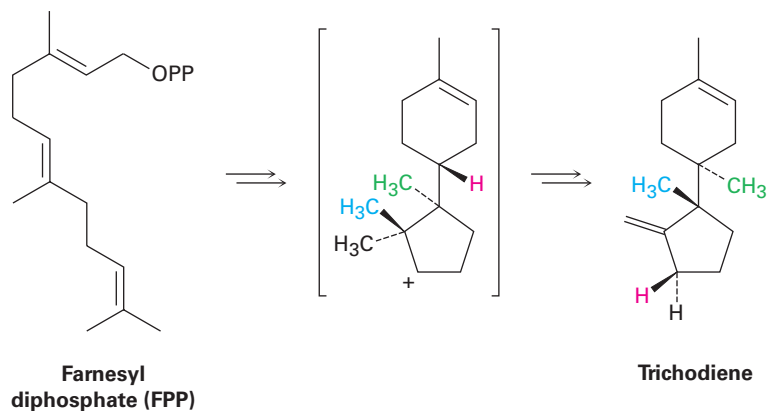


Propose a structure for cembrene that is consistent with its formation from geranylgeranyl diphosphate (Problem 23.48).

- 23.52** α -Fenchone is a pleasant-smelling terpenoid isolated from oil of lavender. Propose a pathway for the formation of α -fenchone from geranyl diphosphate. A carbocation rearrangement is required.



- 23.53 Propose a mechanism for the biosynthesis of the sesquiterpene trichodiene from farnesyl diphosphate. The process involves cyclization to give an intermediate secondary carbocation, followed by several carbocation rearrangements.



24

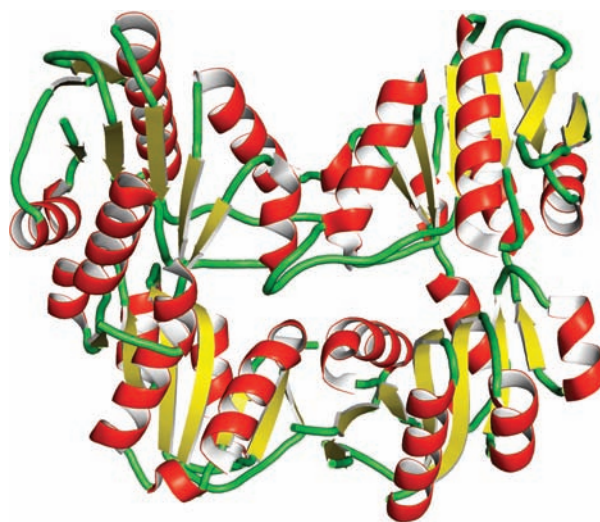
Biomolecules: Nucleic Acids and Their Metabolism

CONTENTS

- 24-1 Nucleotides and Nucleic Acids
- 24-2 Base Pairing in DNA: The Watson–Crick Model
- 24-3 Replication of DNA
- 24-4 Transcription of DNA
- 24-5 Translation of RNA: Protein Biosynthesis
- 24-6 DNA Sequencing
- 24-7 DNA Synthesis
- 24-8 The Polymerase Chain Reaction
- 24-9 Catabolism of Nucleotides
- 24-10 Biosynthesis of Nucleotides

SOMETHING EXTRA

DNA Fingerprinting



Phosphoribosyl diphosphate synthetase catalyzes the phosphorylation of ribose 5-phosphate during the biosynthesis of pyrimidine nucleotides.

WHY THIS CHAPTER?

Nucleic acids are the last of the four major classes of biomolecules we'll consider. So much has been written and spoken about DNA in the media that the basics of DNA replication and transcription are probably known to you. Thus, we'll move fairly quickly through the fundamentals and then look more closely at the chemical details of DNA sequencing, synthesis, and metabolism. The field is moving very rapidly, and there's probably a lot you may not be familiar with.

The nucleic acids, **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)**, are the chemical carriers of a cell's genetic information. Coded in a cell's DNA is the information that determines the nature of the cell, controls the cell's growth and division, and directs biosynthesis of the enzymes and other proteins required for cellular functions.

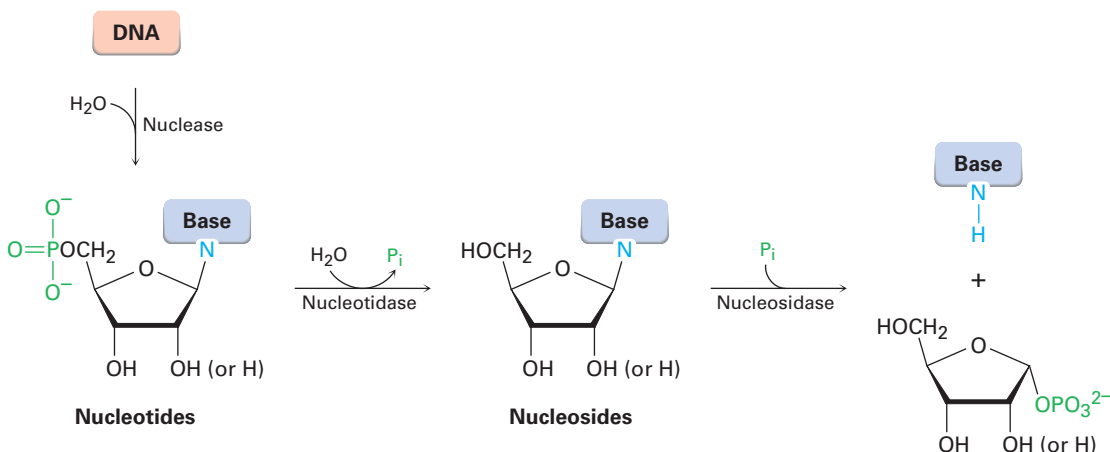
In addition to nucleic acids themselves, nucleic acid derivatives such as ATP are involved as phosphorylating agents in many biochemical pathways, and several important coenzymes, including NAD^+ , FAD, and coenzyme A, have nucleic acid components. See Table 19.3 on pages 706 and 707 for the structures.

24-1 Nucleotides and Nucleic Acids

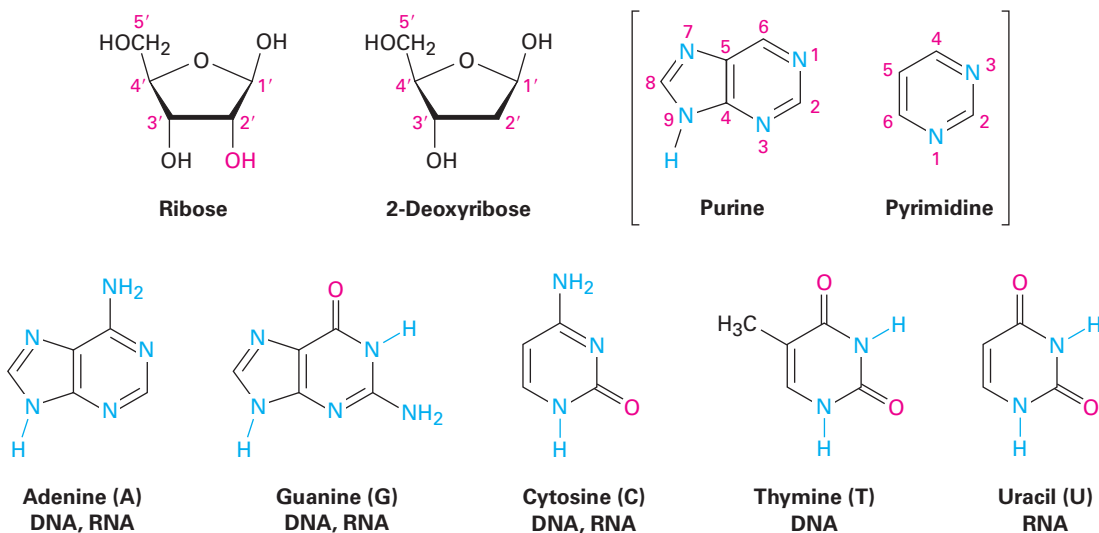
Just as proteins are biopolymers made of amino acids, nucleic acids are biopolymers made of **nucleotides**, joined together to form a long chain. Each nucleotide is composed of a **nucleoside** bonded to a phosphate group, and each



nucleoside is composed of an aldopentose sugar linked through its anomeric carbon to the nitrogen atom of a heterocyclic purine or pyrimidine base.



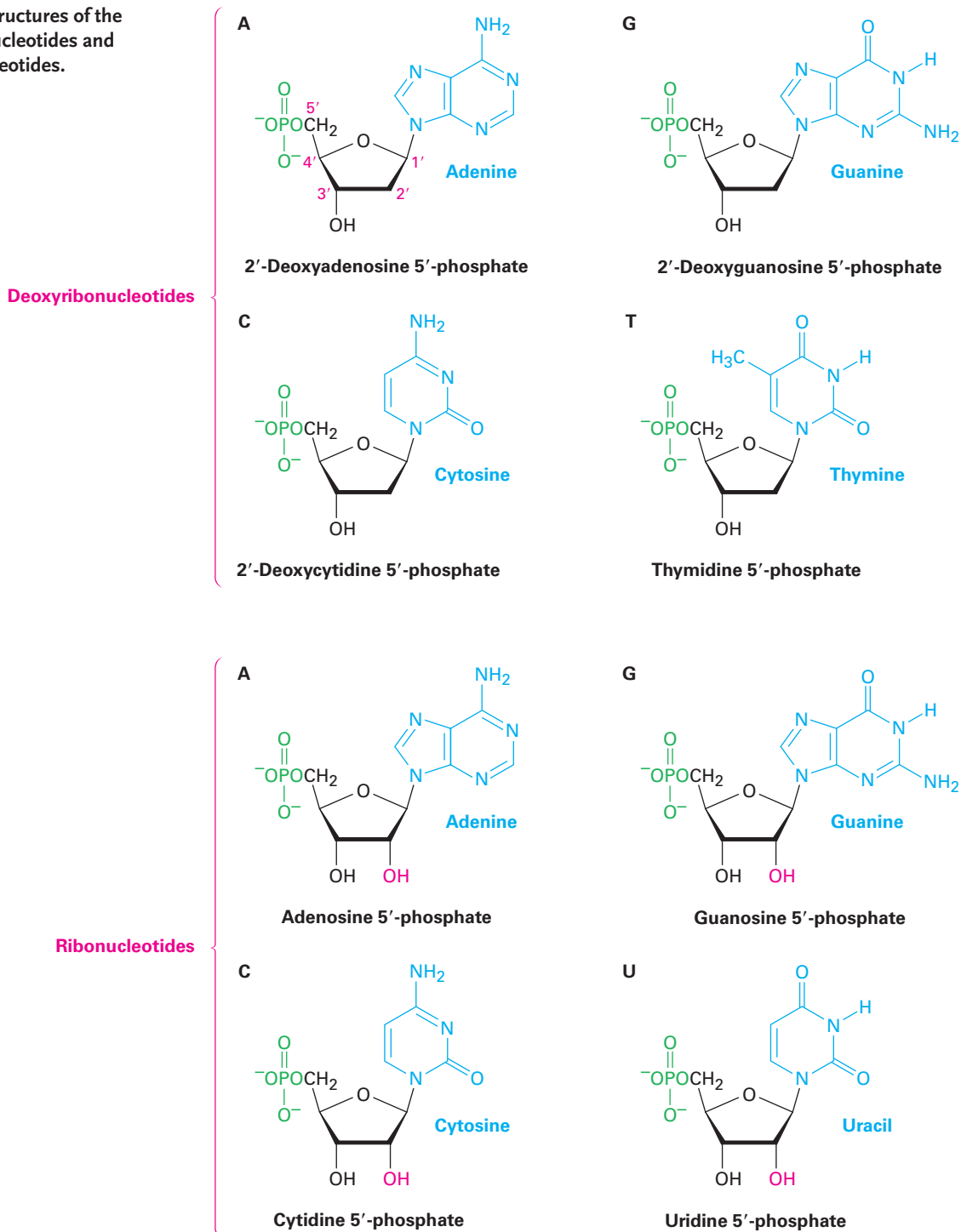
The sugar component in RNA is ribose, and the sugar in DNA is 2'-deoxyribose. (In naming and numbering nucleotides, numbers with a prime superscript refer to positions on the sugar and numbers without a prime superscript refer to positions on the heterocyclic base. Thus, the prefix 2'-deoxy indicates that oxygen is missing from C2' of ribose.) DNA contains four different amine bases, two substituted purines (adenine and guanine) and two substituted pyrimidines (cytosine and thymine). Adenine, guanine, and cytosine also occur in RNA, but thymine is replaced in RNA by a closely related pyrimidine base called uracil.



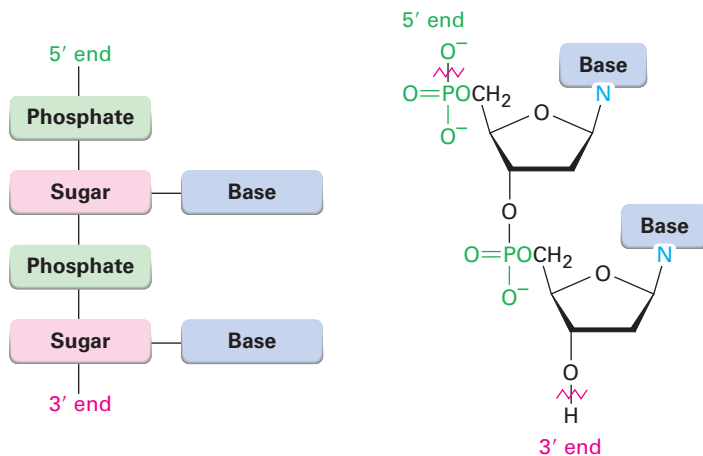
The structures of the four deoxyribonucleotides and the four ribonucleotides are shown in **FIGURE 24.1**. Although similar chemically, DNA and RNA

differ dramatically in size. Molecules of DNA are enormous, containing as many as 245 million nucleotides and having molecular weights as high as 75 billion. Molecules of RNA, by contrast, are much smaller, containing as few as 21 nucleotides and having molecular weights as low as 7000.

FIGURE 24.1 Structures of the four deoxyribonucleotides and the four ribonucleotides.



Nucleotides are linked together in DNA and RNA by *phosphodiester* bonds $[\text{RO}-(\text{PO}_2^-)-\text{OR}']$ between phosphate, the 5' hydroxyl group on one nucleoside, and the 3'-hydroxyl group on another nucleoside. One end of the nucleic acid polymer has a free hydroxyl at C3' (the **3' end**), and the other end has a phosphate at C5' (the **5' end**). The sequence of nucleotides in a chain is described by starting at the 5' end and identifying the bases in order of occurrence, using the abbreviations G, C, A, and T (or U for RNA). Thus, a typical DNA sequence might be written as TAGGCT.



PROBLEM 24.1

Draw the full structure of the DNA dinucleotide AG.

PROBLEM 24.2

Draw the full structure of the RNA dinucleotide UA.

24-2 Base Pairing in DNA: The Watson–Crick Model

Samples of DNA isolated from different tissues of the same species have the same proportions of heterocyclic bases, but samples from different species often have greatly different proportions of bases. Human DNA, for example, contains about 30% each of adenine and thymine and about 20% each of guanine and cytosine. The bacterium *Clostridium perfringens*, however, contains about 37% each of adenine and thymine and only 13% each of guanine and cytosine. Note that in both examples the bases occur in pairs. Adenine and thymine are present in equal amounts, as are cytosine and guanine. Why?

In 1953, James Watson and Francis Crick made their classic proposal for the secondary structure of DNA. According to the Watson–Crick model, DNA under physiological conditions consists of two polynucleotide strands, running in opposite directions and coiled around each other in a **double helix**

like the handrails on a spiral staircase. The two strands are complementary rather than identical and are held together by hydrogen bonds between specific pairs of bases, A with T and C with G. That is, whenever an A base occurs in one strand, a T base occurs opposite it in the other strand; when a C base occurs in one, a G occurs in the other (FIGURE 24.2). This complementary base pairing thus explains why A and T are always found in equal amounts, as are G and C.

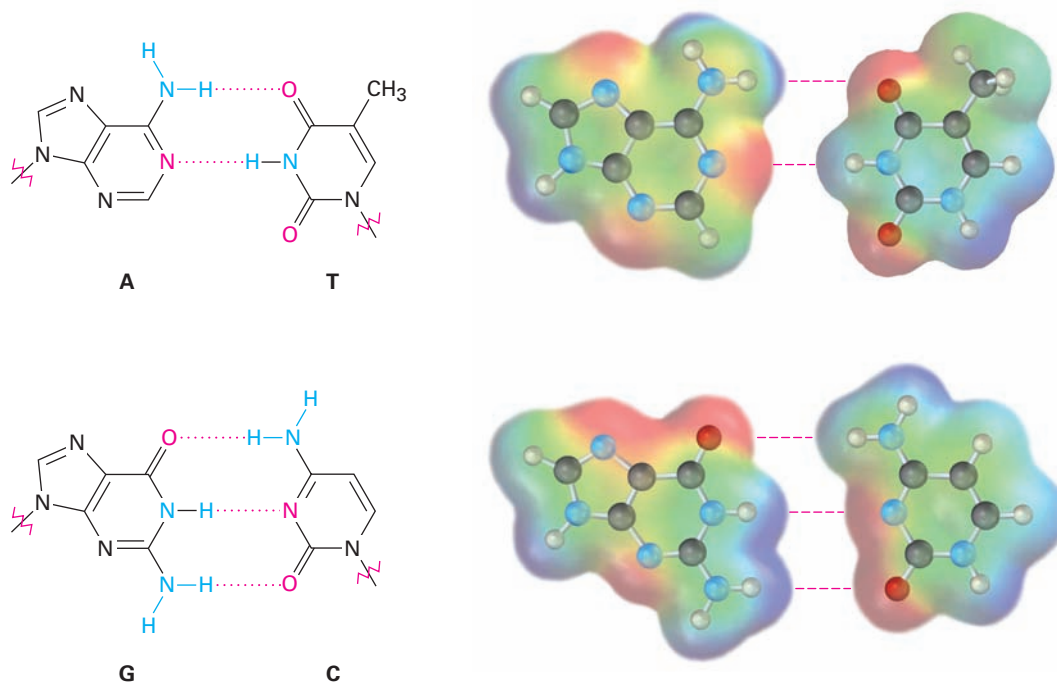


FIGURE 24.2 Hydrogen-bonding between base pairs in the DNA double helix. Electrostatic potential maps show that the faces of the bases are relatively neutral (green), while the edges have positive and negative regions. Pairing G with C and A with T brings together oppositely charged regions.

A full turn of the DNA double helix is shown in FIGURE 24.3. The helix is 20 Å wide, there are 10 base pairs per turn, and each turn is 34 Å in length. Note in Figure 24.3 that the two strands of the double helix coil in such a way that two kinds of “grooves” result, a *major groove* 12 Å wide and a *minor groove* 6 Å wide. The major groove is slightly deeper than the minor groove, and both are lined by flat heterocyclic bases. As a result, a variety of other flat polycyclic aromatic molecules are able to slip sideways, or *intercalate*, between the stacked bases. Many cancer-causing and cancer-preventing agents function by interacting with DNA in this way.

An organism’s genetic information is stored as a sequence of deoxyribonucleotides strung together in the DNA chain. For the information to be preserved and passed on to future generations, a mechanism must exist for copying DNA. For the information to be used, a mechanism must exist for decoding the DNA message and implementing the instructions it contains.

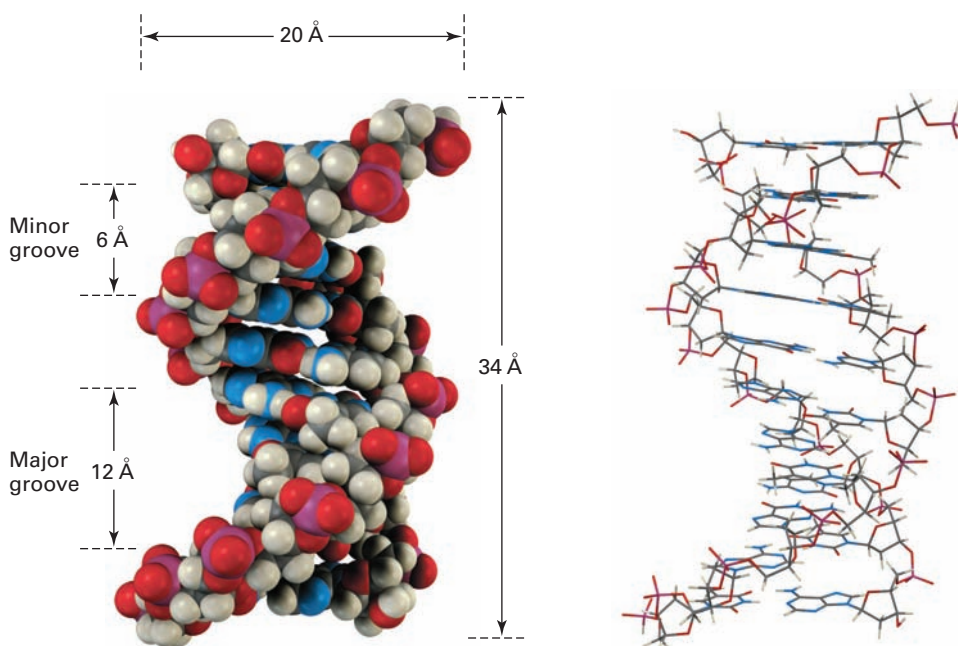
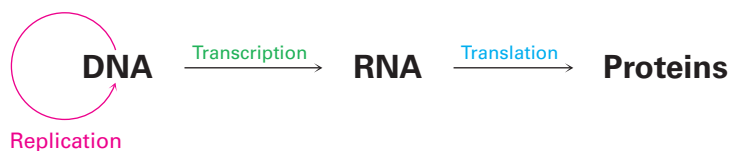


FIGURE 24.3 A turn of the DNA double helix in both space-filling and wire-frame formats. The sugar–phosphate backbone runs along the outside of the helix, and the amine bases hydrogen bond to one another on the inside. Both major and minor grooves are visible.

What Crick called the “central dogma of molecular genetics” says that the function of DNA is to store information and pass it on to RNA. The function of RNA, in turn, is to read, decode, and use the information received from DNA to make proteins. This view is greatly oversimplified but is nevertheless a good place to start. Three fundamental processes take place:

- **Replication**—the process by which identical copies of DNA are made so that information can be preserved and handed down to offspring.
- **Transcription**—the process by which the genetic messages are read and carried out of the cell nucleus to ribosomes, where protein synthesis occurs.
- **Translation**—the process by which the genetic messages are decoded and used to synthesize proteins.



Predicting the Complementary Base Sequence in Double-Stranded DNA

WORKED EXAMPLE 24.1

What sequence of bases on one strand of DNA is complementary to the sequence TATGCAT on another strand?

Strategy

Remember that A and G form complementary pairs with T and C, respectively, and then go through the sequence replacing A by T, G by C, T by A, and C by G. Remember also that the 5′ end is on the left and the 3′ end is on the right in the original strand.

Solution

Original: (5') TATGCAT (3')

Complement: (3') ATACGTA (5') or (5') ATGCATA (3')

PROBLEM 24.3

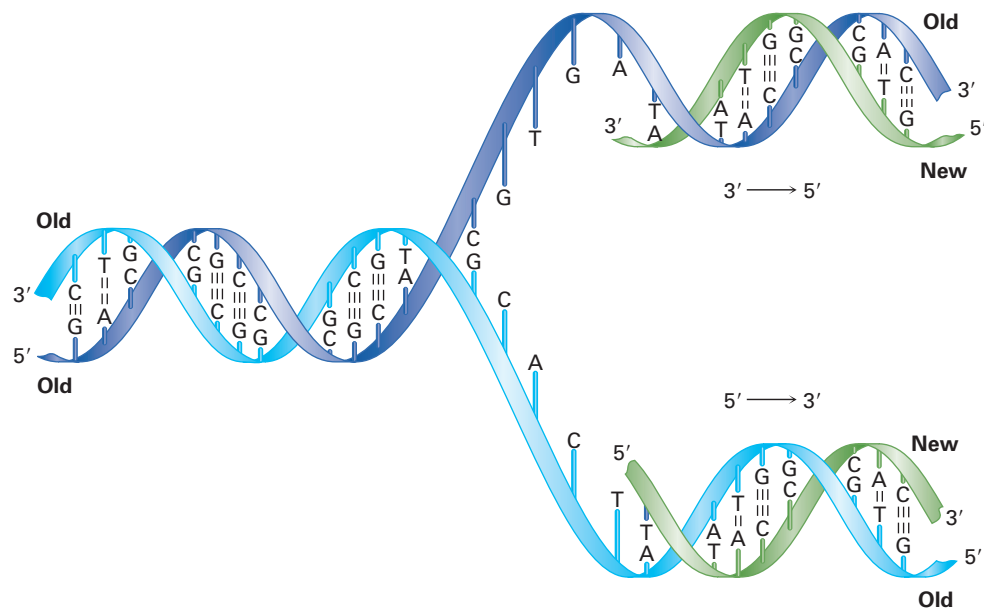
What sequence of bases on one strand of DNA is complementary to the following sequence on another strand?

(5') GGCTAATCCGT (3')

24-3 Replication of DNA

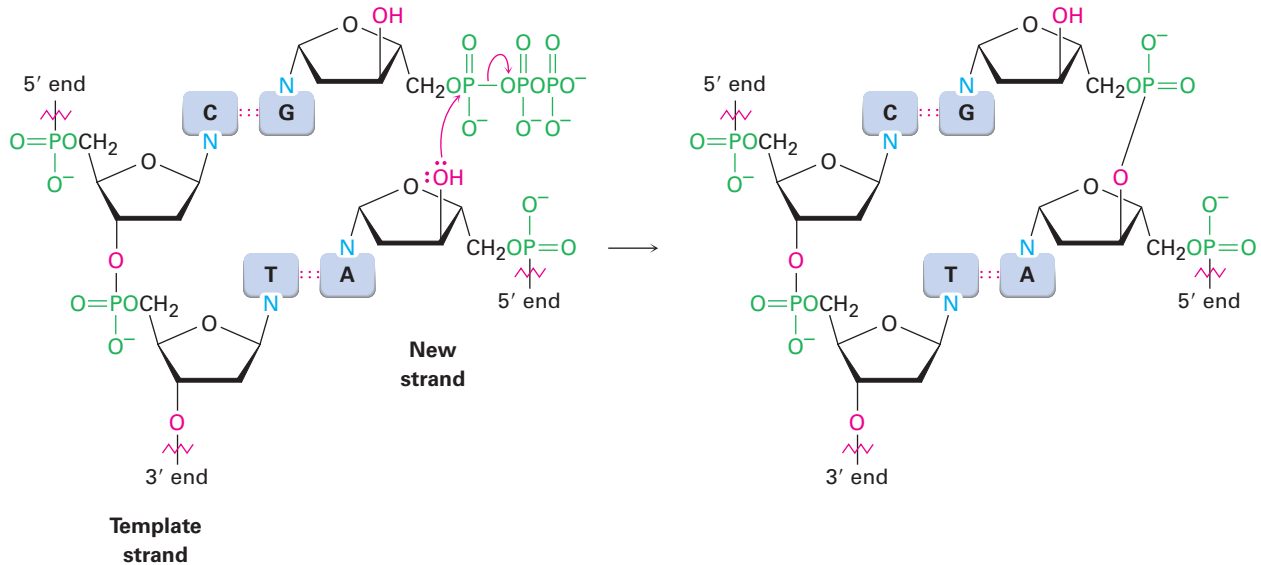
DNA **replication** begins with a partial unwinding of the double helix at various points along the chain, brought about by enzymes called *helicases*. Hydrogen bonds are broken, the two strands separate to form a “bubble,” and bases are exposed. New nucleotides then line up on each strand in a complementary manner, A to T and G to C, and two new strands begin to grow from the ends of the bubble, called the *replication forks*. Each new strand is complementary to its old template strand, so two identical DNA double helices are produced (FIGURE 24.4). Because each of the new DNA molecules contains one old strand and one new strand, the process is described as *semiconservative replication*.

FIGURE 24.4 A representation of semiconservative DNA replication. The original double-stranded DNA partially unwinds, bases are exposed, nucleotides line up on each strand in a complementary manner, and two new strands begin to grow. Both strands are synthesized in the same 5' → 3' direction, one continuously and one in fragments.



Addition of nucleotides to a growing chain takes place in the 5' → 3' direction and is catalyzed by DNA polymerase. The key step is the addition of

a nucleoside 5'-triphosphate to the free 3'-hydroxyl group of the growing chain, with loss of a diphosphate leaving group.



Because both new DNA strands are synthesized in the 5' → 3' direction, they can't be made in exactly the same way. One new strand must have its 3' end nearer a replication fork, while the other new strand has its 5' end nearer the replication fork. What happens is that the complement of the original 5' → 3' strand is synthesized continuously in a single piece to give a newly synthesized copy called the *leading strand*, while the complement of the original 3' → 5' strand is synthesized discontinuously in small pieces called *Okazaki fragments*, which are subsequently linked by DNA ligases to form the *lagging strand*.

The magnitude of the replication process is staggering. The nucleus of every human cell contains 2 copies of 22 chromosomes plus an additional 2 sex chromosomes, for a total of 46. Each chromosome consists of one very large DNA molecule, and the sum of the DNA in each of the two sets of chromosomes is estimated to be 3.0 billion base pairs, or 6.0 billion nucleotides. Despite the size of these enormous molecules, their base sequence is faithfully copied during replication. The entire copying process takes only a few hours and, after proofreading and repair, an error gets through only about once each 10 to 100 billion bases. About 60 of these random mutations are passed on from parent to child in a human generation.

24-4 Transcription of DNA

As noted previously, RNA is structurally similar to DNA but contains ribose rather than deoxyribose and uracil rather than thymine. RNA is of three major kinds, each of which serves a specific purpose. In addition, there are a number of small RNAs that appear to control a wide variety of important cellular

functions. All RNA molecules are much smaller than DNA, and all remain single-stranded rather than double-stranded.

- **Messenger RNA (mRNA)** carries genetic messages from DNA to ribosomes, small granular particles in the cytoplasm of a cell where protein synthesis takes place.
- **Ribosomal RNA (rRNA)** complexed with protein provides the physical makeup of the ribosomes.
- **Transfer RNA (tRNA)** transports amino acids to the ribosomes, where they are joined together to make proteins.
- **Small RNAs**, also called *functional RNAs*, have a variety of functions within the cell, including silencing transcription and catalyzing chemical modifications of other RNA molecules.

The genetic information in DNA is contained in segments called *genes*, each of which consists of a specific nucleotide sequence that encodes a specific protein. The conversion of that information from DNA into proteins begins in the nucleus of cells with the synthesis of mRNA by **transcription** of DNA. In bacteria, the process begins when RNA polymerase recognizes and binds to a *promoter sequence* on DNA, typically consisting of around 40 base pairs located upstream (5') of the transcription start site. Within the promoter are two hexameric *consensus sequences*, one located 10 base pairs upstream of the start and the second located 35 base pairs upstream.

Following formation of the polymerase–promoter complex, several turns of the DNA double helix unwind, forming a bubble and exposing 14 or so base pairs of the two strands. Appropriate ribonucleotides then line up by hydrogen-bonding to their complementary bases on DNA, bond formation occurs in the 5' → 3' direction, the RNA polymerase moves along the DNA chain, and the growing RNA molecule unwinds from DNA (**FIGURE 24.5**). At any one time, about 12 base pairs of the growing RNA remain hydrogen-bonded to the DNA template.

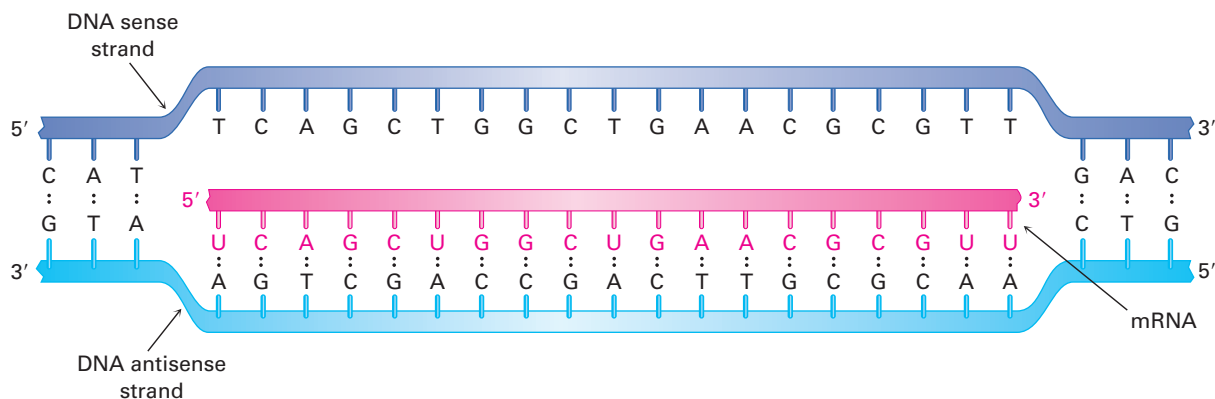


FIGURE 24.5 Biosynthesis of RNA using a DNA base segment as template.

Unlike what happens in DNA replication, where both strands are copied, only one of the two DNA strands is transcribed into mRNA. The DNA

strand that contains the gene is often called the **sense strand**, or *coding strand*, and the DNA strand that gets transcribed to give RNA is called the **antisense strand**, or *noncoding strand*. Because the sense strand and the antisense strand in DNA are complementary, and because the DNA antisense strand and the newly formed RNA strand are also complementary, the RNA molecule produced during transcription is a copy of the DNA sense strand. That is, the complement of the complement is the same as the original. The only difference is that the RNA molecule has a U everywhere the DNA sense strand has a T.

Another part of the picture in vertebrates and flowering plants is that genes are often not continuous segments of the DNA chain. Instead, a gene will begin in one small section of DNA called an *exon*, then be interrupted by a noncoding section called an *intron*, and then take up again farther down the chain in another exon. The final mRNA molecule results only after the non-coded sections are cut out of the transcribed mRNA and the remaining pieces are joined together by spliceosomes. The gene for triose phosphate isomerase in maize, for instance, contains eight noncoding introns accounting for approximately 70% of the DNA base pairs and nine coding exons accounting for only 30% of the base pairs.

PROBLEM 24.4

Show how uracil can form strong hydrogen bonds to adenine.

PROBLEM 24.5

What mRNA base sequence is complementary to the following DNA base sequence?

(5') GATTACCGTA (3')

PROBLEM 24.6

From what DNA base sequence was the following mRNA sequence transcribed?

(5') UUCGCAGAGU (3')

24-5 Translation of RNA: Protein Biosynthesis

The primary cellular function of mRNA is to direct biosynthesis of the thousands of diverse peptides and proteins required by an organism—as many as 500,000 in a human. The mechanics of protein biosynthesis take place on ribosomes, small granular particles in the cytoplasm of a cell that consist of about 60% ribosomal RNA and 40% protein.

The specific ribonucleotide sequence in mRNA forms a message that determines the order in which amino acid residues are to be joined. Each “word,” or **codon**, along the mRNA chain consists of a sequence of three ribonucleotides

that is specific for a given amino acid. For example, the series UUC on mRNA is a codon directing incorporation of the amino acid phenylalanine into the growing protein. Of the $4^3 = 64$ possible triplets of the four bases in RNA, 61 code for specific amino acids and 3 code for chain termination. **TABLE 24.1** shows the meaning of each codon.

TABLE 24.1 Codon Assignments of Base Triplets

First base (5' end)	Second base	Third base (3' end)			
		U	C	A	G
U	U	Phe	Phe	Leu	Leu
	C	Ser	Ser	Ser	Ser
	A	Tyr	Tyr	Stop	Stop
	G	Cys	Cys	Stop	Trp
C	U	Leu	Leu	Leu	Leu
	C	Pro	Pro	Pro	Pro
	A	His	His	Gln	Gln
	G	Arg	Arg	Arg	Arg
A	U	Ile	Ile	Ile	Met
	C	Thr	Thr	Thr	Thr
	A	Asn	Asn	Lys	Lys
	G	Ser	Ser	Arg	Arg
G	U	Val	Val	Val	Val
	C	Ala	Ala	Ala	Ala
	A	Asp	Asp	Glu	Glu
	G	Gly	Gly	Gly	Gly

The message embedded in mRNA is read by transfer RNA (tRNA) in a process called **translation**. There are 61 different tRNAs, one for each of the 61 codons that specifies an amino acid. A typical tRNA is single-stranded and has roughly the shape of a cloverleaf, as shown in **FIGURE 24.6**. It consists of about 70 to 100 ribonucleotides and is bonded to a specific amino acid by an ester linkage through the 3' hydroxyl on ribose at the 3' end of the tRNA. Each tRNA also contains on its middle leaf a segment called an **anticodon**, a sequence of three ribonucleotides complementary to the codon sequence. For example, the codon sequence UUC present on mRNA is read by a phenylalanine-bearing tRNA having the complementary anticodon base sequence GAA. [Remember that nucleotide sequences are written in the 5' → 3' direction, so the sequence in an anticodon must be reversed. That is, the complement to (5')-UUC-(3') is (3')-AAG-(5'), which is written as (5')-GAA-(3').]

As each successive codon on mRNA is read, different tRNAs bring the correct amino acids into position for enzyme-mediated transfer to the growing peptide. When synthesis of the proper protein is completed, a “stop” codon signals the end and the protein is released from the ribosome. The process is illustrated in **FIGURE 24.7**.

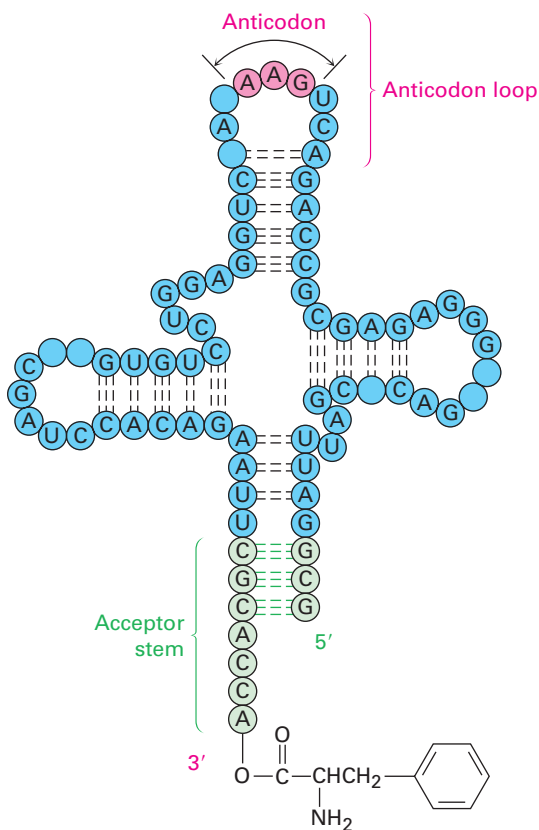


FIGURE 24.6 Structure of a tRNA molecule. The tRNA molecule is roughly cloverleaf-shaped and contains an anticodon triplet on one leaf and an amino acid unit attached covalently at its 3' end. The example shown is a yeast tRNA that codes for phenylalanine. The nucleotides not specifically identified are chemically modified analogs of the four common ribonucleotides.

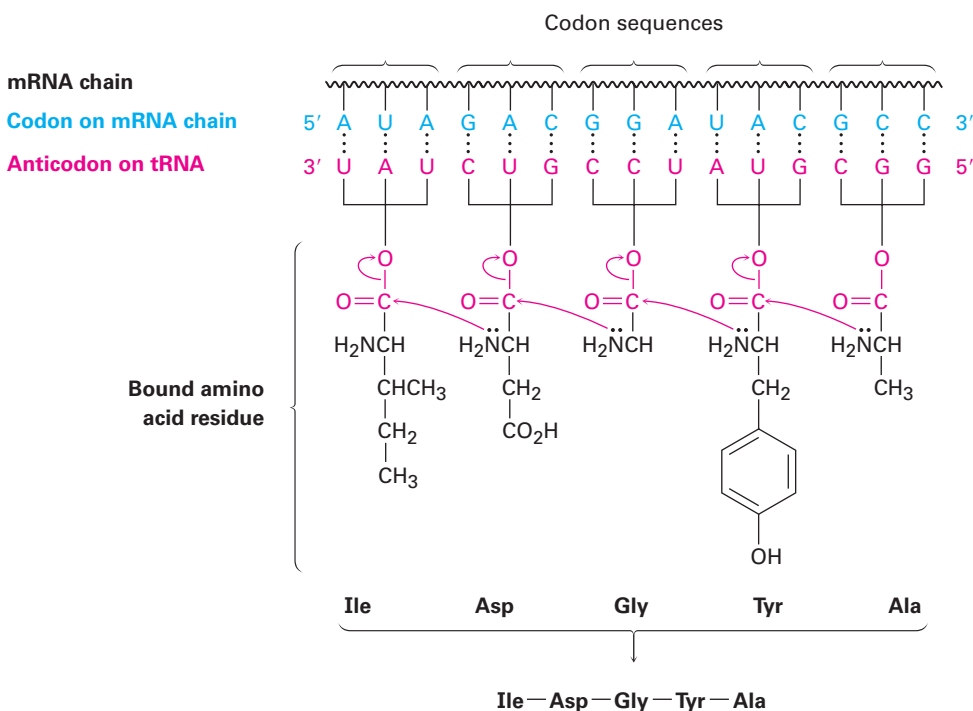
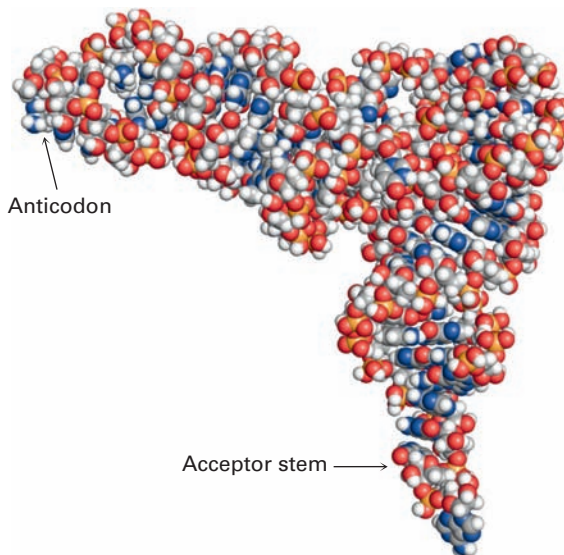


FIGURE 24.7 A representation of protein biosynthesis.

The codon base sequences on mRNA are read by tRNAs containing complementary anticodon base sequences. Transfer RNAs assemble the proper amino acids into position for incorporation into the growing peptide.

WORKED EXAMPLE 24.2

Predicting the Amino Acid Sequence Transcribed from DNA

What amino acid sequence is coded by the following segment of a DNA sense strand?

(5') CTA-ACT-AGC-GGG-TCG-CCG (3')

Strategy

The mRNA produced during translation is a copy of the DNA sense strand, with each T replaced by U. Thus, the mRNA has the following sequence:

(5') CUA-ACU-AGC-GGG-UCG-CCG (3')

Each set of three bases forms a codon, whose meaning can be found in Table 24.1.

Solution

Leu-Thr-Ser-Gly-Ser-Pro

PROBLEM 24.7

List anticodon sequences on the tRNAs carrying the following amino acids:

(a) Ala (b) Phe (c) Leu (d) Tyr

PROBLEM 24.8

What amino acid sequence is coded by the following mRNA base sequence?

(5') CUU-AUG-GCU-UGG-CCC-UAA (3')

PROBLEM 24.9

What is the base sequence in the original DNA strand on which the mRNA sequence in Problem 24.8 was made?

24-6 DNA Sequencing

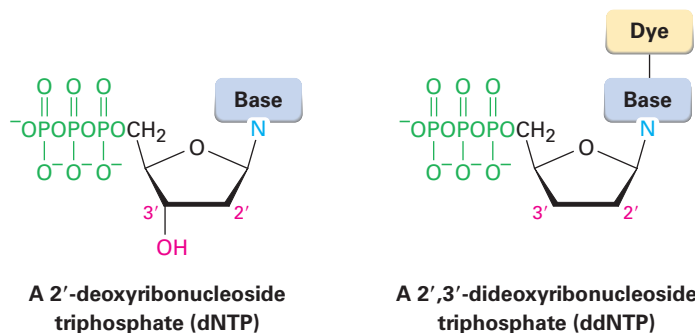
One of the greatest scientific revolutions in history is now underway in molecular biology, as scientists are learning how to manipulate and harness the genetic machinery of organisms. None of the extraordinary advances of the past two decades would have been possible, however, were it not for the discovery in 1977 of methods for sequencing immense DNA chains.

The first step in DNA sequencing is to cleave the enormous chain at known points to produce smaller, more manageable pieces, a task accomplished by the use of *restriction endonucleases*. Each different restriction enzyme, of which more than 3800 are known and approximately 375 are commercially available, cleaves a DNA molecule at a point in the chain where a specific base sequence occurs. For example, the restriction enzyme *AluI* cleaves between G and C in the four-base sequence AG-CT. Note that the sequence is a *palindrome*, meaning that the sequence (5')-AGCT-(3') is the same as its complement (3')-TCGA-(5') when both are read in the same 5' → 3' direction. The same is true for other restriction endonucleases.

If the original DNA molecule is cut with another restriction enzyme that has a different specificity for cleavage, still other segments are produced whose sequences partially overlap those produced by the first enzyme. Sequencing of all the segments, followed by identification of the overlapping regions, allows complete DNA sequencing.

A dozen or so different methods of DNA sequencing are now available, and at least a half-dozen others are under development. The **Sanger dideoxy method** is currently the most frequently used and was the method responsible for first sequencing the entire human genome of 3.0 billion base pairs. In commercial sequencing instruments, the dideoxy method begins with a mixture of the following:

- The restriction fragment to be sequenced
- A small piece of DNA called a *primer*, whose sequence is complementary to that on the 3' end of the restriction fragment
- The four 2'-deoxyribonucleoside triphosphates (dNTPs)
- Very small amounts of the four 2',3'-dideoxyribonucleoside triphosphates (ddNTPs), each of which is labeled with a fluorescent dye of a different color. (A 2',3'-dideoxyribonucleoside triphosphate is one in which both 2' and 3' -OH groups are missing from ribose.)



DNA polymerase is added to the mixture, and a strand of DNA complementary to the restriction fragment begins to grow from the end of the primer. Most of the time, only normal deoxyribonucleotides are incorporated into the growing chain because of their much higher concentration in the mixture, but every so often, a dideoxyribonucleotide is incorporated. When that happens, DNA synthesis stops because the chain end no longer has a 3'-hydroxyl group for adding further nucleotides.

When reaction is complete, the product consists of a mixture of DNA fragments of all possible lengths, each terminated by one of the four dye-labeled dideoxyribonucleotides. This product mixture is then separated according to the size of the pieces by gel electrophoresis (Section 19-2), and the identity of the terminal dideoxyribonucleotide in each piece—and thus the sequence of the restriction fragment—is identified by noting the color with which it fluoresces. **FIGURE 24.8** shows a typical result.

So efficient is the automated dideoxy method that sequences up to 1100 nucleotides in length, with a throughput of up to 19,000 bases per hour, can be sequenced with greater than 99% accuracy. After a decade of work, preliminary sequence information for the entire human genome of 3.0 billion base pairs was announced early in 2001 and complete information was released in

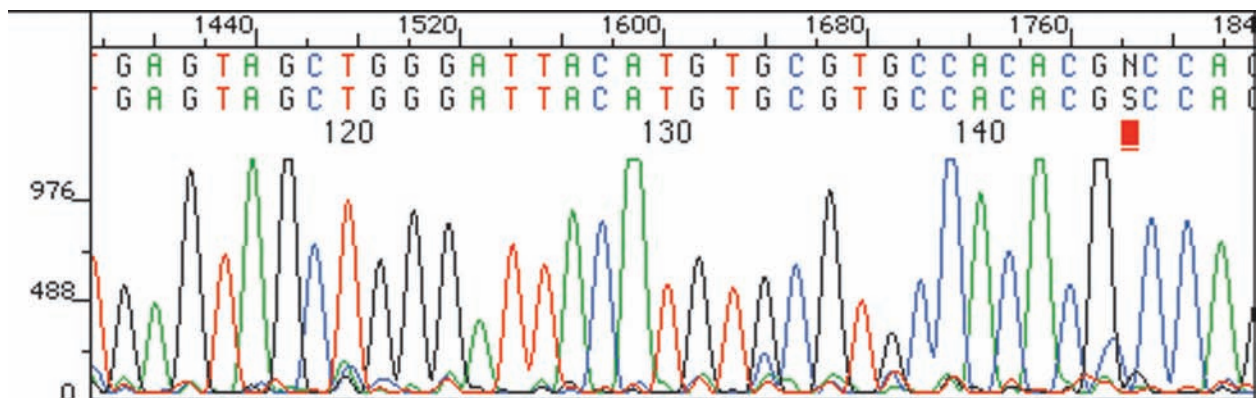


FIGURE 24.8 Determining the sequence of a restriction fragment by the Sanger dideoxy method. The sequence is read by noting the colors of the dye attached to each of the various terminal nucleotides.

2003. More recently, the genome sequencing of specific individuals, including that of James Watson, discoverer of the double helix, has been accomplished. The sequencing price per genome is dropping rapidly as newer methods are introduced and was approaching \$5,000 in early 2013, meaning that the routine sequencing of individuals is now possible.

Remarkably, our genome appears to contain only about 21,000 genes, less than one-fourth the previously predicted number and only about twice the number found in the common roundworm. It's also interesting to note that the number of genes in a human (21,000) is much smaller than the number of kinds of proteins (perhaps 500,000). The discrepancy arises because most proteins are modified in various ways after translation (*posttranslational modifications*), so a single gene can ultimately give many different proteins.

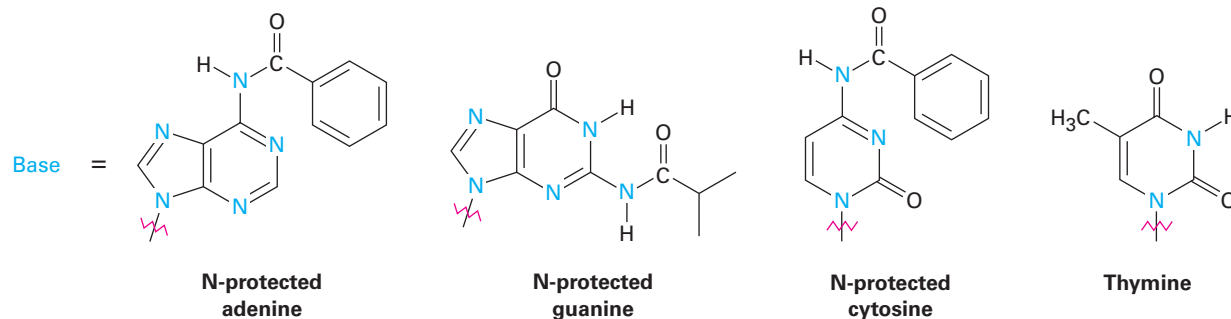
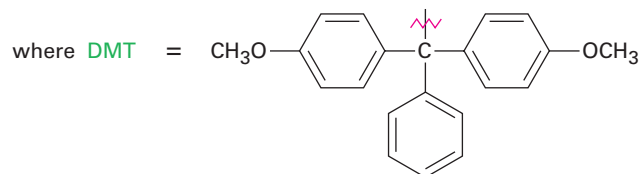
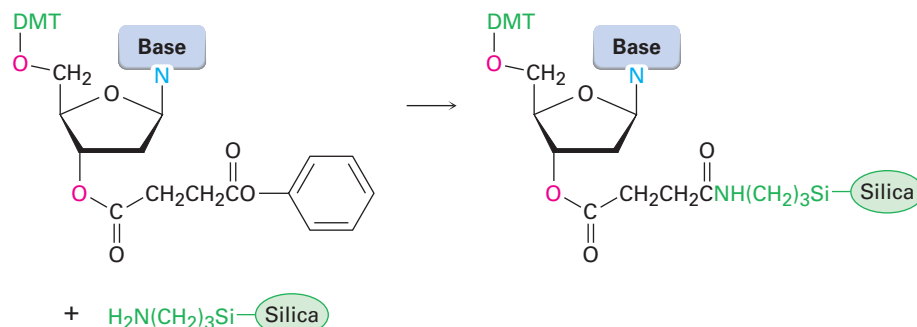
24-7 DNA Synthesis

The ongoing revolution in molecular biology has brought with it an increased demand for the efficient chemical synthesis of short DNA segments, called *oligonucleotides*, or simply *oligos*. The problems of DNA synthesis are similar to those of protein synthesis (Section 19-7) but are more difficult because of the complexity of the nucleotide monomers. Each nucleotide has multiple reactive sites that must be selectively protected and deprotected at the proper times, and coupling of the four nucleotides must be carried out in the proper sequence. Automated DNA synthesizers are available, however, that allow the fast and reliable synthesis of DNA segments up to 200 nucleotides in length.

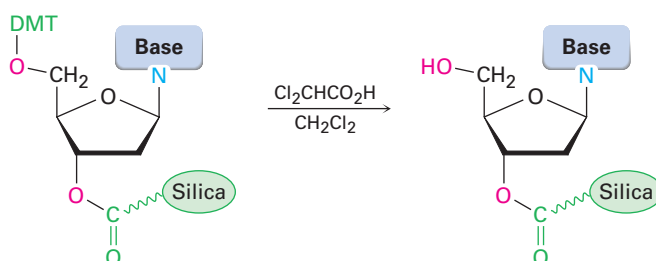
DNA synthesizers operate on a principle similar to that of the Merrifield solid-phase peptide synthesizer (Section 19-7). In essence, a protected nucleotide is covalently bonded to a solid support, and one nucleotide at a time is added to the growing chain by the use of a coupling reagent. After the final nucleotide has been added, all the protecting groups are removed and the synthetic DNA is cleaved from the solid support. Five steps are needed:

Step 1 The first step in DNA synthesis is to attach a protected deoxynucleoside to a silica (SiO_2) support by an ester linkage to the 3' -OH group

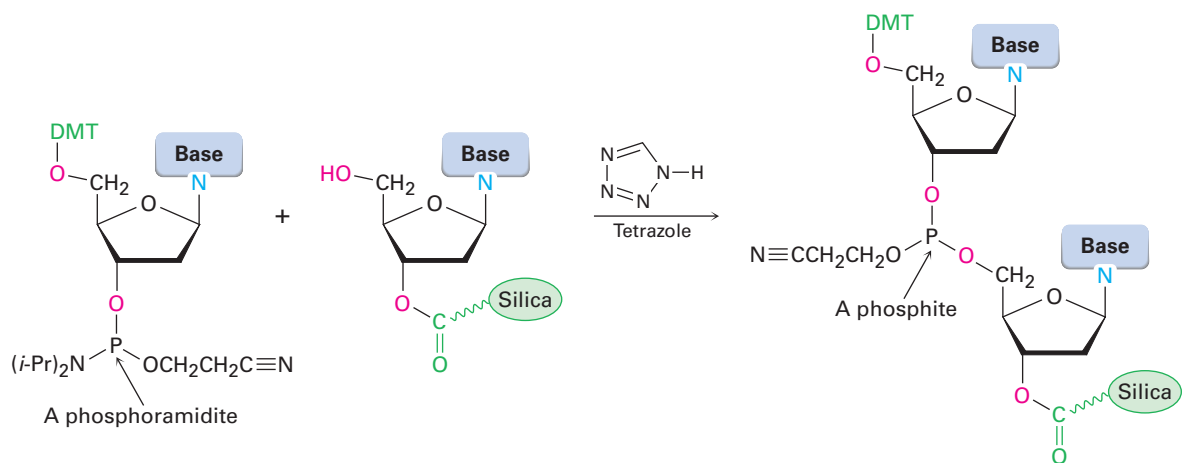
of the deoxynucleoside. Both the 5' –OH group on the sugar and free –NH₂ groups on the heterocyclic bases must be protected. Adenine and cytosine bases are protected by benzoyl groups, guanine is protected by an isobutyryl group, and thymine requires no protection. The deoxyribose 5' –OH is protected as its *p*-dimethoxytrityl (DMT) ether.



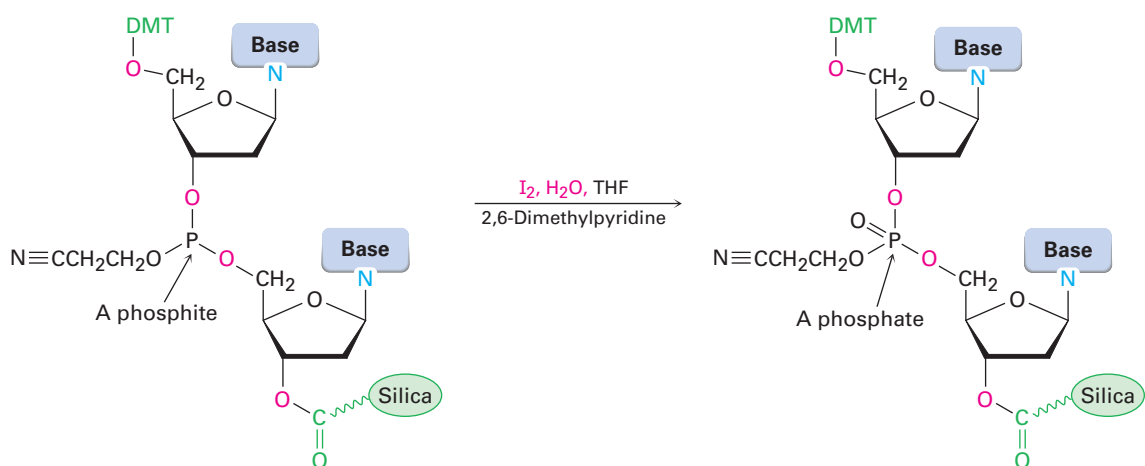
Step 2 The second step is removal of the DMT protecting group by treatment with dichloroacetic acid in CH_2Cl_2 . The reaction occurs by an $\text{S}_{\text{N}}1$ mechanism and proceeds rapidly because of the stability of the tertiary, benzylic dimethoxytrityl cation.



Step 3 The third step is the coupling of the polymer-bonded deoxynucleoside with a protected deoxynucleoside containing a *phosphoramidite* group $[R_2NP(OR)_2]$ at its 3' position. The coupling reaction takes place in the polar aprotic solvent acetonitrile, requires catalysis by the heterocyclic amine tetrazole, and yields a *phosphite*, $P(OR)_3$, as product. Note that one of the phosphorus oxygen atoms is protected by a β -cyanoethyl group, $-OCH_2CH_2C\equiv N$. The coupling step takes place in better than 99% yield.

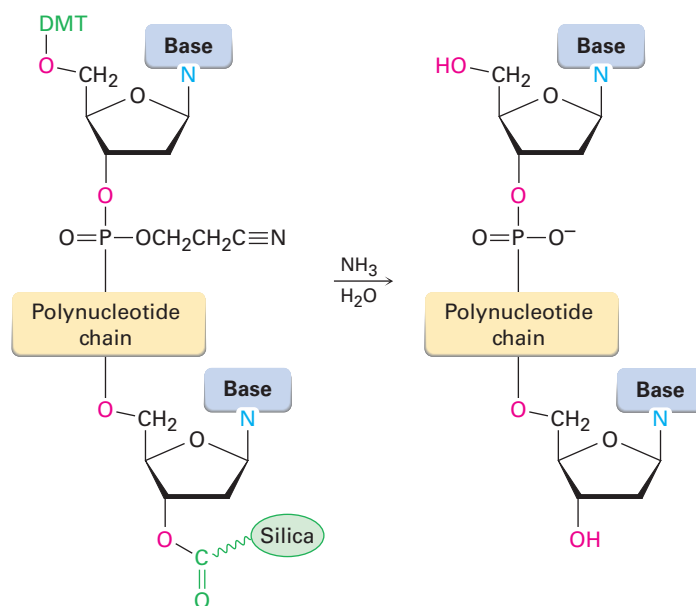


Step 4 With the coupling accomplished, the phosphite product is oxidized to a phosphate by treatment with iodine in aqueous tetrahydrofuran in the presence of 2,6-dimethylpyridine. The cycle (1) deprotection, (2) coupling, and (3) oxidation is then repeated until an oligonucleotide chain of the desired sequence has been built.



Step 5 The final step is removal of all protecting groups and cleavage of the ester bond holding the DNA to the silica. All these reactions are done

at the same time by treatment with aqueous NH_3 . Purification by electrophoresis then yields the synthetic DNA.



PROBLEM 24.10

p-Dimethoxytrityl (DMT) ethers are easily cleaved by mild acid treatment. Show the mechanism of the cleavage reaction.

PROBLEM 24.11

Propose a mechanism to account for cleavage of the β -cyanoethyl protecting group from the phosphate groups on treatment with aqueous ammonia. (Acrylonitrile, $\text{H}_2\text{C}=\text{CHCN}$, is a by-product.) What kind of reaction is occurring?

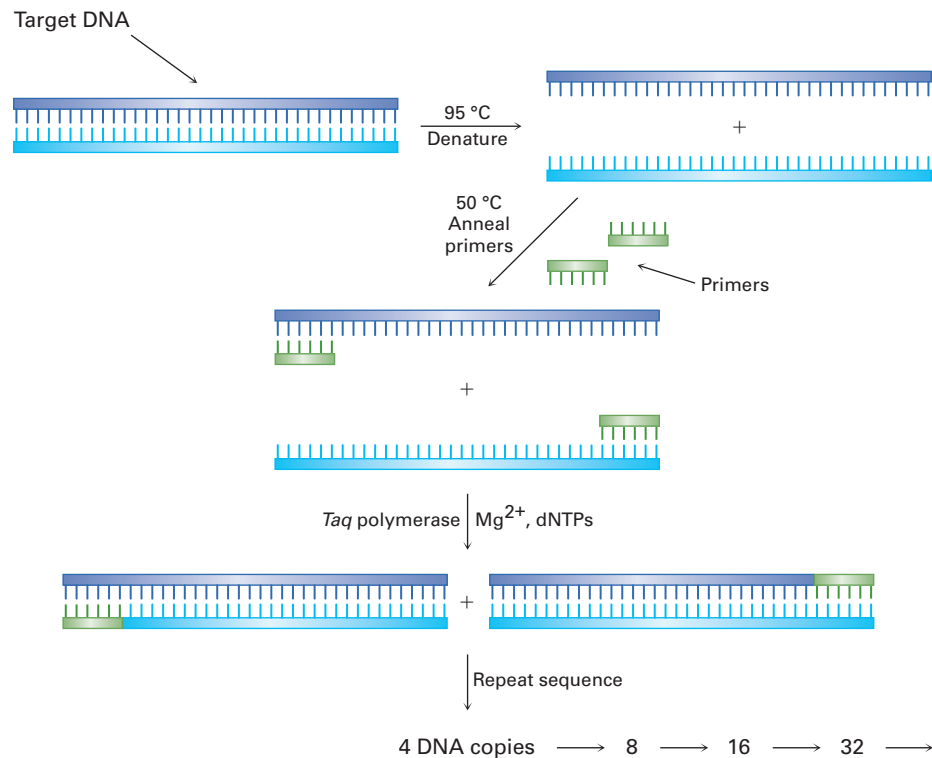
24-8 The Polymerase Chain Reaction

It often happens that only a tiny amount of DNA can be obtained directly, as might occur at a crime scene, so methods for obtaining larger amounts are sometimes needed to carry out the sequencing and characterization. The invention of the **polymerase chain reaction (PCR)** by Kary Mullis in 1986 has been described as being to genes what Gutenberg's invention of the printing press was to the written word. Just as the printing press produces multiple copies of a book, PCR produces multiple copies of a given DNA sequence. Starting from less than 1 picogram of DNA with a chain length of 10,000 nucleotides ($1 \text{ pg} = 10^{-12} \text{ g}$; about 100,000 molecules), PCR makes it possible to obtain several micrograms ($1 \text{ } \mu\text{g} = 10^{-6} \text{ g}$; about 10^{11} molecules) in just a few hours.

The key to the polymerase chain reaction is *Taq* DNA polymerase, a heat-stable enzyme isolated from the thermophilic bacterium *Thermus aquaticus* found in a hot spring in Yellowstone National Park. *Taq* polymerase is able to take a single strand of DNA that has a short, primer segment of complementary chain at one end and then finish constructing the entire complementary strand. The overall process takes three steps, as shown in **FIGURE 24.9**. (More

recently, improved heat-stable DNA polymerases have become available, including Vent polymerase and *Pfu* polymerase, both isolated from bacteria growing near geothermal vents in the ocean floor. The error rate of both enzymes is substantially less than that of *Taq*.)

FIGURE 24.9 The polymerase chain reaction. Details are explained in the text.



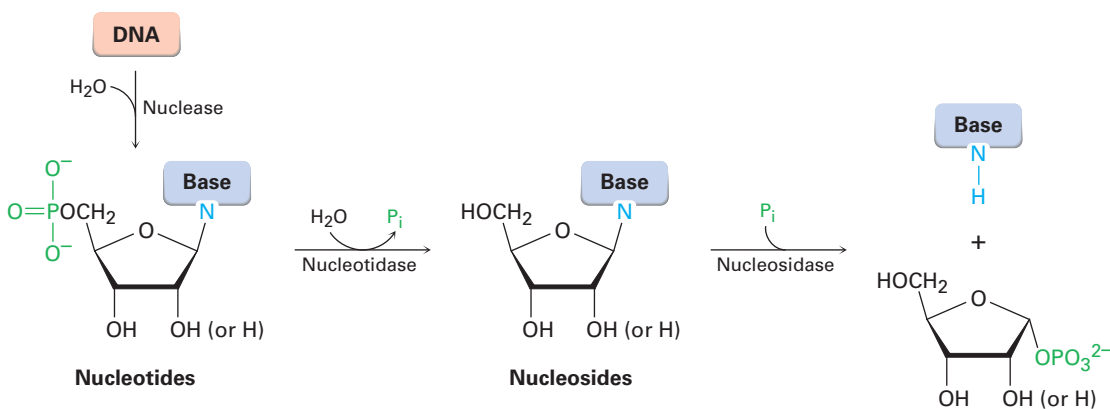
- Step 1** The double-stranded DNA to be amplified is heated in the presence of *Taq* polymerase, Mg^{2+} ion, the four deoxynucleotide triphosphate monomers (dNTPs), and a large excess of two short oligonucleotide primers of about 20 bases each. Each primer is complementary to the sequence at the end of one of the target DNA segments. At a temperature of 95 °C, double-stranded DNA denatures, spontaneously breaking apart into two single strands.
- Step 2** The temperature is lowered to between 37 and 50 °C, allowing the primers, because of their relatively high concentration, to anneal by hydrogen-bonding to their complementary sequence at the end of each target strand.
- Step 3** The temperature is then raised to 72 °C, and *Taq* polymerase catalyzes the addition of further nucleotides to the two primed DNA strands. When replication of each strand is finished, *two* copies of the original DNA now exist. Repeating the denature–anneal–synthesize cycle a second time yields four DNA copies, repeating a third time yields eight copies, and so on, in an exponential series.

PCR has been automated, and 30 or so cycles can be carried out in an hour, resulting in a theoretical amplification factor of 2^{30} ($\sim 10^9$). In practice, however, the efficiency of each cycle is less than 100%, and an experimental amplification of about 10^6 to 10^8 is routinely achieved for 30 cycles.

24-9 Catabolism of Nucleotides

The catabolism of nucleotides is generally more complex than that of amino acids, carbohydrates, or fatty acids because the structures of the nucleotides themselves are more complex. As a result, we'll treat the subject lightly and look only at one example.

Dietary nucleic acids first pass through the stomach to the intestines, where they are hydrolyzed to their constituent nucleotides by a variety of different nucleases. Dephosphorylation by various nucleotidases next gives nucleosides, and cleavage by nucleosidases then gives the constituent bases, which are catabolized to produce intermediates that enter other metabolic processes or are excreted.



As an example of nucleoside catabolism, let's look at guanosine, which is degraded by a three-step pathway that begins with cleavage to give β -ribose 1-phosphate plus guanine. Hydrolysis of guanine then yields xanthine, and oxidation of xanthine gives uric acid, which is excreted in the urine (FIGURE 24.10).

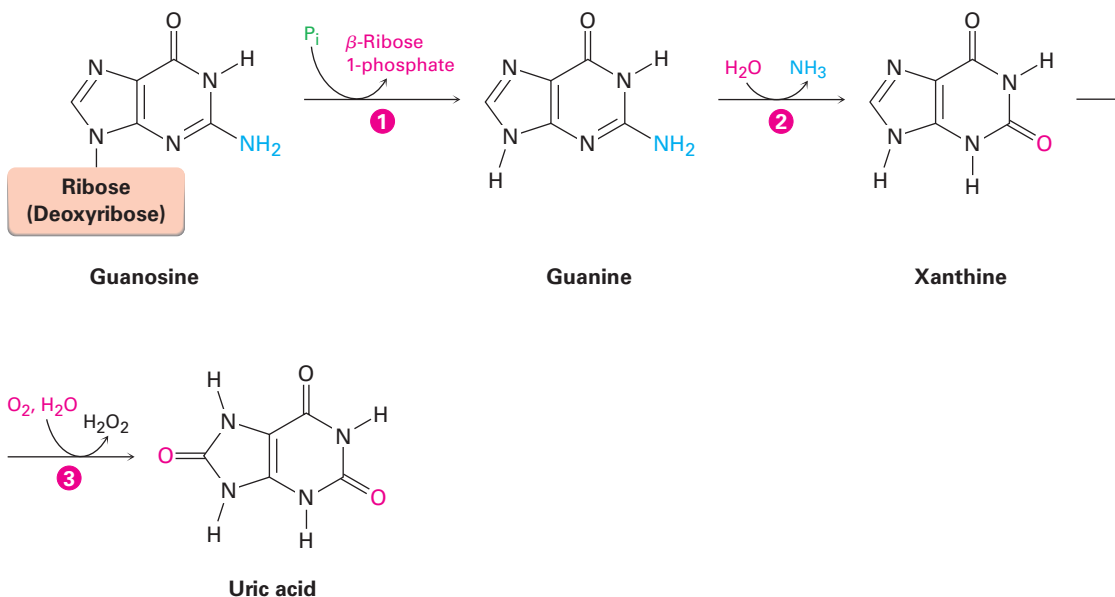
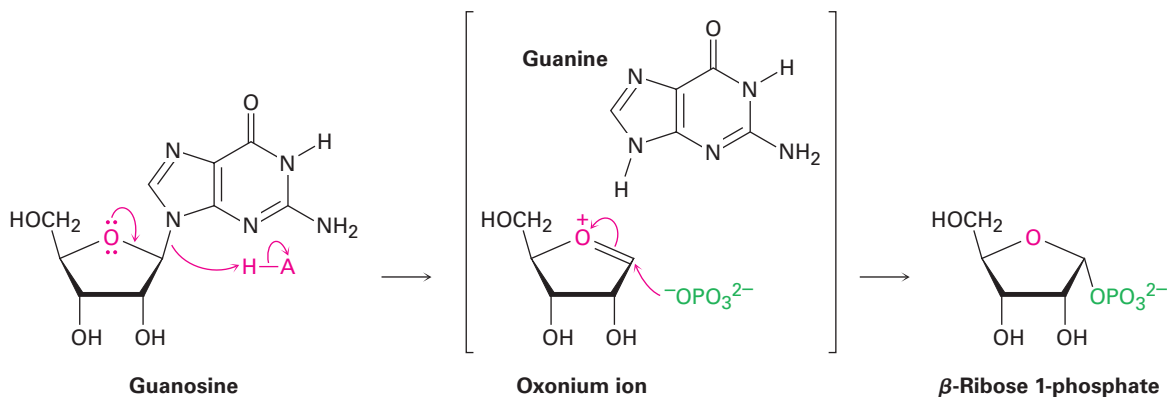
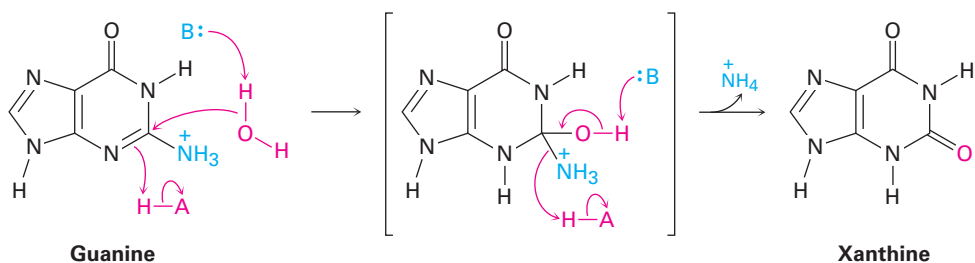


FIGURE 24.10 Pathway for the catabolism of guanosine to uric acid. Individual steps are explained in the text.

STEP 1 OF FIGURE 24.10: PHOSPHOROLYSIS The cleavage of guanosine is catalyzed by purine nucleoside phosphorylase and gives β -ribose 1-phosphate plus guanine. The reaction probably occurs by an S_N1 -like replacement of guanine by phosphate ion through an oxonium-ion intermediate, analogous to what occurs during the hydrolysis of a glycoside with an inverting glycosidase (Figure 22.2 on page 775).



STEP 2 OF FIGURE 24.10: HYDROLYSIS The hydrolysis of guanine to give xanthine is catalyzed by guanine deaminase and occurs by nucleophilic addition of water to the C=N bond, followed by expulsion of ammonium ion—essentially a nucleophilic acyl substitution reaction.



STEP 3 OF FIGURE 24.10: OXIDATION The only unusual step in guanosine catabolism is the oxidation of xanthine by xanthine oxidase, a complex enzyme that contains FAD and an oxo-molybdenum(VI) cofactor. Current evidence suggests the mechanism in **FIGURE 24.11**, in which a base deprotonates the Mo-OH group and the resulting anion does a nucleophilic addition to a C=N bond in xanthine. The nitrogen anion then expels hydride ion, which adds to an Mo=S bond, thereby reducing the molybdenum center from Mo(VI) to Mo(IV). Hydrolysis of the Mo-O bond gives an enol that tautomerizes to uric acid, and the reduced molybdenum is reoxidized by O_2 in a complex redox pathway.

The transformation may look complicated because you're probably unfamiliar with molybdenum. Note, though, that the reactions taking place on xanthine *are* familiar and we've seen them numerous times. Thus, the initial nucleophilic addition of an oxygen anion to C=N is similar to what occurs in step 2 when water adds to guanine, and the subsequent expulsion of hydride

ion by the adjacent nitrogen atom is analogous to what occurs during NADH reductions (Section 14-10).

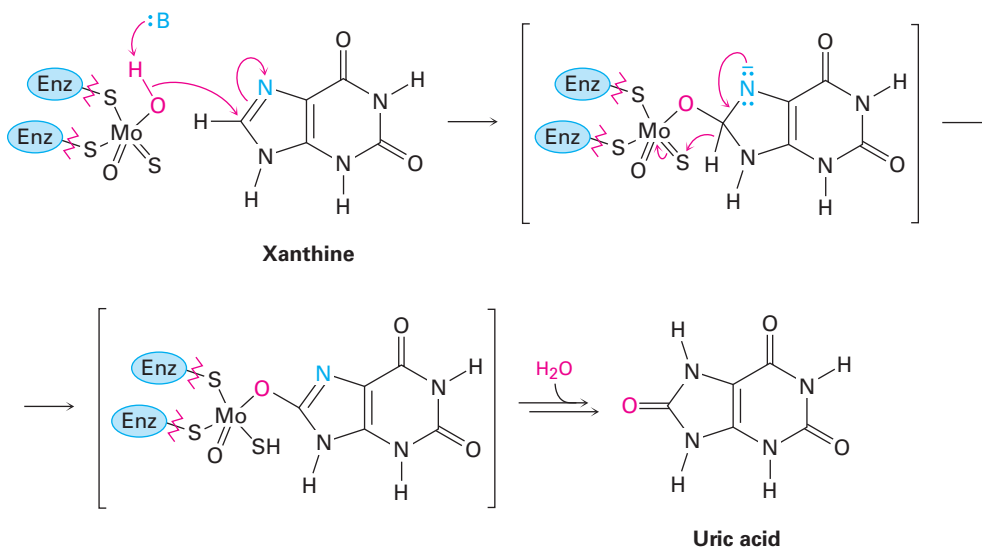
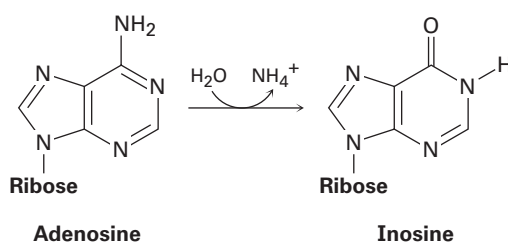


FIGURE 24.11 The mechanism of step 3 in Figure 24.10. Xanthine is oxidized to yield uric acid.

Adenosine, the other purine nucleotide, is degraded by a strategy similar to that used for guanosine, but the order of steps is different. Rather than having the base first cleaved off and then degraded, the base in adenosine is first degraded and then removed.

PROBLEM 24.12

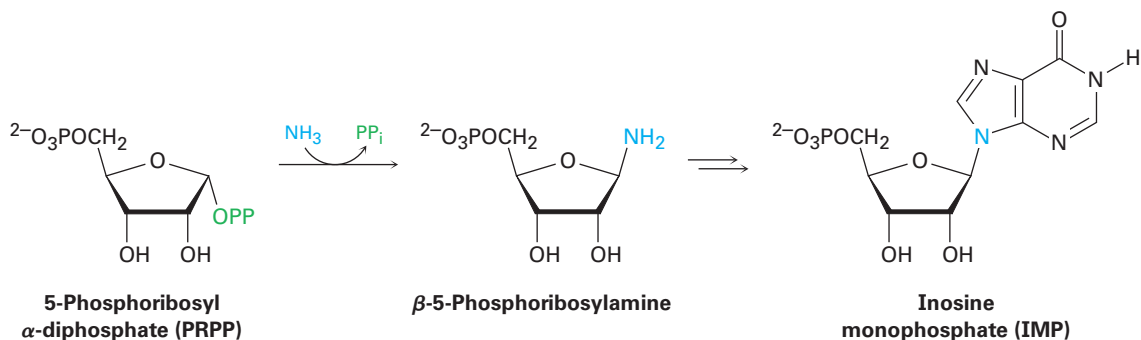
Write a likely mechanism for the first step in adenosine catabolism, the hydrolysis of adenosine to yield inosine.



24-10 Biosynthesis of Nucleotides

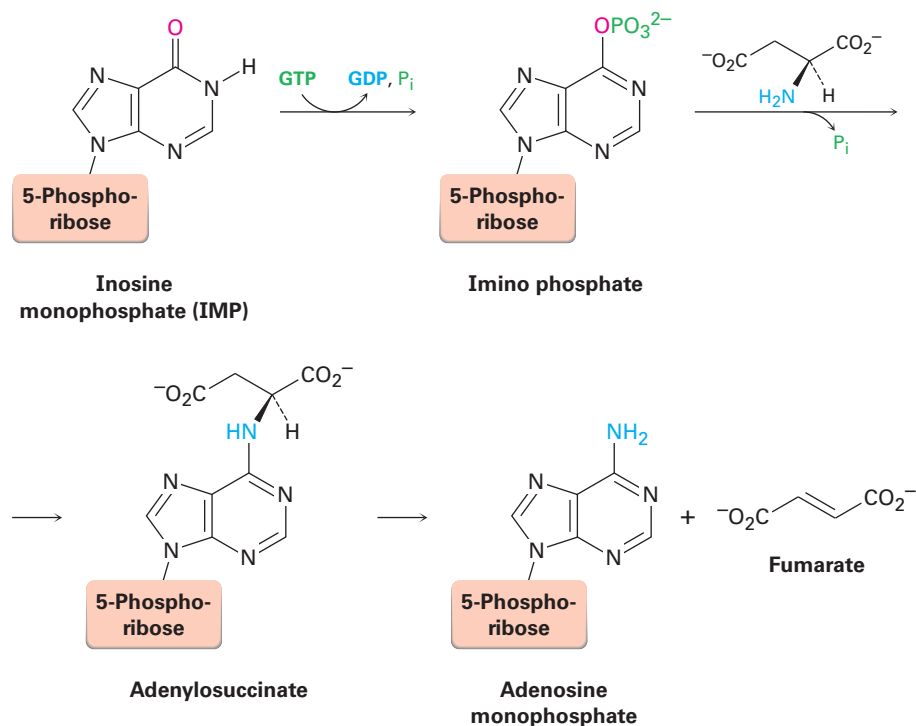
Nucleotide biosynthesis, like nucleotide catabolism, is relatively complex. Thus, we'll again look at only one example, adenosine monophosphate. Purine nucleotides are formed by initial attachment of an -NH_2 group to ribose, followed by multistep buildup of the heterocyclic base. The attachment of -NH_2 takes place by a nucleophilic substitution reaction of ammonia with 5-phosphoribosyl α -diphosphate to give β -5-phosphoribosylamine and

probably involves an S_N1 -like loss of diphosphate ion with formation of an oxonium-ion intermediate. Although we'll not cover the details of its formation, inosine monophosphate (IMP) is the first fully formed purine ribonucleotide, with adenosine monophosphate (AMP) derived from it.



Adenosine monophosphate is biosynthesized from IMP in a three-step sequence: initial phosphorylation with GTP to form an imino phosphate, reaction with aspartate to give adenylosuccinate, and elimination of fumarate (FIGURE 24.12). The reaction of the imino phosphate with aspartate is simply a nucleophilic acyl substitution reaction, and the elimination of fumarate is an E1cB reaction, analogous to the third step in the urea cycle in which argininosuccinate is converted to arginine (Figure 20.5 on page 725).

FIGURE 24.12 Pathway for the conversion of inosine monophosphate to adenosine monophosphate.



PROBLEM 24.13

Write the mechanism of the formation of adenylosuccinate from inosine monophosphate, the second step in adenosine biosynthesis (Figure 24.12).

PROBLEM 24.14

Show the mechanism of the formation of adenosine monophosphate from adenylosuccinate, the third step in adenosine biosynthesis (Figure 24.12).

SOMETHING EXTRA

DNA Fingerprinting

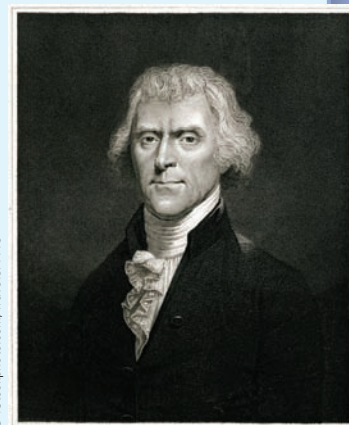
The invention of DNA sequencing has affected society in many ways, few more dramatic than those stemming from the development of *DNA fingerprinting*. DNA fingerprinting arose from the discovery in 1984 that human genes contain short, repeating sequences of noncoding DNA, called *short tandem repeat (STR)* loci. Furthermore, the STR loci are slightly different for every individual, except identical twins. By sequencing these loci, a pattern unique to each person can be obtained.

Perhaps the most common and well-publicized use of DNA fingerprinting is that carried out by crime laboratories to link suspects to biological evidence—blood, hair follicles, skin, or semen—found at a crime scene. Many thousands of court cases have now been decided based on DNA evidence.

For use in criminal cases, forensic laboratories in the United States have agreed on 13 core STR loci that are most accurate for identification of an individual. Based on these 13 loci, a Combined DNA Index System (CODIS) has been established to serve as a registry of convicted offenders. When a DNA sample is obtained from a crime scene, the sample is subjected to cleavage with restriction endonucleases to cut out fragments containing the STR loci, the fragments are amplified using the polymerase chain reaction, and the sequences of the fragments are determined.

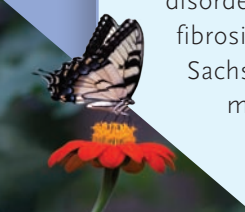
If the profile of sequences from a known individual and the profile from DNA obtained at a crime scene

Historians have wondered for many years whether Thomas Jefferson fathered a child by his slave, Sally Hemings. DNA fingerprinting evidence obtained in 1998 strongly suggests that he did.



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match, the probability is approximately 82 billion to 1 that the DNA is from the same individual. In paternity cases, where the DNA of father and offspring are related but not fully identical, the identity of the father can be established with a probability of around 100,000 to 1. Even after several generations have passed, paternity can still be inferred from DNA analysis of the Y chromosome of direct male-line descendants. The most well-known such case is that of Thomas Jefferson, who likely fathered a child by his slave Sally Hemings. Although Jefferson himself has no male-line descendants, DNA analysis of the male-line descendants of Jefferson's paternal uncle contained the same Y chromosome as a male-line descendant of Eston Hemings, the youngest son of Sally Hemings. Thus, a mixing of the two genomes is clear, although the male individual responsible for that mixing can't be conclusively identified.



Among its many other applications, DNA fingerprinting is widely used for the diagnosis of genetic disorders, both prenatally and in newborns. Cystic fibrosis, hemophilia, Huntington's disease, Tay-Sachs disease, sickle cell anemia, and thalassemia are among the many diseases that can be detected, enabling early treatment of an affected child. Furthermore, by

studying the DNA fingerprints of relatives with a history of a particular disorder, it's possible to identify DNA patterns associated with the disease and perhaps obtain clues for eventual cure. In addition, the U.S. Department of Defense now requires blood and saliva samples from all military personnel. The samples are stored, and DNA is extracted should the need for identification of a casualty arise.

KEY WORDS

anticodon, 862
 antisense strand, 861
 codon, 861
 deoxyribonucleic acid (DNA), 852
 double helix, 855
 3' end, 855
 5' end, 855
 messenger RNA (mRNA), 860
 nucleoside, 852
 nucleotide, 852
 polymerase chain reaction (PCR), 869
 replication, 858
 ribonucleic acid (RNA), 852
 ribosomal RNA (rRNA), 860
 Sanger dideoxy method, 865
 sense strand, 861
 small RNAs, 860
 transcription, 860
 transfer RNA (tRNA), 860
 translation, 862

SUMMARY

DNA (deoxyribonucleic acid) and **RNA (ribonucleic acid)** are biological polymers that act as chemical carriers of an organism's genetic information. Enzyme-catalyzed hydrolysis of nucleic acids yields **nucleotides**, the monomer units from which RNA and DNA are constructed. Further enzyme-catalyzed hydrolysis of the nucleotides yields **nucleosides** plus phosphate. Nucleosides, in turn, consist of a purine or pyrimidine base linked to C1 of an aldopentose sugar—ribose in RNA and 2-deoxyribose in DNA. The nucleotides are joined by phosphate links between the 5' phosphate of one nucleotide and the 3' hydroxyl on the sugar of another nucleotide.

Molecules of DNA consist of two complementary polynucleotide strands held together by hydrogen bonds between heterocyclic bases on the different strands and coiled into a **double helix**. Adenine and thymine form hydrogen bonds to each other, as do cytosine and guanine.

Three processes take place in deciphering the genetic information of DNA:

- **Replication** of DNA is the process by which identical DNA copies are made. The DNA double helix unwinds, complementary deoxyribonucleotides line up in order, and two new DNA molecules are produced.
- **Transcription** is the process by which RNA is produced to carry genetic information from the nucleus to the ribosomes. A short segment of the DNA double helix unwinds, and complementary ribonucleotides line up to produce **messenger RNA (mRNA)**.
- **Translation** is the process by which mRNA directs protein synthesis. Each mRNA is divided into **codons**, ribonucleotide triplets that are recognized by small amino acid carrying molecules of **transfer RNA (tRNA)**, which deliver the appropriate amino acids needed for protein synthesis.

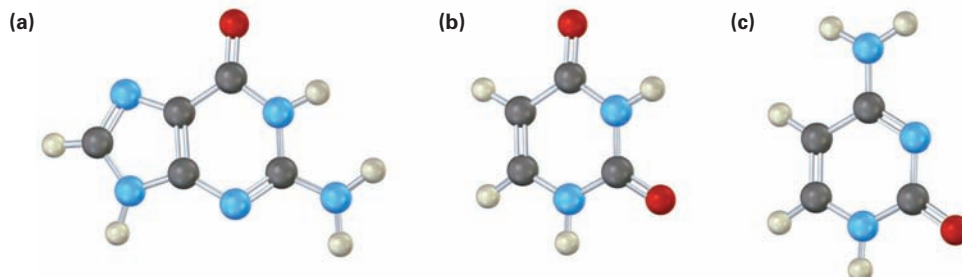
Sequencing of DNA is carried out by the **Sanger dideoxy method**, and small DNA segments can be synthesized in the laboratory by automated instruments. Small amounts of DNA can be amplified by a factor of 10^6 using the **polymerase chain reaction (PCR)**. Nucleotide catabolism and biosynthesis are generally more complex than that of other classes of biomolecules, but the reactions that occur are similar.

EXERCISES

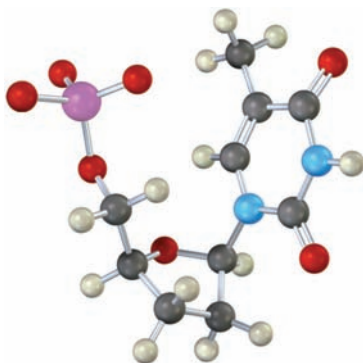
VISUALIZING CHEMISTRY

(Problems 24.1–24.14 appear within the chapter.)

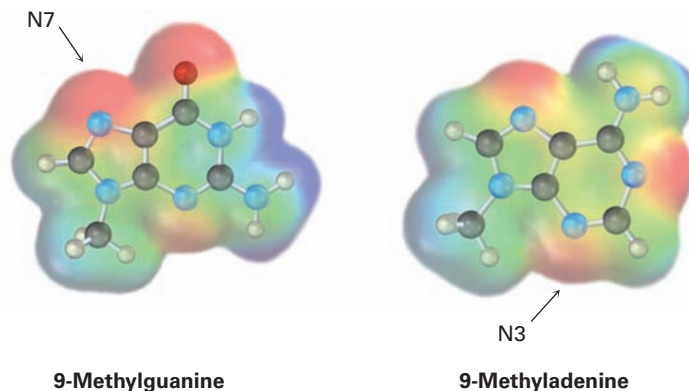
24.15 Identify the following bases, and tell whether each is found in DNA, RNA, or both:



24.16 Identify the following nucleotide, and tell how it is used:



24.17 Amine bases in nucleic acids can react with alkylating agents in typical S_N2 reactions. Look at the following electrostatic potential maps, and tell which is the better nucleophile, guanine or adenine. The reactive positions in each are indicated.

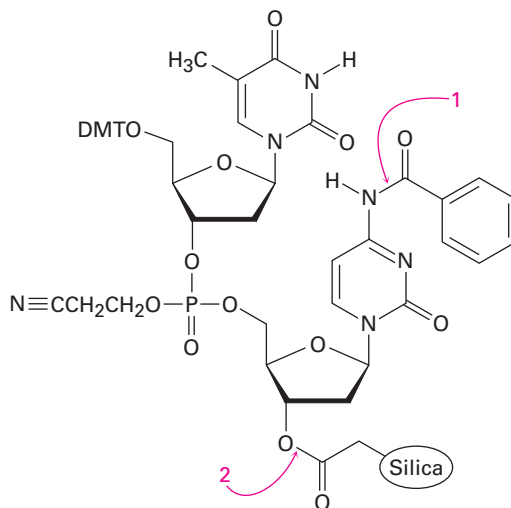


ADDITIONAL PROBLEMS

- 24.18** Human brain natriuretic peptide (BNP) is a small peptide of 32 amino acids used in the treatment of congestive heart failure. How many nitrogen bases are present in the DNA that codes for BNP?
- 24.19** Human and horse insulin both have two polypeptide chains, with one chain containing 21 amino acids and the other containing 30 amino acids. They differ in primary structure at two places. At position 9 in one chain, human insulin has Ser and horse insulin has Gly; at position 30 in the other chain, human insulin has Thr and horse insulin has Ala. How must the DNA for the two insulins differ?
- 24.20** The DNA of sea urchins contains about 32% A. What percentages of the other three bases would you expect in sea urchin DNA?
- 24.21** The codon UAA stops protein synthesis. Why does the sequence UAA in the following stretch of mRNA not cause any problems?
-GCA-UUC-GAG-GUA-ACG-CCC-
- 24.22** Which of the following base sequences would most likely be recognized by a restriction endonuclease? Explain.
(a) GAATTC **(b)** GATTACA **(c)** CTCGAG
- 24.23** For what amino acids do the following ribonucleotide triplets code?
(a) AAU **(b)** GAG **(c)** UCC **(d)** CAU
- 24.24** From what DNA sequences were each of the mRNA codons in Problem 24.23 transcribed?
- 24.25** What anticodon sequences of tRNAs are coded for by the codons in Problem 24.23?
- 24.26** Draw the complete structure of the ribonucleotide codon UAC. For what amino acid does this sequence code?
- 24.27** Draw the complete structure of the deoxyribonucleotide sequence from which the mRNA codon in Problem 24.26 was transcribed.
- 24.28** Give an mRNA sequence that will code for synthesis of met-enkephalin:
Tyr-Gly-Gly-Phe-Met
- 24.29** Give an mRNA sequence that will code for the synthesis of angiotensin II:
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe
- 24.30** What amino acid sequence is coded for by the following DNA sense strand?
(5') CTT-CGA-CCA-GAC-AGC-TTT (3')
- 24.31** What amino acid sequence is coded for by the following mRNA base sequence?
(5') CUA-GAC-CGU-UCC-AAG-UGA (3')
- 24.32** If the DNA sense sequence -CAA-CCG-GAT- were miscopied during replication and became -CGA-CCG-GAT-, what effect would there be on the sequence of the protein produced?

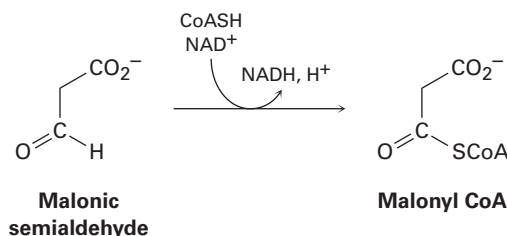
24.33 Show the steps involved in a laboratory synthesis of the DNA fragment with the sequence CTAG.

24.34 The final step in DNA synthesis is deprotection by treatment with aqueous ammonia. Show the mechanisms by which deprotection occurs at the points indicated in the following structure:

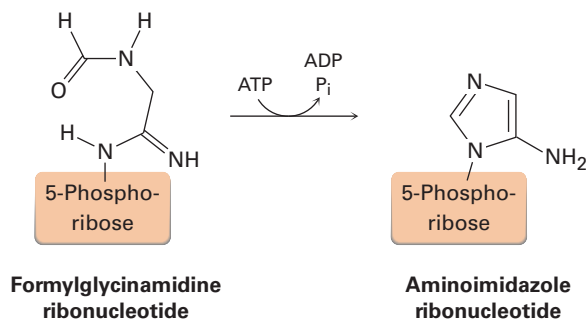


24.35 Draw the structure of cyclic adenosine monophosphate (cAMP), a messenger involved in the regulation of glucose production in the body. Cyclic AMP has a phosphate ring connecting the 3' and 5' hydroxyl groups on adenosine.

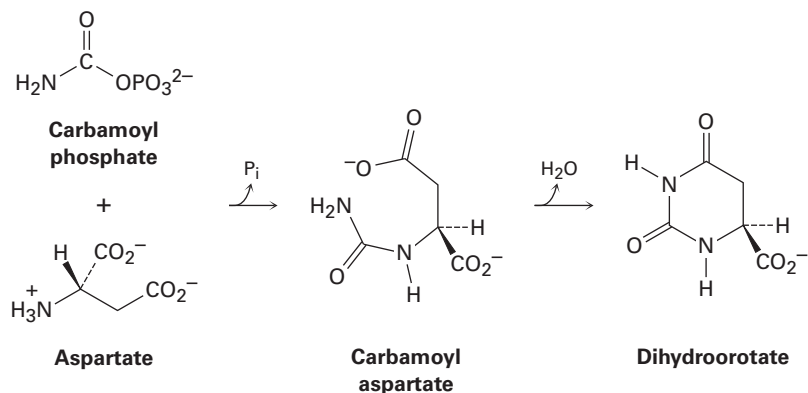
24.36 Write a mechanism for the oxidation of malonic semialdehyde to give malonyl CoA, one of the steps in uracil catabolism. The process is similar to what occurs in step 6 of glycolysis.



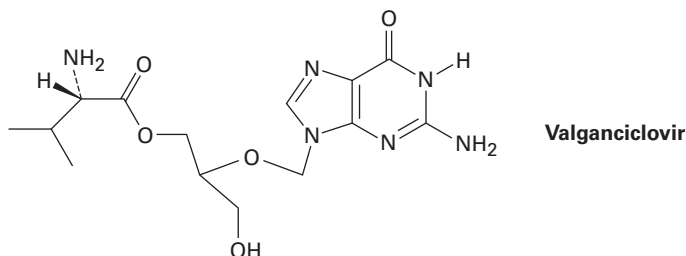
24.37 One of the steps in the biosynthesis of inosine monophosphate is the formation of aminoimidazole ribonucleotide from formylglycinamide ribonucleotide. Propose a mechanism.



- 24.38** One of the steps in the biosynthesis of uridine monophosphate is the reaction of aspartate with carbamoyl phosphate to give carbamoyl aspartate followed by cyclization to form dihydroorotate. Zn^{2+} ion is required as a Lewis acid to catalyze the cyclization. Propose mechanisms for both steps.



- 24.39** Valganciclovir, marketed as Valcyte, is an antiviral agent used for the treatment of cytomegalovirus. Called a *prodrug*, valganciclovir is inactive by itself but is rapidly converted in the intestine by hydrolysis of its ester bond to produce an active drug called ganciclovir, along with an amino acid.



- What amino acid is produced by hydrolysis of the ester bond in valganciclovir?
- What is the structure of ganciclovir?
- What atoms present in the nucleotide deoxyguanine are missing from ganciclovir?
- What role do the atoms missing from deoxyguanine play in DNA replication?
- How might valganciclovir interfere with DNA synthesis?

Secondary Metabolites: An Introduction to Natural Products Chemistry

e25

Norcoclaurine synthase catalyzes the coupling of dopamine with *p*-hydroxyphenylacetaldehyde, a step in morphine biosynthesis.



CONTENTS

- 25-1** Classifying Natural Products
- 25-2** Biosynthesis of Pyridoxal Phosphate
- 25-3** Biosynthesis of Morphine
- 25-4** Biosynthesis of Erythromycin

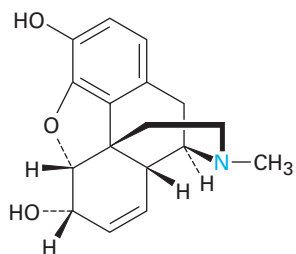
SOMETHING EXTRA

Bioprospecting: Hunting for Natural Products

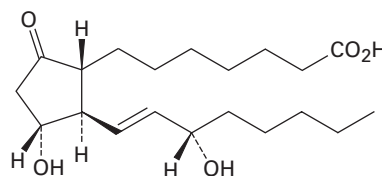
WHY THIS CHAPTER?

In the past six chapters, we've looked at the chemistry and metabolism of the four major classes of biomolecules—proteins, carbohydrates, lipids, and nucleic acids. But there is far more to do, for all living organisms also contain a vast diversity of substances usually grouped under the heading *natural products*. The term **natural product** really refers to *any* naturally occurring substance but is generally taken to mean a **secondary metabolite**—a small molecule that is not essential to the growth and development of the producing organism and is not classified by structure. In this chapter, we'll look at some familiar natural products and see how they are biosynthesized.

It has been estimated that well over 300,000 secondary metabolites exist, and it's thought that their primary function is to increase the likelihood of an organism's survival by repelling or attracting other organisms. Alkaloids, such as morphine; eicosanoids, such as prostaglandin E₁; and antibiotics, such as erythromycin and the penicillins, are examples.

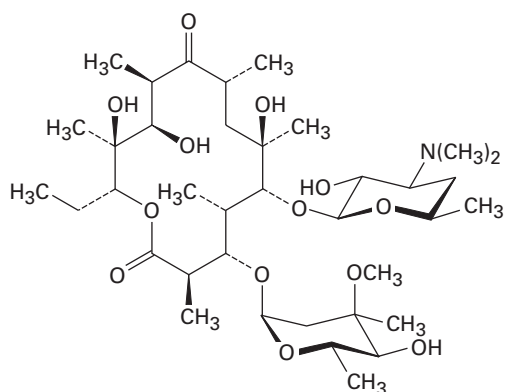


Morphine

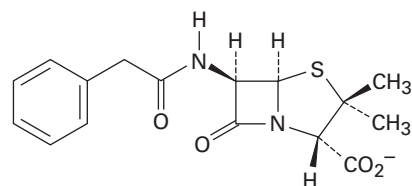


Prostaglandin E₁





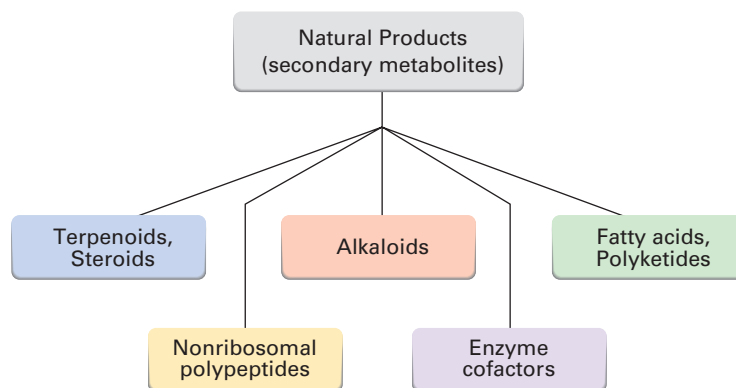
Erythromycin A



Benzylpenicillin

25-1 Classifying Natural Products

There is no rigid scheme for classifying natural products—their immense diversity in structure, function, and biosynthesis is too great to allow them to fit neatly into a few simple categories. In practice, however, workers in the field often speak of five main classes of natural products: terpenoids and steroids, fatty acid–derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors.



- **Terpenoids** and **steroids**, as discussed previously in Chapter 23, are a vast group of substances—more than 35,000 are known—derived biosynthetically from isopentenyl diphosphate. Terpenoids have an immense variety of apparently unrelated structures, while steroids have a common tetracyclic carbon skeleton and are modified terpenoids that are biosynthesized from the triterpene lanosterol. We looked at terpenoid and steroid biosynthesis in Sections 23-8–23-10.

- **Alkaloids**, like terpenoids, are a large and diverse class of compounds, with more than 12,000 examples known at present. They contain a basic amine group in their structure and are derived biosynthetically from amino acids. We'll look at morphine biosynthesis as an example in Section 25-3.
- **Fatty acid–derived substances** and **polyketides**, of which more than 10,000 are known, are biosynthesized from simple acyl precursors such as acetyl CoA, propionyl CoA, and methylmalonyl CoA. Natural products derived from fatty acids generally have most of the oxygen atoms removed, but polyketides, such as the antibiotic erythromycin A, often have many oxygen substituents remaining. We'll look at erythromycin biosynthesis in Section 25-4.
- **Nonribosomal polypeptides** are peptidelike compounds that are biosynthesized from amino acids by a multifunctional enzyme complex without direct RNA transcription. The penicillins are good examples, but their chemistry is a bit complicated and we'll not discuss their biosynthesis.
- **Enzyme cofactors** don't fit one of the other general categories of natural products and are usually classed separately. We've seen numerous examples of coenzymes in past chapters (see the list in Table 19.3) and will look at the biosynthesis of pyridoxal phosphate (PLP) in Section 25-2.

As you might imagine, unraveling the biosynthetic pathways by which specific natural products are made is difficult and time-consuming work. Small precursor molecules have to be identified, guesses about likely routes made, and individual enzymes that catalyze each step isolated, characterized, and mechanistically studied. The payoff for all this painstaking work is a fundamental understanding of how organisms function at the molecular level, an understanding that can be used to design new pharmaceutical agents.

25-2 Biosynthesis of Pyridoxal Phosphate

Let's begin this quick tour of natural-products chemistry by looking at the biosynthesis of pyridoxal 5'-phosphate (PLP), a relatively simple but enormously important enzyme cofactor we've encountered several times in different metabolic pathways. An overview of PLP biosynthesis is shown in **FIGURE 25.1**.

STEPS 1–2 OF FIGURE 25.1: OXIDATION Pyridoxal phosphate biosynthesis begins with oxidation of the aldehyde group in D-erythrose 4-phosphate to give the corresponding carboxylic acid, D-erythronate 4-phosphate. The oxidation requires NAD^+ as cofactor and occurs by a mechanism similar to that of step 6 in glycolysis, in which glyceraldehyde 3-phosphate is oxidized to the corresponding acid (Figure 22.6; page 780). A cysteine $-\text{SH}$ group in the enzyme adds to the aldehyde carbonyl group of D-erythrose 4-phosphate to give an intermediate hemithioacetal, which is then oxidized by NAD^+ to a

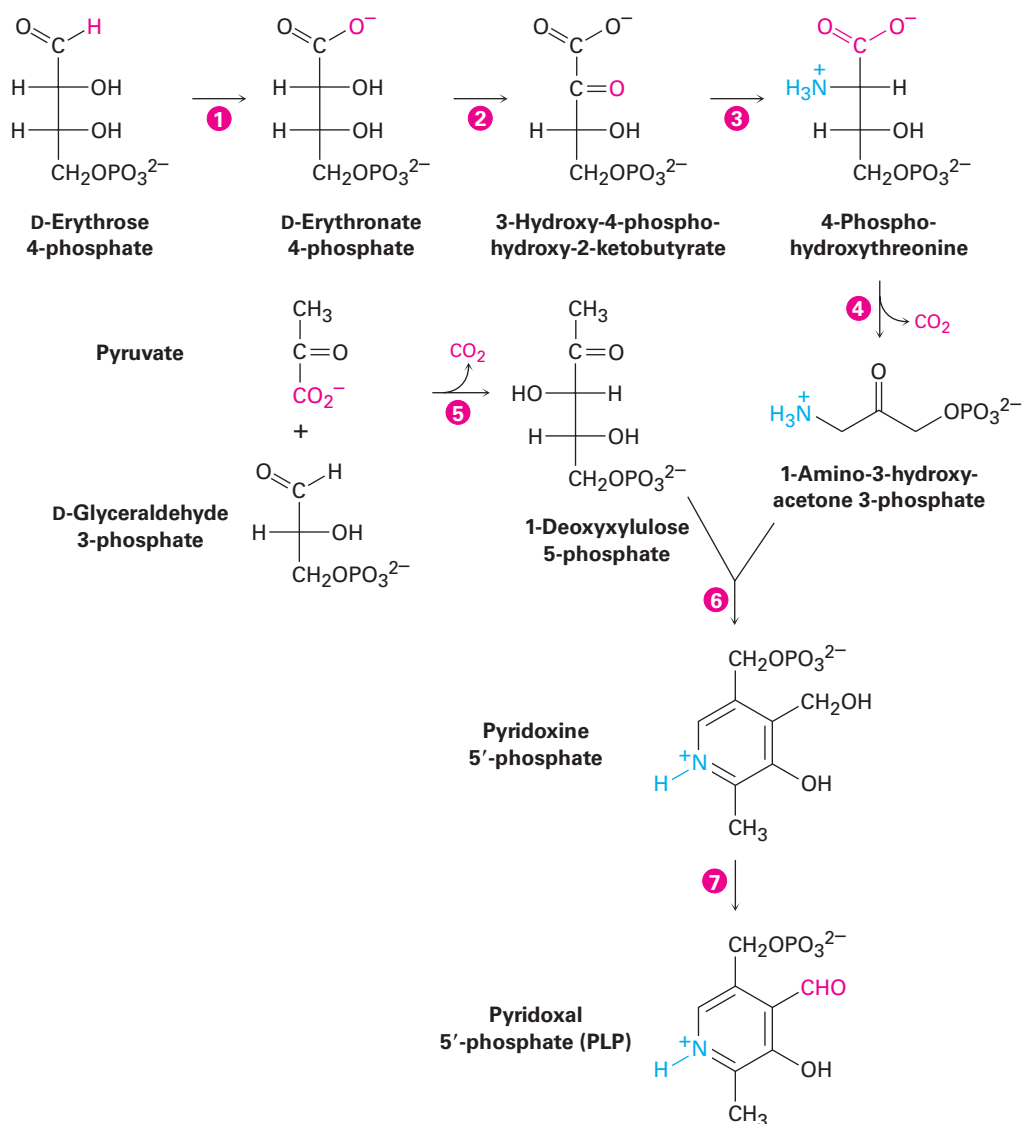


FIGURE 25.1 An overview of the pathway for pyridoxal 5'-phosphate biosynthesis. Individual steps are explained in the text.

thioester. Hydrolysis of the thioester yields erythronate 4-phosphate, and a further oxidation of the $-\text{OH}$ group at C2 by NAD^+ gives 3-hydroxy-4-phosphohydroxy-2-ketobutyrate (FIGURE 25.2).

STEPS 3–4 OF FIGURE 25.1: TRANSAMINATION AND OXIDATION-DECARBOXYLATION 3-Hydroxy-4-phosphohydroxy-2-ketobutyrate undergoes a transamination in step 3 on reaction with α -ketoglutarate by the usual PLP-dependent mechanism, shown previously in Figure 20.2 on page 720. The product, 4-phosphohydroxythreonine, is then oxidized by NAD^+ to give an intermediate β -keto ester, which undergoes concurrent decarboxylation and yields 1-amino-3-hydroxyacetone 3-phosphate. The reactions are shown in FIGURE 25.3.

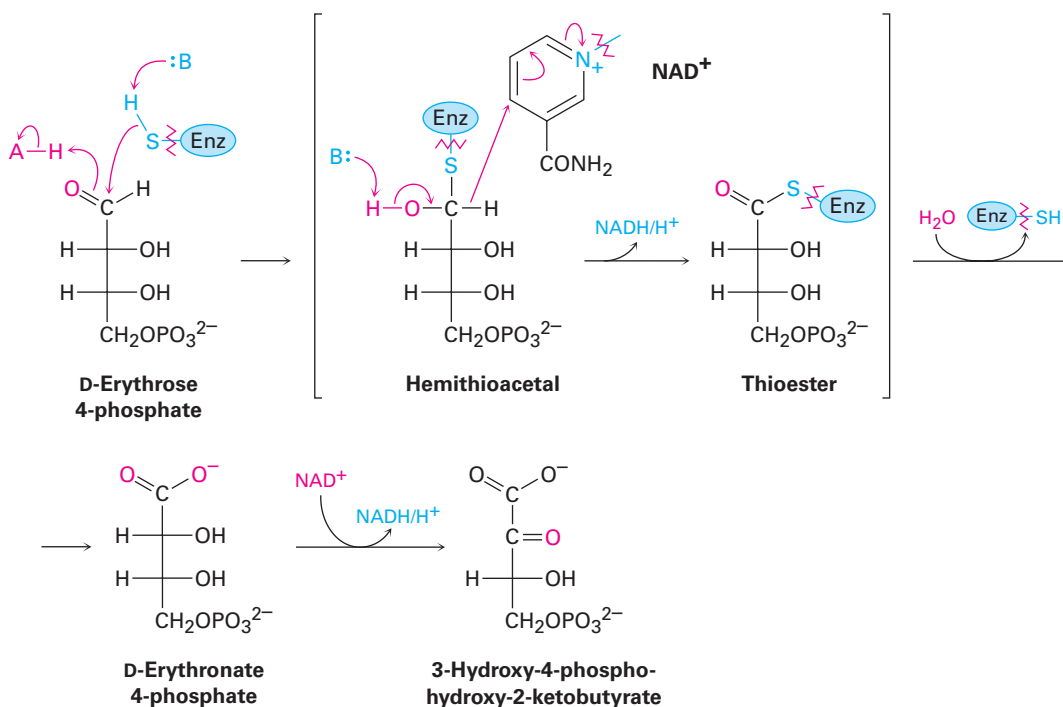


FIGURE 25.2 Mechanism of steps 1 and 2 in PLP biosynthesis. Oxidation of D-erythrose 4-phosphate gives 3-hydroxy-4-phospho-hydroxy-2-ketobutyrate.

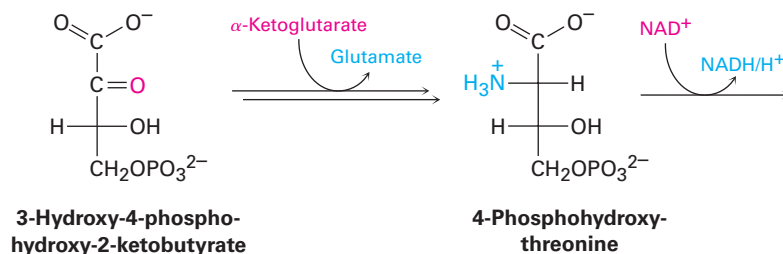
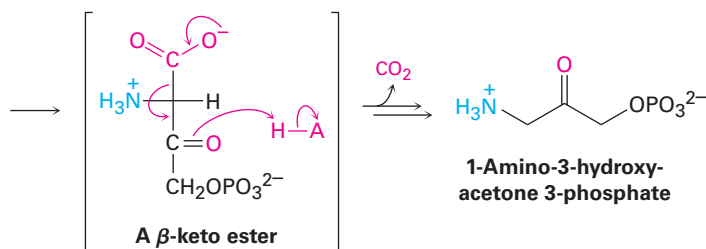


FIGURE 25.3 Mechanism of steps 3 and 4 in PLP biosynthesis.



STEP 5 OF FIGURE 25.1: FORMATION OF 1-DEOXYXYLULOSE 5-PHOSPHATE The 1-amino-3-hydroxyacetone 3-phosphate formed in step 4 of PLP biosynthesis reacts in step 6 with 1-deoxyxylulose 5-phosphate (DXP). DXP arises in step 5 by an aldol-like condensation of D-glyceraldehyde 3-phosphate with pyruvate in a thiamin-dependent reaction catalyzed by DXP synthase.

You might recall from Figure 22.7 on page 784 that pyruvate is converted to acetyl CoA by a process that begins with addition of thiamin diphosphate

(TPP) ylide to the ketone carbonyl group, followed by decarboxylation to give hydroxyethylthiamin diphosphate (HETPP). Exactly the same reaction occurs in DXP biosynthesis, but instead of reacting with lipoamide to give a thioester, as in the formation of acetyl CoA, HETPP adds to glyceraldehyde 3-phosphate in an aldol-like reaction. The tetrahedral intermediate that results expels TPP ylide as leaving group and yields DXP. The mechanism is shown in **FIGURE 25.4**.

FIGURE 25.4
Mechanism of
step 5 in pyridoxal
phosphate biosynthesis.

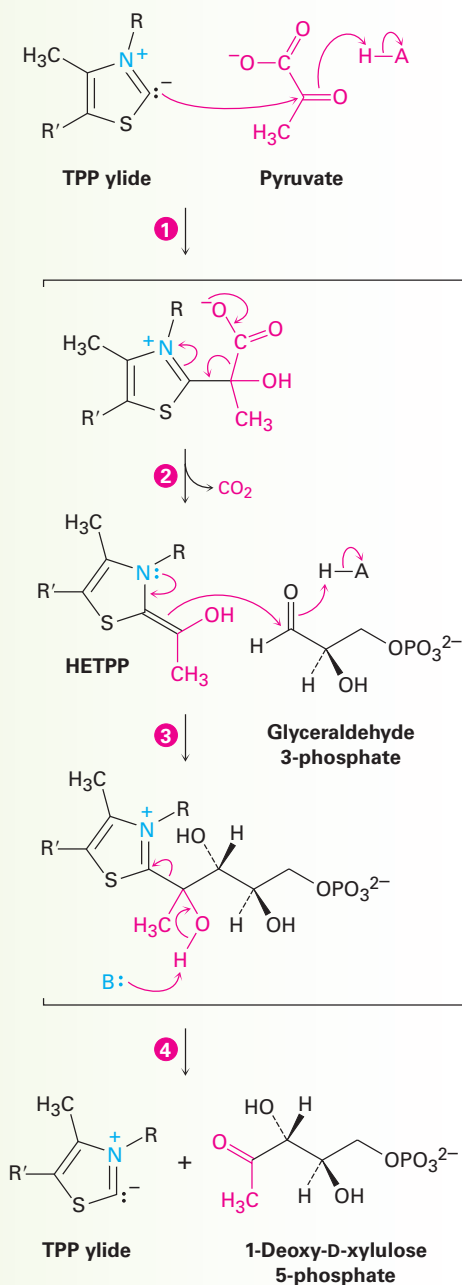
The thiamin-dependent aldol reaction of D-glyceraldehyde 3-phosphate with pyruvate gives 1-deoxyxylulose 5-phosphate.

1 Thiamin diphosphate ylide adds to the ketone carbonyl group of pyruvate to yield an alcohol addition product.

2 The addition product contains a C=N bond two carbons away from the carboxylate and is structurally similar to a β -keto acid. It therefore loses CO_2 , giving the enamine HETPP.

3 The enamine adds to glyceraldehyde 3-phosphate in an aldol-like reaction.

4 Cleavage of the adduct in a retro-aldol reaction gives 1-deoxy-D-xylulose 5-phosphate and regenerates TPP ylide.



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STEP 6 OF FIGURE 25.1: CONDENSATION AND CYCLIZATION 1-Deoxy-D-xylulose 5-phosphate is dephosphorylated and then condenses with 1-amino-

3-hydroxyacetone 3-phosphate in step 6 to give pyridoxine 5'-phosphate. The reaction begins with formation of an enamine, followed by loss of water to form an enol that also contains a ketone group six atoms away. The enol adds to the ketone in an intramolecular aldol reaction (Section 17-8) to form a six-membered ring, which then loses water. Tautomerization of the resultant unsaturated ketone gives an aromatic pyridine ring. Note that a loss of phosphate ion occurs at some point in the process, although the exact point at which this happens is not known. The mechanism is shown in **FIGURE 25.5**.

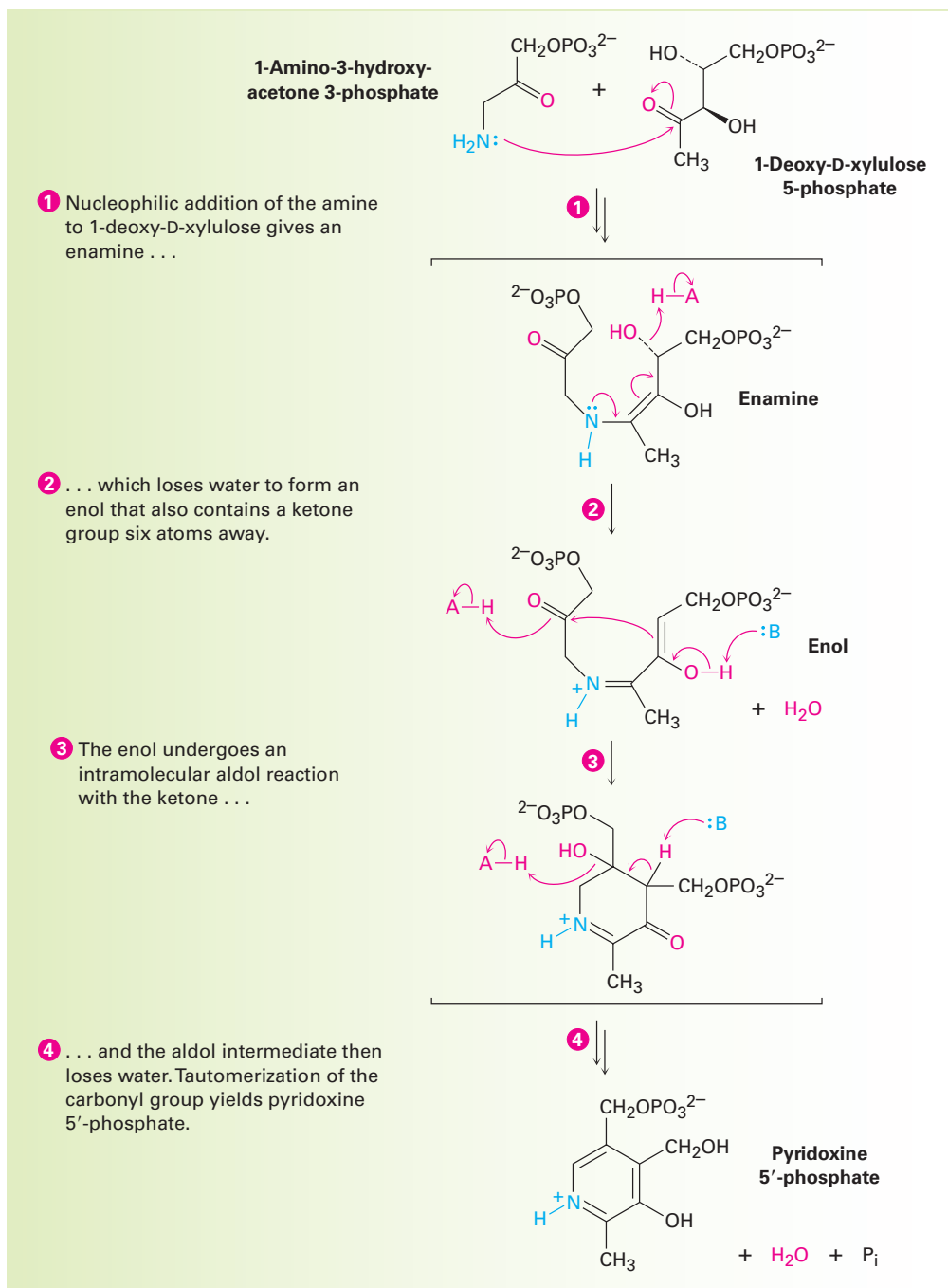
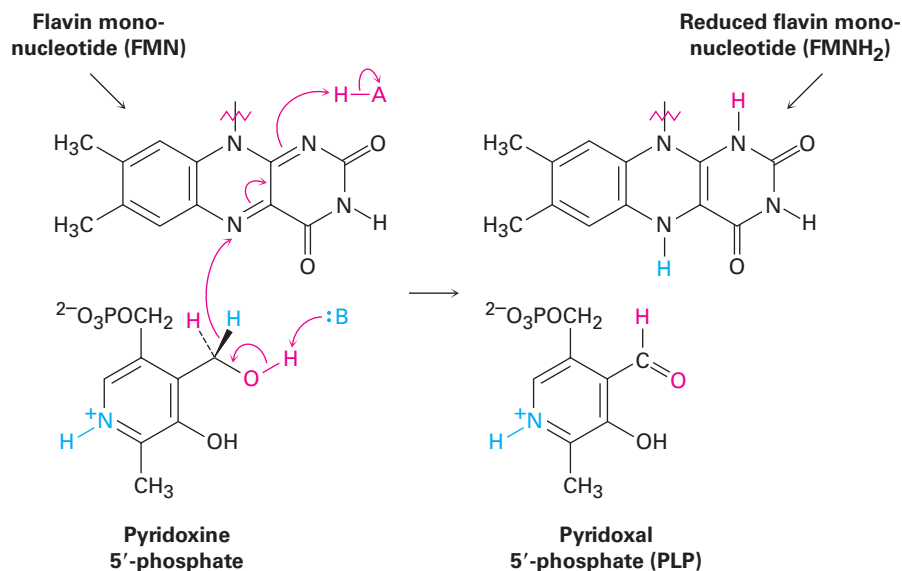


FIGURE 25.5 Mechanism of step 6 in PLP biosynthesis. The reaction of 1-amino-3-hydroxyacetone 3-phosphate with 1-deoxy-D-xylulose 5-phosphate gives pyridoxine 5'-phosphate.

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STEP 7 OF FIGURE 25.1: OXIDATION The final step in PLP biosynthesis is oxidation of the primary alcohol group in pyridoxine 5'-phosphate to the corresponding aldehyde. Typically, as we've seen on numerous occasions, alcohol oxidations are carried out by either NAD^+ or NADP^+ . In this instance, however, flavin mononucleotide (FMN) is involved as the oxidizing coenzyme and reduced flavin mononucleotide (FMNH_2) is the by-product. The details of the reaction are not clear, but evidence suggests that a hydride transfer is involved, just as in NAD^+ oxidations.



PROBLEM 25.1

In the addition of HETPP to glyceraldehyde 3-phosphate shown in Figure 25.4, does the reaction take place on the *Re* face or the *Si* face of the glyceraldehyde carbonyl group?

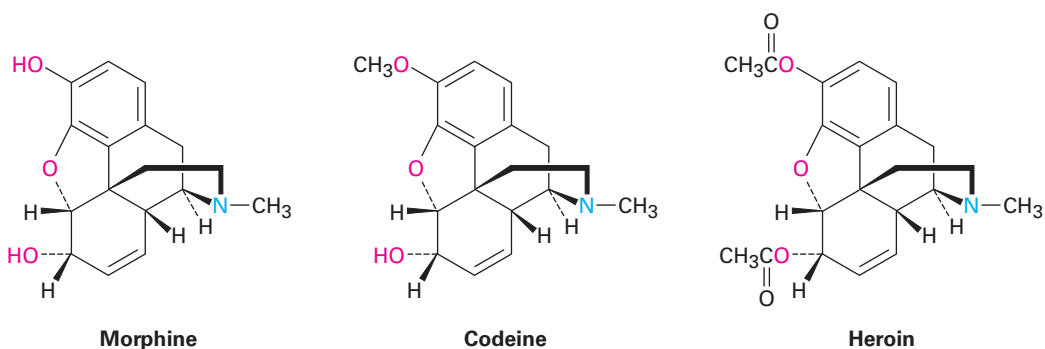
PROBLEM 25.2

Show a likely mechanism for the final tautomerization in the reaction of 1-amino-3-hydroxyacetone 3-phosphate with 1-deoxy-D-xylulose to give pyridoxine 5'-phosphate (Figure 25.5).

25-3 Biosynthesis of Morphine

Having looked at the biosynthesis of pyridoxal 5'-phosphate in the previous section, let's now go up a level in complexity by looking at morphine biosynthesis. Morphine, perhaps the oldest and best known of all alkaloids, is obtained from the opium poppy, *Papaver somniferum*, which has been cultivated for more than 6000 years. Medical uses of the poppy have been known since the early 1500s, when crude extracts, called *opium*, were used for the relief of pain. Morphine was the first pure compound to be isolated from opium, but its close relative codeine also occurs naturally. Codeine, which is

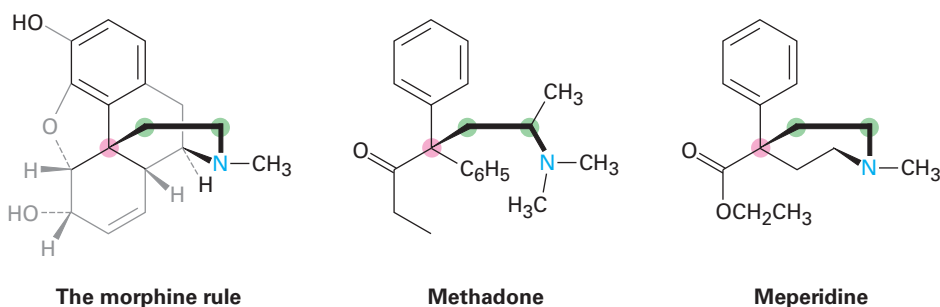
simply the methyl ether of morphine and is converted to morphine in the body, is used in prescription cough medicines and as an analgesic. Heroin, another close relative of morphine, does not occur naturally but is synthesized in the laboratory by diacetylation of morphine.



Chemical investigations into the structure of morphine occupied some of the finest chemical minds of the 19th and early 20th centuries, and it was not until 1924 that the puzzle was finally solved by Robert Robinson, who received the 1947 Nobel Prize in Chemistry for this and other work with alkaloids.

Morphine and its relatives are extremely useful pharmaceutical agents, yet they also pose an enormous social problem because of their addictive properties. Much effort has therefore gone into understanding how morphine works and into developing modified morphine analogs that retain the analgesic activity but don't cause physical dependence. Our present understanding is that morphine functions by binding to so-called mu opioid receptor sites in both the spinal cord, where it interferes with the transmission of pain signals, and brain neurons, where it changes the brain's reception of the signal.

Hundreds of morphine-like molecules have been synthesized and tested for their analgesic properties. Research has shown that not all the complex framework of morphine is necessary for biological activity. According to the "morphine rule," biological activity requires (1) an aromatic ring attached to (2) a quaternary carbon atom, followed by (3) two more carbon atoms and (4) a tertiary amine. Meperidine (Demerol), a widely used analgesic, and methadone, a substance used in the treatment of heroin addiction, are two compounds that fit the morphine rule.



An aromatic ring
attached to a quaternary carbon (●)
followed by two more carbons (●)
and a tertiary amine (N)

Morphine is biosynthesized from two molecules of the amino acid tyrosine. One tyrosine is converted into dopamine, the second is converted into *p*-hydroxyphenylacetaldehyde, and the two are coupled to give morphine. The entire pathway is a bit complex at several points, but an abbreviated scheme is given in **FIGURE 25.6**.

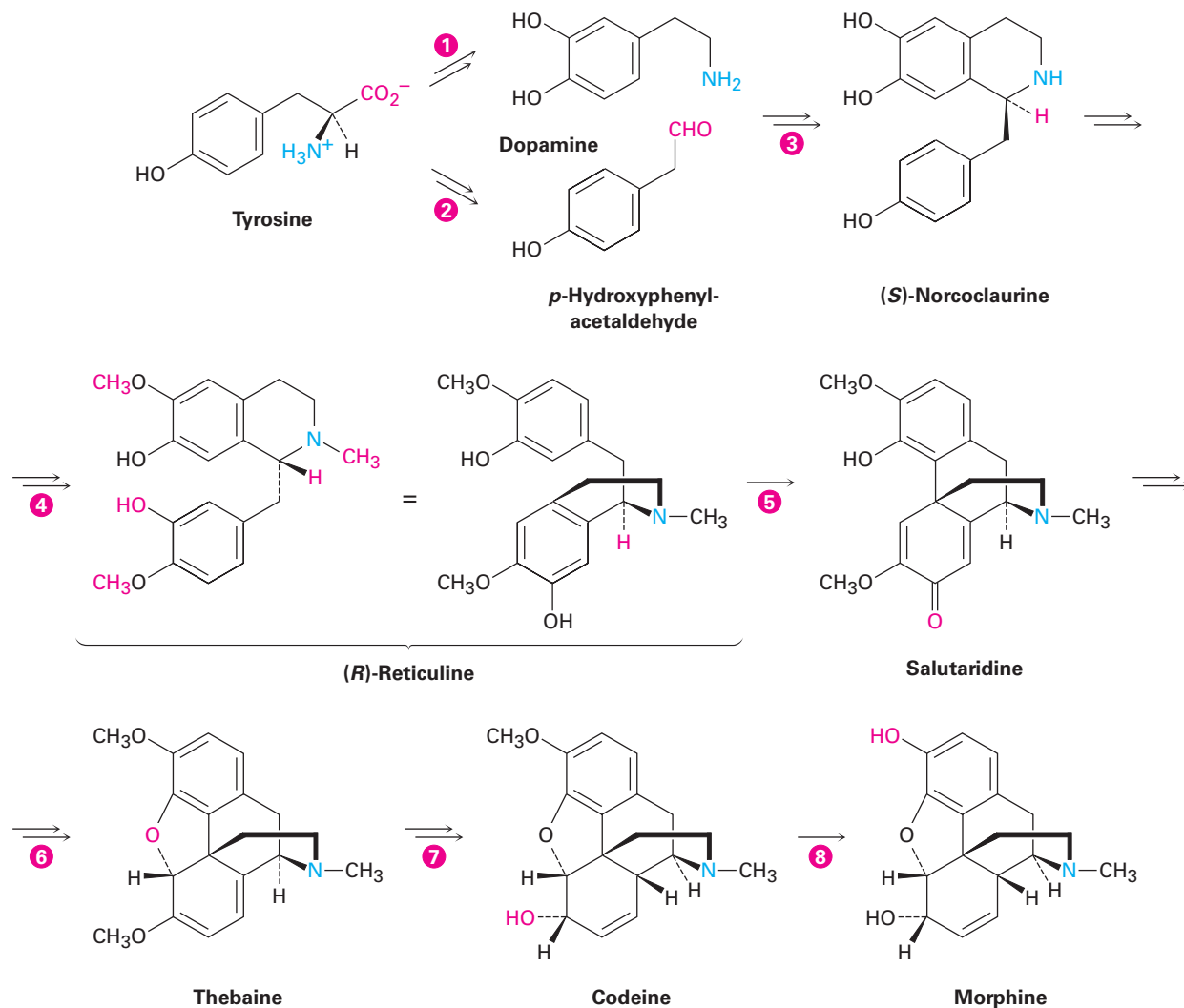
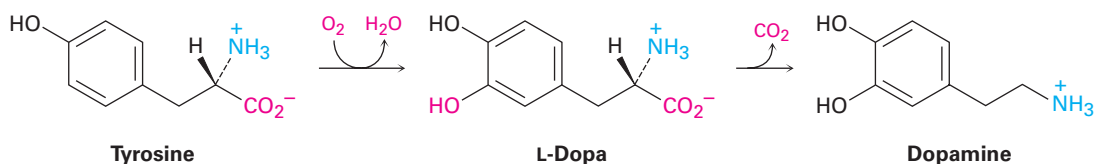


FIGURE 25.6 An abbreviated pathway for the biosynthesis of morphine from two molecules of tyrosine. Individual steps are explained in the text.

STEP 1 OF FIGURE 25.6: DOPAMINE BIOSYNTHESIS Dopamine is formed from tyrosine in two steps: an initial hydroxylation of the aromatic ring, followed by decarboxylation. The hydroxylation is catalyzed by tyrosine 3-monooxygenase, requires a cofactor called tetrahydrobiopterin, and occurs through a somewhat complex pathway that involves an iron–oxo ($\text{Fe}=\text{O}$) complex analogous to that involved in prostaglandin biosynthesis (Figure 8.11).

The decarboxylation is catalyzed by the PLP-dependent enzyme aromatic L-amino acid decarboxylase.



Recall from Section 20-2 that pyridoxal 5'-phosphate reacts with the α amino group of an α -amino acid to form an imine, or Schiff base. When L-dopa reacts with PLP, the resultant imine undergoes decarboxylation, with the pyridinium ion of PLP acting as the electron acceptor. Hydrolysis then gives dopamine and regenerated PLP. The mechanism is shown in **FIGURE 25.7**.

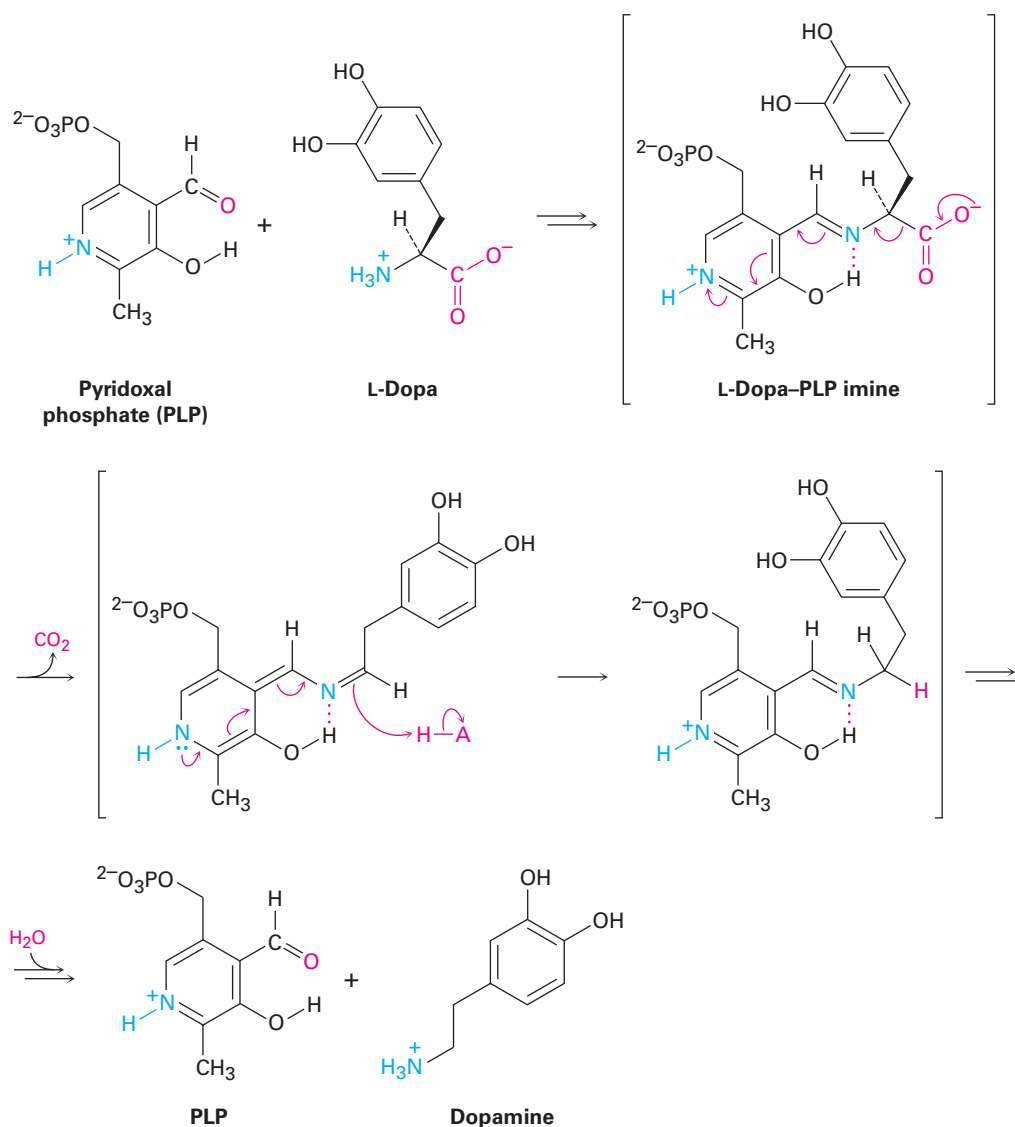


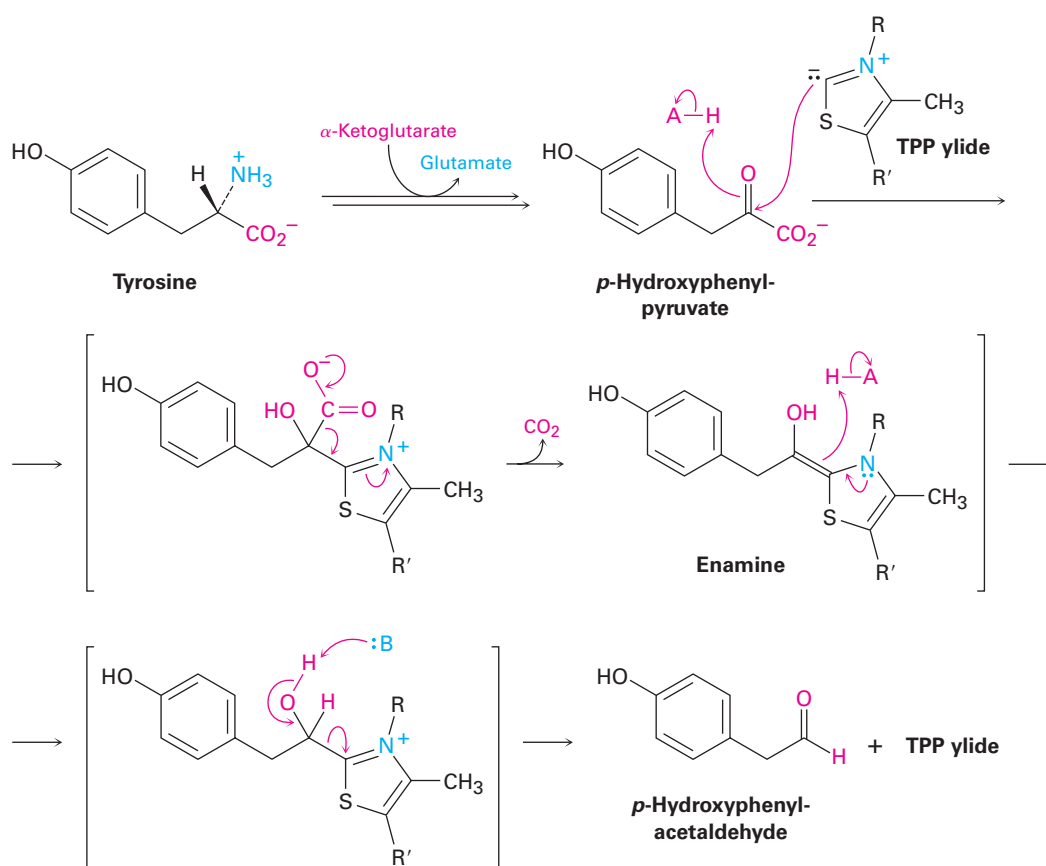
FIGURE 25.7
Mechanism of step 1 in morphine biosynthesis. The PLP-dependent decarboxylation of L-dopa gives dopamine.

STEP 2 OF FIGURE 25.6: P-HYDROXYPHENYLACETALDEHYDE BIOSYNTHESIS

p-Hydroxyphenylacetaldehyde, the second tyrosine-derived precursor of morphine, is also formed in two steps: an initial PLP-dependent transamination with α -ketoglutarate to give *p*-hydroxyphenylpyruvate, followed by decarboxylation of the α keto acid. The transamination occurs by the mechanism previously shown in Figure 20.2 on page 720. The decarboxylation requires thiamin diphosphate as coenzyme and occurs by a slight variant of the mechanism described previously in Figure 22.7 on page 784, for the formation of acetyl CoA from pyruvate.

Decarboxylation of *p*-hydroxyphenylpyruvate begins with nucleophilic addition of TPP ylide to the ketone carbonyl group, followed by loss of CO₂ to give an enamine in the usual way. But whereas the enamine formed from pyruvate decarboxylation reacts with lipoamide to give a thioester and regenerated TPP ylide, the enamine from *p*-hydroxyphenylpyruvate decarboxylation is simply protonated to give an aldehyde plus TPP ylide. The mechanism is shown in **FIGURE 25.8**.

FIGURE 25.8
Mechanism of step 2 in morphine biosynthesis. TPP-dependent decarboxylation of *p*-hydroxyphenylpyruvate gives *p*-hydroxyphenylacetaldehyde.



STEP 3 OF FIGURE 25.6: COUPLING The coupling of dopamine and *p*-hydroxyphenylacetaldehyde is catalyzed by (*S*)-norcoclaurine synthase and is relatively straightforward. The reaction proceeds through initial formation of an intermediate iminium ion, followed by intramolecular electrophilic aromatic substitution at a position *para* to one of the hydroxyl groups (**FIGURE 25.9**).

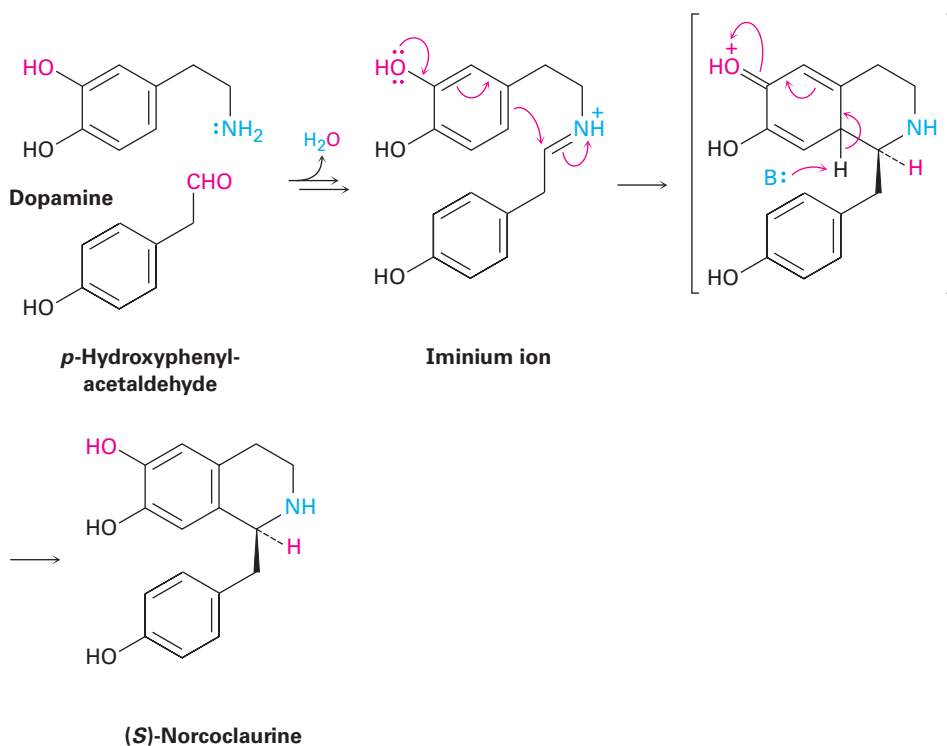


FIGURE 25.9 Mechanism of step 3 in morphine biosynthesis.

Coupling of dopamine and *p*-hydroxyphenylacetaldehyde gives (*S*)-norcoclaurine.

STEP 4 OF FIGURE 25.6: METHYLATION, HYDROXYLATION, AND EPIMERIZATION (*S*)-Norcoclaurine next undergoes two methylations and a hydroxylation to give (*S*)-3'-hydroxy-*N*-methylcoclaurine, which is methylated a third time to produce (*S*)-reticuline. Epimerization of (*S*)-reticuline then yields (*R*)-reticuline (FIGURE 25.10).

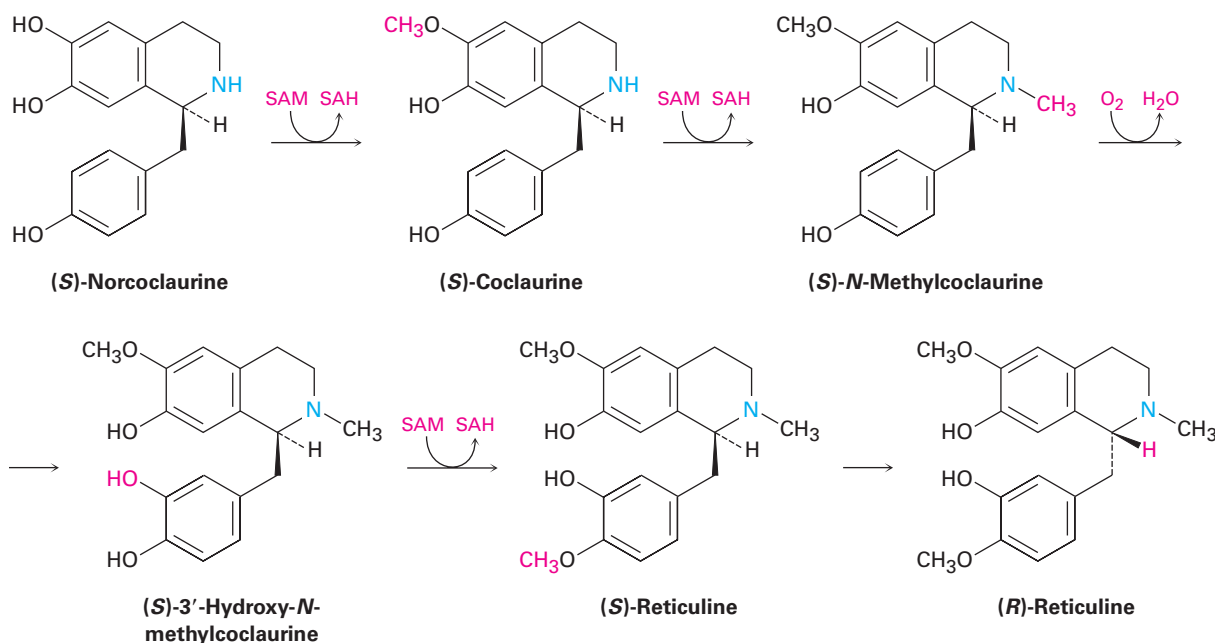
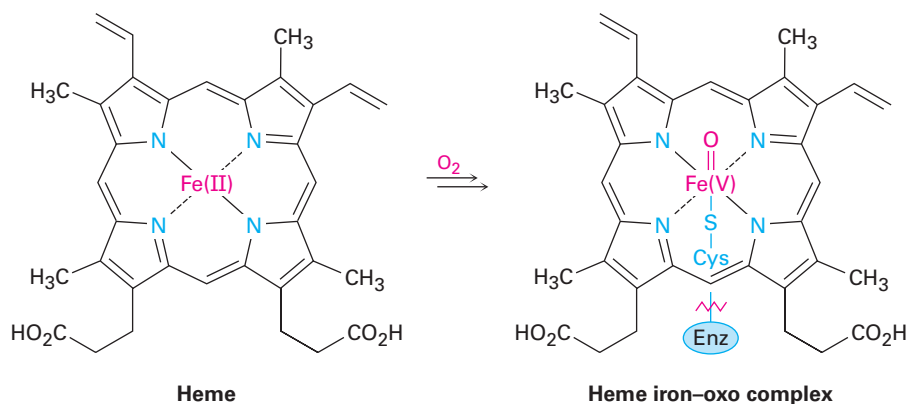


FIGURE 25.10 An overview of the reactions in step 4 of morphine biosynthesis.

(*S*)-Norcoclaurine is converted to (*R*)-reticuline.

Both initial methylations use *S*-adenosylmethionine (SAM) as the methyl donor, as discussed in Section 12-11. *S*-Adenosylhomocysteine (SAH) is the by-product in each case, and the reactions occur by the usual S_N2 substitution pathway. The first methylation occurs on a phenol oxygen, and the second takes place on the amine nitrogen.

The hydroxylation of (*S*)-*N*-methylcoclaurine to give (*S*)-3'-hydroxy-*N*-methylcoclaurine is superficially similar to the hydroxylation of tyrosine in step 1 in that both involve an iron–oxo complex as the active hydroxylating agent. Unlike the enzyme in the tyrosine hydroxylation, however, that responsible for hydroxylation of *N*-methylcoclaurine is a so-called cytochrome P450 enzyme. These enzymes, of which more than 500 are known, contain an iron–heme cofactor ligated to the sulfur atom of a cysteine residue in the enzyme. The details of the hydroxylation itself are not clear, although it may well occur through a straightforward electrophilic aromatic substitution mechanism.



Methylation of a phenolic –OH group in (*S*)-3'-hydroxy-*N*-methylcoclaurine by SAM gives (*S*)-reticuline through the usual S_N2 pathway, and epimerization of the chirality center forms (*R*)-reticuline. The epimerization is a two-step process, the first an oxidation of the tertiary amine to an intermediate iminium ion, and the second a hydride reduction of the iminium ion. The mechanism of the oxidation step is not yet known, but the reduction of the iminium ion requires NADPH as cofactor (FIGURE 25.11).

Why does morphine biosynthesis proceed through initial formation of (*S*)-reticuline as an intermediate, followed by epimerization, rather than through (*R*)-reticuline directly? There is no obvious answer other than to say that many metabolic pathways contain such small inefficiencies, probably as a result of the evolutionary development of the responsible enzymes—what some people have called “unintelligent design.”

STEP 5 OF FIGURE 25.6: OXIDATIVE COUPLING (*R*)-Reticuline is converted into salutaridine in step 5 by an oxidative coupling between the ortho position of one phenol ring and the para position of the other. The reaction is catalyzed by another cytochrome P450 enzyme like that involved in the hydroxylation of (*S*)-*N*-methylcoclaurine in step 4. Formation of the phenoxide ions and abstraction of a nonbonding electron from each oxygen atom to give radicals occurs, followed by radical coupling and a keto–enol tautomerization to yield salutaridine (FIGURE 25.12).

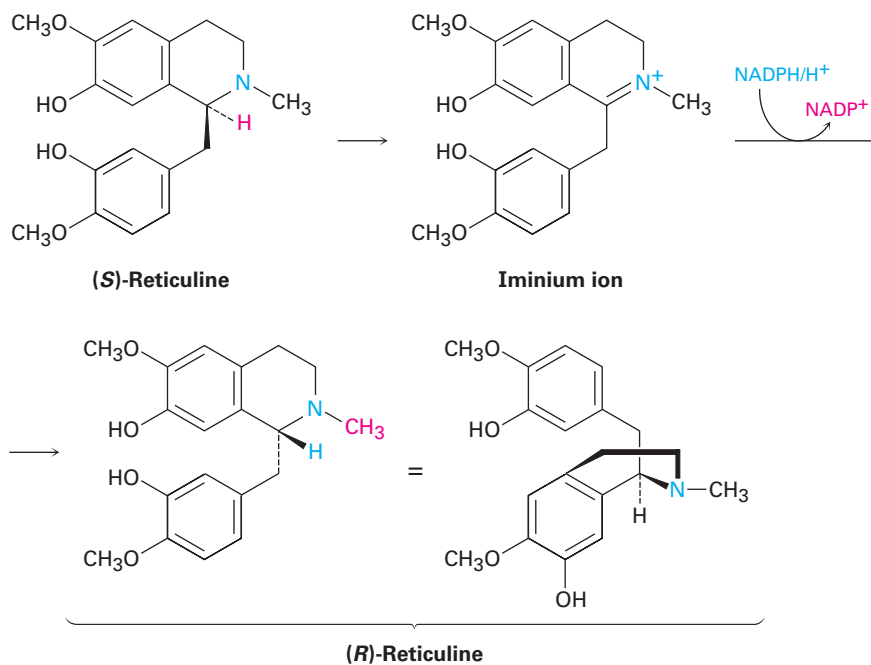


FIGURE 25.11 Mechanism of the epimerization of (S)-reticuline to (R)-reticuline in step 4 of morphine biosynthesis.

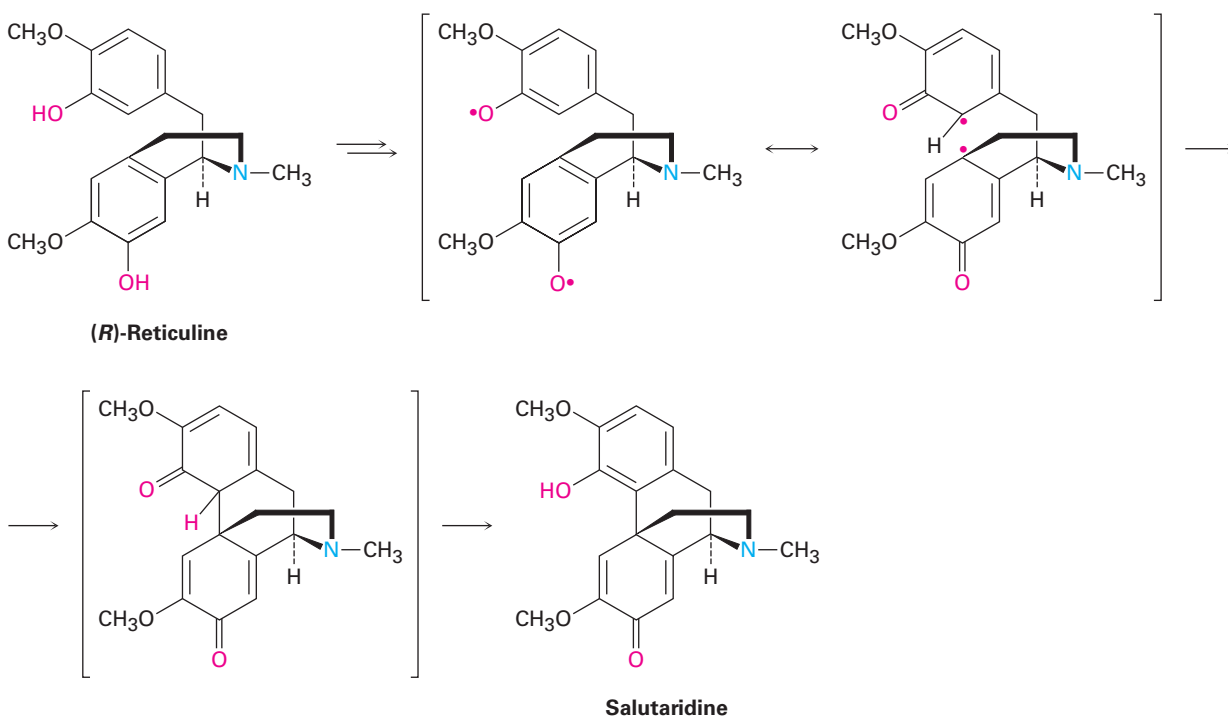


FIGURE 25.12 Mechanism of step 5 in morphine biosynthesis. Oxidative phenol coupling of (R)-reticuline gives salutaridin.

STEP 6 OF FIGURE 25.6: REDUCTION AND CYCLIZATION Reduction of salutaridine to salutaridinol is catalyzed by salutaridine reductase, with NADPH as cofactor. This alcohol then undergoes a nucleophilic acyl substitution reaction with acetyl CoA to give a doubly allylic acetate, which spontaneously eliminates acetate ion in an S_N1 -like process and cyclizes to thebaine (FIGURE 25.13).

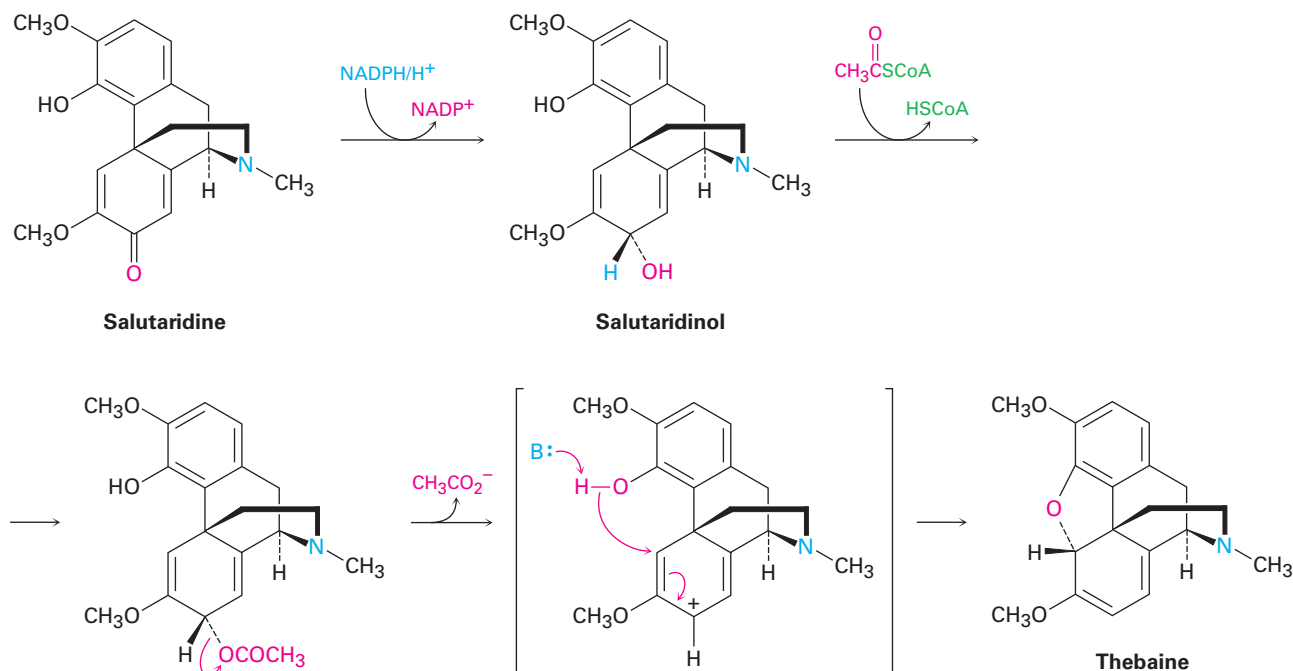


FIGURE 25.13 Mechanism of step 6 in morphine biosynthesis. Thebaine is formed from salutaridine.

STEPS 7–8 OF FIGURE 25.6: DEMETHYLATION AND REDUCTION The remaining steps in the biosynthesis of morphine involve two demethylation reactions and a reduction. The first demethylation is catalyzed by a cytochrome P450 enzyme, which hydroxylates the $-OCH_3$ group of thebaine to form $-OCH_2OH$, a hemiacetal. Loss of formaldehyde then gives an enol that tautomerizes to codeinone. Reduction of the resultant ketone by NADPH yields codeine, and demethylation by a P450 enzyme produces morphine (FIGURE 25.14).

PROBLEM 25.3

Show the mechanism of the reaction of (*S*)-norcoclaurine with *S*-adenosylmethionine to give (*S*)-coclaurine (Figure 25.10).

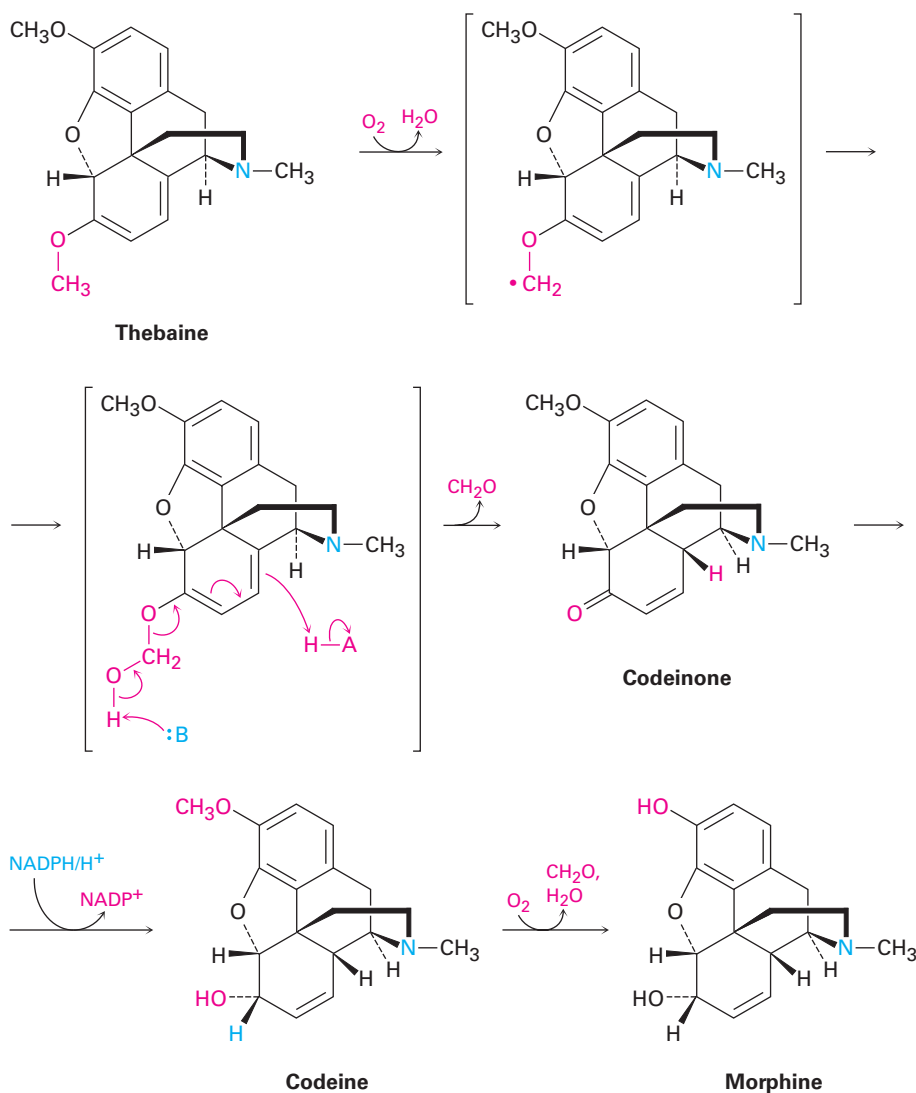
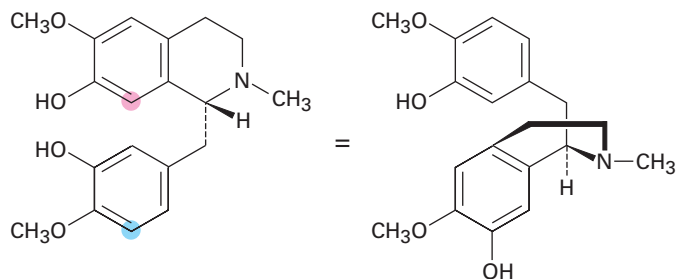


FIGURE 25.14 Mechanism of step 7 in morphine biosynthesis. Demethylation of thebaine to give codeinone is catalyzed by a P450 enzyme. Reduction of codeinone with NADPH then yields codeine, and a final demethylation produces morphine.

PROBLEM 25.4

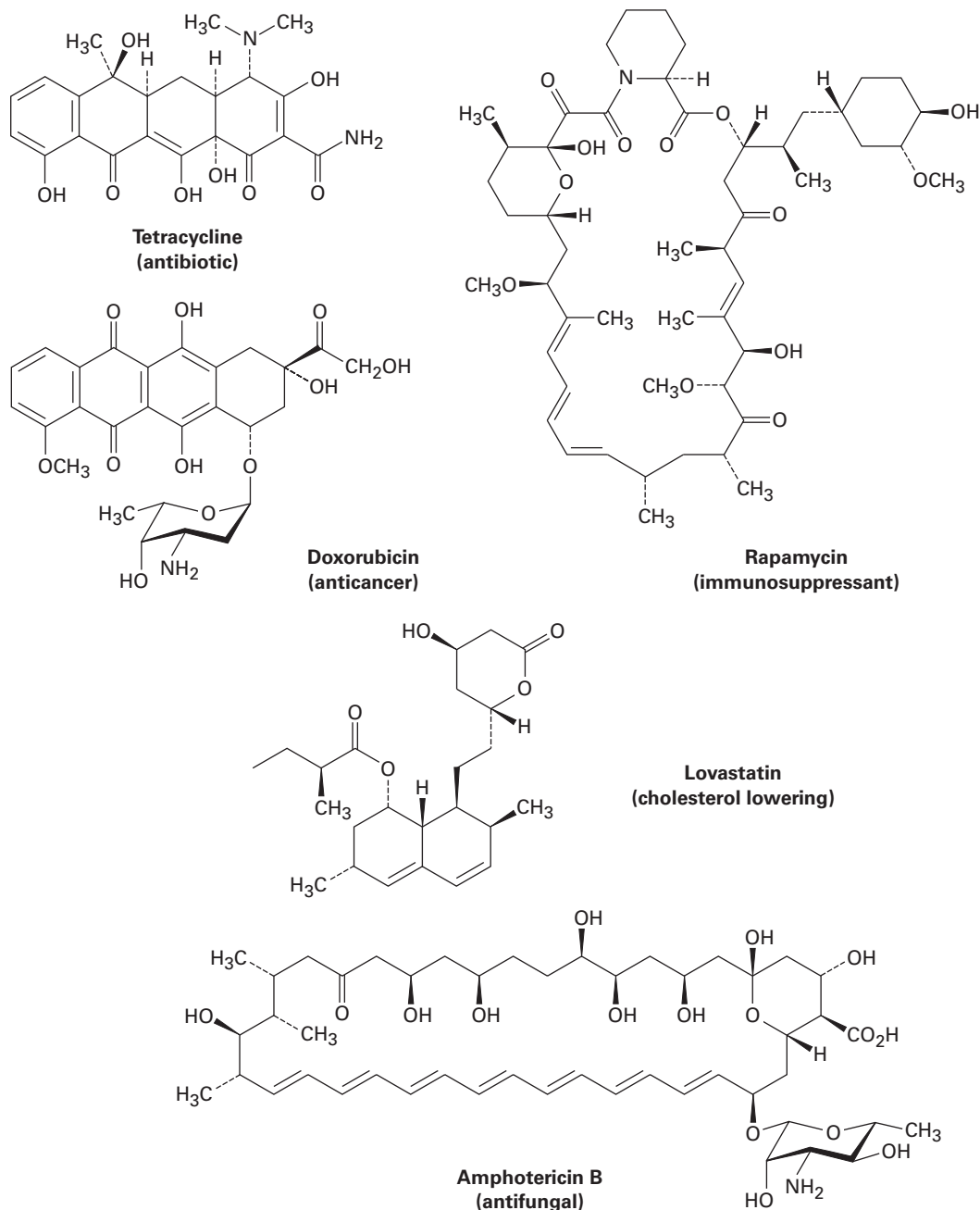
Convince yourself that the following two structures both represent (*R*)-reticuline. Which carbon atoms in the structure on the right correspond to the two carbons indicated in the structure on the left?



25-4 Biosynthesis of Erythromycin

Having discussed the biosynthesis of pyridoxal phosphate and morphine in the preceding two sections, we'll end this chapter on natural-products chemistry by going up yet one more level in complexity and looking at polyketide biosynthesis. Unlike what happens in many metabolic pathways, where each separate step is catalyzed by a separate, relatively small enzyme, erythromycin

FIGURE 25.15
Structures of some polyketides used as pharmaceutical agents.



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and other polyketides are assembled by a single massive synthase. The synthase contains many enzyme domains linked together, with each domain catalyzing a specific biosynthetic step in sequence.

Polyketides are an extraordinarily valuable class of natural products, numbering over 10,000 compounds. Commercially important polyketides include antibiotics (erythromycin A, tetracycline) and immunosuppressants (rapamycin), as well as anticancer (doxorubicin), antifungal (amphotericin B), and cholesterol-lowering (lovastatin) agents (FIGURE 25.15). It has been estimated that the sales of these and other polyketide pharmaceuticals total more than \$15 billion per year.

Polyketides are biosynthesized by the joining together of the simple acyl CoA's acetyl CoA, propionyl CoA, methylmalonyl CoA, and (less frequently) butyryl CoA. The key carbon-carbon bond-forming step in each joining is a Claisen condensation (Section 17-9). Once the carbon chain is assembled and released from the enzyme, further transformations take place to give the final product. Erythromycin A, for instance, is prepared from one propionate and six methylmalonate units by the pathway outlined in FIGURE 25.16. Following initial assembly of the acyl units into the macrocyclic lactone 6-deoxyerythronolide B, two hydroxylations, two glycosylations, and a final methylation complete the biosynthesis.

The initial assembly of seven acyl CoA precursors to build a polyketide carbon chain is carried out by a multienzyme complex called a *polyketide synthase*, or PKS. The 6-deoxyerythronolide B synthase (DEBS) is a massive structure of greater than 2 million molecular weight and containing more than 20,000 amino acids. Furthermore, it is a *homodimer*, meaning that it consists of two identical protein chains held together by noncovalent interactions, with each chain containing all the enzymes necessary for constructing the polyketide.

Each separate enzyme domain in the erythromycin synthase is a folded, globular region within a huge protein chain that catalyzes a specific biosynthetic step. The domains are grouped into modules, where each module carries out the sequential addition and processing of an acyl CoA to the growing polyketide. In addition, adjacent modules form three larger groups (DEBS 1, DEBS 2, and DEBS 3) that are linked by peptide spacers. As shown in FIGURE 25.17, the erythromycin PKS consists of an initial *loading module* to attach the first acyl group, six *extension modules* to add six further acyl groups, and an *ending module* to cleave the thioester bond and release the polyketide. The ending module also catalyzes cyclization to give a macrocyclic lactone.

The loading module has two domains: an acyl transfer (AT) domain and an acyl carrier protein (ACP) domain. The AT selects the first acyl CoA (propionyl CoA in the case of erythromycin) and transfers it to the adjacent ACP, which binds it through a thioester linkage and holds it for further reaction. Each extension module has a minimum of three domains: an AT, an ACP, and a ketosynthase (KS), which catalyzes the Claisen condensation reaction that builds the polyketide chain. In addition to the three minimum domains, some extension modules also contain a ketoreductase (KR) to reduce a ketone carbonyl group and produce an alcohol, a dehydratase (DH) to dehydrate the alcohol and produce a C=C bond, and an enoyl reductase (ER) to reduce the C=C bond. Finally, the ending domain is a thioesterase (TE), which releases the product by catalyzing a lactonization.

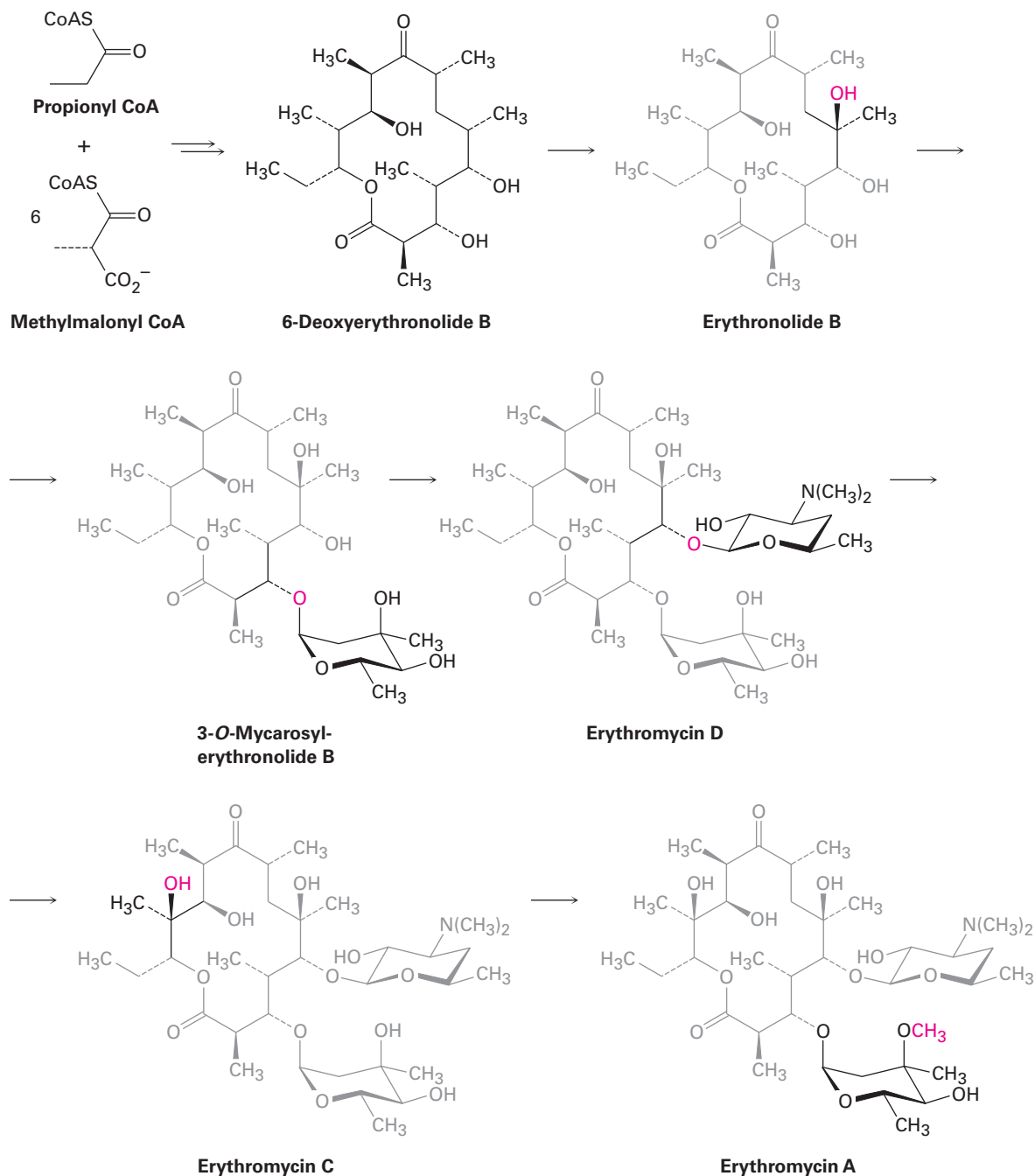


FIGURE 25.16 An outline of the pathway for the biosynthesis of erythromycin A. One propionate and six methylmalonate units are first assembled into the macrocyclic lactone 6-deoxyerythronolide B, which is then hydroxylated, glycosylated by two different sugars, hydroxylated again, and finally methylated.

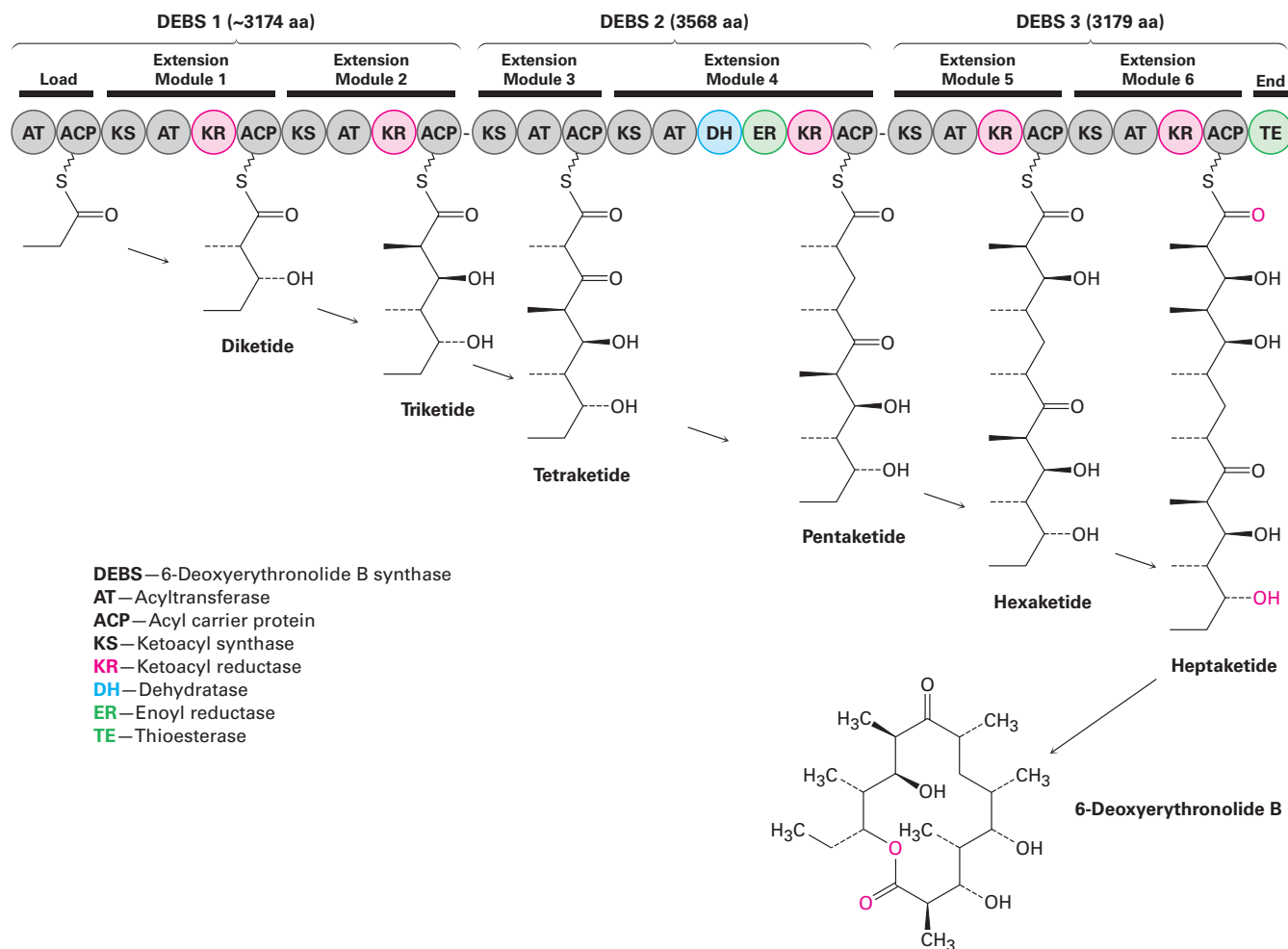


FIGURE 25.17 A schematic view of the 6-deoxyerythronolide B synthase (DEBS). Locations of the enzyme domains within the loading module and the six extension modules are shown. The figure is explained in detail in the text.

Polyketide chain extension occurs when an extension module AT selects a new acyl CoA, transfers it to the ACP, and the KS then catalyzes a Claisen condensation reaction between the newly bonded acyl group and the acyl group of the previous module. **FIGURE 25.18** shows the steps occurring in the first extension cycle; other extension cycles take place similarly.

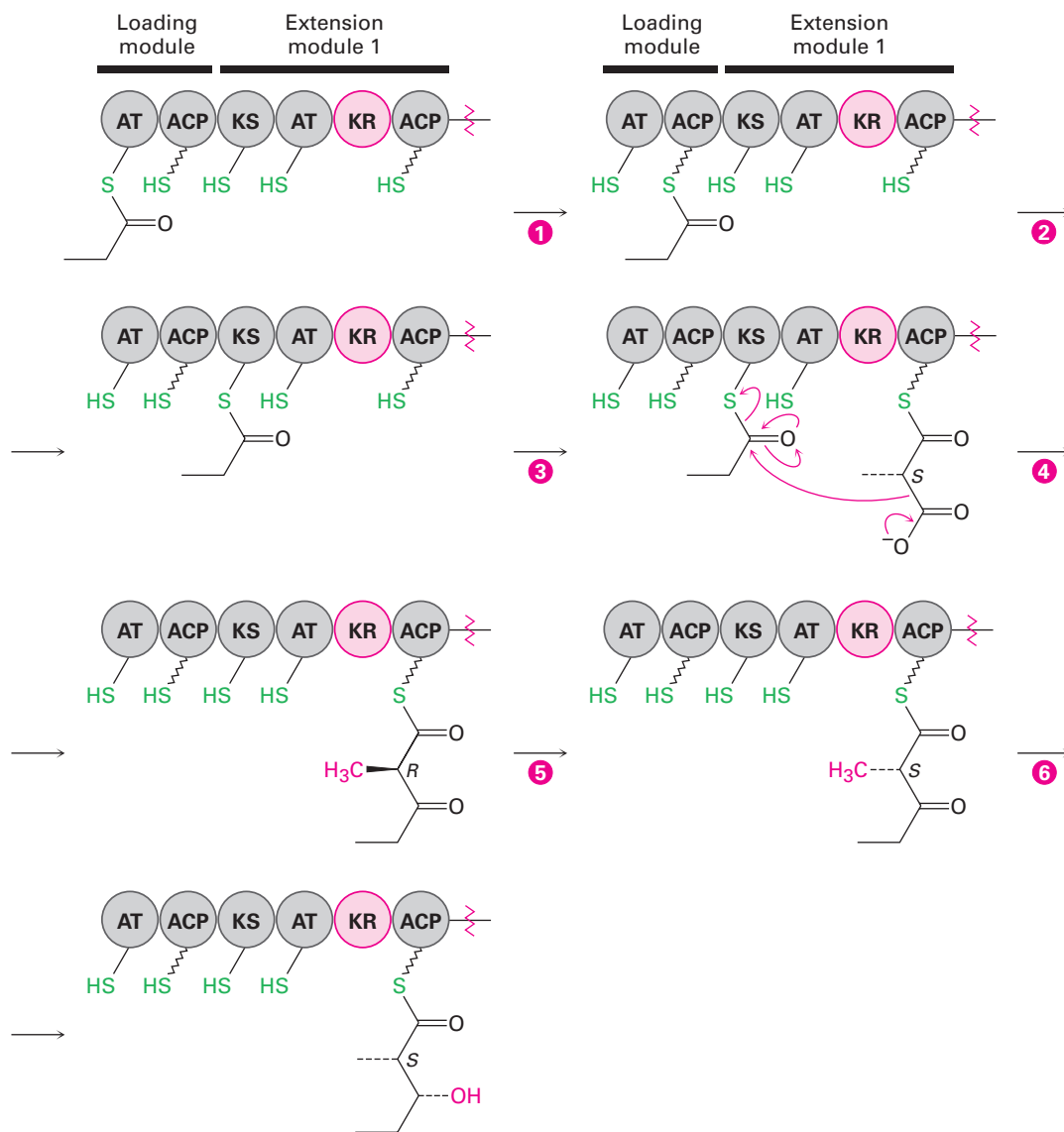


FIGURE 25.18 The initial loading and first chain-extension cycle catalyzed by the erythromycin PKS. Individual steps are explained in the text.

STEP 1 OF FIGURE 25.18: LOADING The loading AT domain begins the erythromycin biosynthesis by binding a propionyl CoA through a thioester bond to the -SH of a cysteine residue. The AT then transfers the propionyl group to the adjacent ACP. Each ACP in the synthase contains a phosphopantetheine bonded to the hydroxyl of a serine residue, and bonding of the acyl group to the enzyme occurs by thioester formation with the phosphopantetheine -SH (**FIGURE 25.19**). The phosphopantetheine effectively acts as a long, flexible arm to allow movement of the acyl group from one catalytic domain to another.

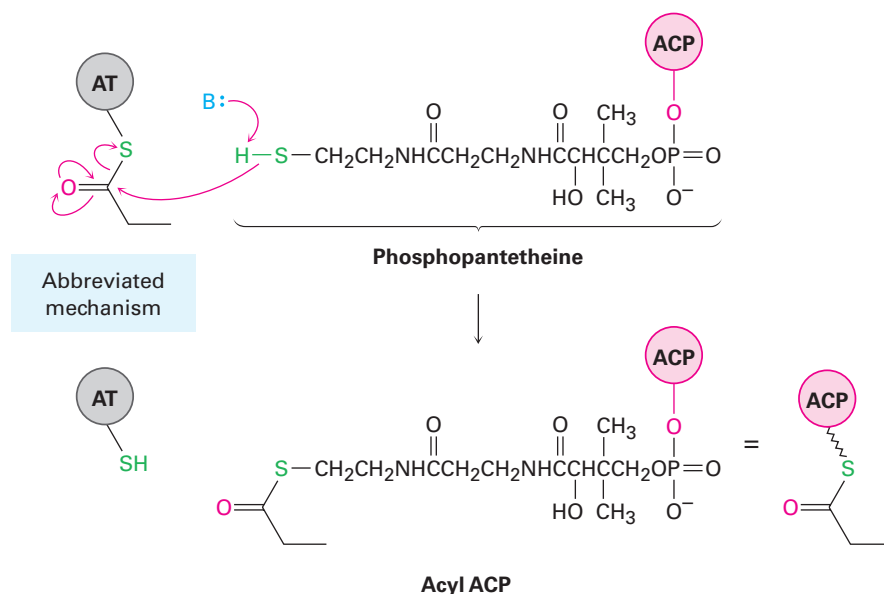
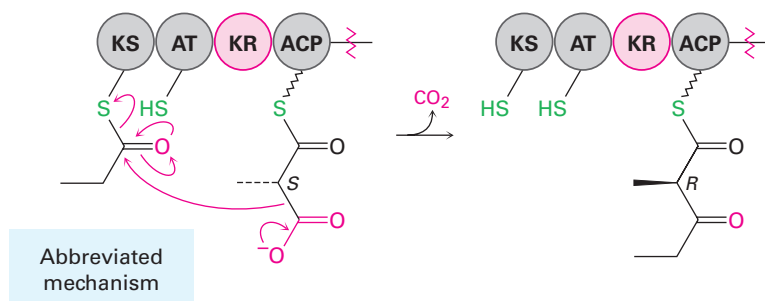


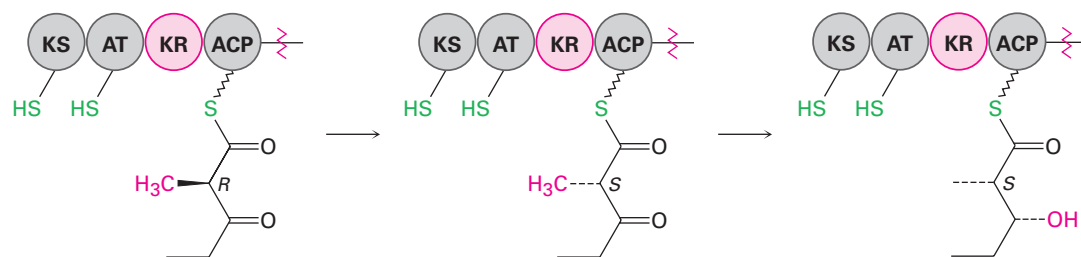
FIGURE 25.19 Formation of an acyl ACP during polyketide biosynthesis. Phosphopantetheine, symbolized by a zigzag line between S and ACP, acts as a long, flexible arm to allow the acyl group to move from one catalytic domain to another.

STEPS 2–4 OF FIGURE 25.18: CHAIN EXTENSION Polyketide chain extension begins (step 2) when the acyl ACP of the loading module transfers the propionyl group to the ketosynthase of module 1 (KS1), again forming a thioester bond to a cysteine residue. At the same time (step 3), the AT and ACP of module 1 load a (2*S*)-methylmalonyl CoA onto the thiol terminus of the ACP1 phosphopantetheine. The key carbon–carbon bond formation occurs in step 4 when KS1 catalyzes a Claisen condensation and decarboxylation to form an enzyme-bound β -keto thioester. It's likely that the decarboxylation occurs simultaneously with the Claisen condensation, giving the enolate ion necessary for nucleophilic addition to the second thioester.



STEPS 5–6 OF FIGURE 25.18: EPIMERIZATION AND REDUCTION Interestingly, the Claisen condensation occurs with inversion of configuration at the methyl-bearing chirality center so that the initially formed diketide has (*R*) stereochemistry. Base catalyzed epimerization of the (*R*) product, an acidic β -diketone, occurs in step 5, however, so the product that goes on to the next step regains the (*S*) configuration. Finally, KR1 reduces the ketone to a β -hydroxy thioester in step 6 by transfer of the *pro-S* hydrogen from NADPH

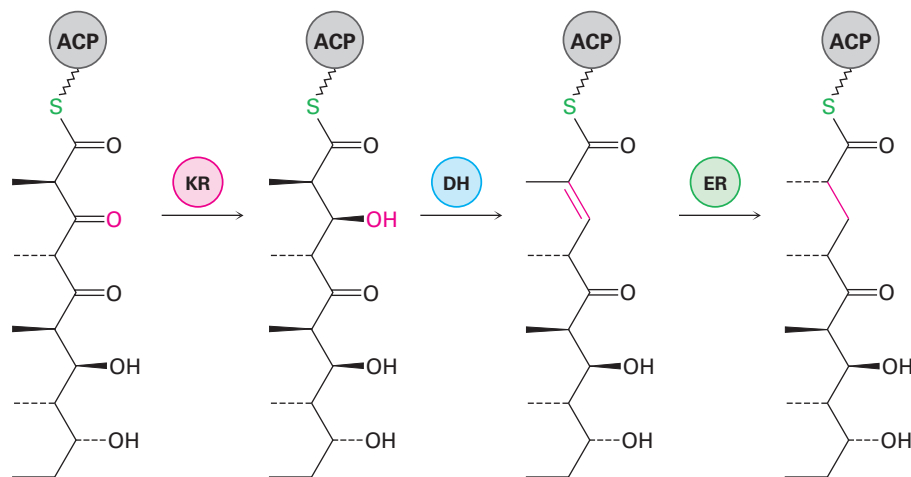
as cofactor. Module 1 is now finished, so the diketide is transferred to KS2 for another chain extension.



The reactions catalyzed by extension modules 2, 5, and 6 are similar to those of module 1, although the stereochemistries of the Claisen condensation and reduction steps may differ. The reactions in modules 3 and 4, however, are different. Module 3 lacks a KR domain, so no reduction occurs and the tetraketide product contains a ketone carbonyl group (Figure 25.17). Module 4 contains a KR and two additional enzyme domains, so it catalyzes a ketone reduction plus two additional reactions. Following the reduction by KR4 of the pentaketide, a dehydratase (DH) dehydrates the pentaketide alcohol to an α,β -unsaturated thioester and the double bond is then reduced by an enoyl reductase (ER) domain (FIGURE 25.20).

Note that the complete sequence of reactions carried out by module 4—Claisen condensation, ketone reduction, dehydration, and double-bond reduction—is identical to the series of reactions found in fatty-acid biosynthesis (Figure 23.6; page 822). In fact, all fatty-acid synthases have the same set of AT, ACP, KS, KR, DH, and ER domains as the polyketide synthases.

FIGURE 25.20 Additional processing of the pentaketide intermediate in module 4. A carbonyl group is removed by a reduction–dehydration–reduction sequence.



A pentaketide

Release of 6-deoxyerythronolide B from the PKS is catalyzed by the ending thioesterase module. A serine residue on the TE module first carries out a nucleophilic acyl substitution on the ACP-bound heptaketide, and the acyl enzyme that results undergoes lactonization. A histidine residue in the TE acts as base to catalyze nucleophilic acyl substitution of the serine ester by the terminal $-\text{OH}$ group in the heptaketide (FIGURE 25.21).

Following its release from the PKS, 6-deoxyerythronolide B is hydroxylated at C6 with retention of configuration to give erythronolide B. The reaction

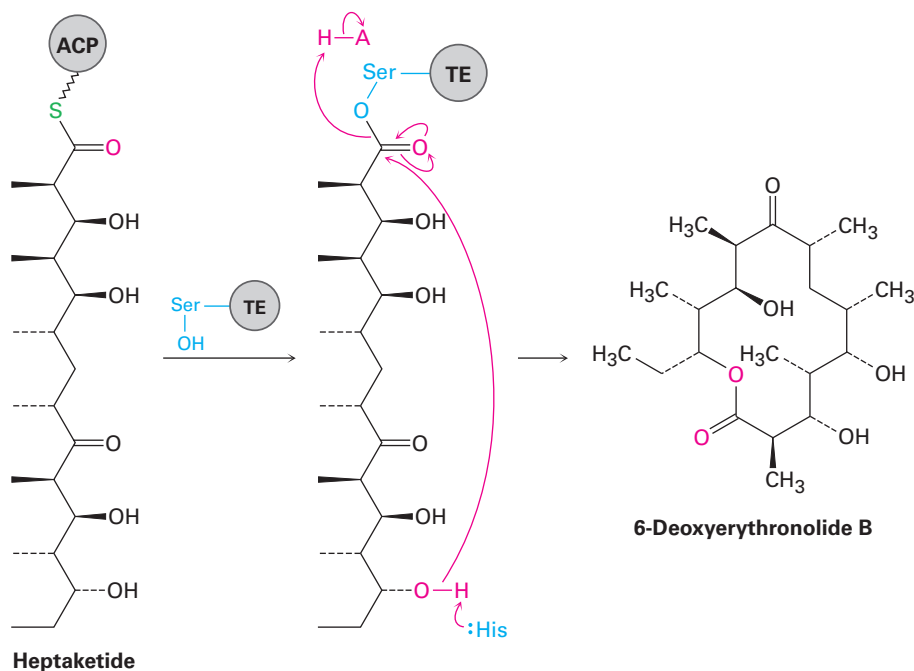


FIGURE 25.21 Release of **6-deoxyerythronolide** from the **PKS**. The reaction occurs by lactonization of an acyl enzyme, formed by reaction of a serine residue in the TE module with the heptaketide.

is catalyzed by a P450 hydroxylase analogous to that involved in morphine biosynthesis (Section 25-3, Figure 25.14). L-Mycarose is then attached to the C3 hydroxyl group by reaction with thymidyl diphosphomycarose through an S_N1 -like process that proceeds by initial formation of the mycarosyl carbocation (**FIGURE 25.22**).

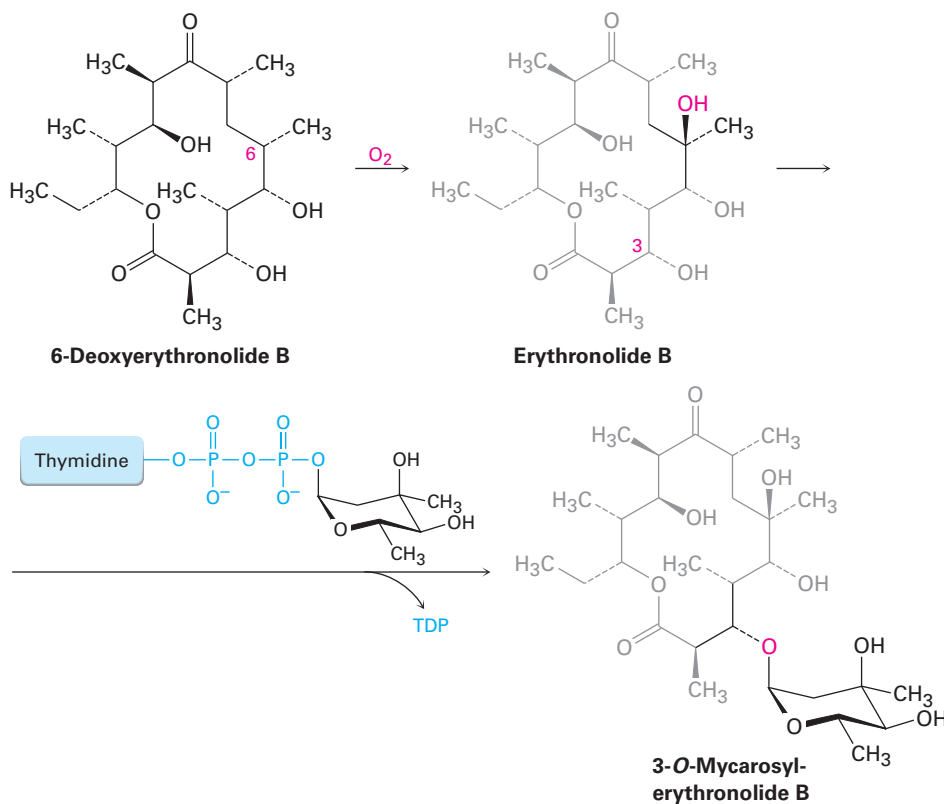


FIGURE 25.22 Hydroxylation and glycosylation of **6-deoxyerythronolide B** to give **3-O-mycarosylerythronolide B**.

The final steps in erythromycin A biosynthesis are a further glycosylation, a further hydroxylation, and a methylation (FIGURE 25.23). As in the attachment of mycarose, the attachment of the amino sugar D-desosamine also takes place by transfer from a thymidyl diphosphosugar. C12 hydroxylation by another P450 enzyme occurs with retention of configuration to give erythromycin C, and methylation of the C3' hydroxyl group of the mycarose unit by reaction with *S*-adenosylmethionine gives erythromycin A.

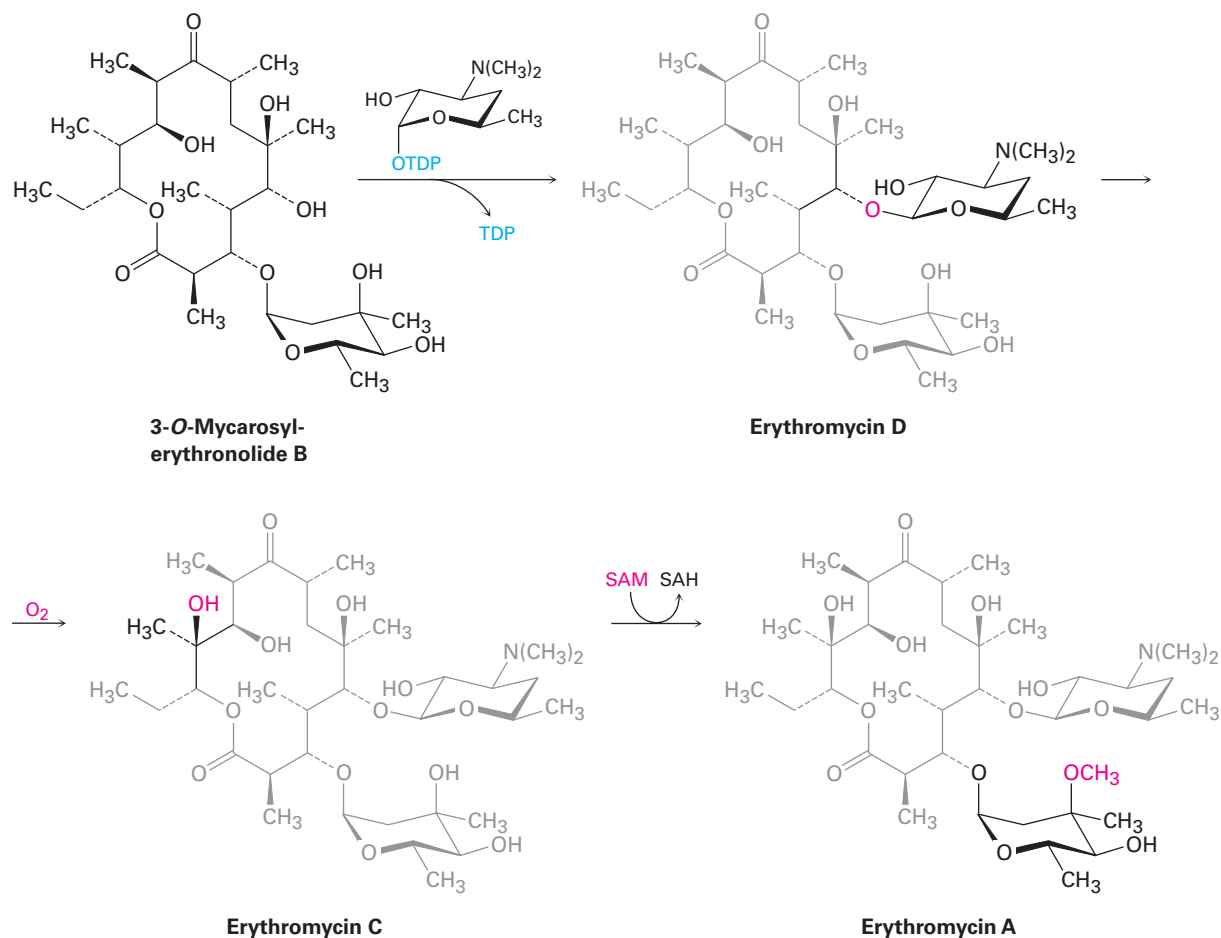
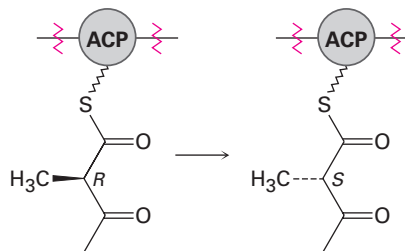


FIGURE 25.23 Final steps in the biosynthesis of erythromycin A.

PROBLEM 25.5

Show a likely mechanism for the epimerization that occurs in step 5 of Figure 25.18.



PROBLEM 25.6

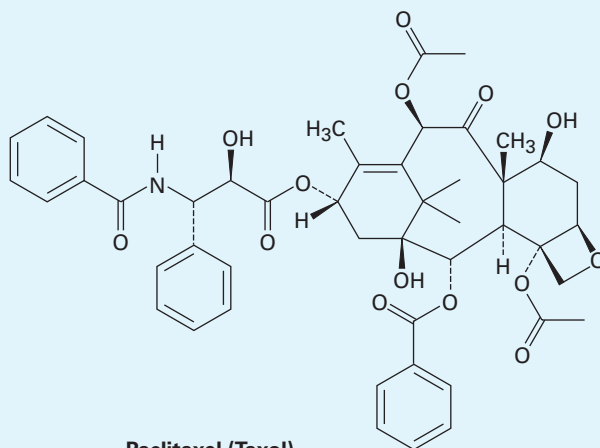
Propose a mechanism for the reaction of erythronolide B with thymidyl diphosphomycarose to give 3-*O*-mycarosylerythronolide B (Figure 25.22).

SOMETHING EXTRA

Bioprospecting: Hunting for Natural Products

Most chemists and biologists spend the majority of their time in the laboratory. A few, however, spend their days scuba diving on South Pacific islands or trekking through the rainforests of South America and Southeast Asia. They aren't on vacation, though; they're at work as bioprospectors, and their job is to hunt for new and unusual natural products that might be useful as drugs.

As noted in the Chapter 6 *Something Extra*, more than half of all new drug candidates come either directly or indirectly from natural products. All four natural products shown in the introduction to this chapter, for instance, are used as drugs: morphine from the opium poppy, prostaglandin E₁ from sheep prostate glands, erythromycin A from a *Streptomyces erythreus*



Corbis

Rapamycin, an immunosuppressant natural product used during organ transplants, was originally isolated from a soil sample found on Easter Island, or Rapa Nui, an island 2200 miles off the coast of Chile known for its giant Moai statues.

bacterium cultured from a Philippine soil sample, and benzylpenicillin from *Penicillium notatum*. Still other examples include rapamycin (Figure 25.15), an immunosuppressant isolated from a *Streptomyces hygrosopicus* bacterium first found in a soil sample from Easter Island (Rapa Nui), and paclitaxel (Taxol), an anticancer drug isolated from the bark of the Pacific yew tree found in the American Northwest.

With less than 1% of living organisms yet investigated, bioprospectors have a lot of work to do. But there is a race going on. Rainforests throughout the world are being destroyed at an alarming rate, causing many species of both plants and animals to become extinct before they can even be examined. Fortunately, the governments in many countries seem aware of the problem, but there is as yet no international treaty on biodiversity that could help preserve vanishing species.

KEY WORDS

fatty-acid derived substance,
879

natural product, 877

nonribosomal polypeptide,
879

polyketide, 879

secondary metabolite, 877

SUMMARY

In this brief chapter, we've just tickled the surface of natural-products chemistry, looking at the pathways by which several well-known natural products are synthesized in living organisms.

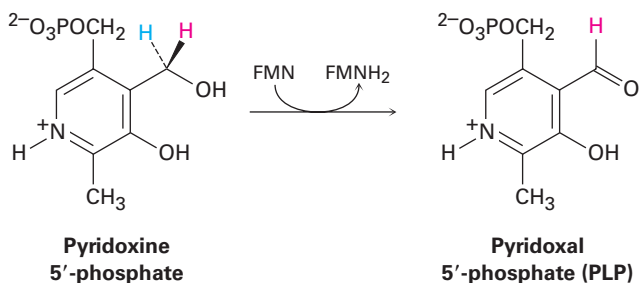
The term **natural product** is generally taken to mean a **secondary metabolite**—a small molecule that is not essential to the growth and development of the producing organism and is not classified by structure. Well over 300,000 secondary metabolites probably exist, generally classified into five categories: **terpenoids** and **steroids**, **fatty acid-derived substances** and **polyketides**, **alkaloids**, **nonribosomal polypeptides**, and **enzyme cofactors**.

Unraveling the biosynthetic pathways by which natural products are made is difficult and time-consuming work, but the payoff is a fundamental understanding of how organisms function at the molecular level. The molecules are sometimes complex, but the individual chemical steps by which they are made are familiar.

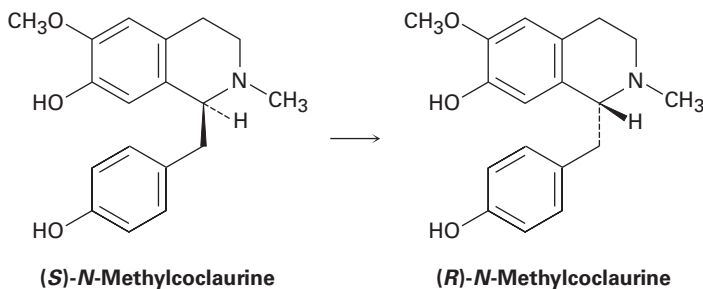
EXERCISES

(Problems 25.1–25.6 appear within the chapter.)

- 25.7 Which hydrogen, *pro-R* or *pro-S* is removed from pyridoxine 5'-phosphate in the final step of PLP biosynthesis?

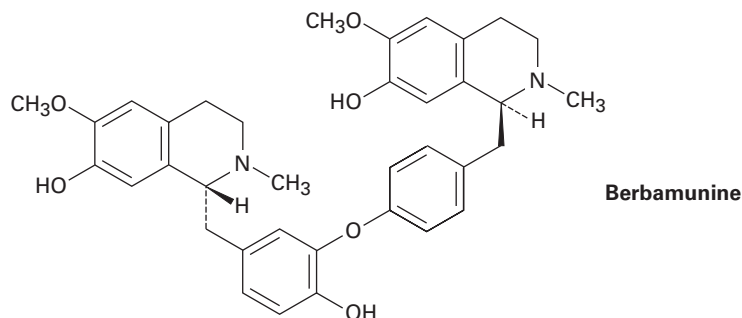


- 25.8 Does the ketone reduction step catalyzed by KR1 in erythromycin biosynthesis occur on the *Re* or the *Si* face of the substrate carbonyl group? (See Figure 25.18.)
- 25.9 When the enoyl reductase domain (ER4) in the erythromycin PKS is deactivated by gene mutation, all further steps still occur normally. What is the structure of the lactone that results?
- 25.10 One of the steps in the biosynthesis of the alkaloid berbaminine is an epimerization of (*S*)-*N*-methylcoclaurine. Review the morphine biosynthesis in Figure 25.6, and propose a mechanism for the epimerization.

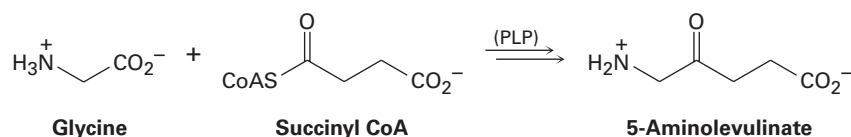


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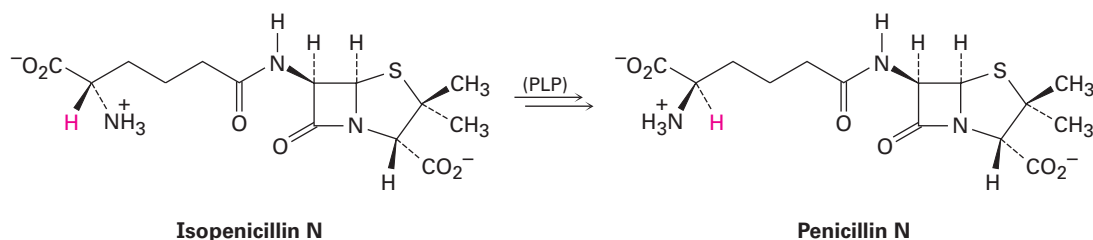
- 25.11 The final step in the biosynthesis of berbaminine is a coupling reaction of (*S*)-*N*-methylcoclaurine with (*R*)-*N*-methylcoclaurine (Problem 25.10). Propose a mechanism.



- 25.12 5-Aminolevulinate is the precursor from which the large class of alkaloids called *tetrapyrroles* are biosynthesized. It arises by a PLP-dependent reaction of glycine and succinyl CoA. Review the mechanism of the formation of dopamine from L-dopa in Figure 25.7, and propose a mechanism for 5-aminolevulinate biosynthesis.

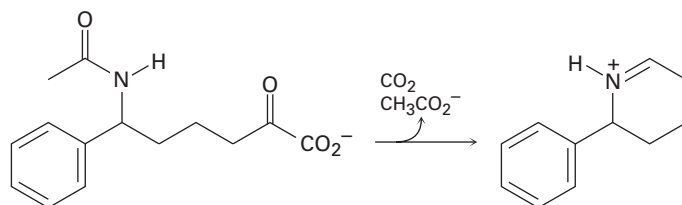


- 25.13 One of the steps in the biosynthesis of penicillins is a PLP-dependent epimerization of isopenicillin N to penicillin N.

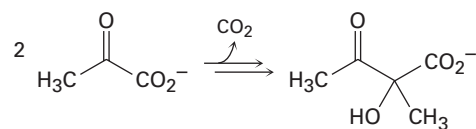


The reaction occurs by initial formation of an imine, followed by a base-catalyzed isomerization. Propose a mechanism.

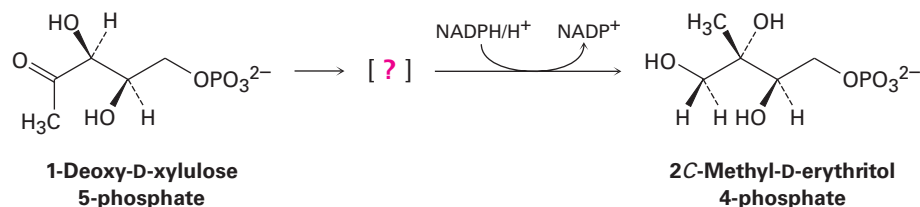
- 25.14 Propose a mechanism for the following biosynthetic conversion. What cofactors are likely to be involved?



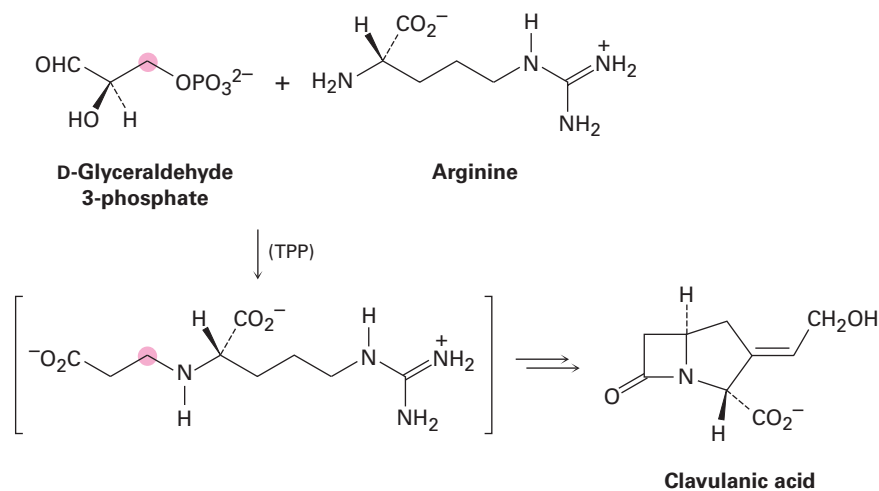
- 25.15 The enzyme acetolactate synthase catalyzes the thiamin diphosphate-dependent conversion of two molecules of pyruvate to acetolactate. Propose a mechanism.



- 25.16 1-Deoxy-D-xylulose 5-phosphate (DXP), in addition to being a precursor to PLP, is also a precursor to isopentenyl diphosphate in terpenoid biosynthesis. The initial step in the pathway is a base-catalyzed rearrangement, followed by reduction with NADPH to give 2C-methyl-D-erythritol 4-phosphate. Show the structure of the rearranged intermediate, and propose a mechanism for its formation.



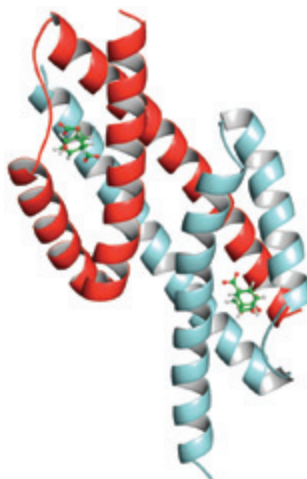
- 25.17 Biosynthesis of the β -lactam antibiotic clavulanic acid begins with a TPP-dependent reaction between D-glyceraldehyde 3-phosphate and arginine.



- (a) The first step is the reaction of D-glyceraldehyde 3-phosphate with TPP ylide, followed by dehydration to give an enol. Show the mechanism, and draw the structure of the product.
- (b) The second step is loss of hydrogen phosphate from the enol to give an unsaturated carbonyl compound. Show the mechanism, and draw the structure of the product.
- (c) The third step is a conjugate addition of arginine to the unsaturated carbonyl compound. Show the mechanism, and draw the structure of the product.
- (d) The final step is a base-catalyzed hydrolysis to give the final product and regenerate TPP ylide. Show the mechanism.

Orbitals and Organic Chemistry: Pericyclic Reactions

e26



Chorismate mutase catalyzes a pericyclic reaction that converts chorismate to prephenate, a step in the biosynthesis of the aromatic amino acids phenylalanine and tyrosine.

WHY THIS CHAPTER?

The broad outlines of both polar and radical reactions have been known for more than a century, but our understanding of pericyclic reactions emerged more recently. Prior to the mid-1960s, in fact, they were even referred to on occasion as “no-mechanism reactions” because they seemed so unusual. They occur largely in the laboratory rather than in biological processes, but a knowledge of them is necessary, both for completeness in studying organic chemistry and in understanding those biological pathways where they do occur.

Most organic reactions take place by polar mechanisms, in which a nucleophile donates two electrons to an electrophile in forming a new bond. Other reactions take place by radical mechanisms, in which each of two reactants donates one electron in forming a new bond. Both kinds of reactions occur frequently in the laboratory and in living organisms. Less common, however, is the third major class of organic reactions — *pericyclic reactions*.

A **pericyclic reaction** is one that occurs by a concerted process through a cyclic transition state. The word *concerted* means that all bonding changes occur simultaneously; no intermediates are involved. Rather than try to expand this definition now, we'll begin by briefly reviewing some of the ideas of molecular orbital theory introduced in Chapters 1 and 9 and then looking individually at the three main classes of pericyclic reactions: *electrocyclic reactions*, *cycloadditions*, and *sigmatropic rearrangements*.

26-1 Molecular Orbitals of Conjugated Pi Systems

A conjugated polyene, as we saw in Section 8-12, is one with alternating double and single bonds. According to molecular orbital (MO) theory, the *p* orbitals on the *sp*²-hybridized carbons of a conjugated polyene interact to form a set of

CONTENTS

- 26-1 Molecular Orbitals of Conjugated Pi Systems
- 26-2 Electrocyclic Reactions
- 26-3 Stereochemistry of Thermal Electrocyclic Reactions
- 26-4 Photochemical Electrocyclic Reactions
- 26-5 Cycloaddition Reactions
- 26-6 Stereochemistry of Cycloadditions
- 26-7 Sigmatropic Rearrangements
- 26-8 Some Examples of Sigmatropic Rearrangements
- 26-9 A Summary of Rules for Pericyclic Reactions

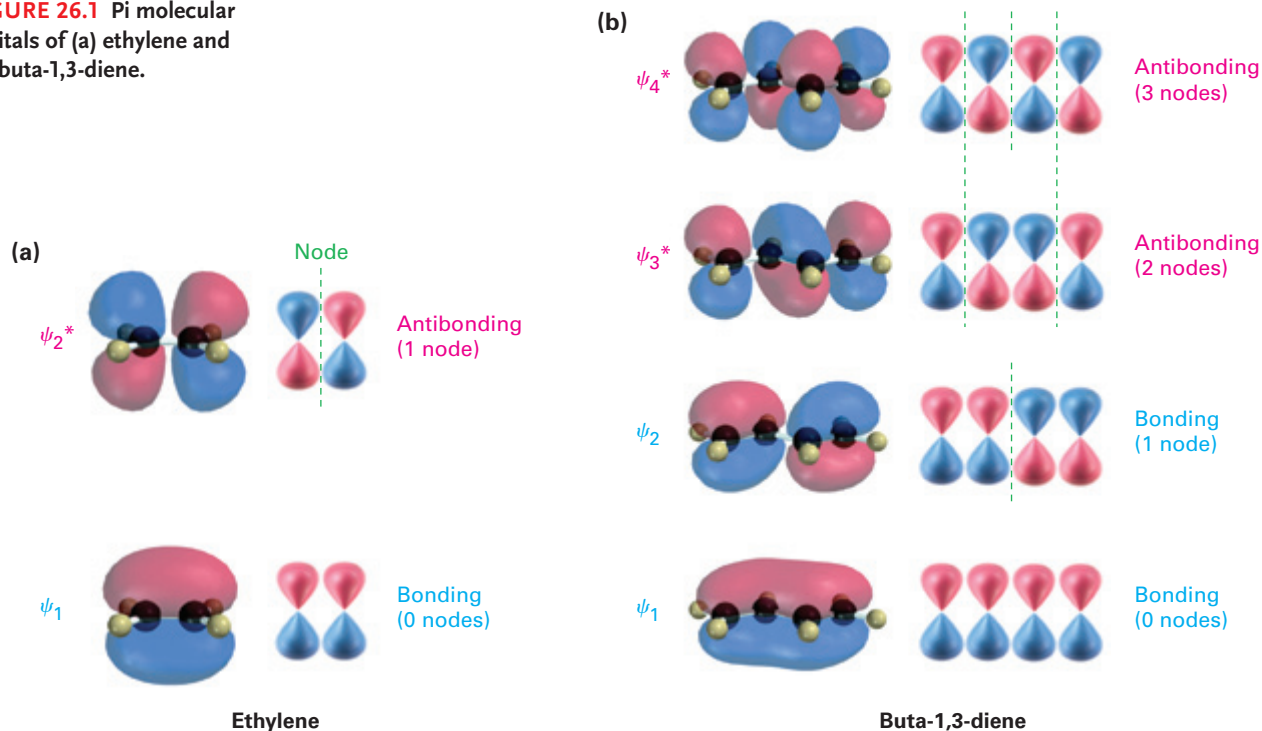
SOMETHING EXTRA

Vitamin D, the Sunshine Vitamin



π molecular orbitals whose energies depend on the number of nodes they have between nuclei. Those molecular orbitals with fewer nodes are lower in energy than the isolated p atomic orbitals and are *bonding MOs*; those molecular orbitals with more nodes are higher in energy than the isolated p orbitals and are *antibonding MOs*. Pi molecular orbitals of ethylene and buta-1,3-diene are shown in **FIGURE 26.1**.

FIGURE 26.1 Pi molecular orbitals of (a) ethylene and (b) buta-1,3-diene.



A similar sort of molecular orbital description can be derived for any conjugated π electron system. Hexa-1,3,5-triene, for example, has three double bonds and six π MOs, as shown in **FIGURE 26.2**. In the ground state, only the three bonding orbitals, ψ_1 , ψ_2 , and ψ_3 , are filled. On irradiation with ultraviolet light, however, an electron is promoted from the highest-energy filled orbital (ψ_3) to the lowest-energy unfilled orbital (ψ_4^*) to give an excited state (Section 10-9), in which ψ_3 and ψ_4^* are each half-filled. (An asterisk denotes an antibonding orbital.)

What do molecular orbitals and their nodes have to do with pericyclic reactions? The answer is: *everything*. According to a series of rules formulated in the mid-1960s by R. B. Woodward and Roald Hoffmann, a pericyclic reaction can take place only if the symmetries of the reactant MOs are the same as the symmetries of the product MOs. In other words, the lobes of reactant MOs must be of the correct algebraic sign for bonding to occur in the transition state leading to product.

If the symmetries of reactant and product orbitals match up, or correlate, the reaction is said to be **symmetry-allowed**. If the symmetries of reactant and product orbitals don't correlate, the reaction is **symmetry-disallowed**. Symmetry-allowed reactions often occur under relatively mild conditions, but symmetry-disallowed reactions can't occur by concerted paths. Either

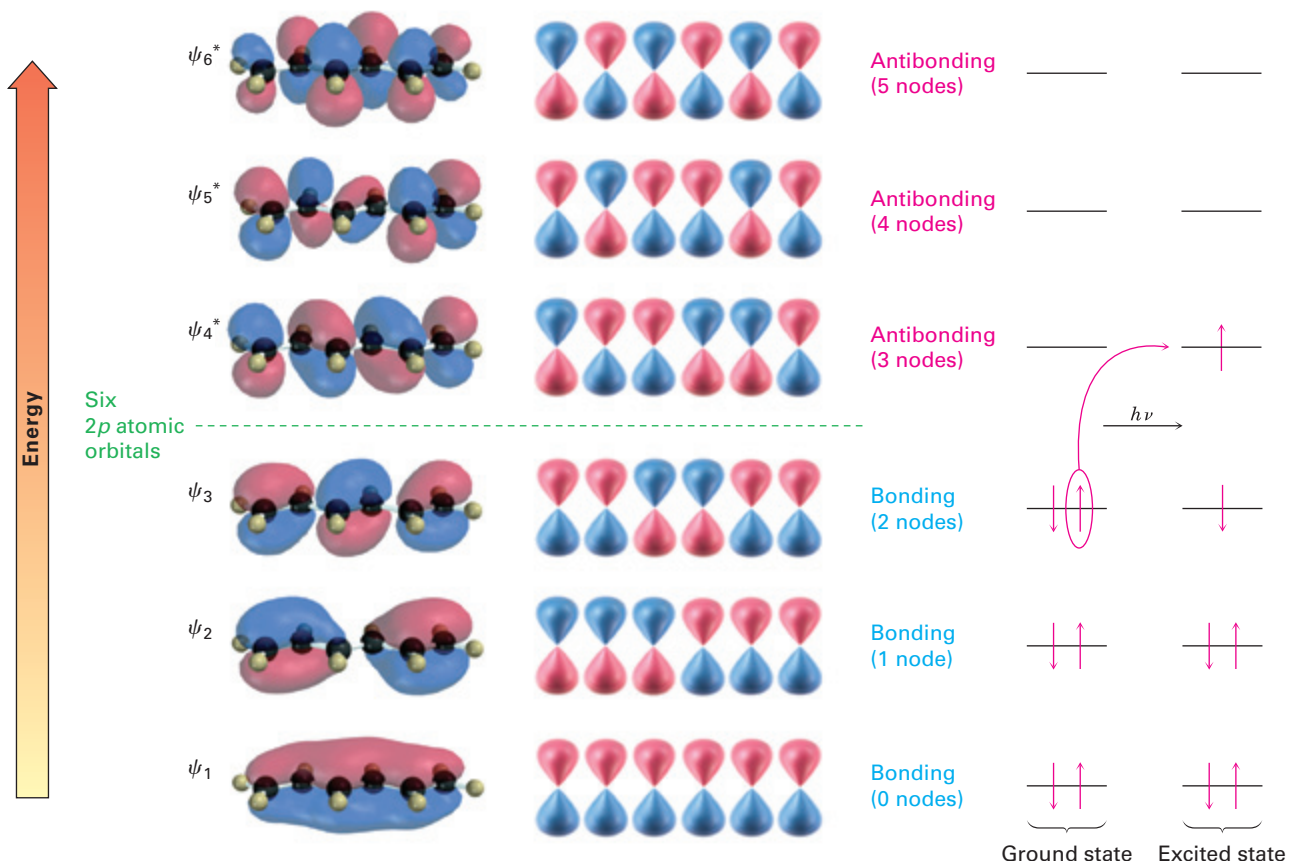


FIGURE 26.2 The six π molecular orbitals of hexa-1,3,5-triene. In the ground state, the three bonding MOs, ψ_1 , ψ_2 , and ψ_3 , are filled. In the excited state, ψ_3 and ψ_4^* are both half-filled.

they take place by nonconcerted, higher-energy pathways, or they don't take place at all.

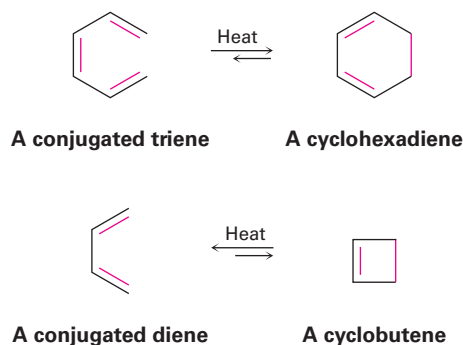
The Woodward–Hoffmann rules for pericyclic reactions require an analysis of all reactant and product molecular orbitals, but Kenichi Fukui at Kyoto Imperial University in Japan introduced a simplified version. According to Fukui, we need to consider only two molecular orbitals, called the **frontier orbitals**. These frontier orbitals are the **highest occupied molecular orbital (HOMO)** and the **lowest unoccupied molecular orbital (LUMO)**. In ground-state hexa-1,3,5-triene, for example, ψ_3 is the HOMO and ψ_4^* is the LUMO (Figure 26.2). In excited-state hexa-1,3,5-triene, however, ψ_4^* is the HOMO and ψ_5^* is the LUMO.

PROBLEM 26.1

Look at Figure 26.1, and tell which molecular orbital is the HOMO and which is the LUMO for both ground and excited states of ethylene and buta-1,3-diene.

26-2 Electrocyclic Reactions

The best way to understand how orbital symmetry affects pericyclic reactions is to look at some examples. Let's look first at a group of polyene rearrangements called *electrocyclic reactions*. An **electrocyclic reaction** is a pericyclic process that involves the cyclization of a conjugated acyclic polyene. One π bond is broken, the other π bonds change position, a new σ bond is formed, and a cyclic compound results. For example, a conjugated triene can be converted into a cyclohexadiene, and a conjugated diene can be converted into a cyclobutene.

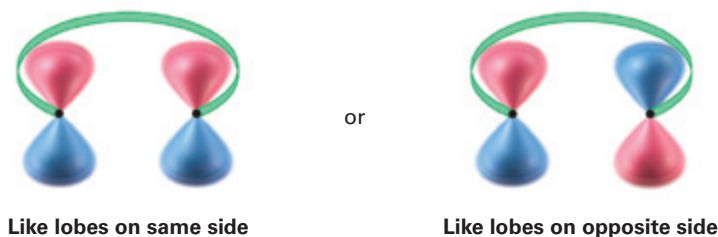


Pericyclic reactions are reversible, and the position of the equilibrium depends on the specific case. In general, the triene \rightleftharpoons cyclohexadiene equilibrium favors the cyclic product, whereas the diene \rightleftharpoons cyclobutene equilibrium favors the less strained open-chain product.

The most striking feature of electrocyclic reactions is their stereochemistry. For example, (2*E*,4*Z*,6*E*)-octa-2,4,6-triene yields only *cis*-5,6-dimethylcyclohexa-1,3-diene when heated, and (2*E*,4*Z*,6*Z*)-octa-2,4,6-triene yields only *trans*-5,6-dimethylcyclohexa-1,3-diene. Remarkably, however, the stereochemical results change completely when the reactions are carried out under what are called **photochemical**, rather than thermal, conditions. Irradiation, or *photolysis*, of (2*E*,4*Z*,6*E*)-octa-2,4,6-triene with ultraviolet light yields *trans*-5,6-dimethylcyclohexa-1,3-diene (FIGURE 26.3).

A similar result is obtained for the thermal electrocyclic ring-opening of 3,4-dimethylcyclobutene. The *trans* isomer yields only (2*E*,4*E*)-hexa-2,4-diene when heated, and the *cis* isomer yields only (2*E*,4*Z*)-hexa-2,4-diene. On UV irradiation, however, the results are opposite. Cyclization of the 2*E*,4*E* isomer under photochemical conditions yields *cis* product (FIGURE 26.4).

To account for these results, we need to look at the two outermost lobes of the polyene MOs—the lobes that interact when cyclization occurs. There are two possibilities: the lobes of like sign can be either on the same side or on opposite sides of the molecule.



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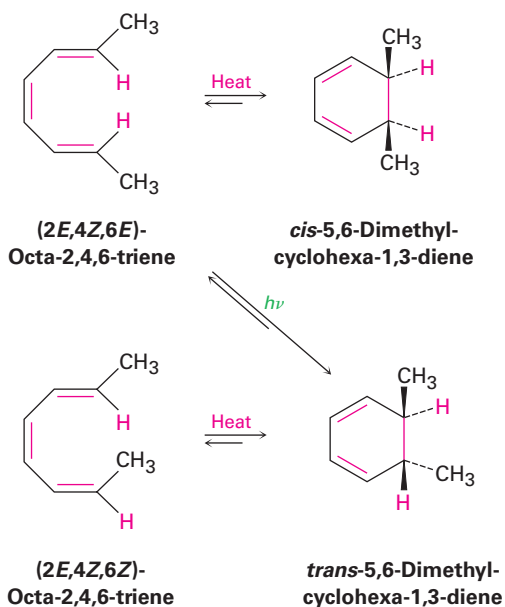


FIGURE 26.3 Electrocyclic interconversions of octa-2,4,6-triene isomers and 5,6-dimethylcyclohexa-1,3-diene isomers.

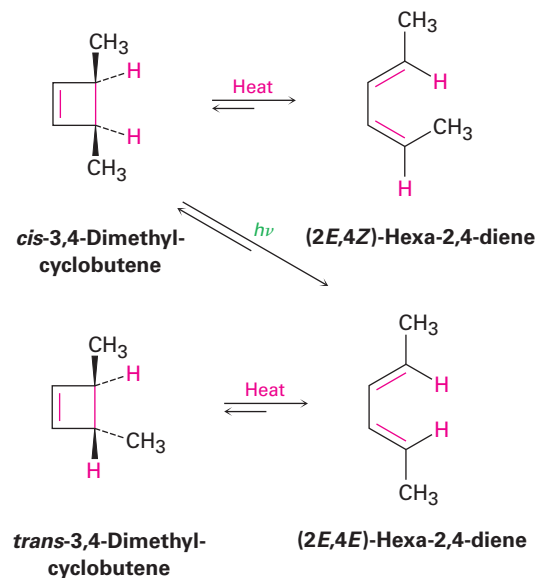
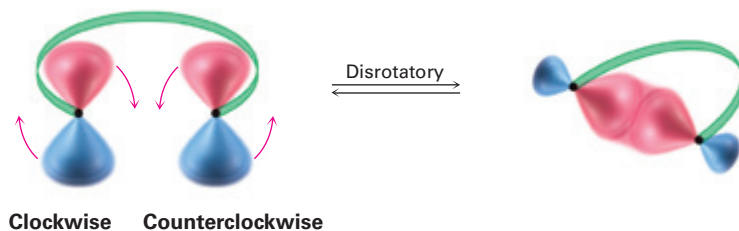
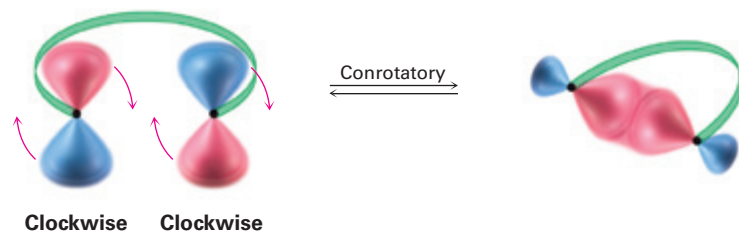


FIGURE 26.4 Electrocyclic interconversions of hexa-2,4-diene isomers and 3,4-dimethylcyclobutene isomers.

For a bond to form, the outermost π lobes must rotate so that favorable bonding interaction is achieved—a positive lobe with a positive lobe or a negative lobe with a negative lobe. If two lobes of like sign are on the *same* side of the molecule, the two orbitals must rotate in *opposite* directions—one clockwise and one counterclockwise. This kind of motion is referred to as **disrotatory**.



Conversely, if lobes of like sign are on *opposite* sides of the molecule, both orbitals must rotate in the *same* direction, either both clockwise or both counterclockwise. This kind of motion is called **conrotatory**.

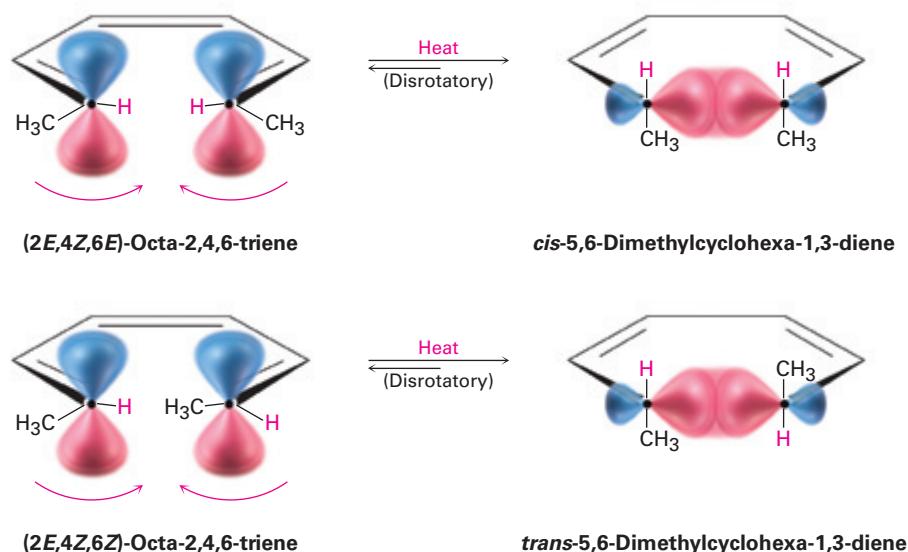


26-3 Stereochemistry of Thermal Electrocyclic Reactions

How can we predict whether conrotatory or disrotatory motion will occur in a given case? According to frontier orbital theory, *the stereochemistry of an electrocyclic reaction is determined by the symmetry of the polyene HOMO*. The electrons in the HOMO are the highest-energy, most loosely held electrons and are therefore most easily moved during reaction. For thermal reactions, the ground-state electron configuration is used to identify the HOMO; for photochemical reactions, the excited-state electron configuration is used.

Let's look again at the thermal ring-closure of conjugated trienes. According to Figure 26.2, the HOMO of a conjugated triene in its ground state has lobes of like sign on the same side of the molecule, a symmetry that predicts disrotatory ring closure. This disrotatory cyclization is exactly what is observed in the thermal cyclization of octa-2,4,6-triene. The *2E,4Z,6E* isomer yields *cis* product, and the *2E,4Z,6Z* isomer yields *trans* product (FIGURE 26.5).

FIGURE 26.5 Thermal cyclizations of octa-2,4,6-trienes. The reactions occur by disrotatory ring closures.



In the same way, the ground-state HOMO of conjugated dienes (Figure 26.1) has a symmetry that predicts conrotatory ring closure. In practice, however, the conjugated diene reaction can be observed only in the reverse direction (cyclobutene \rightarrow diene) because of the position of the equilibrium. We therefore find that the 3,4-dimethylcyclobutene ring *opens* in a conrotatory fashion. *cis*-3,4-Dimethylcyclobutene yields (*2E,4Z*)-hexa-2,4-diene, and *trans*-3,4-dimethylcyclobutene yields (*2E,4E*)-hexa-2,4-diene by conrotatory opening (FIGURE 26.6).

Note that a conjugated diene and a conjugated triene react with opposite stereochemistry. The diene opens and closes by a conrotatory path, whereas

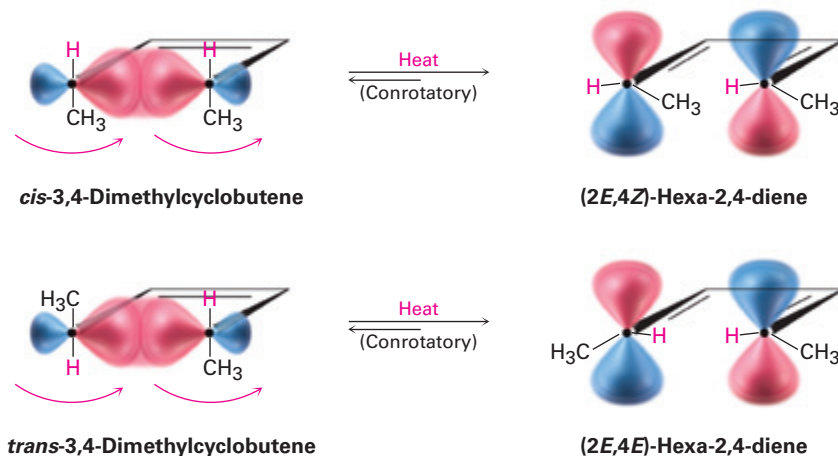
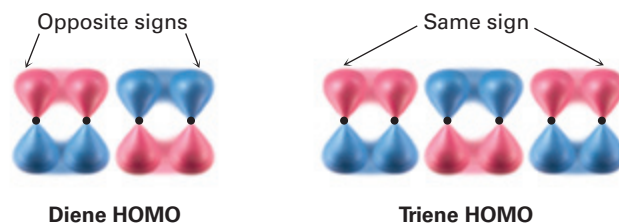


FIGURE 26.6 Thermal ring-openings of *cis*- and *trans*-dimethylcyclobutene. The reactions occur by conrotatory paths.

the triene opens and closes by a disrotatory path. The difference is due to the different symmetries of the diene and triene HOMOs.



It turns out that there is an alternating relationship between the number of electron pairs (double bonds) undergoing bond reorganization and the stereochemistry of ring opening or closure. Polyenes with an even number of electron pairs undergo thermal electrocyclic reactions in a conrotatory sense, whereas polyenes with an odd number of electron pairs undergo the same reactions in a disrotatory sense.

PROBLEM 26.2

Draw the products you would expect from conrotatory and disrotatory cyclizations of (2*Z*,4*Z*,6*Z*)-octa-2,4,6-triene. Which of the two paths would you expect the thermal reaction to follow?

PROBLEM 26.3

trans-3,4-Dimethylcyclobutene can open by two conrotatory paths to give either (2*E*,4*E*)-hexa-2,4-diene or (2*Z*,4*Z*)-hexa-2,4-diene. Explain why both products are symmetry-allowed, and then account for the fact that only the 2*E*,4*E* isomer is obtained in practice.

26-4 Photochemical Electrocyclic Reactions

We noted previously that photochemical electrocyclic reactions take a different stereochemical course than their thermal counterparts, and we can now explain this difference. Ultraviolet irradiation of a polyene causes an excitation of one electron from the ground-state HOMO to the ground-state LUMO, thus changing their symmetries. But because electronic excitation changes the symmetries of HOMO and LUMO, it also changes the reaction stereochemistry. $(2E,4E)$ -Hexa-2,4-diene, for instance, undergoes photochemical cyclization by a disrotatory path, whereas the thermal reaction is conrotatory. Similarly, $(2E,4Z,6E)$ -octa-2,4,6-triene undergoes photochemical cyclization by a conrotatory path, whereas the thermal reaction is disrotatory (FIGURE 26.7).

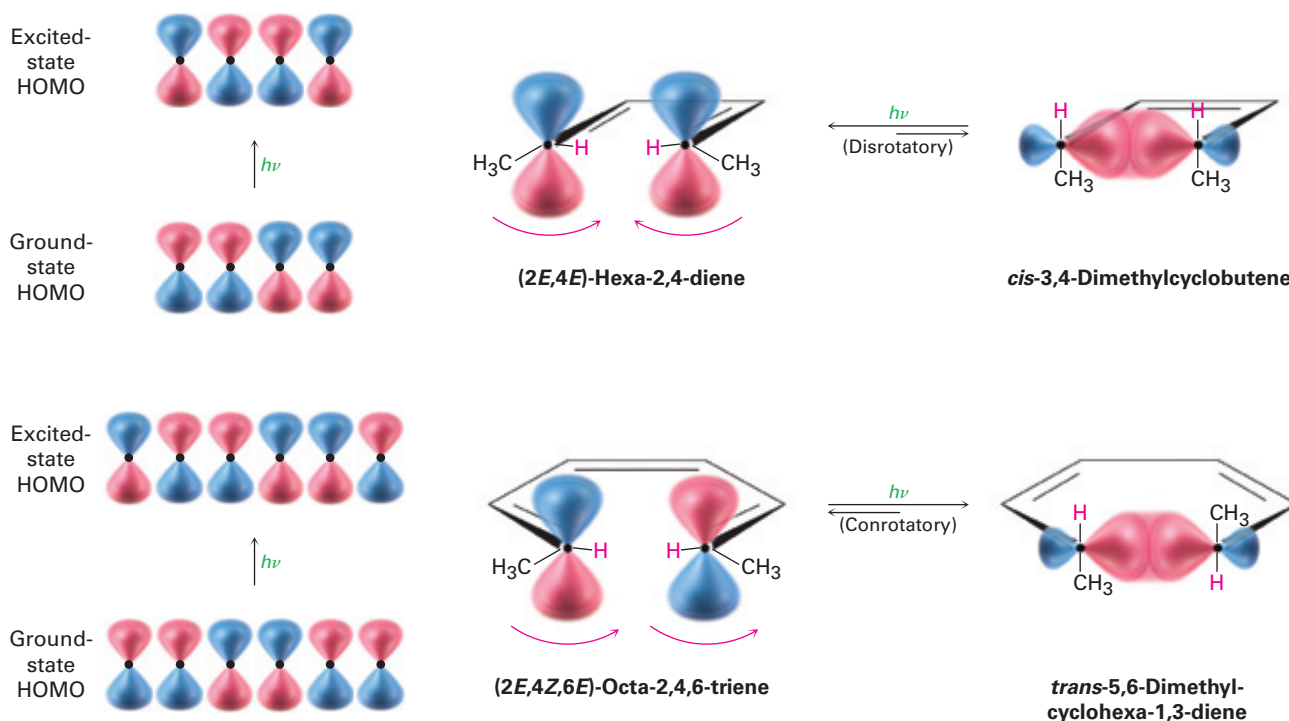


FIGURE 26.7 Photochemical cyclizations of conjugated dienes and trienes. The two processes occur with different stereochemistry because of their different orbital symmetries.

Thermal and photochemical electrocyclic reactions always take place with opposite stereochemistry because the symmetries of the frontier orbitals are always different. TABLE 26.1 gives some simple rules that make it possible to predict the stereochemistry of electrocyclic reactions.

TABLE 26.1 Stereochemical Rules for Electrocyclic Reactions

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Conrotatory	Disrotatory
Odd number	Disrotatory	Conrotatory

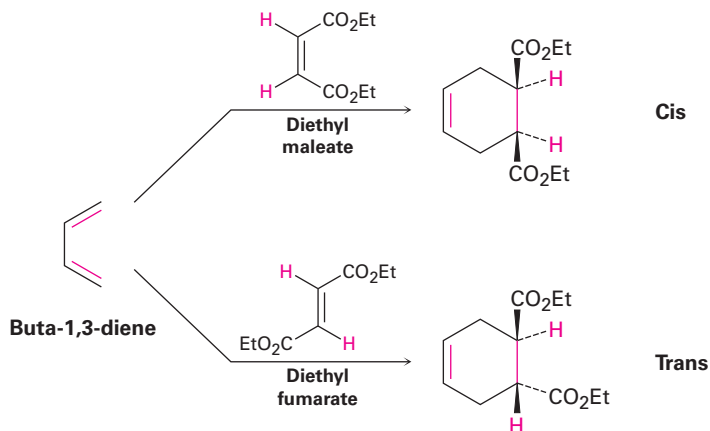
PROBLEM 26.4

What product would you expect to obtain from the photochemical cyclization of (2*E*,4*Z*,6*E*)-octa-2,4,6-triene? Of (2*E*,4*Z*,6*Z*)-octa-2,4,6-triene?

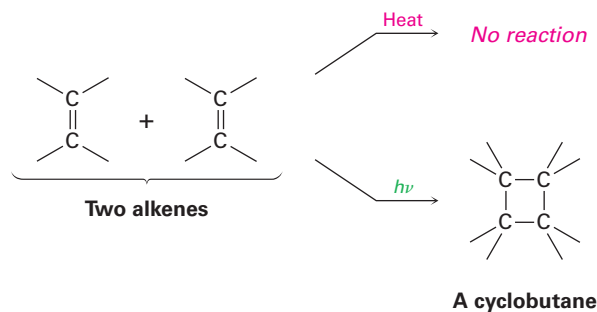
26-5 Cycloaddition Reactions

A **cycloaddition reaction** is one in which two unsaturated molecules add to one another to yield a cyclic product. As with electrocyclic reactions, cycloadditions are controlled by the orbital symmetry of the reactants. Symmetry-allowed processes often take place readily, but symmetry-disallowed processes take place with difficulty, if at all, and then only by nonconcerted pathways. Let's look at two examples to see how they differ.

The Diels–Alder cycloaddition reaction (Section 8-14) is a pericyclic process that takes place between a diene (four π electrons) and a dienophile (two π electrons) to yield a cyclohexene product. Many thousands of examples of Diels–Alder reactions are known. They often take place easily at room temperature or slightly above, and they are stereospecific with respect to substituents. For example, room-temperature reaction between buta-1,3-diene and diethyl maleate (*cis*) yields exclusively the *cis*-disubstituted cyclohexene product. A similar reaction between buta-1,3-diene and diethyl fumarate (*trans*) yields exclusively the *trans*-disubstituted product.



In contrast to the $[4 + 2]$ - π -electron Diels–Alder reaction, the $[2 + 2]$ - π -electron cycloaddition between two alkenes does not occur thermally. The $[2 + 2]$ cycloaddition takes place only on irradiation, yielding cyclobutane products.

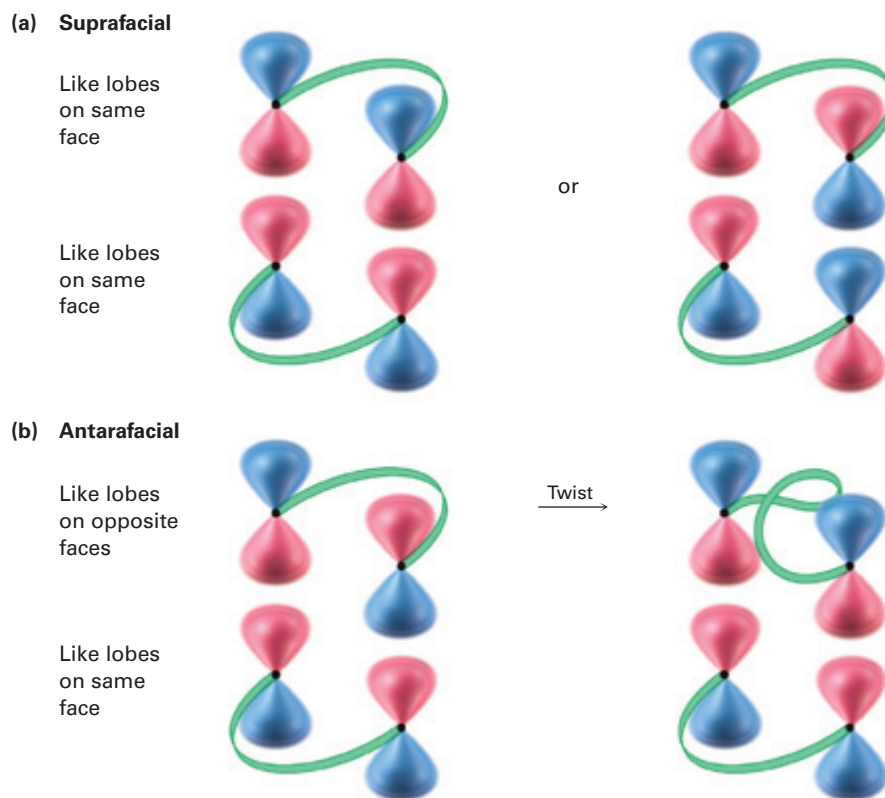


For a successful cycloaddition to take place, the terminal π lobes of the two reactants must have the correct symmetry for bonding to occur. This can happen in either of two ways, called *suprafacial* and *antarafacial*. **Suprafacial** cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on the same face of the other reactant. **Antarafacial** cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on *opposite* faces of the other reactant (**FIGURE 26.8**).

FIGURE 26.8 Suprafacial and antarafacial cycloadditions.

(a) Suprafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on the same face of the other reactant.

(b) Antarafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on opposite faces of the other, which requires a twist in one π system.



Note that both suprafacial and antarafacial cycloadditions are symmetry-allowed. Geometric constraints often make antarafacial reactions difficult, however, because there must be a twisting of the π orbital system in one of the reactants. Thus, suprafacial cycloadditions are much more common for small π systems.

26-6 Stereochemistry of Cycloadditions

How can we predict whether a given cycloaddition reaction will occur with suprafacial or with antarafacial geometry? According to frontier orbital theory, a cycloaddition reaction takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other. An intuitive

explanation of this rule is to imagine that one reactant donates electrons to the other. As with electrocyclic reactions, it's the electrons in the HOMO of the first reactant that are least tightly held and most likely to be donated. But of course when the second reactant accepts those electrons, they must go into a vacant, unoccupied orbital—the LUMO.

For a [4 + 2] cycloaddition (Diels–Alder reaction), let's arbitrarily select the diene LUMO and the alkene HOMO. The symmetries of the two ground-state orbitals are such that bonding of the terminal lobes can occur with suprafacial geometry (FIGURE 26.9), so the Diels–Alder reaction takes place readily under thermal conditions. Note that, as with electrocyclic reactions, we need be concerned only with the terminal lobes. For purposes of prediction, interactions among the interior lobes need not be considered.

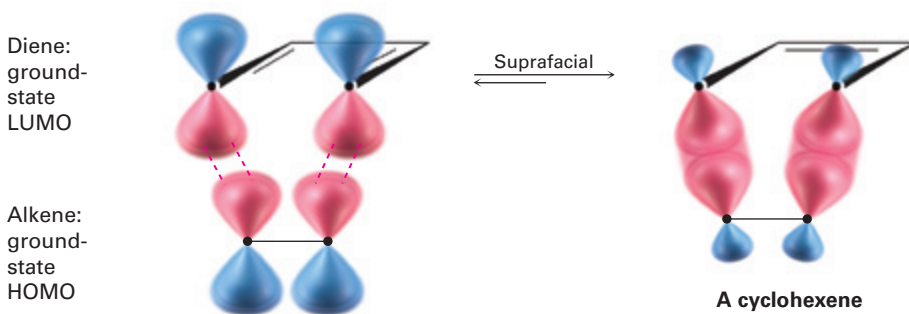


FIGURE 26.9 Orbital interactions in the Diels–Alder reaction. Interaction of diene LUMO and alkene HOMO in a suprafacial [4 + 2] cycloaddition reaction (Diels–Alder reaction).

In contrast with the thermal [4 + 2] Diels–Alder reaction, the [2 + 2] cycloaddition of two alkenes to yield a cyclobutane can only be observed photochemically. The explanation follows from orbital-symmetry arguments. Looking at the ground-state HOMO of one alkene and the LUMO of the second alkene, it's apparent that a thermal [2 + 2] cycloaddition must take place by an antarafacial pathway (FIGURE 26.10a). Geometric constraints make the antarafacial transition state difficult, however, and so concerted thermal [2 + 2] cycloadditions are not observed. Photochemical [2 + 2] cycloadditions, however, *are* observed. Irradiation of an alkene with UV light excites an electron from ψ_1 , the ground-state HOMO, to ψ_2^* , which becomes the excited-state HOMO. Interaction between the excited-state HOMO of one alkene and the LUMO of the second alkene allows a photochemical [2 + 2] cycloaddition reaction to occur by a suprafacial pathway (FIGURE 26.10b).

The photochemical [2 + 2] cycloaddition reaction occurs smoothly, particularly with α,β -unsaturated carbonyl compounds, and represents one of the best methods known for synthesizing cyclobutane rings. For example:

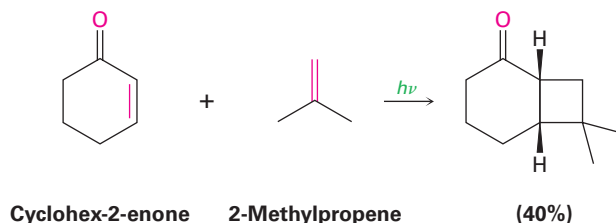
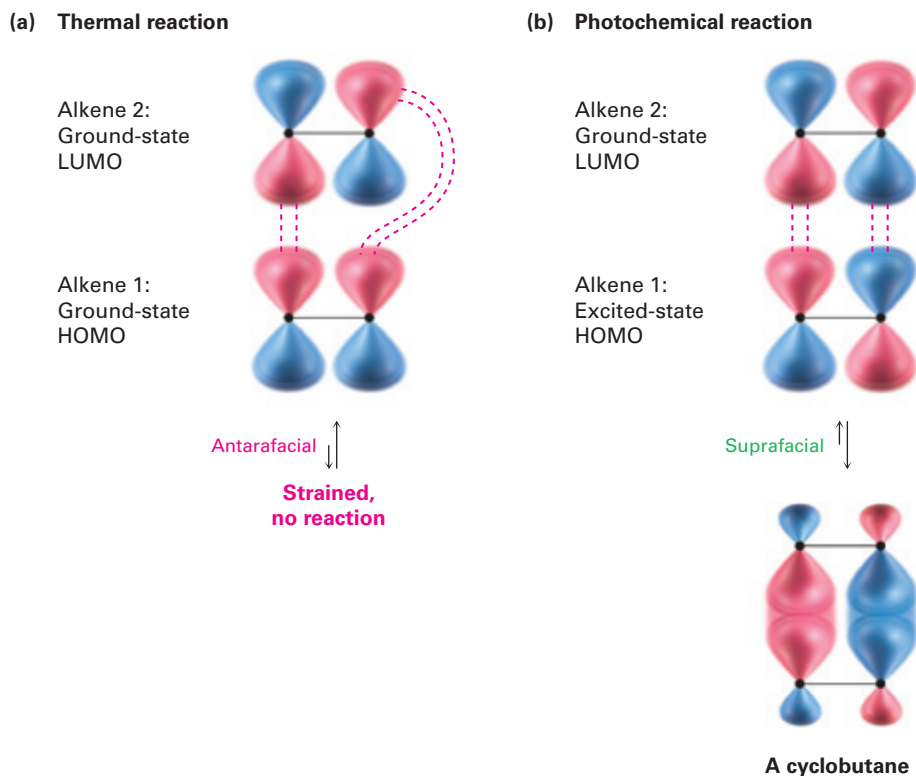


FIGURE 26.10 Thermal and photochemical [2 + 2] cycloadditions. (a) Interaction of a ground-state HOMO and a ground-state LUMO in a potential [2 + 2] cycloaddition does not occur thermally because the antarafacial geometry is too strained. (b) Interaction of an excited-state HOMO and a ground-state LUMO in a photochemical [2 + 2] cycloaddition reaction is less strained, however, and occurs with suprafacial geometry.



Thermal and photochemical cycloaddition reactions always take place with opposite stereochemistry. As with electrocyclic reactions, we can categorize cycloadditions according to the total number of electron pairs (double bonds) involved in the rearrangement. Thus, a thermal [4 + 2] Diels–Alder reaction between a diene and a dienophile involves an odd number (three) of electron pairs and takes place by a suprafacial pathway. A thermal [2 + 2] reaction between two alkenes involves an even number (two) of electron pairs and must take place by an antarafacial pathway. For photochemical cyclizations, these selectivities are reversed. The general rules are given in [TABLE 26.2](#).

TABLE 26.2 Stereochemical Rules for Cycloaddition Reactions

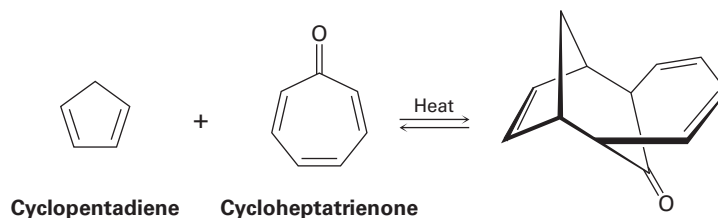
Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

PROBLEM 26.5

What stereochemistry would you expect for the product of the Diels–Alder reaction between (2*E*,4*E*)-hexa-2,4-diene and ethylene? What stereochemistry would you expect if (2*E*,4*Z*)-hexa-2,4-diene were used instead?

PROBLEM 26.6

Cyclopenta-1,3-diene reacts with cycloheptatrienone to give the product shown. Tell what kind of reaction is involved, and explain the observed result. Is the reaction suprafacial or antarafacial?

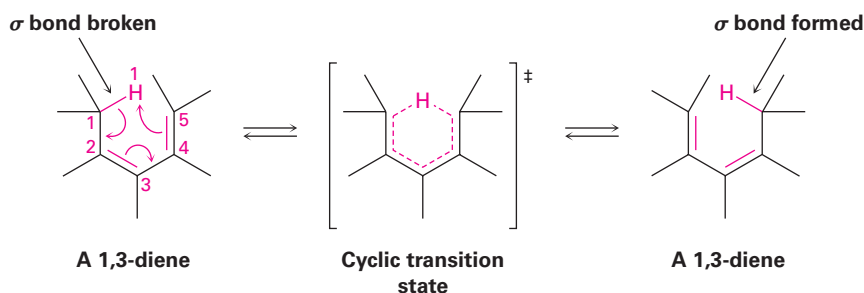


26-7

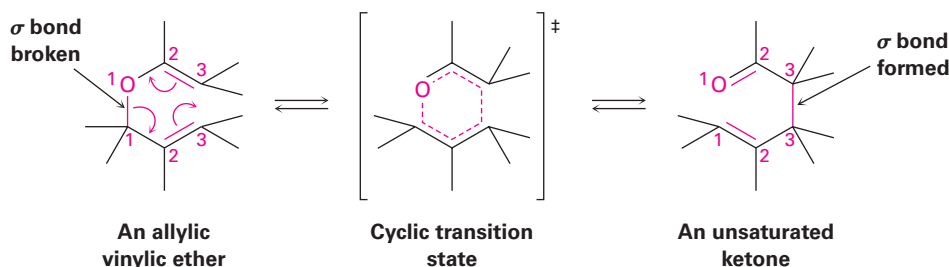
Sigmatropic Rearrangements

A **sigmatropic rearrangement**, the third general kind of pericyclic reaction, is a process in which a σ -bonded substituent atom or group migrates across a π electron system from one position to another. A σ bond is broken in the reactant, the π bonds move, and a new σ bond is formed in the product. The σ -bonded group can be either at the end or in the middle of the π system, as the following [1,5] and [3,3] rearrangements illustrate:

A [1,5] sigmatropic rearrangement



A [3,3] sigmatropic rearrangement

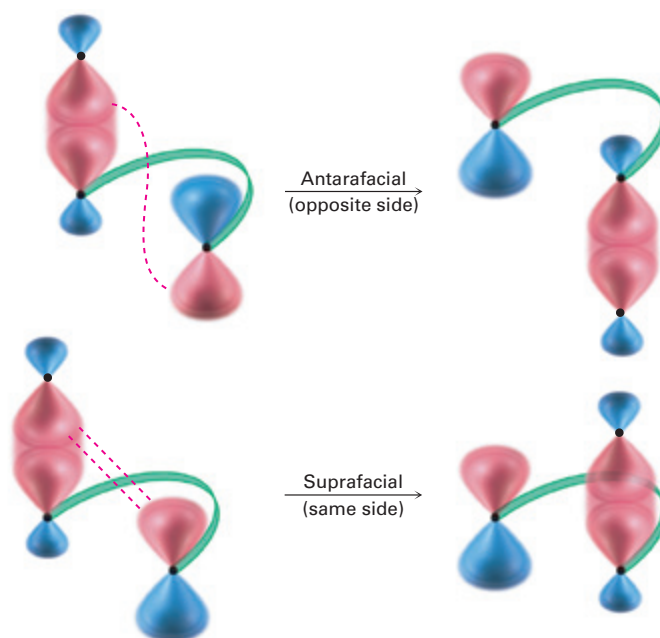


The notations [1,5] and [3,3] describe the kind of rearrangement that is occurring. The numbers refer to the two groups connected by the σ bond in

the reactant and designate the positions in those groups to which migration occurs. For example, in the [1,5] sigmatropic rearrangement of a 1,3-diene, the two groups connected by the σ bond are a hydrogen atom and a pentadienyl group. Migration occurs to position 1 of the H group (the only possibility) and to position 5 of the pentadienyl group. In the [3,3] Claisen rearrangement of an allylic vinylic ether, the two groups connected by the σ bond are an allylic group and a vinylic ether group. Migration occurs to position 3 of the allylic group and also to position 3 of the vinylic ether.

Like electrocyclic reactions and cycloadditions, sigmatropic rearrangements are controlled by orbital symmetries. There are two possible modes of reaction: migration of a group across the same face of the π system is suprafacial, and migration of a group from one face of the π system to the other face is antarafacial (FIGURE 26.11).

FIGURE 26.11 Suprafacial and antarafacial sigmatropic rearrangements.



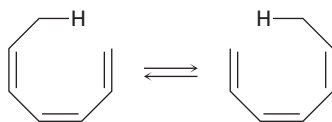
Both suprafacial and antarafacial sigmatropic rearrangements are symmetry-allowed, but suprafacial rearrangements are often easier for geometric reasons. The rules for sigmatropic rearrangements are identical to those for cycloaddition reactions (TABLE 26.3).

TABLE 26.3 Stereochemical Rules for Sigmatropic Rearrangements

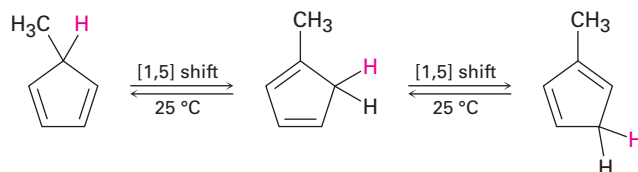
Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

PROBLEM 26.7

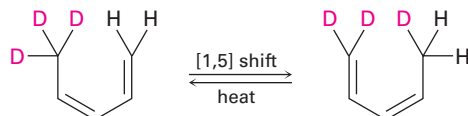
Classify the following sigmatropic reaction by order $[x,y]$, and tell whether it will proceed with suprafacial or antarafacial stereochemistry:

**26-8 Some Examples of Sigmatropic Rearrangements**

Because a $[1,5]$ sigmatropic rearrangement involves three electron pairs (two π bonds and one σ bond), the orbital-symmetry rules in Table 26.3 predict a suprafacial reaction. In fact, the $[1,5]$ suprafacial shift of a hydrogen atom across two double bonds of a π system is one of the most commonly observed of all sigmatropic rearrangements. For example, 5-methylcyclopenta-1,3-diene rapidly rearranges at room temperature to yield a mixture of 1-methyl-, 2-methyl-, and 5-methyl-substituted products.



As another example, heating 5,5,5-trideuterio-(3*Z*)-penta-1,3-diene causes scrambling of deuterium between positions 1 and 5.



Both these $[1,5]$ hydrogen shifts occur by a symmetry-allowed suprafacial pathway, as illustrated in **FIGURE 26.12**. In contrast with these thermal $[1,5]$ sigmatropic hydrogen shifts, however, thermal $[1,3]$ hydrogen shifts are unknown. Were they to occur, they would have to proceed by a strained antarafacial reaction pathway.

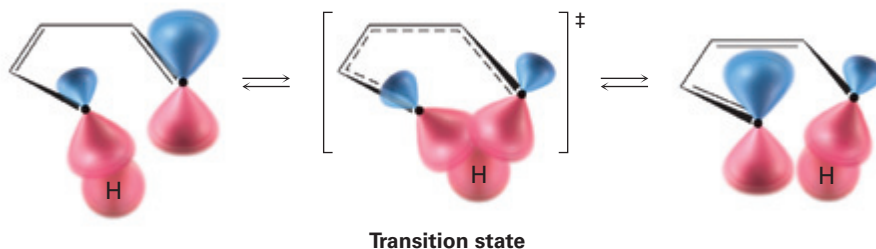
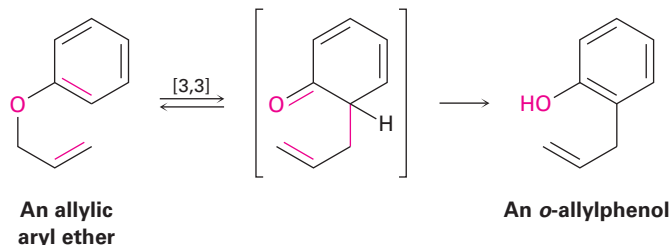


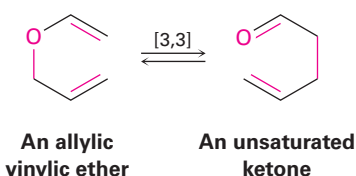
FIGURE 26.12 An orbital view of a suprafacial $[1,5]$ hydrogen shift.

Two other important sigmatropic reactions are the *Cope rearrangement* of a hexa-1,5-diene and the *Claisen rearrangement* of an aryl allyl ether or a vinyl allyl ether (Section 13-10). These two, along with the Diels–Alder reaction, are the most useful pericyclic reactions for organic synthesis; many thousands of examples of all three are known.

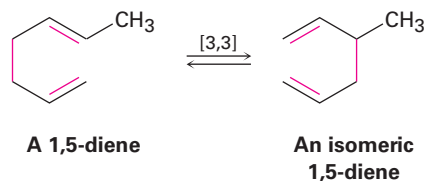
Claisen rearrangement



Claisen rearrangement



Cope rearrangement

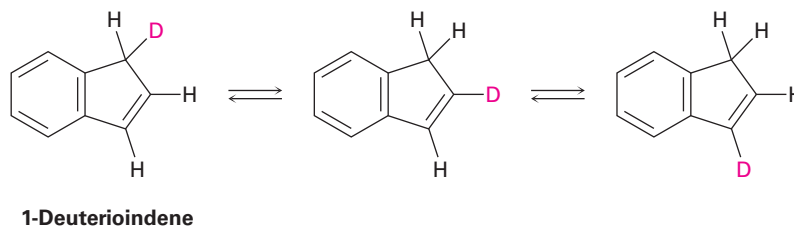


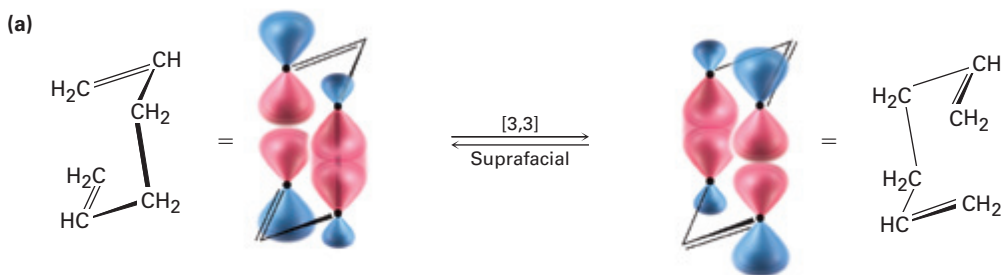
Both Cope and Claisen rearrangements involve reorganization of an odd number of electron pairs (two π bonds and one σ bond), and both react by suprafacial pathways (FIGURE 26.13).

As noted in Section 13-10, biological examples of pericyclic reactions are relatively rare, although one much-studied example occurs during our body's synthesis of vitamin D. That process is discussed in the *Something Extra* at the end of this chapter.

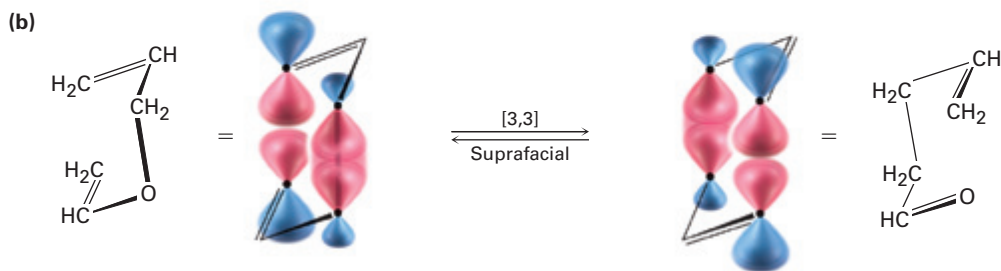
PROBLEM 26.8

Propose a mechanism to account for the fact that heating 1-deuterioindene scrambles the isotope label to all three positions on the five-membered ring.





Cope rearrangement of a hexa-1,5-diene

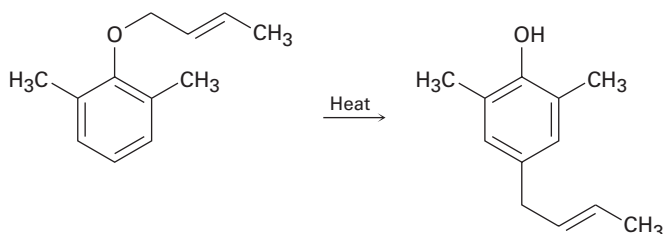


Claisen rearrangement of an allylic vinylic ether

FIGURE 26.13
Suprafacial [3,3]
(a) Cope and (b) Claisen
rearrangements.

PROBLEM 26.9

When a 2,6-disubstituted allyl phenyl ether is heated in an attempted Claisen rearrangement, migration occurs to give the *p*-allyl product as the result of two sequential pericyclic reactions. Explain.



26-9 A Summary of Rules for Pericyclic Reactions

How can you keep straight all the rules about pericyclic reactions? The summary information in Tables 26.1 to 26.3 can be distilled into one mnemonic phrase that provides an easy way to predict the stereochemical outcome of any pericyclic reaction:

The Electrons Circle Around (TECA)

Thermal reactions with an *Even* number of electron pairs are
Conrotatory or Antarafacial.

A change either from thermal to photochemical or from an even to an odd number of electron pairs changes the outcome from conrotatory/antarafacial to disrotatory/suprafacial. A change from both thermal and even to photochemical and odd causes no change because two negatives make a positive.

These selection rules are summarized in TABLE 26.4; knowing them gives you the ability to predict the stereochemistry of literally thousands of pericyclic reactions.

TABLE 26.4 Stereochemical Rules for Pericyclic Reactions

Electronic state	Electron pairs	Stereochemistry
Ground state (thermal)	Even number	Antara-con
	Odd number	Supra-dis
Excited state (photochemical)	Even number	Supra-dis
	Odd number	Antara-con

PROBLEM 26.10

Predict the stereochemistry of the following pericyclic reactions:

- The thermal cyclization of a conjugated tetraene
- The photochemical cyclization of a conjugated tetraene
- A photochemical [4 + 4] cycloaddition
- A thermal [2 + 6] cycloaddition
- A photochemical [3,5] sigmatropic rearrangement

SOMETHING EXTRA

Vitamin D, the Sunshine Vitamin

Vitamin D, discovered in 1918, is a general name for two related compounds, *cholecalciferol* (vitamin D₃) and *ergocalciferol* (vitamin D₂). Both are derived from steroids (Section 23-9) and differ only in the nature of the hydrocarbon side chain attached to the five-membered ring. Cholecalciferol comes primarily from dairy products and fish; ergocalciferol comes from some vegetables.



Art Directors & TRIP/Alamy

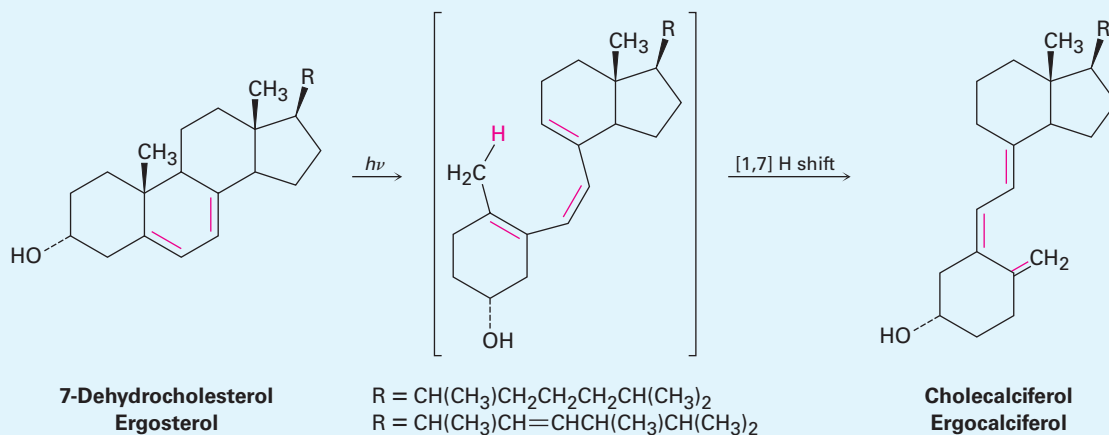
Synthesizing vitamin D takes dedication and hard work.

The function of vitamin D in the body is to control the calcification of bones by increasing intestinal absorption of calcium. When sufficient vitamin D is present, approximately 30% of ingested calcium is absorbed, but in the absence of vitamin D, calcium absorption falls to about 10%. A deficiency of vitamin D thus leads to poor bone growth and to the diseases *rickets* in children and *osteoporosis* in adults.

Actually, neither vitamin D₂ nor D₃ is present in foods. Rather, foods contain the precursor molecules 7-dehydrocholesterol and ergosterol. In the presence of sunlight, both precursors are converted in the outer, epidermal layer of skin to the active vitamins, hence the nickname for vitamin D, the “sunshine vitamin.”

Pericyclic reactions are unusual in living organisms, and the photochemical synthesis of vitamin D is one of only a few well-studied examples. The reaction takes place in two steps, an electrocyclic ring-opening of a cyclohexadiene to yield an open-chain hexatriene, followed by a sigmatropic [1,7] H shift to yield an isomeric hexatriene. Only the initial, electrocyclic ring-opening requires irradiation, with so-called UVB light of 295 to 300 nm wavelength required. The subsequent sigmatropic [1,7] H shift occurs spontaneously by a thermal isomerization.

Following synthesis under the skin, further metabolic processing of cholecalciferol and ergocalciferol in the liver and kidney introduces two additional –OH groups to give the active forms of the vitamin, calcitriol and ergocalcitril.



SUMMARY

A **pericyclic reaction** takes place in a single step through a cyclic transition state without intermediates. There are three major classes of pericyclic processes: electrocyclic reactions, cycloaddition reactions, and sigmatropic rearrangements. The stereochemistry of these reactions is controlled by the symmetry of the orbitals involved in bond reorganization.

Electrocyclic reactions involve the cyclization of conjugated acyclic polyenes. For example, hexa-1,3,5-triene cyclizes to cyclohexa-1,3-diene on heating. Electrocyclic reactions can occur by either **conrotatory** or **disrotatory** pathways, depending on the symmetry of the terminal lobes of the π system. Conrotatory cyclization requires that both lobes rotate in the same direction, whereas disrotatory cyclization requires that the lobes rotate in opposite directions. The reaction course in a specific case can be found by looking at the symmetry of the **highest occupied molecular orbital (HOMO)**.

KEY WORDS

- antarafacial, 914
- conrotatory, 909
- cycloaddition reaction, 913
- disrotatory, 909
- electrocyclic reaction, 908
- frontier orbital, 907
- highest occupied molecular orbital (HOMO), 907
- lowest unoccupied molecular orbital (LUMO), 907
- pericyclic reaction, 905

photochemical reaction,
908

sigmatropic rearrangement,
917

suprafacial, 914

symmetry-allowed, 906

symmetry-disallowed, 906

Cycloaddition reactions are those in which two unsaturated molecules add together to yield a cyclic product. For example, Diels–Alder reaction between a diene (four π electrons) and a dienophile (two π electrons) yields a cyclohexene. Cycloadditions can take place either by **suprafacial** or **antarafacial** pathways. Suprafacial cycloaddition involves interaction between lobes on the same face of one component and on the same face of the second component. Antarafacial cycloaddition involves interaction between lobes on the same face of one component and on opposite faces of the other component. The reaction course in a specific case can be found by looking at the symmetry of the HOMO of one component and the **lowest unoccupied molecular orbital (LUMO)** of the other component.

Sigmatropic rearrangements involve the migration of a σ -bonded group across a π electron system. For example, Claisen rearrangement of an allylic vinylic ether yields an unsaturated carbonyl compound, and Cope rearrangement of a hexa-1,5-diene yields an isomeric hexa-1,5-diene. Sigmatropic rearrangements can occur with either suprafacial or antarafacial stereochemistry; the selection rules for a given case are the same as those for cycloaddition reactions.

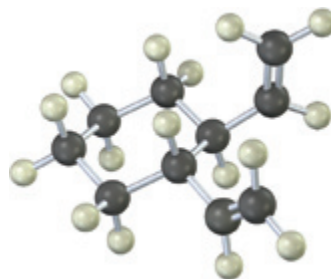
The stereochemistry of any pericyclic reaction can be predicted by counting the total number of electron pairs (bonds) involved in bond reorganization and then applying the mnemonic “The Electrons Circle Around.” That is, **thermal** (ground-state) reactions involving an even number of electron pairs occur with either conrotatory or antarafacial stereochemistry. Exactly the opposite rules apply to **photochemical** (excited-state) reactions.

EXERCISES

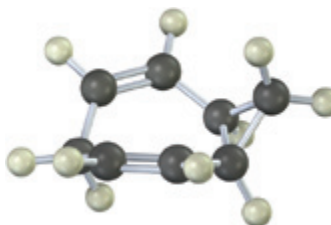
VISUALIZING CHEMISTRY

(Problems 26.1–26.10 appear within the chapter.)

26.11 Predict the product obtained when the following substance is heated:



26.12 The ^{13}C NMR spectrum of homotropilidene taken at room temperature shows only three peaks. Explain.

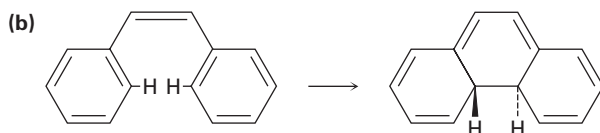
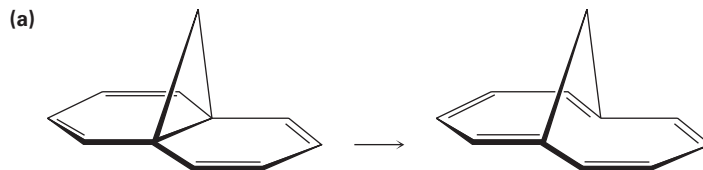


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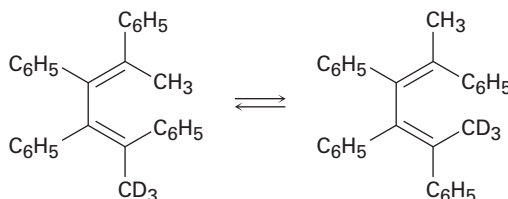
ADDITIONAL PROBLEMS

Electrocyclic Reactions

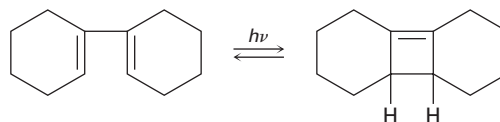
26.13 Have the following electrocyclic reactions taken place in a conrotatory or disrotatory manner? Under what conditions, thermal or photochemical, would you carry out each reaction?



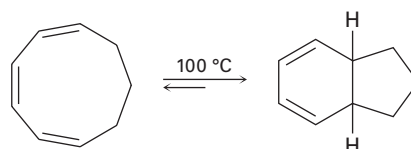
26.14 The following thermal isomerization occurs under relatively mild conditions. Identify the pericyclic reactions involved, and show how the rearrangement occurs.



26.15 Would you expect the following reaction to proceed in a conrotatory or disrotatory manner? Show the stereochemistry of the cyclobutene product, and explain your answer.

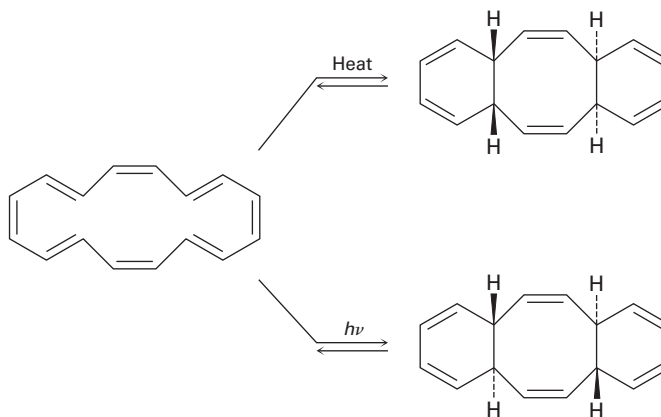


26.16 Heating (1*Z*,3*Z*,5*Z*)-cyclonona-1,3,5-triene to 100 °C causes cyclization and formation of a bicyclic product. Is the reaction conrotatory or disrotatory? What is the stereochemical relationship of the two hydrogens at the ring junctions, cis or trans?



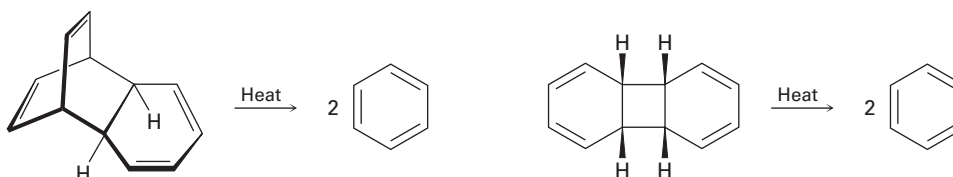
(1*Z*,3*Z*,5*Z*)-Cyclonona-1,3,5-triene

- 26.17** (*2E,4Z,6Z,8E*)-Deca-2,4,6,8-tetraene has been cyclized to give 7,8-dimethylcycloocta-1,3,5-triene. Predict the manner of ring closure—conrotatory or disrotatory—for both thermal and photochemical reactions, and predict the stereochemistry of the product in each case.
- 26.18** Answer Problem 26.17 for the thermal and photochemical cyclizations of (*2E,4Z,6Z,8Z*)-deca-2,4,6,8-tetraene.
- 26.19** The cyclohexadecaoctaene shown isomerizes to two different isomers, depending on reaction conditions. Explain the observed results, and indicate whether each reaction is conrotatory or disrotatory.

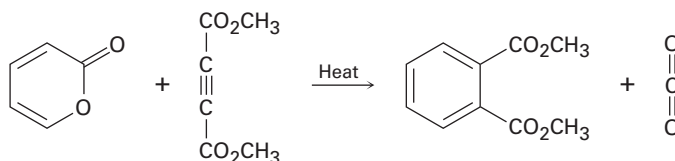


Cycloaddition Reactions

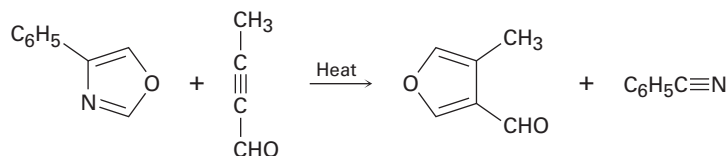
- 26.20** Which of the following reactions is more likely to occur? Explain.



- 26.21** The following reaction takes place in two steps, one of which is a cycloaddition and the other of which is a *reverse* cycloaddition. Identify the two pericyclic reactions, and show how they occur.

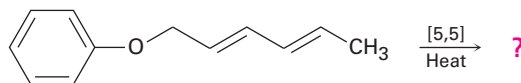


- 26.22** Two sequential pericyclic reactions are involved in the following furan synthesis. Identify them, and propose a mechanism for the transformation.

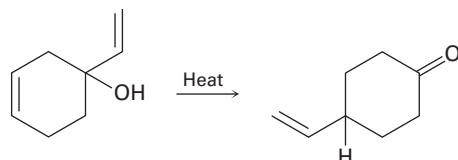


Sigmatropic Rearrangements

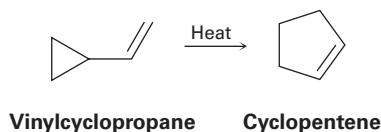
- 26.23 Predict the product of the following pericyclic reaction. Is this [5,5] shift a suprafacial or an antarafacial process?



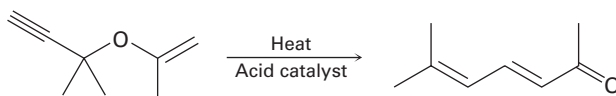
- 26.24 Propose a pericyclic mechanism to account for the following transformation:



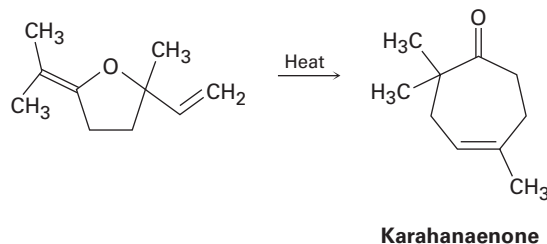
- 26.25 Vinyl-substituted cyclopropanes undergo thermal rearrangement to yield cyclopentenes. Propose a mechanism for the reaction, and identify the pericyclic process involved.



- 26.26 The following synthesis of dienones occurs readily. Propose a mechanism to account for the results, and identify the kind of pericyclic reaction involved.



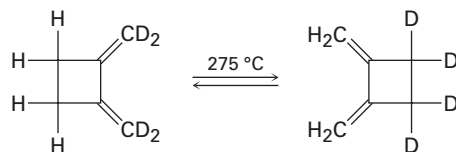
- 26.27 Karahanaenone, a terpenoid isolated from oil of hops, has been synthesized by the thermal reaction shown. Identify the kind of pericyclic reaction, and explain how karahanaenone is formed.



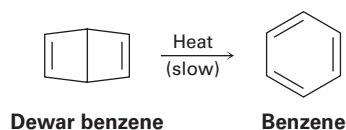
General Problems

- 26.28 What stereochemistry—antarafacial or suprafacial—would you expect to observe in the following reactions?
- A photochemical [1,5] sigmatropic rearrangement
 - A thermal [4 + 6] cycloaddition
 - A thermal [1,7] sigmatropic rearrangement
 - A photochemical [2 + 6] cycloaddition

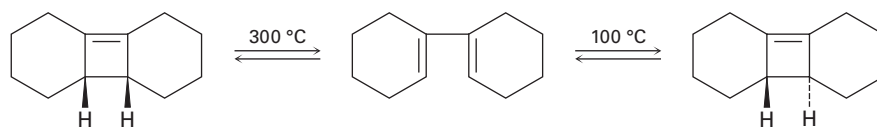
- 26.29** The following thermal rearrangement involves two pericyclic reactions in sequence. Identify them, and propose a mechanism to account for the observed result.



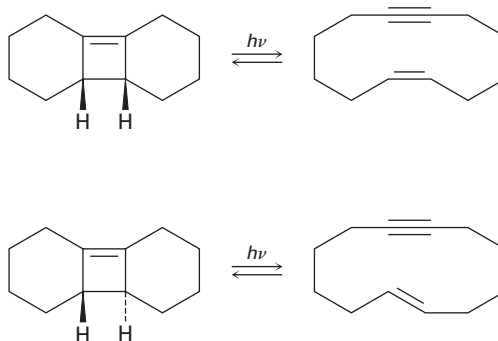
- 26.30** Bicyclohexadiene, also known as *Dewar benzene*, is extremely stable despite the fact that its rearrangement to benzene is energetically favored. Explain why the rearrangement is so slow.



- 26.31** Ring-opening of the *trans*-cyclobutene isomer shown takes place at much lower temperature than a similar ring-opening of the *cis*-cyclobutene isomer. Explain the temperature effect, and identify the stereochemistry of each reaction as either conrotatory or disrotatory.



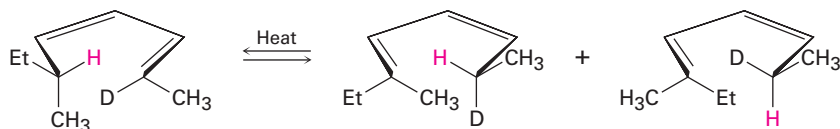
- 26.32** Photolysis of the *cis*-cyclobutene isomer in Problem 26.31 yields *cis*-cyclododecaen-7-yne, but photolysis of the *trans* isomer yields *trans*-cyclododecaen-7-yne. Explain these results, and identify the type and stereochemistry of the pericyclic reaction.



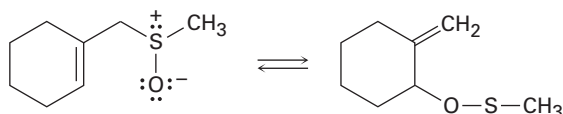
- 26.33** The ^1H NMR spectrum of bullvalene at 100 °C consists only of a single peak at 4.22 δ . Explain.



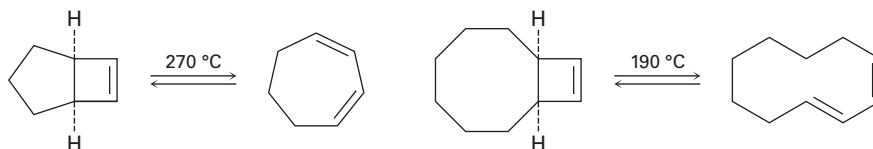
- 26.34** The following rearrangement was devised and carried out to prove the stereochemistry of [1,5] sigmatropic hydrogen shifts. Explain how the observed result confirms the predictions of orbital symmetry.



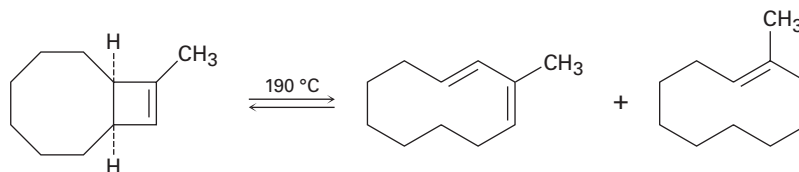
- 26.35** The following reaction is an example of a [2,3] sigmatropic rearrangement. Would you expect the reaction to be suprafacial or antarafacial? Explain.



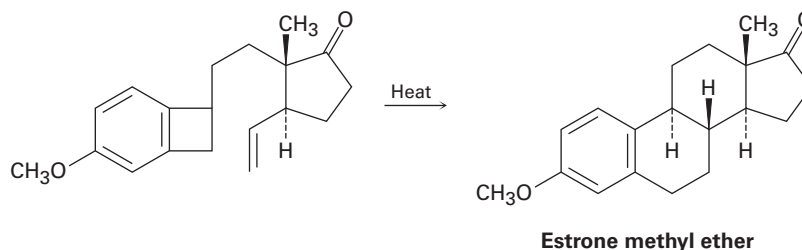
- 26.36** When the compound having a cyclobutene fused to a five-membered ring is heated, (1*Z*,3*Z*)-cyclohepta-1,3-diene is formed. When the related compound having a cyclobutene fused to an eight-membered ring is heated, however, (1*E*,3*Z*)-cyclodeca-1,3-diene is formed. Explain these results, and suggest a reason why opening of the eight-membered ring occurs at a lower temperature.



- 26.37** In light of your answer to Problem 26.36, explain why a mixture of products occurs in the following reaction:



- 26.38** The sex hormone estrone has been synthesized by a route that involves the following step. Identify the pericyclic reactions involved, and propose a mechanism.

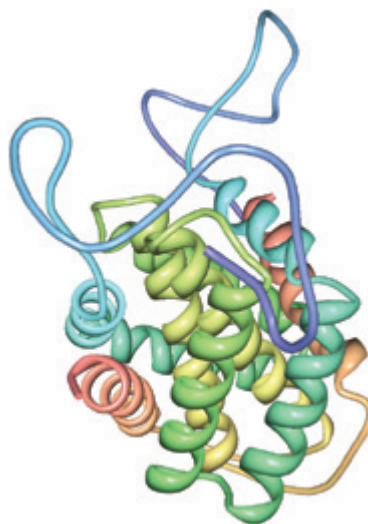


CONTENTS

- 27-1** Chain-Growth Polymers
- 27-2** Stereochemistry of Polymerization: Ziegler–Natta Catalysts
- 27-3** Copolymers
- 27-4** Step-Growth Polymers
- 27-5** Olefin Metathesis Polymerization
- 27-6** Polymer Structure and Physical Properties

SOMETHING EXTRA

Biodegradable Polymers



Structure of the C-terminal domain of spider dragline silk protein, a biopolymer used to make the outer rim and spokes of a spider web.

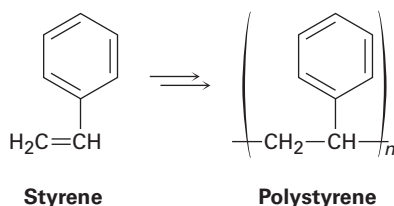
Image from the RCSB PDB (www.rcsb.org) of PDB ID 3LR2 (G. Askarieh, M. Hedhammar, K. Nordling, A. Saenz, C. Casals, A Rising, J. Johansson, S.D. Knight (2010) Self-assembly of spider silk proteins is controlled by a pH-sensitive relay Nature 465(7295): 236-238).

WHY THIS CHAPTER?

Our treatment of polymers has thus far been dispersed over several chapters, but it's also important to take a more comprehensive view. In the present chapter, we'll look further at how polymers are made, and we'll see how polymer structure correlates with physical properties. No course in organic chemistry would be complete without a look at polymers.

Polymers are a fundamental part of the modern world, used in everything from coffee cups to cars to clothing. In medicine, too, their importance is growing for purposes as diverse as cardiac pacemakers, artificial heart valves, and biodegradable sutures.

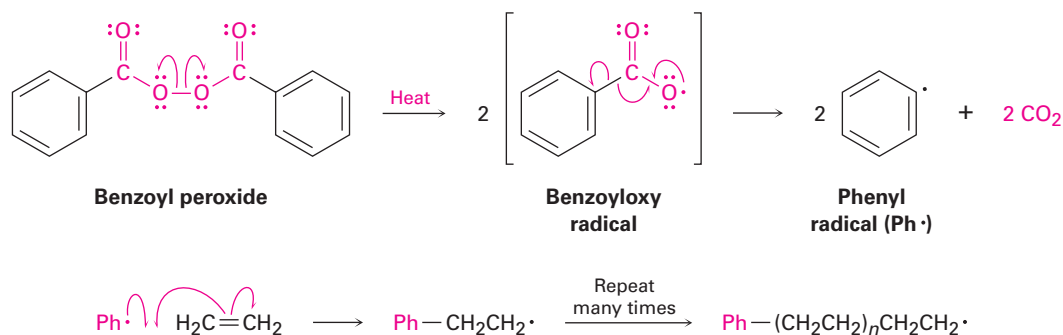
We've seen on several occasions in previous chapters that a **polymer**, whether synthetic or biological, is a large molecule built up by repetitive bonding together of many smaller units, or **monomers**. Polyethylene, for instance, is a synthetic polymer made from ethylene (Section 8-10), nylon is a synthetic polyamide made from a diacid and a diamine (Section 16-9), and proteins are biological polyamides made from amino acids. Note that polymers are often drawn by indicating their repeating unit in parentheses. The repeat unit in polystyrene, for example, comes from the monomer styrene.



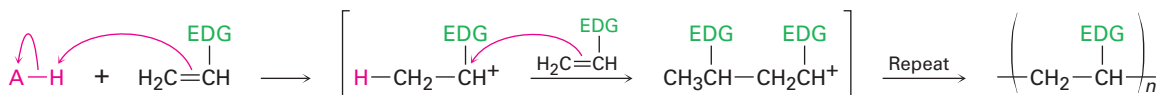
27-1 Chain-Growth Polymers

Synthetic polymers are classified by their method of synthesis as either *chain-growth* or *step-growth*. The categories are somewhat imprecise but nevertheless provide a useful distinction. Chain-growth polymers are produced by chain-reaction polymerization in which an initiator adds to a carbon-carbon double bond of an unsaturated substrate (a *vinyl monomer*) to yield a reactive intermediate. This intermediate reacts with a second molecule of monomer to yield a new intermediate, which reacts with a third monomer unit, and so on.

The initiator can be a radical, an acid, or a base. Historically, as we saw in Section 8-10, radical polymerization was the most common method because it can be carried out with practically any vinyl monomer.

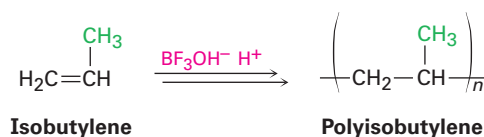


Acid-catalyzed (cationic) polymerization, by contrast, is effective only with vinyl monomers that contain an electron-donating group (EDG) capable of stabilizing the chain-carrying carbocation intermediate.

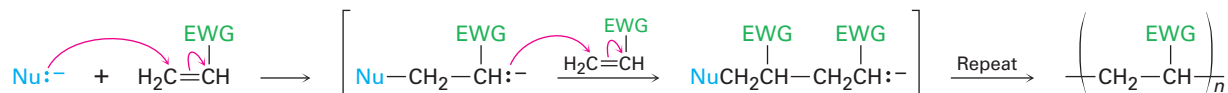


where **EDG** = an electron-donating group

Isobutylene (2-methylpropene) is a good example of a monomer that polymerizes rapidly under cationic conditions. The reaction is carried out commercially at -80°C , using BF_3 and a small amount of water to generate the $\text{BF}_3\text{OH}^- \text{H}^+$ catalyst. The product is used in the manufacture of truck and bicycle inner tubes.

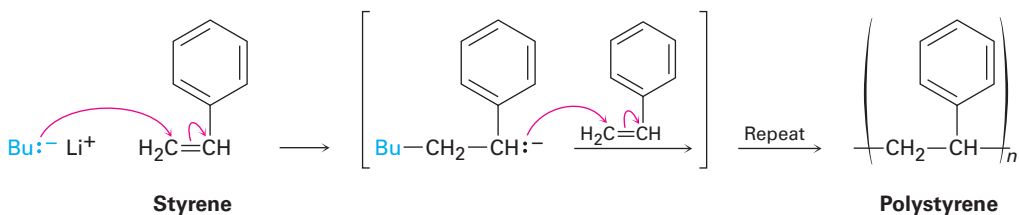


Vinyl monomers with electron-withdrawing groups (EWG) can be polymerized by basic (anionic) catalysts. The chain-carrying step is conjugate nucleophilic addition of an anion to the unsaturated monomer (Section 14-11).

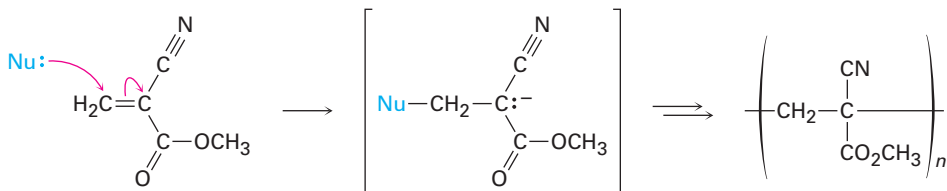


where EWG = an electron-withdrawing group

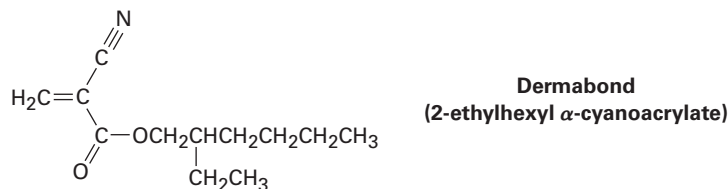
Acrylonitrile ($\text{H}_2\text{C}=\text{CHCN}$), methyl methacrylate [$\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{CO}_2\text{CH}_3$], and styrene ($\text{H}_2\text{C}=\text{CHC}_6\text{H}_5$) can all be polymerized anionically. The polystyrene used in foam coffee cups, for example, is prepared by anionic polymerization of styrene using butyllithium as the catalyst.



An interesting example of anionic polymerization accounts for the remarkable properties of “super glue,” one drop of which can support up to 2000 lb. Super glue is simply a solution of pure methyl α -cyanoacrylate, which has two electron-withdrawing groups that make anionic addition particularly easy. Trace amounts of water or bases on the surface of an object are sufficient to initiate polymerization of the cyanoacrylate and bind articles together. Skin is a good source of the necessary basic initiators, and many people have found their fingers stuck together after inadvertently touching super glue. So good is super glue at binding tissues together that related cyanoacrylate esters, such as Dermabond, are often used in place of sutures to close wounds.

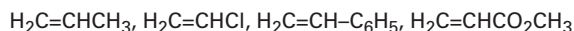


Methyl α -cyanoacrylate



PROBLEM 27.1

Order the following monomers with respect to their expected reactivity toward cationic polymerization, and explain your answer:

**PROBLEM 27.2**

Order the following monomers with respect to their expected reactivity toward anionic polymerization, and explain your answer:

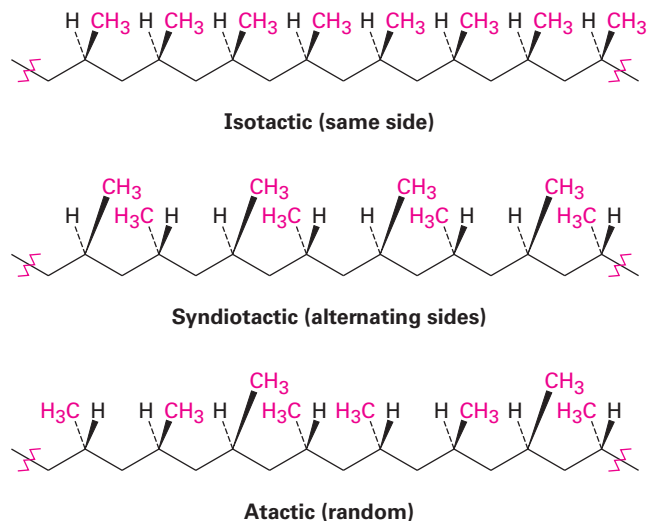
**PROBLEM 27.3**

Polystyrene is produced commercially by reaction of styrene with butyllithium as an anionic initiator. Using resonance structures, explain how the chain-carrying intermediate is stabilized.

27-2 Stereochemistry of Polymerization: Ziegler–Natta Catalysts

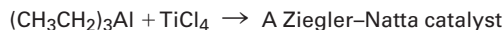
Although we didn't point it out when discussing chain-growth polymers in Section 8-10, the polymerization of a substituted vinyl monomer can lead to a polymer with numerous chirality centers in its chain. Propylene, for example, might polymerize with any of the three stereochemical outcomes shown in **FIGURE 27.1**. The polymer having all methyl groups on the same side of the zig-zag backbone is called **isotactic**, the one in which the methyl groups alternate regularly on opposite sides of the backbone is called **syndiotactic**, and the one having the methyl groups randomly oriented is called **atactic**.

FIGURE 27.1 Isotactic, syndiotactic, and atactic forms of polypropylene.



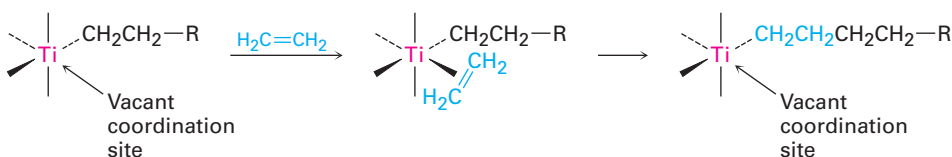
The three different stereochemical forms of polypropylene all have somewhat different properties, and all can be made by using the right polymerization catalyst. Propylene polymerization using radical initiators does not work well, but polymerization using *Ziegler–Natta catalysts* allows preparation of isotactic, syndiotactic, and atactic polypropylene.

Ziegler–Natta catalysts—there are many different formulations—are organometallic transition-metal complexes prepared by treatment of an alkylaluminum with a titanium compound. Triethylaluminum and titanium tetrachloride form a typical preparation.



Following their introduction in 1953, Ziegler–Natta catalysts revolutionized the field of polymer chemistry because of two advantages: first, the resultant polymers are linear, with practically no chain branching, and second, they are stereochemically controllable. Isotactic, syndiotactic, and atactic forms can all be produced, depending on the catalyst system used.

The active form of a Ziegler–Natta catalyst is an alkyltitanium intermediate with a vacant coordination site on the metal. Coordination of alkene monomer to the titanium occurs, and the coordinated alkene then inserts into the carbon–titanium bond to extend the alkyl chain. A new coordination site opens up during the insertion step, so the process repeats indefinitely.



The linear polyethylene produced by the Ziegler–Natta process, called *high-density polyethylene*, is a highly crystalline polymer with 4000 to 7000 ethylene units per chain and molecular weights in the range 100,000 to 200,000 amu. High-density polyethylene has greater strength and heat resistance than the branched product of radical-induced polymerization, called *low-density polyethylene*, and is used to produce plastic squeeze bottles and molded housewares.

Polyethylenes of even higher molecular weights are produced for specialty applications. So-called high-molecular-weight (HMW) polyethylene contains 10,000 to 18,000 monomer units per chain (MW = 300,000 to 500,000 amu) and is used for underground pipes and large containers. Ultrahigh-molecular-weight (UHMW) polyethylene contains more than 100,000 monomer units per chain and has molecular weights ranging from 3,000,000 to 6,000,000 amu. It is used in bearings, conveyor belts, and bulletproof vests, among other applications requiring unusual wear resistance.

PROBLEM 27.4

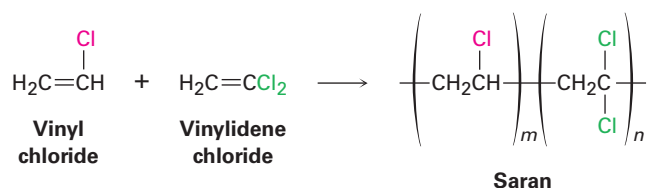
Vinylidene chloride, $\text{H}_2\text{C}=\text{CCl}_2$, does not polymerize in isotactic, syndiotactic, and atactic forms. Explain.

PROBLEM 27.5

Polymers such as polypropylene contain a large number of chirality centers. Would you therefore expect samples of isotactic, syndiotactic, or atactic polypropylene to rotate plane-polarized light? Explain.

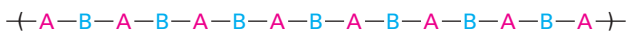
27-3 Copolymers

Up to this point we've discussed only **homopolymers**—polymers that are made up of identical repeating units. In practice, however, *copolymers* are more important commercially. **Copolymers** are obtained when two or more different monomers are allowed to polymerize together. For example, copolymerization of vinyl chloride with vinylidene chloride (1,1-dichloroethylene) in a 1:4 ratio leads to the polymer Saran.



Copolymerization of monomer mixtures often leads to materials with properties quite different from those of either corresponding homopolymer, giving the polymer chemist a vast amount of flexibility for devising new materials. **TABLE 27.1** lists some common copolymers and their commercial applications.

Several different types of copolymers can be defined, depending on the distribution of monomer units in the chain. If monomer A is copolymerized with monomer B, for instance, the resultant product might have a random distribution of the two units throughout the chain, or it might have an alternating distribution.

**Random copolymer****Alternating copolymer**

The exact distribution of monomer units depends on the initial proportions of the two reactant monomers and their relative reactivities. In practice, neither perfectly random nor perfectly alternating copolymers are usually found. Most copolymers have many random imperfections.

Two other forms of copolymers that can be prepared under certain conditions are called *block copolymers* and *graft copolymers*. **Block copolymers** are those in which different blocks of identical monomer units alternate with each other; **graft copolymers** are those in which homopolymer branches

TABLE 27.1 Some Common Copolymers and Their Uses

Monomers	Structures	Trade name	Uses
Vinyl chloride Vinylidene chloride	$\begin{array}{c} \text{H} \quad \text{Cl} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} + \begin{array}{c} \text{H} \quad \text{Cl} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{Cl} \end{array}$	Saran	Fibers, food packaging
Styrene Buta-1,3-diene	$\begin{array}{c} \text{H} \quad \text{C}_6\text{H}_5 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} + \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	SBR (styrene–butadiene rubber)	Tires, rubber articles
Hexafluoropropene Vinylidene fluoride	$\begin{array}{c} \text{F} \quad \text{CF}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{F} \quad \text{F} \end{array} + \begin{array}{c} \text{H} \quad \text{F} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{F} \end{array}$	Viton	Gaskets, seals
Acrylonitrile Buta-1,3-diene	$\begin{array}{c} \text{H} \quad \text{CN} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} + \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	Nitrile rubber	Adhesives, hoses
Isobutylene Buta-1,3-diene	$\begin{array}{c} \text{H} \quad \text{CH}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{CH}_3 \end{array} + \begin{array}{c} \text{H}_3\text{C} \quad \text{H} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	Butyl rubber	Inner tubes
Acrylonitrile Buta-1,3-diene Styrene	$\begin{array}{c} \text{H} \quad \text{CN} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} + \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} + \begin{array}{c} \text{H} \quad \text{C}_6\text{H}_5 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	ABS (monomer initials)	Pipes, high-impact applications

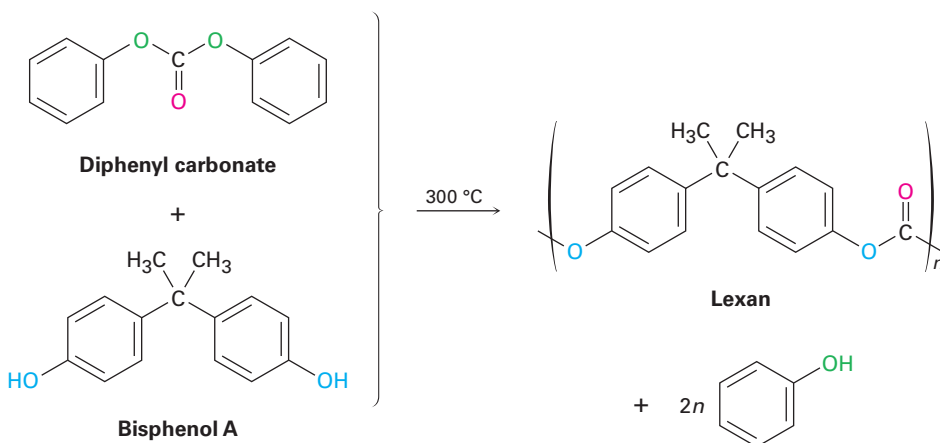
of one monomer unit are “grafted” onto a homopolymer chain of another monomer unit.



Block copolymers are prepared by initiating the polymerization of one monomer as if growing a homopolymer chain and then adding an excess of the second monomer to the still-active reaction mix. Graft copolymers are made by gamma irradiation of a completed homopolymer chain in the presence of the second monomer. The high-energy irradiation knocks hydrogen atoms off

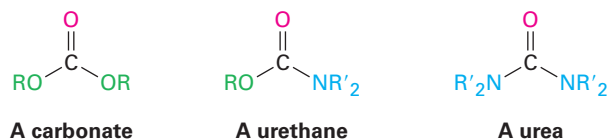
Polycarbonates

Polycarbonates are like polyesters, but their carbonyl group is linked to two $-OR$ groups, $[O=C(OR)_2]$. Lexan, for instance, is a polycarbonate prepared from diphenyl carbonate and a diphenol called bisphenol A. Lexan has an unusually high impact strength, making it valuable for use in machinery housings, telephones, bicycle safety helmets, and bulletproof glass.

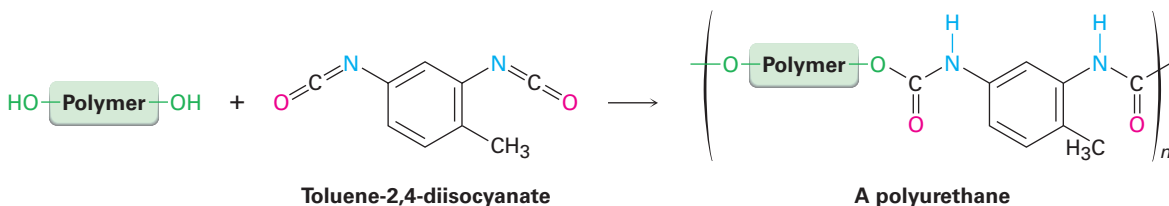


Polyurethanes

A *urethane* is a carbonyl-containing functional group in which the carbonyl carbon is bonded to both an $-OR$ group and an $-NR_2$ group. As such, a urethane is halfway between a carbonate and a urea.

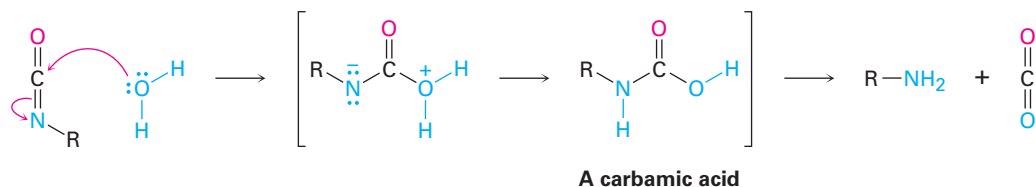


A urethane is typically prepared by nucleophilic addition reaction between an alcohol and an isocyanate ($R-N=C=O$), so a **polyurethane** is prepared by reaction between a diol and a diisocyanate. The diol is usually a low-molecular-weight polymer (MW \approx 1000 amu) with hydroxyl end-groups; the diisocyanate is often toluene-2,4-diisocyanate.



Several different kinds of polyurethanes are produced, depending on the nature of the polymeric alcohol used. One major use of polyurethane is in the stretchable spandex fibers used for bathing suits and athletic gear. These

polyurethanes have a fairly low degree of cross-linking so that the resultant polymer is soft and elastic. A second major use of polyurethanes is in the foams used for insulation. Foaming occurs when a small amount of water is added during polymerization, giving a carbamic acid intermediate that spontaneously loses bubbles of CO_2 .



Polyurethane foams are generally made using a *polyalcohol* rather than a diol as the monomer so that the polymer has a high amount of three-dimensional cross-linking. The result is a rigid but very light foam suitable for use as thermal insulation in building construction and portable ice chests.

PROBLEM 27.8

Poly(ethylene terephthalate), or PET, is a polyester used to make soft-drink bottles. It is prepared by reaction of ethylene glycol with benzene-1,4-dicarboxylic acid (terephthalic acid). Draw the structure of PET.

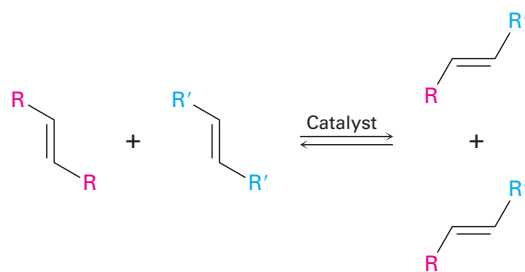
PROBLEM 27.9

Show the mechanism of the nucleophilic addition reaction of an alcohol with an isocyanate to yield a urethane.

27-5 Olefin Metathesis Polymerization

Perhaps the most important advance in polymer synthesis in recent years has been the development of *olefin metathesis polymerization*. At its simplest, an olefin metathesis reaction is one in which two olefins (alkenes) exchange substituents on their double bonds.

An olefin metathesis reaction



Olefin metathesis catalysts, such as the Grubbs catalyst now in common use, contain a carbon–metal double bond (usually to ruthenium, Ru) and have the general structure $\text{M}=\text{CHR}$. They function by reacting reversibly with an alkene to form a four-membered, metal-containing intermediate called a

metallacycle, which immediately opens to give a different catalyst and a different alkene. The mechanism is shown in **FIGURE 27.2**.

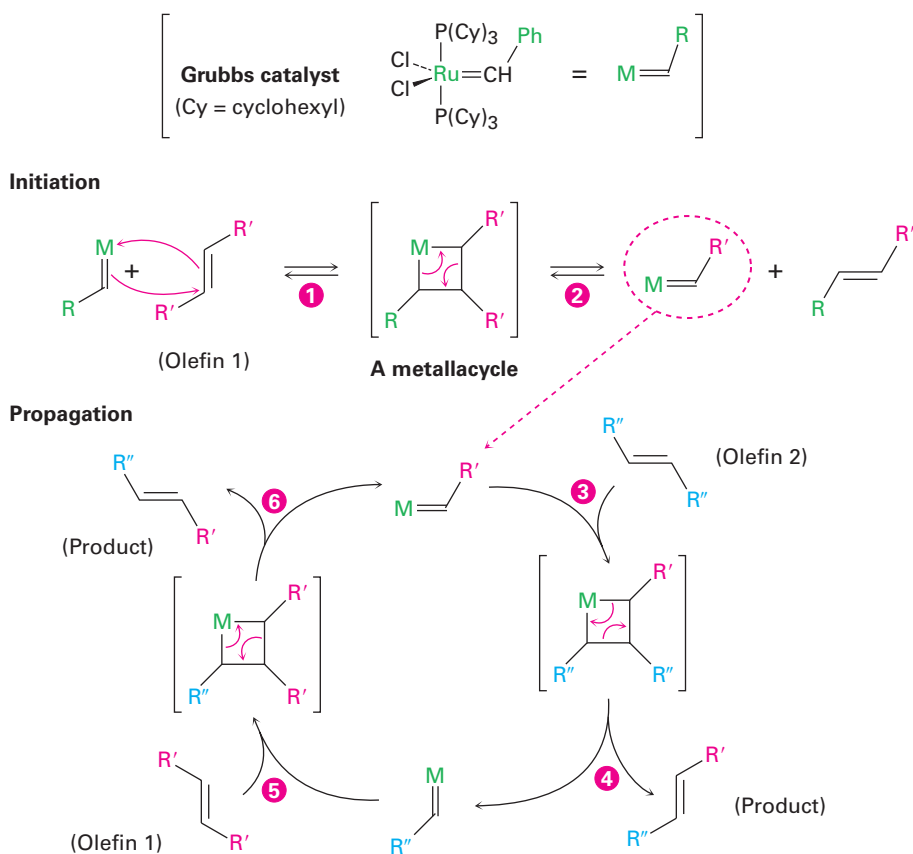
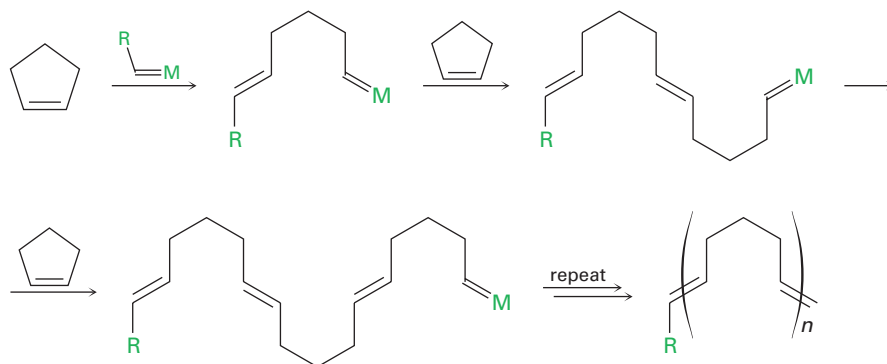


FIGURE 27.2 Mechanism of the olefin metathesis reaction. The process is initiated by a two-step sequence that involves **1** reaction of the catalyst and olefin 1 to give a four-membered metallacycle intermediate, followed by **2** ring-opening to give a different form of catalyst that contains part of olefin 1. **3** Reaction of this new catalyst with olefin 2 gives another metallacycle intermediate, **4** which opens to give metathesis product and another form of catalyst. **5**, **6** The repeating ring-forming and ring-opening steps then continue.

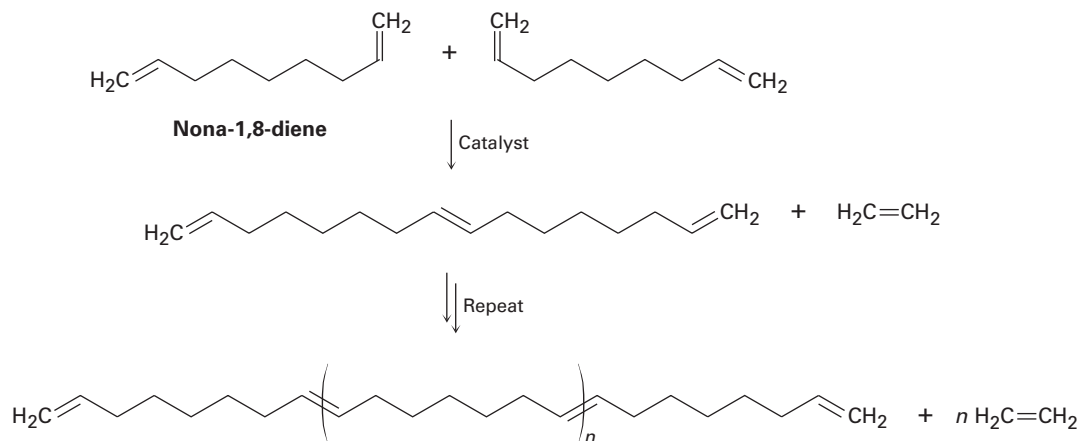
There are several methods for implementing the olefin metathesis reaction to prepare polymers. One method, called *ring-opening metathesis polymerization*, or ROMP, involves use of a moderately strained cycloalkene, such as cyclopentene. The strain of the ring favors ring-opening, thereby driving formation of the open-chain product. The polymer that results has double bonds spaced regularly along the chain, allowing for either hydrogenation or further functionalization if desired.

Ring-opening metathesis polymerization (ROMP)

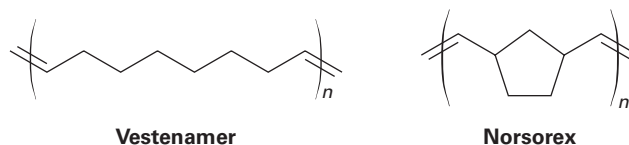


A second method of using olefin metathesis to prepare polymers is by *acyclic diene metathesis*, or ADMET. As the name suggests, ADMET involves olefin metathesis of an open-chain substrate with two double bonds at the ends of a long chain, such as nona-1,8-diene. As the reaction proceeds, the gaseous ethylene by-product escapes, thereby driving the equilibrium toward polymer product. So efficient is the reaction that polymers with molecular weights as high as 80,000 amu have been prepared.

Acyclic diene metathesis (ADMET)



The ROMP and ADMET procedures are particularly valuable because the metathesis reaction is compatible with the presence in the olefin monomer of many different functional groups. In addition, the double bonds in the polymers allow still more flexibility for further manipulations. Among the commercial polymers produced by olefin metathesis are Vestenamer, used in the manufacture of tires and other molded rubber objects, and Norsorex, used in the automobile industry as a sealing material.



PROBLEM 27.10

Look at the structures of Vestenamer and Norsorex, and show how they might be made by olefin metathesis polymerization.

27-6 Polymer Structure and Physical Properties

Polymers aren't really that different from other organic molecules. They're much larger, of course, but their chemistry is similar to that of analogous small molecules. Thus, the alkane chains of polyethylene undergo radical-initiated halogenation, the aromatic rings of polystyrene undergo typical electrophilic

aromatic substitution reactions, and the amide linkages of a nylon are hydrolyzed by aqueous base.

The major difference between small and large organic molecules is in their physical properties. For instance, their large size means that polymers experience substantially larger van der Waals forces than do small molecules (Section 2-12). But because van der Waals forces operate only at close distances, they are strongest in polymers like high-density polyethylene in which chains can pack together closely in a regular way. Many polymers, in fact, have regions that are essentially crystalline. These regions, called **crystallites**, consist of highly ordered portions in which the zigzag polymer chains are held together by van der Waals forces (**FIGURE 27.3**).

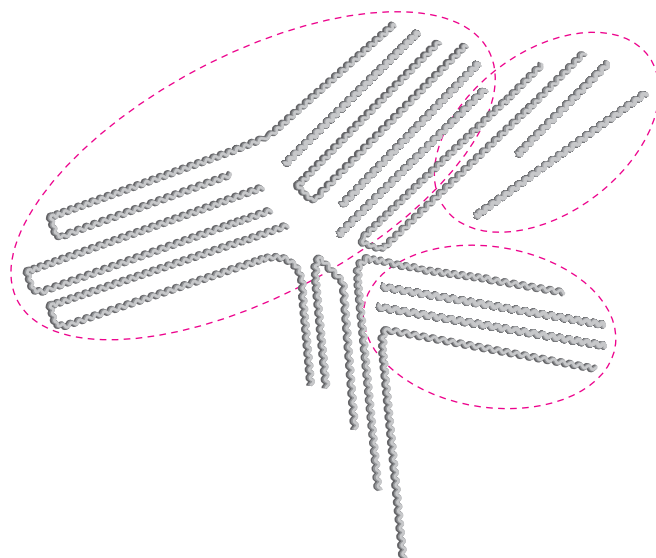


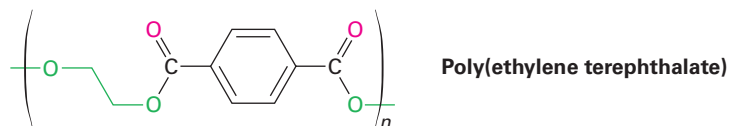
FIGURE 27.3 Crystallites in linear polyethylene. The long polymer chains are arranged in parallel lines in the crystallite regions.

As you might expect, polymer crystallinity is strongly affected by the steric requirements of substituent groups on the chains. Linear polyethylene is highly crystalline, but poly(methyl methacrylate) is noncrystalline because the chains can't pack closely together in a regular way. Polymers with a high degree of crystallinity are generally hard and durable. When heated, the crystalline regions melt at the **melt transition temperature, T_m** , to give an amorphous material.

Noncrystalline, amorphous polymers like poly(methyl methacrylate), sold under the trade name Plexiglas, have little or no long-range ordering among chains but can nevertheless be very hard at room temperature. When heated, the hard amorphous polymer becomes soft and flexible at a point called the **glass transition temperature, T_g** . Much of the art in polymer synthesis lies in finding methods for controlling the degree of crystallinity and the glass transition temperature, thereby imparting useful properties to the polymer.

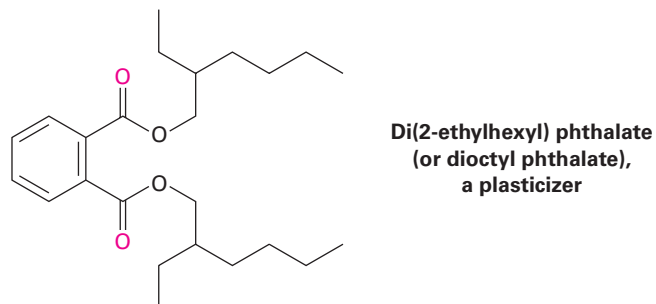
In general, polymers can be divided into four major categories, depending on their physical behavior: *thermoplastics*, *fibers*, *elastomers*, and *thermosetting resins*. **Thermoplastics** are the polymers most people think of when the word *plastic* is mentioned. These polymers have a high T_g and are therefore hard at room temperature but become soft and viscous when heated. As a result, they can be molded into toys, beads, telephone housings, or any of a thousand other items. Because thermoplastics have little or no cross-linking,

the individual chains can slip past one another in the melt. Some thermoplastic polymers, such as poly(methyl methacrylate) and polystyrene, are amorphous and noncrystalline; others, such as polyethylene and nylon, are partially crystalline. Among the better-known thermoplastics is poly(ethylene terephthalate), or PET, used for making plastic soft-drink bottles.



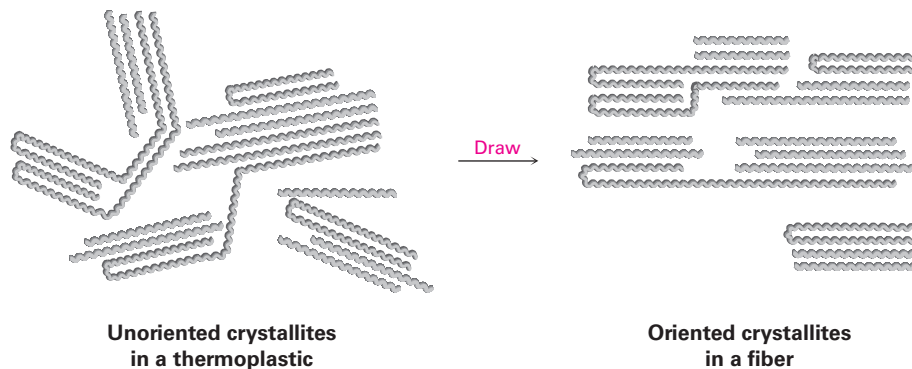
Plasticizers—small organic molecules that act as lubricants between chains—are usually added to thermoplastics to keep them from becoming brittle at room temperature. An example is poly(vinyl chloride), which is brittle when pure but becomes supple and pliable when a plasticizer is added. In fact, most drip bags used in hospitals to deliver intravenous saline solutions are made of poly(vinyl chloride), although replacements are appearing.

Dialkyl phthalates such as di(2-ethylhexyl) phthalate (generally called dioctyl phthalate) are commonly used as plasticizers although questions about their safety have been raised. The U.S. Food and Drug Administration (FDA) has advised the use of alternative materials in compromised patients and infants but has found no evidence of toxicity for healthy individuals. In addition, children's toys that contain phthalates have been banned in the United States.



Fibers are thin threads produced by extruding a molten polymer through small holes in a die, or spinneret. The fibers are then cooled and drawn out, which orients the crystallite regions along the axis of the fiber and adds considerable tensile strength (FIGURE 27.4). Nylon, Dacron, and polyethylene all have the semicrystalline structure necessary for drawing into oriented fibers.

FIGURE 27.4 Oriented crystallite regions in a polymer fiber.



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Elastomers are amorphous polymers that have the ability to stretch out and spring back to their original shapes. These polymers must have low T_g values and a small amount of cross-linking to prevent the chains from slipping over one another. In addition, the chains must have an irregular shape to prevent crystallite formation. When stretched, the randomly coiled chains straighten out and orient along the direction of the pull. Van der Waals forces are too weak and too few to maintain this orientation, however, so the elastomer reverts to its random coiled state when the stretching force is released (**FIGURE 27.5**).

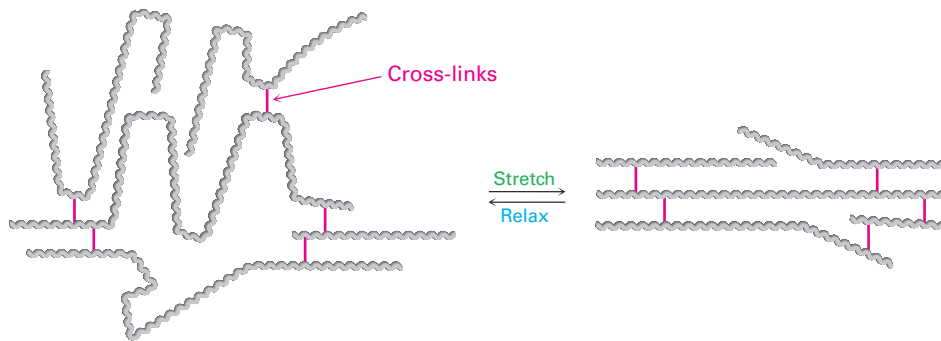


FIGURE 27.5 Unstretched and stretched forms of an elastomer.

Natural rubber (Chapter 8 *Something Extra*) is the most common example of an elastomer. Rubber has the long chains and occasional cross-links needed for elasticity, but its irregular geometry prevents close packing of the chains into crystallites. Gutta-percha, by contrast, is highly crystalline and is not an elastomer (**FIGURE 27.6**).

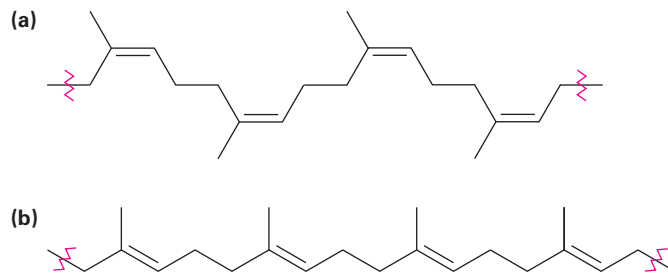
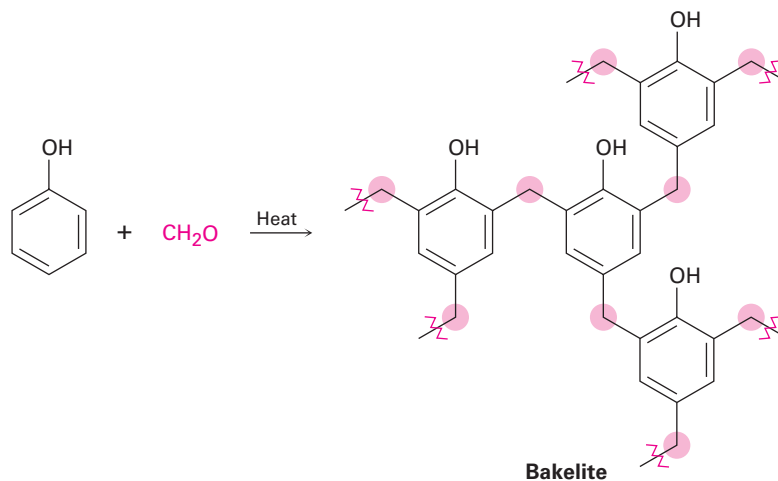


FIGURE 27.6 Natural rubber and gutta percha. (a) Natural rubber is elastic and noncrystalline because of its cis double-bond geometry, but (b) gutta-percha is nonelastic and crystalline because its geometry allows for better packing together of chains.

Thermosetting resins are polymers that become highly cross-linked and solidify into a hard, insoluble mass when heated. *Bakelite*, a thermosetting resin first produced in 1907, has been in commercial use longer than any other synthetic polymer. It is widely used for molded parts, adhesives, coatings, and even high-temperature applications such as missile nose cones.

Chemically, Bakelite is a *phenolic resin*, produced by reaction of phenol and formaldehyde. On heating, water is eliminated, many cross-links form, and the polymer sets into a rocklike mass. The cross-linking in Bakelite and

other thermosetting resins is three-dimensional and is so extensive that we can't really speak of polymer "chains." A piece of Bakelite is essentially one large molecule.



PROBLEM 27.11

What product would you expect to obtain from catalytic hydrogenation of natural rubber? Would the product be syndiotactic, atactic, or isotactic?

PROBLEM 27.12

Propose a mechanism to account for the formation of Bakelite from acid-catalyzed polymerization of phenol and formaldehyde.

SOMETHING EXTRA

Biodegradable Polymers

The high chemical stability of many polymers is both a blessing and a curse. Heat resistance, wear resistance, and long life are valuable characteristics of clothing fibers, bicycle helmets, underground pipes, food wrappers, and many other items. Yet when those items outlive their usefulness, disposal becomes a problem.

Recycling of unwanted polymers is the best solution, and six types of plastics in common use are frequently stamped with identifying codes assigned



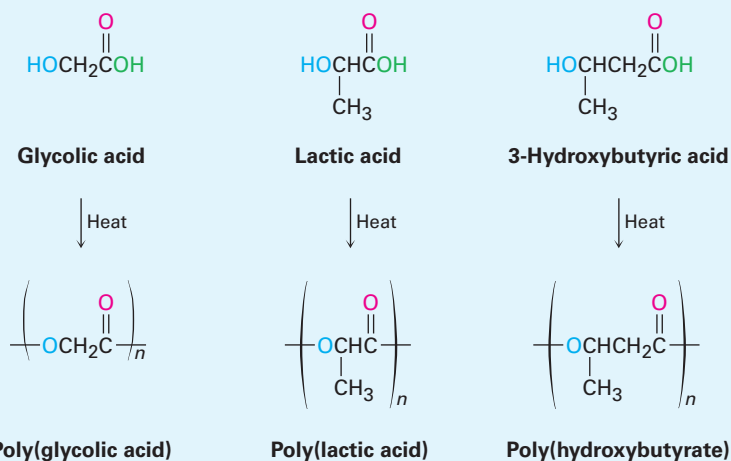
What happens to the plastics that end up here?

by the Society of the Plastics Industry (TABLE 27.2). After being sorted by type, the items to be recycled are shredded into small chips, washed, dried, and melted for reuse. Soft-drink bottles, for instance, are made from recycled poly(ethylene terephthalate), trash bags are made from recycled low-density polyethylene, and garden furniture is made from recycled polypropylene and mixed plastics.

Frequently, however, plastics are simply thrown away rather than recycled, and much work has therefore been carried out on developing *biodegradable* polymers,

TABLE 27.2 Recyclable Plastics

Polymer	Recycling code	Use
Poly(ethylene terephthalate)	1 – PET	Soft-drink bottles
High-density polyethylene	2 – HDPE	Bottles
Poly(vinyl chloride)	3 – V	Floor mats
Low-density polyethylene	4 – LDPE	Grocery bags
Polypropylene	5 – PP	Furniture
Polystyrene	6 – PS	Molded articles
Mixed plastics	7	Benches, plastic lumber



which can be broken down rapidly in landfills by soil microorganisms. Among the most common biodegradable polymers are polyglycolic acid (PGA), polylactic acid (PLA), and polyhydroxybutyrate (PHB). All are polyesters and are therefore susceptible to hydrolysis of their ester links. Copolymers of PGA with PLA have found a particularly wide range of uses. A 90/10 copolymer of polyglycolic acid with polylactic acid is used to make absorbable sutures that are degraded and absorbed by the body within 90 days after surgery.

In Europe, interest has centered particularly on poly(hydroxybutyrate), which can be made into films for packaging as well as into molded items. The polymer degrades within 4 weeks in landfills, both by ester hydrolysis and by an E1cB elimination reaction of the oxygen atom β to the carbonyl group. The use of poly(hydroxybutyrate) is limited at present by its cost—about four times that of polypropylene.

SUMMARY

Synthetic polymers can be classified as either chain-growth or step-growth. Chain-growth polymers are prepared by chain-reaction polymerization of vinyl monomers in the presence of a radical, an anion, or a cation initiator. Radical polymerization is sometimes used, but alkenes such as 2-methylpropene that have electron-donating substituents on the double bond polymerize easily by a cationic route through carbocation intermediates. Similarly, monomers such as methyl α -cyanoacrylate that have electron-withdrawing substituents on the double bond polymerize by an anionic, conjugate addition pathway.

KEY WORDS

atactic, 928
 block copolymer, 930
 copolymer, 930
 crystallite, 937
 elastomer, 939
 fiber, 938

glass transition temperature (T_g), 937
 graft copolymer, 930
 homopolymer, 930
 isotactic, 928
 melt transition temperature (T_m), 937
 monomer, 925
 plasticizer, 938
 polycarbonate, 933
 polymer, 925
 polyurethane, 933
 syndiotactic, 928
 thermoplastic, 937
 thermosetting resin, 939
 Ziegler–Natta catalyst, 929

Copolymerization of two monomers gives a product with properties different from those of either homopolymer. **Graft copolymers** and **block copolymers** are two examples.

Alkene polymerization can be carried out in a controlled manner using a **Ziegler–Natta catalyst**. Ziegler–Natta polymerization minimizes the amount of chain branching in the polymer and leads to stereoregular chains—either **isotactic** (substituents on the same side of the chain) or **syndiotactic** (substituents on alternate sides of the chain), rather than **atactic** (substituents randomly disposed).

Step-growth polymers, the second major class of polymers, are prepared by reactions between difunctional molecules, with the individual bonds in the polymer formed independently of one another. **Polycarbonates** are formed from a diester and a diol, and **polyurethanes** are formed from a diisocyanate and a diol.

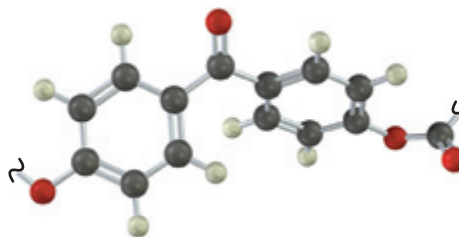
The chemistry of synthetic polymers is similar to the chemistry of small molecules with the same functional groups, but the physical properties of polymers are greatly affected by size. Polymers can be classified by physical property into four groups: **thermoplastics**, **fibers**, **elastomers**, and **thermosetting resins**. The properties of each group can be accounted for by the structure, the degree of crystallinity, and the amount of cross-linking they contain.

EXERCISES

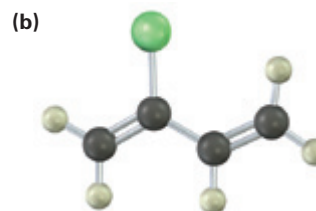
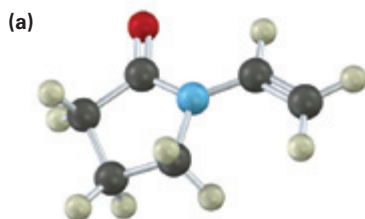
VISUALIZING CHEMISTRY

(Problems 27.1–27.12 appear within the chapter.)

- 27.13** Identify the structural class to which the following polymer belongs, and show the structure of the monomer units used to make it:

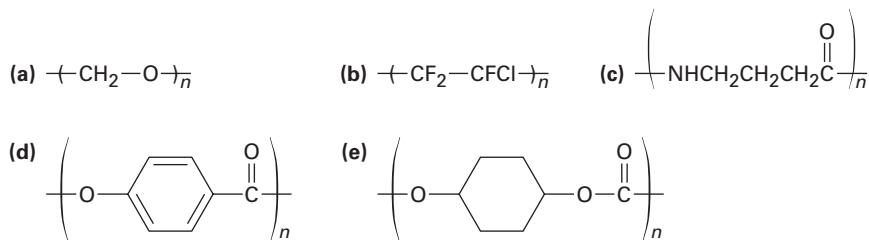


- 27.14** Show the structures of the polymers that could be made from the following monomers (green = Cl):



ADDITIONAL PROBLEMS

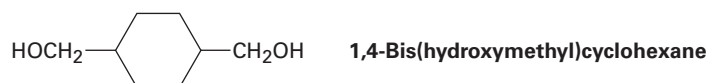
27.15 Identify the monomer units from which each of the following polymers is made, and tell whether each is a chain-growth or a step-growth polymer:



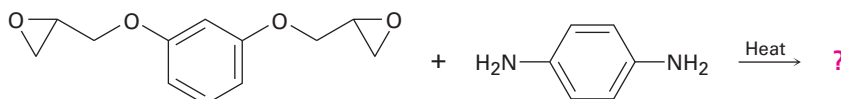
27.16 Draw a three-dimensional representation of segments of the following polymers:

- (a) Syndiotactic polyacrylonitrile
 (b) Atactic poly(methyl methacrylate)
 (c) Isotactic poly(vinyl chloride)

27.17 Draw the structure of Kodel, a polyester prepared by heating dimethyl benzene-1,4-dicarboxylate with 1,4-bis(hydroxymethyl)cyclohexane.



27.18 Show the structure of the polymer that results from heating the following diepoxide and diamine:



27.19 Nomex, a polyamide used in such applications as fire-retardant clothing, is prepared by reaction of benzene-1,3-diamine with benzene-1,3-dicarbonyl chloride. Show the structure of Nomex.

27.20 Nylon 10,10 is an extremely tough, strong polymer used to make reinforcing rods for concrete. Draw a segment of nylon 10,10, and show its monomer units.

27.21 Cyclopenta-1,3-diene undergoes thermal polymerization to yield a polymer that has no double bonds in the chain. On strong heating, the polymer breaks down to regenerate cyclopentadiene. Propose a structure for the polymer.

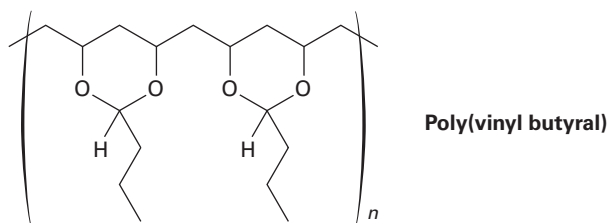
27.22 When styrene, $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$, is copolymerized in the presence of a few percent *p*-divinylbenzene, a hard, insoluble, cross-linked polymer is obtained. Show how this cross-linking of polystyrene chains occurs.

- 27.23** Poly(ethylene glycol), or Carbowax, is made by anionic polymerization of ethylene oxide using NaOH as the catalyst. Propose a mechanism.



- 27.24** Nitroethylene, $\text{H}_2\text{C=CHNO}_2$, is a sensitive compound that must be prepared with great care. Attempted purification of nitroethylene by distillation often results in low recovery of product and a white coating on the inner walls of the distillation apparatus. Explain.

- 27.25** Poly(vinyl butyral) is used as the plastic laminate in the preparation of automobile windshield safety glass. How would you synthesize this polymer?

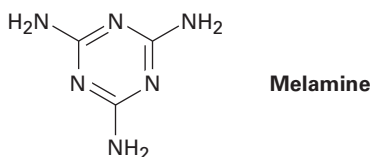


- 27.26** What is the structure of the polymer produced by anionic polymerization of β -propiolactone using NaOH as the catalyst?

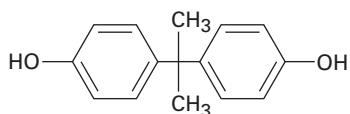
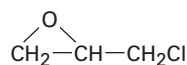


- 27.27** Glyptal is a highly cross-linked thermosetting resin produced by heating glycerol and phthalic anhydride (benzene-1,2-dicarboxylic acid anhydride). Show the structure of a representative segment of glyptal.

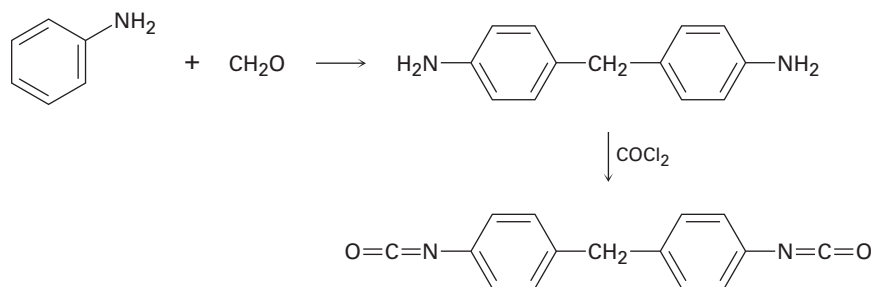
- 27.28** Melmac, a thermosetting resin often used to make plastic dishes, is prepared by heating melamine with formaldehyde. Look at the structure of Bakelite shown in Section 27-6, and then propose a structure for Melmac.



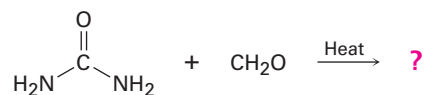
- 27.29** Epoxy adhesives are cross-linked resins prepared in two steps. The first step involves S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin to form a low-molecular-weight prepolymer. This prepolymer is then “cured” into a cross-linked resin by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.

**Bisphenol A****Epichlorohydrin**

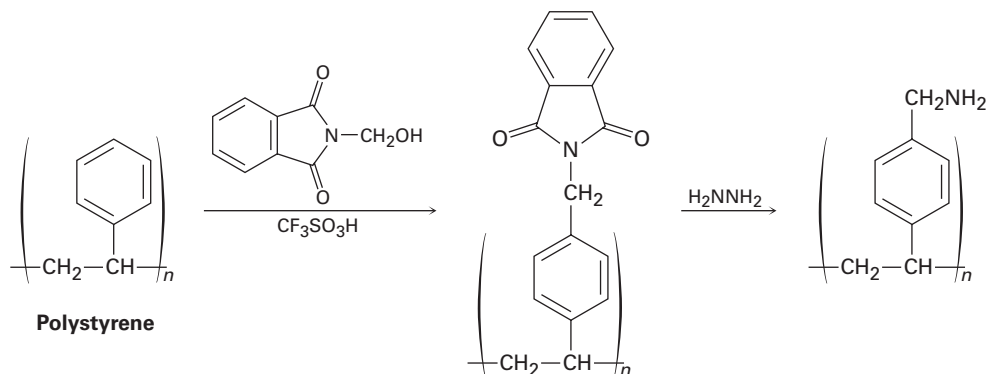
- (a) What is the structure of the prepolymer?
- (b) How does addition of the triamine to the prepolymer result in cross-linking?
- 27.30** The polyurethane foam used for home insulation uses methanediphenyl-diisocyanate (MDI) as monomer. The MDI is prepared by acid-catalyzed reaction of aniline with formaldehyde, followed by treatment with phosgene, $COCl_2$. Propose mechanisms for both steps.

**MDI**

- 27.31** Write the structure of a representative segment of polyurethane prepared by reaction of ethylene glycol with MDI (Problem 27.30).
- 27.32** The smoking salons of the Hindenburg and other hydrogen-filled dirigibles of the 1930s were insulated with urea-formaldehyde polymer foams. The structure of this polymer is highly cross-linked, like that of Bakelite (Section 27-6). Propose a structure.

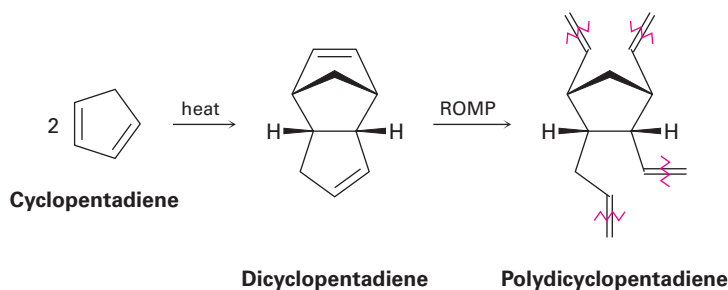


- 27.33** The polymeric resin used for Merrifield solid-phase peptide synthesis (Section 19-7) is prepared by treating polystyrene with *N*-(hydroxymethyl)phthalimide and trifluoromethanesulfonic acid, followed by reaction with hydrazine. Propose a mechanism for both steps.



- 27.34** 2-Ethylhexan-1-ol, used in the synthesis of di(2-ethylhexyl) phthalate plasticizer, is made commercially from butanal. Show the likely synthesis route.

- 27.35** Polydicyclopentadiene (PDCPD), marketed as Telene and Metton, is a highly cross-linked thermosetting resin used for molding such impact-resistant parts as cabs for large trucks and earth-moving equipment. PDCPD is prepared by ring-opening metathesis polymerization of dicyclopentadiene, which is itself prepared from cyclopenta-1,3-diene. The polymerization occurs by initial metathesis of the more highly strained double bond in the bicyclo[2.2.1]heptane part of the molecule (Section 4-9) to give a linear polymer, followed by cross-linking of different chains in a second metathesis of the remaining cyclopentene double bond.



- Show the mechanism of the formation of dicyclopentadiene from cyclopentadiene.
- Draw the structure of a representative sample of the initially formed linear polymer containing three monomer units.
- Draw the structure of a representative sample of PDCPD that shows how cross-linking of the linear chains takes place.

Nomenclature of Polyfunctional Organic Compounds

A

With more than 70 million organic compounds now known and thousands more being created daily, naming them all is a real problem. Part of the problem is due to the sheer complexity of organic structures, but part is also due to the fact that chemical names have more than one purpose. For Chemical Abstracts Service (CAS), which catalogs and indexes the worldwide chemical literature, each compound must have only one correct name. It would be chaos if half the entries for CH_3Br were indexed under “M” for methyl bromide and half under “B” for bromomethane. Furthermore, a CAS name must be strictly systematic so that it can be assigned and interpreted by computers; common names are not allowed.

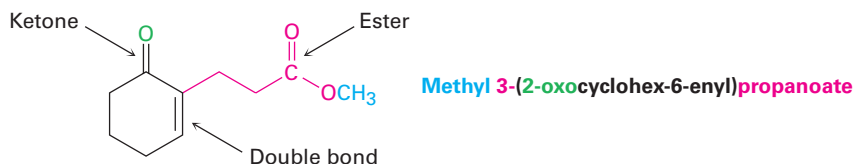
People, however, have different requirements than computers. For people—students and professional chemists in their spoken and written communications—it’s best that a chemical name be pronounceable and that it be as easy as possible to assign and interpret. Furthermore, it’s convenient if names follow historical precedents, even if that means a particularly well-known compound might have more than one name. People can readily understand that bromomethane and methyl bromide both refer to CH_3Br .

As noted in the text, chemists overwhelmingly use the nomenclature system devised and maintained by the International Union of Pure and Applied Chemistry, or IUPAC. Rules for naming monofunctional compounds were given throughout the text as each new functional group was introduced, and a list of where these rules can be found is given in **TABLE A.1**.

TABLE A.1 Nomenclature Rules for Functional Groups

Functional group	Text section	Functional group	Text section
Acid anhydride	16-1	Aromatic compound	9-1
Acid halide	16-1	Carboxylic acid	15-1
Acyl phosphate	16-1	Cycloalkane	4-1
Alcohol	13-1	Ester	16-1
Aldehyde	14-1	Ether	13-8
Alkane	3-4	Ketone	14-1
Alkene	7-2	Nitrile	15-1
Alkyl halide	12-1	Phenol	13-1
Alkyne	7-2	Sulfide	13-8
Amide	16-1	Thiol	13-1
Amine	18-1	Thioester	16-1

Naming a monofunctional compound is reasonably straightforward, but even experienced chemists often encounter problems when faced with naming a complex polyfunctional compound. Take the following compound, for instance. It has three functional groups—ester, ketone, and C=C—but how should it be named? As an ester with an *-oate* ending, a ketone with an *-one* ending, or an alkene with an *-ene* ending? It's actually named methyl 3-(2-oxocyclohex-6-enyl)propanoate.



The name of a polyfunctional organic molecule has four parts—suffix, parent, prefixes, and locants—that must be identified and expressed in the proper order and format. Let's look at each of the four.

Name Part 1. The Suffix: Functional-Group Precedence

Although a polyfunctional organic molecule might contain several different functional groups, we must choose just one suffix for nomenclature purposes. It's not correct to use two suffixes. Thus, keto ester **1** must be named either as a ketone with an *-one* suffix or as an ester with an *-oate* suffix, but it can't be named as an *-onoate*. Similarly, amino alcohol **2** must be named either as an alcohol (*-ol*) or as an amine (*-amine*), but it can't be named as an *-olamine* or *-aminol*.



The only exception to the rule requiring a single suffix is when naming compounds that have double or triple bonds. Thus, the unsaturated acid $\text{H}_2\text{C}=\text{CHCH}_2\text{CO}_2\text{H}$ is but-3-enoic acid, and the acetylenic alcohol $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{OH}$ is pent-5-yn-1-ol.

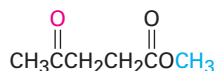
How do we choose which suffix to use? Functional groups are divided into two classes, **principal groups** and **subordinate groups**, as shown in **TABLE A.2**. Principal groups can be cited either as prefixes or as suffixes, while subordinate groups are cited only as prefixes. Within the principal groups, an order of priority has been established, with the proper suffix for a given compound determined by choosing the principal group of highest priority. For example, Table A.2 indicates that keto ester **1** should be named as an ester rather than as a ketone because an ester functional group is higher in priority than a ketone.

TABLE A.2 Classification of Functional Groups^a

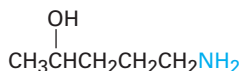
Functional group	Name as suffix	Name as prefix
Principal groups		
Carboxylic acid	-oic acid -carboxylic acid	carboxy
Acid anhydride	-oic anhydride -carboxylic anhydride	—
Ester	-oate -carboxylate	alkoxycarbonyl
Thioester	-thioate -carbothioate	alkylthiocarbonyl
Acid halide	-oyl halide -carbonyl halide	halocarbonyl
Amide	-amide -carboxamide	carbamoyl
Nitrile	-nitrile -carbonitrile	cyano
Aldehyde	-al -carbaldehyde	oxo
Ketone	-one	oxo
Alcohol	-ol	hydroxy
Phenol	-ol	hydroxy
Thiol	-thiol	mercapto
Amine	-amine	amino
Imine	-imine	imino
Ether	ether	alkoxy
Sulfide	sulfide	alkylthio
Disulfide	disulfide	—
Alkene	-ene	—
Alkyne	-yne	—
Alkane	-ane	—
Subordinate groups		
Azide	—	azido
Halide	—	halo
Nitro compound	—	nitro

^aPrincipal groups are listed in order of decreasing priority; subordinate groups have no priority order.

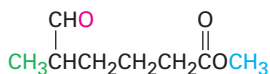
Similarly, amino alcohol **2** should be named as an alcohol rather than as an amine. Thus, the name of **1** is methyl 4-oxopentanoate, and the name of **2** is 5-aminopentan-2-ol. Further examples are shown:



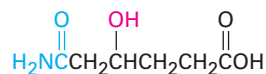
1. Methyl 4-oxopentanoate
(an ester with a ketone group)



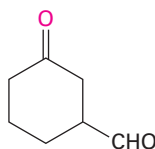
2. 5-Aminopentan-2-ol
(an alcohol with an amine group)



3. Methyl 5-methyl-6-oxohexanoate
(an ester with an aldehyde group)



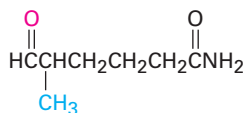
4. 5-Carbamoyl-4-hydroxypentanoic acid
(a carboxylic acid with amide and alcohol groups)



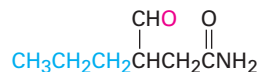
5. 3-Oxocyclohexanecarbaldehyde
(an aldehyde with a ketone group)

Name Part 2. The Parent: Selecting the Main Chain or Ring

The parent, or base, name of a polyfunctional organic compound is usually easy to identify. If the principal group of highest priority is part of an open chain, the parent name is that of the longest chain containing the largest number of principal groups. For example, compounds **6** and **7** are isomeric aldehyde amides, which must be named as amides rather than as aldehydes according to Table A.2. The longest chain in compound **6** has six carbons, and the substance is named 5-methyl-6-oxohexanamide. Compound **7** also has a chain of six carbons, but the longest chain that contains both principal functional groups has only four carbons. Thus, compound **7** is named 4-oxo-3-propylbutanamide.



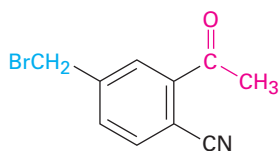
6. 5-Methyl-6-oxohexanamide



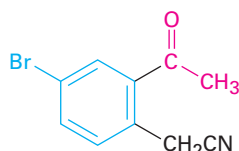
7. 4-Oxo-3-propylbutanamide

If the highest-priority principal group is attached to a ring, the parent name is that of the ring system. Compounds **8** and **9**, for instance, are isomeric keto nitriles and must both be named as nitriles according to Table A.2. Substance **8** is named as a benzonitrile because the $-\text{CN}$ functional group is a substituent on the aromatic ring, but substance **9** is named as an acetonitrile because the $-\text{CN}$ functional group is on an open chain. The names are 2-acetyl-(4-bromomethyl)benzonitrile (**8**) and (2-acetyl-4-bromophenyl)acetonitrile (**9**). As further examples, compounds **10** and **11** are both keto acids and must be named as acids, but the parent name in (**10**) is that of a ring system (cyclohexanecarboxylic acid) and the parent name in (**11**) is that of an open chain

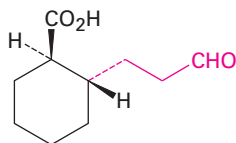
(propanoic acid). The names are *trans*-2-(3-oxopropyl)cyclohexanecarboxylic acid (**10**) and 3-(2-oxocyclohexyl)propanoic acid (**11**).



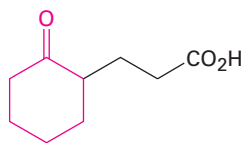
8. 2-Acetyl-(4-bromomethyl)benzonitrile



9. (2-Acetyl-4-bromophenyl)acetonitrile



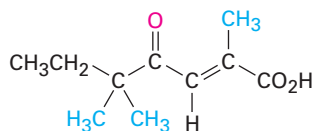
10. *trans*-2-(3-oxopropyl)cyclohexanecarboxylic acid



11. 3-(2-Oxocyclohexyl)propanoic acid

Name Parts 3 and 4. The Prefixes and Locants

With the parent name and the suffix established, the next step is to identify and give numbers, or *locants*, to all substituents on the parent chain or ring. The substituents include all alkyl groups and all functional groups other than the one cited in the suffix. For example, compound **12** contains three different functional groups (carboxyl, keto, and double bond). Because the carboxyl group is highest in priority and the longest chain containing the functional groups has seven carbons, compound **12** is a heptenoic acid. In addition, the parent chain has a keto (oxo) substituent and three methyl groups. Numbering from the end nearer the highest-priority functional group gives the name (*E*)-2,5,5-trimethyl-4-oxohept-2-enoic acid. Look back at some of the other compounds we've named to see other examples of how prefixes and locants are assigned.

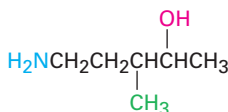


12. (*E*)-2,5,5-Trimethyl-4-oxohept-2-enoic acid

Writing the Name

Once the name parts have been established, the entire name is written out. Several additional rules apply:

- Order of prefixes** When the substituents have been identified, the parent chain has been numbered, and the proper multipliers such as *di*- and *tri*- have been assigned, the name is written with the substituents listed in alphabetical, rather than numerical, order. Multipliers such as *di*- and *tri*- are not used for alphabetization purposes, but the italicized prefixes *iso*- and *sec*- are used.

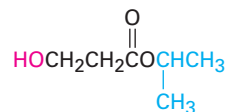


13. 5-Amino-3-methylpentan-2-ol

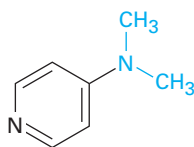
2. **Use of hyphens; single- and multiple-word names** The general rule is to determine whether the parent is itself an element or compound. If it is, then the name is written as a single word; if it isn't, then the name is written as multiple words. Methylbenzene is written as one word, for instance, because the parent—benzene—is itself a compound. Diethyl ether, however, is written as two words because the parent—ether—is a class name rather than a compound name. Additional examples follow:



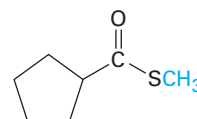
14. **Dimethylmagnesium**
(one word, because magnesium is an element)



15. **Isopropyl 3-hydroxypropanoate**
(two words, because "propanoate" is not a compound)

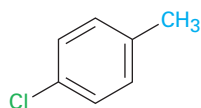


16. **4-(Dimethylamino)pyridine**
(one word, because pyridine is a compound)

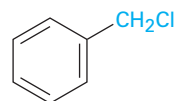


17. **Methyl cyclopentanecarbothioate**
(two words, because "cyclopentanecarbothioate" is not a compound)

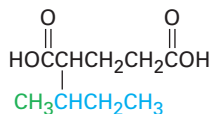
3. **Parentheses** Parentheses are used to denote complex substituents when ambiguity would otherwise arise. For example, chloromethylbenzene has two substituents on a benzene ring, but (chloromethyl)benzene has only one complex substituent. Note that the expression in parentheses is not set off by hyphens from the rest of the name.



18. **p-Chloromethylbenzene**



19. **(Chloromethyl)benzene**



20. **2-(1-Methylpropyl)pentanedioic acid**

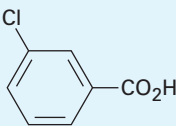
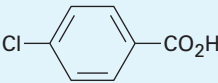
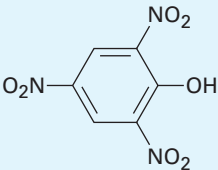
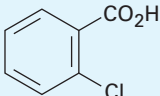
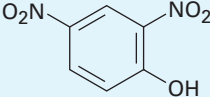
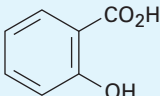
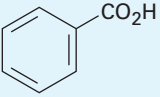
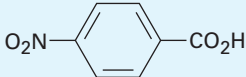
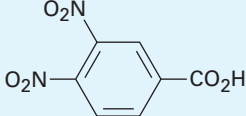
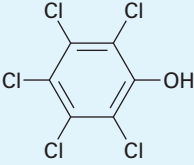
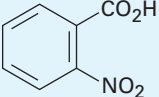
Additional Reading

Further explanations of the rules of organic nomenclature can be found online at <http://www.acdlabs.com/iupac/nomenclature/> (accessed November, 2013) and in the following references:


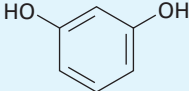
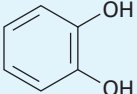
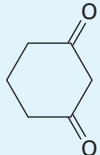
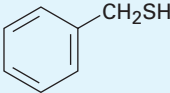
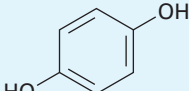
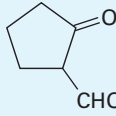
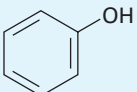
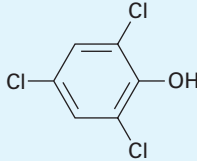
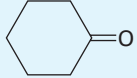
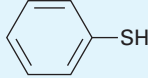
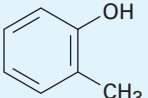
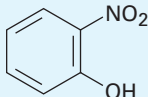
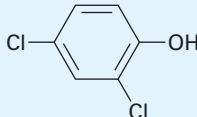
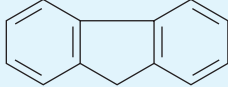
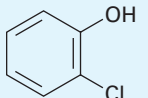
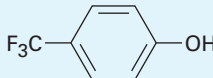

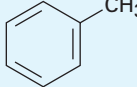

1. *A Guide to IUPAC Nomenclature of Organic Compounds*, CRC Press, Boca Raton, FL, 1993.
2. *Nomenclature of Organic Chemistry*, Sections A, B, C, D, E, F, and H, International Union of Pure and Applied Chemistry, Pergamon Press, Oxford, 1979.

Acidity Constants for Some Organic Compounds

B

Compound	pK _a	Compound	pK _a	Compound	pK _a
CH ₃ SO ₃ H	-1.8	CH ₂ ClCO ₂ H	2.8		3.8
CH(NO ₂) ₃	0.1	HO ₂ CCH ₂ CO ₂ H	2.8; 5.6		4.0
	0.3	CH ₂ BrCO ₂ H	2.9	BrCH ₂ CH ₂ CO ₂ H	4.0
CCl ₃ CO ₂ H	0.5		3.0		4.1
CF ₃ CO ₂ H	0.5		3.0		4.2
CBr ₃ CO ₂ H	0.7	CH ₂ I CO ₂ H	3.2	H ₂ C=CHCO ₂ H	4.2
HO ₂ C≡CCO ₂ H	1.2; 2.5	CHOCO ₂ H	3.2	HO ₂ CCH ₂ CH ₂ CO ₂ H	4.2; 5.7
HO ₂ CCO ₂ H	1.2; 3.7		3.4	HO ₂ CCH ₂ CH ₂ CH ₂ CO ₂ H	4.3; 5.4
CHCl ₂ CO ₂ H	1.3		3.5		4.5
CH ₂ (NO ₂)CO ₂ H	1.3	HSCH ₂ CO ₂ H	3.5; 10.2	H ₂ C=C(CH ₃)CO ₂ H	4.7
HC≡CCO ₂ H	1.9	CH ₂ (NO ₂) ₂	3.6	CH ₃ CO ₂ H	4.8
(Z) HO ₂ CCH=CHCO ₂ H	1.9; 6.3	CH ₃ OCH ₂ CO ₂ H	3.6		
	2.4	CH ₃ COCH ₂ CO ₂ H	3.6		
CH ₃ COCO ₂ H	2.4	HOCH ₂ CO ₂ H	3.7		
NCCH ₂ CO ₂ H	2.5	HCO ₂ H	3.7		
CH ₃ C≡CCO ₂ H	2.6				
CH ₂ FCO ₂ H	2.7				

(continued)

Compound	pK _a	Compound	pK _a	Compound	pK _a
CH ₃ CH ₂ CO ₂ H	4.8	CH ₃ COCH ₂ COCH ₃	9.0		15.4
(CH ₃) ₃ CCO ₂ H	5.0		9.3; 11.1	CH ₃ OH	15.5
CH ₃ COCH ₂ NO ₂	5.1		9.3; 12.6	H ₂ C=CHCH ₂ OH	15.5
	5.3		9.4	CH ₃ CH ₂ OH	16.0
O ₂ NCH ₂ CO ₂ CH ₃	5.8		9.9; 11.5	CH ₃ CH ₂ CH ₂ OH	16.1
	5.8		9.9	CH ₃ COCH ₂ Br	16.1
	6.2	CH ₃ COCH ₂ SOCH ₃	10.0		16.7
	6.6		10.3	CH ₃ CHO	17
HCO ₃ H	7.1	CH ₃ NO ₂	10.3	(CH ₃) ₂ CHCHO	17
	7.2	CH ₃ SH	10.3	(CH ₃) ₂ CHOH	17.1
(CH ₃) ₂ CHNO ₂	7.7	CH ₃ COCH ₂ CO ₂ CH ₃	10.6	(CH ₃) ₃ COH	18.0
	7.8	CH ₃ COCHO	11.0	CH ₃ COCH ₃	19.3
CH ₃ CO ₃ H	8.2	CH ₂ (CN) ₂	11.2		23
	8.5	CCl ₃ CH ₂ OH	12.2	CH ₃ CO ₂ CH ₂ CH ₃	25
CH ₃ CH ₂ NO ₂	8.5	Glucose	12.3	HC≡CH	25
	8.7	(CH ₃) ₂ C=NOH	12.4	CH ₃ CN	25
		CH ₂ (CO ₂ CH ₃) ₂	12.9	CH ₃ SO ₂ CH ₃	28
		CHCl ₂ CH ₂ OH	12.9	(C ₆ H ₅) ₃ CH	32
		CH ₂ (OH) ₂	13.3	(C ₆ H ₅) ₂ CH ₂	34
		HOCH ₂ CH(OH)CH ₂ OH	14.1	CH ₃ SOCH ₃	35
		CH ₂ ClCH ₂ OH	14.3	NH ₃	36
			15.0	CH ₃ CH ₂ NH ₂	36
				(CH ₃ CH ₂) ₂ NH	40
					41
					43
				H ₂ C=CH ₂	44
				CH ₄	~60

An acidity list covering more than 5000 organic compounds has been published: E.P. Serjeant and B. Dempsey (eds.), *Ionization Constants of Organic Acids in Aqueous Solution*, IUPAC Chemical Data Series No. 23, Pergamon Press, Oxford, 1979.

Absolute configuration (Section 5-5): The exact three-dimensional structure of a given enantiomer. Absolute configurations are specified verbally by the Cahn–Ingold–Prelog *R,S* convention.

Absorbance (Section 10-9): In optical spectroscopy, the logarithm of the intensity of the incident light divided by the intensity of the light transmitted through a sample; $A = \log I_0/I$.

Absorption spectrum (Section 10-5): A plot of wavelength of incident light versus amount of light absorbed. Organic molecules show absorption spectra in both the infrared and the ultraviolet regions of the electromagnetic spectrum.

Acetal (Section 14-8): A functional group consisting of two –OR groups bonded to the same carbon, $R_2C(OR')_2$. Acetals are often used as protecting groups for ketones and aldehydes.

Acetoacetic ester synthesis (Section 17-5): The synthesis of a methyl ketone by alkylation of an alkyl halide with ethyl acetoacetate, followed by hydrolysis and decarboxylation.

Acetyl group (Section 14-1): The CH_3CO- group.

Acetylide anion (Section 8-15): The anion formed by removal of a proton from a terminal alkyne, $R-C\equiv C:^-$.

Achiral (Section 5-2): Having a lack of handedness. A molecule is achiral if it has a plane of symmetry and is thus superimposable on its mirror image.

Acid anhydride (Chapter 16 Introduction): A functional group with two acyl groups bonded to a common oxygen atom, RCO_2COR' .

Acid halide (Chapter 16 Introduction): A functional group with an acyl group bonded to a halogen atom, $RCOX$.

Acidity constant, K_a (Section 2-8): A measure of acid strength in water. For any acid HA, the acidity constant is given by the expression

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Activating group (Section 9-8): An electron-donating group such as hydroxyl (–OH) or amino (–NH₂) that increases the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Activation energy, ΔG^\ddagger (Section 6-9): The difference in energy between ground state and transition state in a reaction. The amount of activation energy determines the rate at which a reaction proceeds. Most organic reactions have activation energies of 40–100 kJ/mol.

Active site (Sections 6-11, 19-10): The pocket in an enzyme where a substrate is bound and undergoes reaction.

Acyclic diene metathesis (ADMET) (Section 27-5): A method of polymer synthesis that uses the olefin metathesis reaction of an open-chain diene.

Acyl group (Sections 9-7, 14-1): A –COR group.

Acyl phosphate (Chapter 16 Introduction): A functional group with an acyl group bonded to a phosphate, $RCO_2PO_3^{2-}$.

Acylation (Section 9-7): The introduction of an acyl group, –COR, onto a molecule. For example, acylation of an alcohol yields an ester, acylation of an amine yields an amide, and acylation of an aromatic ring yields an alkyl aryl ketone.

Acylium ion (Section 9-7): A resonance-stabilized carbocation in which the positive charge is located at a carbonyl-group carbon, $R-C^+=O \leftrightarrow R-C\equiv O^+$. Acylium ions are intermediates in Friedel–Crafts acylation reactions.

Adams catalyst (Section 8-5): The PtO_2 catalyst used for alkene hydrogenations.

1,2-Addition (Sections 8-13, 14-11): Addition of a reactant to the two ends of a double bond.

1,4-Addition (Sections 8-13, 14-11): Addition of a reactant to the ends of a conjugated π system. Conjugated dienes yield 1,4-adducts when treated with electrophiles such as HCl. Conjugated enones yield 1,4-adducts when treated with nucleophiles such as amines.

Addition reaction (Section 6-1): The reaction that occurs when two reactants add together to form a single product with no atoms left over.

Adrenocortical hormone (Section 23-9): A steroid hormone secreted by the adrenal glands. There are two types of adrenocortical hormones: mineralocorticoids and glucocorticoids.

Alcohol (Section 13-2): A compound with an $-OH$ group bonded to a saturated, sp^3 -hybridized carbon, ROH.

Aldaric acid (Section 21-6): The dicarboxylic acid resulting from oxidation of an aldose.

Aldehyde (Section 14-1): A compound containing the $-CHO$ functional group.

Alditol (Section 21-6): The polyalcohol resulting from reduction of the carbonyl group of a sugar.

Aldol reaction (Section 17-6): The carbonyl condensation reaction of an aldehyde or ketone to give a β -hydroxy carbonyl compound.

Aldonic acid (Section 21-6): The monocarboxylic acid resulting from oxidation of the aldehyde group of an aldose.

Aldose (Section 21-1): A carbohydrate with an aldehyde functional group.

Alicyclic (Section 4-1): A nonaromatic cyclic hydrocarbon such as a cycloalkane or cycloalkene.

Aliphatic (Section 3-2): A nonaromatic hydrocarbon such as a simple alkane, alkene, or alkyne.

Alkaloid (Chapter 2 *Something Extra*; Section 25-1): A naturally occurring organic base, such as morphine.

Alkane (Section 3-2): A compound of carbon and hydrogen that contains only single bonds.

Alkene (Chapter 7 Introduction): A hydrocarbon that contains a carbon-carbon double bond, $R_2C=CR_2$.

Alkoxide ion (Section 13-2): The anion RO^- formed by deprotonation of an alcohol.

Alkyl group (Section 3-3): The partial structure that remains when a hydrogen atom is removed from an alkane.

Alkyl halide (Chapter 12 Introduction): A compound with a halogen atom bonded to a saturated, sp^3 -hybridized carbon atom.

Alkylamine (Section 18-1): An amino-substituted alkane, RNH_2 , R_2NH , or R_3N .

Alkylation (Sections 9-7, 17-5): Introduction of an alkyl group onto a molecule. For example, aromatic rings can be alkylated to yield arenes and enolate anions can be alkylated to yield α -substituted carbonyl compounds.

Alkyne (Chapter 7 Introduction): A hydrocarbon that contains a carbon-carbon triple bond, $RC\equiv CR$.

Allyl group (Section 7-2): A $H_2C=CHCH_2-$ substituent.

Allylic (Sections 8-13, 12-2): The position next to a double bond. For example, $H_2C=CHCH_2Br$ is an allylic bromide.

α -Amino acid (Section 19-1): A difunctional compound with an amino group on the carbon atom next to a carboxyl group, $RCH(NH_2)CO_2H$.

α Anomer (Section 21-5): The cyclic hemiacetal form of a sugar that has the hemiacetal $-OH$ group cis to the $-OH$ at the lowest chirality center in a Fischer projection.

α Helix (Section 19-8): A coiled secondary structure of a protein.

α Position (Chapter 17 Introduction): The position next to a carbonyl group.

α -Substitution reaction (Section 17-2): The substitution of the α hydrogen atom of a carbonyl compound by reaction with an electrophile.

Amide (Chapter 16 Introduction): A compound containing the $-CONH_2$, $-CONHR$, or $-CONR_2$ functional group.

Amidomalonate synthesis (Section 19-3): A method for preparing an α -amino acid by alkylation of diethyl amidomalonate with an alkyl halide followed by deprotection and decarboxylation.

Amine (Chapter 18 Introduction): A compound containing one or more organic substituents bonded to a nitrogen atom, RNH_2 , R_2NH , or R_3N .

Amino acid (Section 19-1): *See* α -Amino acid.

Amino sugar (Section 21-7): A sugar with one of its $-OH$ groups replaced by $-NH_2$.

Amphiprotic (Section 19-1): Capable of acting either as an acid or as a base. Amino acids are amphiprotic.

Amplitude (Section 10-5): The height of a wave measured from the midpoint to the maximum. The intensity of radiant energy is proportional to the square of the wave's amplitude.

Amyl group (Section 3-3): An alternative name for a pentyl group.

Anabolic steroid (Section 23-9): A synthetic androgen that mimics the tissue-building effects of natural testosterone.

Anabolism (Section 20-1): The group of metabolic pathways that build up larger molecules from smaller ones.

Androgen (Section 23-9): A male steroid sex hormone.

Angle strain (Section 4-3): The strain introduced into a molecule when a bond angle is deformed from its ideal value. Angle strain is particularly important in small-ring cycloalkanes, where it results from compression of bond angles to less than their ideal tetrahedral values.

Anomeric center (Section 21-5): The hemiacetal carbon atom in the cyclic pyranose or furanose form of a sugar.

Anomers (Section 21-5): Cyclic stereoisomers of sugars that differ only in their configuration at the hemiacetal (anomeric) carbon.

Antarafacial (Section 26-5): A pericyclic reaction that takes place on opposite faces of the two ends of a π electron system.

Anti conformation (Section 3-7): The geometric arrangement around a carbon-carbon single bond in which the two largest substituents are 180° apart as viewed in a Newman projection.

Anti periplanar (Section 12-13): Describing the stereochemical relationship in which two bonds on adjacent carbons lie in the same plane at an angle of 180° .

Anti stereochemistry (Section 8-2): The opposite of syn. An anti addition reaction is one in which the two ends of the double bond are attacked from different sides. An anti elimination reaction is one in which the two groups leave from opposite sides of the molecule.

Antiaromatic (Section 9-3): Describing a planar, conjugated molecule with $4n$ π electrons. Delocalization of the π electrons leads to an increase in energy.

Antibonding MO (Section 1-11): A molecular orbital that is higher in energy than the atomic orbitals from which it is formed.

Anticodon (Section 24-5): A sequence of three bases on tRNA that reads the codons on mRNA and brings the correct amino acids into position for protein synthesis.

Antisense strand (Section 24-4): The template, noncoding strand of double-helical DNA that does not contain the gene.

Arene (Section 9-1): An alkyl-substituted benzene.

Aromaticity (Chapter 9 Introduction; Section 9-3): The special characteristics of cyclic conjugated molecules, including unusual stability and a tendency to undergo substitution reactions rather than addition reactions on treatment with electrophiles. Aromatic molecules are planar, cyclic, conjugated species with $4n + 2$ π electrons.

Arylamine (Section 18-1): An amino-substituted aromatic compound, ArNH_2 .

Atactic (Section 27-2): Describing a chain-growth polymer in which the stereochemistry of the substituents is oriented randomly along the backbone.

Atomic mass (Section 1-1): The weighted average mass of an element's naturally occurring isotopes.

Atomic number, Z (Section 1-1): The number of protons in the nucleus of an atom.

ATZ derivative (Section 19-6): An anilinothiazolinone, formed from an amino acid during Edman degradation of a peptide.

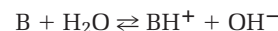
Axial bond (Section 4-6): A bond to chair cyclohexane that lies along the ring axis, perpendicular to the rough plane of the ring.

Azide synthesis (Section 18-6): A method for preparing amines by $\text{S}_{\text{N}}2$ reaction of an alkyl halide with azide ion, followed by reduction.

Backbone (Section 19-4): The continuous chain of atoms running the length of a protein or other polymer.

Base peak (Section 10-1): The most intense peak in a mass spectrum.

Basicity constant, K_{b} (Section 18-3): A measure of base strength in water. For any base B, the basicity constant is given by the expression



$$K_{\text{b}} = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}]}$$

Bent bonds (Section 4-4): The bonds in small rings such as cyclopropane that bend away from the internuclear line and overlap at a slight angle, rather than head-on. Bent bonds are highly strained and highly reactive.

Benzoyl group (Section 14-1): The $\text{C}_6\text{H}_5\text{CO}-$ group.

Benzyl group (Section 9-1): The $\text{C}_6\text{H}_5\text{CH}_2-$ group.

Benzylic (Section 9-10): The position next to an aromatic ring.

β Anomer (Section 21-5): The cyclic hemiacetal form of a sugar that has the hemiacetal $-\text{OH}$ group trans to the $-\text{OH}$ at the lowest chirality center in a Fischer projection.

β Diketone (Section 17-4): A 1,3-diketone.

β -Keto ester (Section 17-4): A 3-oxoester.

β Lactam (Chapter 16 *Something Extra*): A four-membered lactam, or cyclic amide. Penicillin and cephalosporin antibiotics contain β -lactam rings.

β -Oxidation pathway (Section 23-5): The metabolic pathway for degrading fatty acids.

β -Pleated sheet (Section 19-8): A type of secondary structure of a protein.

Betaine (Section 14-9): A neutral dipolar molecule with nonadjacent positive and negative charges. For example, the adduct of a Wittig reagent with a carbonyl compound is a betaine.

Bicycloalkane (Section 4-9): A cycloalkane that contains two rings.

Bimolecular reaction (Section 12-7): A reaction whose rate-limiting step occurs between two reactants.

Block copolymer (Section 27-3): A polymer in which different blocks of identical monomer units alternate with one another.

Boat cyclohexane (Section 4-5): A conformation of cyclohexane that bears a slight resemblance to a boat. Boat cyclohexane has no angle strain but has a large number of eclipsing interactions that make it less stable than chair cyclohexane.

Boc derivative (Section 19-7): A butyloxycarbonyl N-protected amino acid.

Bond angle (Section 1-6): The angle formed between two adjacent bonds.

Bond dissociation energy, D (Section 6-8): The amount of energy needed to break a bond and produce two radical fragments.

Bond length (Section 1-5): The equilibrium distance between the nuclei of two atoms that are bonded to each other.

Bond strength (Sections 1-5, 6-8): An alternative name for bond dissociation energy.

Bonding MO (Section 1-11): A molecular orbital that is lower in energy than the atomic orbitals from which it is formed.

Branched-chain alkane (Section 3-2): An alkane that contains a branching connection of carbons as opposed to a straight-chain alkane.

Bridgehead atom (Section 4-9): An atom that is shared by more than one ring in a polycyclic molecule.

Bromohydrin (Section 8-3): A 1,2 bromoalcohol; obtained by addition of HOBr to an alkene.

Bromonium ion (Section 8-2): A species with a divalent, positively charged bromine, R_2Br^+ .

Brønsted–Lowry acid (Section 2-7): A substance that donates a hydrogen ion (proton; H^+) to a base.

Brønsted–Lowry base (Section 2-7): A substance that accepts H^+ from an acid.

C-terminal amino acid (Section 19-4): The amino acid with a free $-CO_2H$ group at the end of a protein chain.

Cahn–Ingold–Prelog sequence rules (Sections 5-5, 7-4): A series of rules for assigning relative rankings to substituent groups on a chirality center or a double-bond carbon atom.

Cannizzaro reaction (Section 14-10): The disproportionation reaction of an aldehyde on treatment with base to yield an alcohol and a carboxylic acid.

Carbanion (Sections 12-4, 14-6): A carbon anion, or substance that contains a trivalent, negatively charged carbon atom (R_3C^-). Alkyl carbanions are sp^3 -hybridized and have eight electrons in the outer shell of the negatively charged carbon.

Carbene (Section 8-9): A neutral substance that contains a divalent carbon atom having only six electrons in its outer shell ($R_2C:$).

Carbinolamine (Section 14-7): A molecule that contains the $R_2C(OH)NH_2$ functional group. Carbinolamines are produced as intermediates during the nucleophilic addition of amines to carbonyl compounds.

Carbocation (Sections 6-5, 7-8): A carbon cation, or substance that contains a trivalent, positively charged carbon atom having six electrons in its outer shell (R_3C^+).

Carbohydrate (Chapter 21 Introduction): A polyhydroxy aldehyde or ketone. Carbohydrates can be either simple sugars, such as glucose, or complex sugars, such as cellulose.

Carbonyl condensation reaction (Section 17-6): A reaction that joins two carbonyl compounds together by a combination of α -substitution and nucleophilic addition reactions.

Carbonyl group (*Preview of Carbonyl Chemistry*): The $C=O$ functional group.

Carboxyl group (Section 15-1): The $-CO_2H$ functional group.

Carboxylation (Section 15-5): The addition of CO_2 to a molecule.

Carboxylic acid (Chapter 15 Introduction): A compound containing the $-CO_2H$ functional group.

Carboxylic acid derivative (Chapter 16 Introduction): A compound in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in a substitution reaction. Esters, amides, and acid halides are examples.

Catabolism (Section 20-1): The group of metabolic pathways that break down larger molecules into smaller ones.

Catalyst (Section 6-11): A substance that increases the rate of a chemical transformation by providing an alternative mechanism but is not itself changed in the reaction.

Cation radical (Section 10-1): A reactive species, typically formed in a mass spectrometer by loss of an electron from a neutral molecule and having both a positive charge and an odd number of electrons.

Chain-growth polymer (Sections 8-10, 27-1): A polymer whose bonds are produced by chain-reaction mechanisms. Polyethylene and other alkene polymers are examples.

Chain reaction (Section 6-3): A reaction that, once initiated, sustains itself in an endlessly repeating cycle of propagation steps. The radical chlorination of alkanes is an example of a chain reaction that is initiated by irradiation with light and then continues in a series of propagation steps.

Chair conformation (Section 4-5): A three-dimensional conformation of cyclohexane that resembles the rough shape of a chair. The chair form of cyclohexane is the lowest-energy conformation of the molecule.

Chemical shift (Section 11-3): The position on the NMR chart where a nucleus absorbs. By convention, the chemical shift of tetramethylsilane (TMS) is set at zero, and all other absorptions usually occur downfield (to the left on the chart). Chemical shifts are expressed in delta units, δ , where 1 δ equals 1 ppm of the spectrometer operating frequency.

Chiral (Section 5-2): Having handedness. Chiral molecules are those that do not have a plane of symmetry and are therefore not superimposable on their mirror image. A chiral molecule thus exists in two forms, one right-handed and one left-handed. The most common cause of chirality in a molecule is the presence of a carbon atom that is bonded to four different substituents.

Chiral environment (Section 5-12): Chiral surroundings or conditions in which a molecule resides.

Chirality center (Section 5-2): An atom, usually carbon, that is bonded to four different groups.

Chlorohydrin (Section 8-3): A 1,2 chloroalcohol; obtained by addition of HOCl to an alkene.

Chromatography (Section 19-5): A technique for separating a mixture of compounds into pure components. Different compounds adsorb to a stationary support phase and are then carried along at different rates by a mobile phase.

Cis-trans isomers (Sections 4-2, 7-3): Stereoisomers that differ in their stereochemistry about a ring or double bond.

Citric acid cycle (Section 22-4): The metabolic pathway by which acetyl CoA is degraded to CO₂. Also called the tricarboxylic acid (TCA) cycle, or Krebs cycle.

Claisen condensation reaction (Section 17-9): The carbonyl condensation reaction of two ester molecules to give a β -keto ester product.

Claisen rearrangement reaction (Sections 13-10, 26-8): The conversion of an allyl phenyl ether to an *o*-allylphenol by heating.

Coding strand (Section 24-4): The sense strand of double-helical DNA that contains the gene.

Codon (Section 24-5): A three-base sequence on a messenger RNA chain that encodes the genetic information necessary to cause a specific amino acid to be incorporated into a protein. Codons on mRNA are read by complementary anticodons on tRNA.

Coenzyme (Section 19-9): A small organic molecule that acts as a cofactor in a biological reaction.

Cofactor (Section 19-9): A small nonprotein part of an enzyme that is necessary for biological activity.

Complex carbohydrate (Section 21-1): A carbohydrate that is made of two or more simple sugars linked together by glycoside bonds.

Concerted reaction (Chapter 26 Introduction): A reaction that takes place in a single step without intermediates. For example, the Diels-Alder cycloaddition reaction is a concerted process.

Condensed structure (Sections 1-12, 3-2): A shorthand way of writing structures in which C-H and C-C bonds are understood rather than shown explicitly. Propane, for example, has the condensed structure CH₃CH₂CH₃.

Configuration (Section 5-5): The three-dimensional arrangement of atoms bonded to a chirality center.

Conformation (Section 3-6): The three-dimensional shape of a molecule at any given instant, assuming that rotation around single bonds is frozen.

Conformational analysis (Section 4-8): A means of assessing the energy of a substituted cycloalkane by totaling the steric interactions present in the molecule.

Conformer (Section 3-6): A conformational isomer.

Conjugate acid (Section 2-7): The product that results from protonation of a Brønsted-Lowry base.

Conjugate addition (Section 14-11): Addition of a nucleophile to the β carbon atom of an α,β -unsaturated carbonyl compound.

Conjugate base (Section 2-7): The anion that results from deprotonation of a Brønsted-Lowry acid.

Conjugation (Section 8-12): A series of overlapping *p* orbitals, usually in alternating single and multiple bonds. For example, buta-1,3-diene is a conjugated diene, but-3-en-2-one is a conjugated enone, and benzene is a cyclic conjugated triene.

Conrotatory (Section 26-2): A term used to indicate that *p* orbitals must rotate in the same direction during electrocyclic ring-opening or ring-closure.

Constitutional isomers (Sections 3-2, 5-9): Isomers that have their atoms connected in a different order. For example, butane and 2-methylpropane are constitutional isomers.

Cope rearrangement (Section 26-8): The sigmatropic rearrangement of a hexa-1,5-diene.

Copolymer (Section 27-3): A polymer obtained when two or more different monomers are allowed to polymerize together.

Coupled reactions (Section 20-1): Two reactions that share a common intermediate so that the energy released in a favorable step allows an unfavorable step to occur.

Coupling constant, J (Section 11-11): The magnitude (expressed in hertz) of the interaction between nuclei whose spins are coupled.

Covalent bond (Section 1-4): A bond formed by sharing electrons between atoms.

Crown ether (Section 13-11): A large-ring polyether; used as a phase-transfer catalyst.

Crystallite (Section 27-6): A highly ordered crystal-like region within a long polymer chain.

Cyanohydrin (Section 15-7): A compound with an $-OH$ group and a $-CN$ group bonded to the same carbon atom; formed by addition of HCN to an aldehyde or ketone.

Cycloaddition reaction (Sections 8-14, 26-5): A pericyclic reaction in which two reactants add together in a single step to yield a cyclic product. The Diels–Alder reaction between a diene and a dienophile to give a cyclohexene is an example.

Cycloalkane (Section 4-1): An alkane that contains a ring of carbons.

D Sugar (Section 21-3): A sugar whose hydroxyl group at the chirality center farthest from the carbonyl group has the same configuration as D glyceraldehyde and points to the right when drawn in Fischer projection.

d,l form (Section 5-8): The racemic mixture of a chiral compound.

Deactivating group (Section 9-8): An electron-withdrawing substituent that decreases the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Deamination (Section 20-2): The removal of an amino group from a molecule, as occurs with amino acids during metabolic degradation.

Debye, D (Section 2-2): The unit for measuring dipole moments; $1 D = 3.336 \times 10^{-30}$ coulomb meter (C · m).

Decarboxylation (Section 17-5): The loss of carbon dioxide from a molecule. β -Keto acids decarboxylate readily on heating.

Degree of unsaturation (Section 7-1): The number of rings and/or multiple bonds in a molecule.

Dehydration (Sections 8-1, 13-4): The loss of water from an alcohol to yield an alkene.

Dehydrohalogenation (Sections 8-1, 12-12): The loss of HX from an alkyl halide to yield an alkene on treatment with strong base.

Delocalization (Section 8-12): A spreading out of electron density over a conjugated π electron system. For example, allylic cations and allylic anions are delocalized because their charges are spread out over the entire π electron system. Aromatic compounds have $4n + 2$ π electrons delocalized over their ring.

Delta scale (Section 11-3): An arbitrary scale used to calibrate NMR charts. One delta unit (δ) is equal to 1 part per million (ppm) of the spectrometer operating frequency.

Denaturation (Section 19-8): The physical changes that occur in a protein when secondary and tertiary structures are disrupted.

Deoxy sugar (Section 21-7): A sugar with one of its $-OH$ groups replaced by an $-H$.

Deoxyribonucleic acid, DNA (Section 24-1): The biopolymer consisting of deoxyribonucleotide units linked together through phosphate–sugar bonds. Found in the nucleus of cells, DNA contains an organism's genetic information.

DEPT-NMR (Section 11-6): An NMR method for distinguishing among signals due to CH_3 , CH_2 , CH , and quaternary carbons. That is, the number of hydrogens attached to each carbon can be determined.

Deshielding (Section 11-2): An effect observed in NMR that causes a nucleus to absorb toward the left (downfield) side of the chart. Deshielding is caused by a withdrawal of electron density from the nucleus.

Dess–Martin periodinane (Section 13-5): An iodine-based reagent commonly used for the laboratory oxidation of a primary alcohol to an aldehyde or a secondary alcohol to a ketone.

Deuterium isotope effect (Section 12-13): A tool used in mechanistic investigations to establish whether a C–H bond is broken in the rate-limiting step of a reaction.

Dextrorotatory (Section 5-3): A word used to describe an optically active substance that rotates the plane of polarization of plane-polarized light in a right-handed (clockwise) direction.

Diastereomers (Section 5-6): Non-mirror-image stereoisomers; diastereomers have the same configuration at one or more chirality centers but differ at other chirality centers.

Diastereotopic (Section 11-8): Hydrogens in a molecule whose replacement by some other group leads to different diastereomers.

1,3-Diaxial interaction (Section 4-7): The strain energy caused by a steric interaction between axial groups three carbon atoms apart in chair cyclohexane.

Dideoxy DNA sequencing (Section 24-6): A biochemical method for sequencing DNA strands.

Dieckmann cyclization reaction (Section 17-10): An intramolecular Claisen condensation reaction of a diester to give a cyclic β -keto ester.

Diels-Alder cycloaddition reaction (Sections 8-14, 26-5): The cycloaddition reaction of a diene with a dienophile to yield a cyclohexene.

Dienophile (Section 8-14): A compound containing a double bond that can take part in the Diels-Alder cycloaddition reaction. The most reactive dienophiles are those that have electron-withdrawing groups on the double bond.

Digestion (Section 20-1): The first stage of catabolism, in which food is broken down by hydrolysis of ester, glycoside (acetal), and peptide (amide) bonds to yield fatty acids, simple sugars, and amino acids.

Dihedral angle (Section 3-6): The angle between two bonds on adjacent carbons as viewed along the C-C bond.

Dipole moment, μ (Section 2-2): A measure of the net polarity of a molecule. A dipole moment arises when the centers of mass of positive and negative charges within a molecule don't coincide.

Dipole-dipole force (Section 2-12): A noncovalent electrostatic interaction between polar molecules.

Disaccharide (Section 21-8): A carbohydrate formed by linking two simple sugars through an acetal bond.

Dispersion force (Section 2-12): A noncovalent interaction between molecules that arises because of constantly changing electron distributions within the molecules.

Disrotatory (Section 26-2): A term used to indicate that p orbitals rotate in opposite directions during electrocyclic ring-opening or ring-closing reactions.

Disulfide (Section 13-7): A compound of the general structure $RSSR'$.

DNA (Section 24-1): Deoxyribonucleic acid.

Double bond (Section 1-8): A covalent bond formed by sharing two electron pairs between atoms.

Double helix (Section 24-2): The structure of DNA in which two polynucleotide strands coil around each other.

Doublet (Section 11-11): A two-line NMR absorption caused by spin-spin splitting when the spin of the nucleus under observation couples with the spin of a neighboring magnetic nucleus.

Downfield (Section 11-3): Referring to the left-hand portion of the NMR chart.

***E* geometry** (Section 7-4): A term used to describe the stereochemistry of a carbon-carbon double bond. The two groups on each carbon are ranked according to the Cahn-Ingold-Prelog sequence rules, and the two carbons are compared. If the higher-ranked groups on each carbon are on opposite sides of the double bond, the bond has *E* geometry.

E1 reaction (Section 12-14): A unimolecular elimination reaction in which the substrate spontaneously dissociates to give a carbocation intermediate, which loses a proton in a separate step.

E1cB reaction (Section 12-14): A unimolecular elimination reaction in which a proton is first removed to give a carbanion intermediate, which then expels the leaving group in a separate step.

E2 reaction (Section 12-13): A bimolecular elimination reaction in which C-H and C-X bond cleavage are simultaneous.

Eclipsed conformation (Section 3-6): The geometric arrangement around a carbon-carbon single bond in which the bonds to substituents on one carbon are parallel to the bonds to substituents on the neighboring carbon as viewed in a Newman projection.

Eclipsing strain (Section 3-6): The strain energy in a molecule caused by electron repulsions between eclipsed bonds. Eclipsing strain is also called torsional strain.

Edman degradation (Section 19-6): A method for N-terminal sequencing of peptide chains by treatment with *N*-phenylisothiocyanate.

Eicosanoid (Section 23-7): A lipid derived biologically from eicosa-5,8,11,14-tetraenoic acid, or arachidonic acid. Prostaglandins, thromboxanes, and leukotrienes are examples.

Elastomer (Section 27-6): An amorphous polymer that has the ability to stretch out and spring back to its original shape.

Electrocyclic reaction (Section 26-2): A unimolecular pericyclic reaction in which a ring is formed or broken by a concerted reorganization of electrons through a cyclic transition state. For example, the cyclization of hexa-1,3,5-triene to yield cyclohexa-1,3-diene is an electrocyclic reaction.

Electromagnetic spectrum (Section 10-5): The range of electromagnetic energy, including infrared, ultraviolet, and visible radiation.

Electron configuration (Section 1-3): A list of the orbitals occupied by electrons in an atom.

Electron-dot structure (Section 1-4): A representation of a molecule showing valence electrons as dots.

Electron-transport chain (Section 20-1): The final stage of catabolism in which ATP is produced.

Electronegativity (Section 2-1): The ability of an atom to attract electrons in a covalent bond. Electronegativity increases across the periodic table from left to right and from bottom to top.

Electrophile (Section 6-4): An “electron-lover,” or substance that accepts an electron pair from a nucleophile in a polar bond-forming reaction.

Electrophilic addition reaction (Section 7-6): The addition of an electrophile to an alkene to yield a saturated product.

Electrophilic aromatic substitution reaction (Section 9-6): A reaction in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the ring hydrogens.

Electrophoresis (Sections 19-2, 24-6): A technique used for separating charged organic molecules, particularly proteins and DNA fragments. The mixture to be separated is placed on a buffered gel or paper, and an electric potential is applied across the ends of the apparatus. Negatively charged molecules migrate toward the positive electrode, and positively charged molecules migrate toward the negative electrode.

Electrostatic potential map (Section 2-1): A molecular representation that uses color to indicate the charge distribution in the molecule as derived from quantum-mechanical calculations.

Elimination reaction (Section 6-1): What occurs when a single reactant splits into two products.

Embden–Meyerhof pathway (Section 22-2): An alternative name for glycolysis.

Enamine (Section 14-7): A compound with the $R_2N-CR=CR_2$ functional group.

Enantiomers (Section 5-1): Stereoisomers of a chiral substance that have a mirror-image relationship. Enantiomers have opposite configurations at all chirality centers.

Enantioselective synthesis (Chapter 14 *Something Extra*; Section 19-3): A method of synthesis from an achiral precursor that yields only a single enantiomer of a chiral product.

Enantiotopic (Section 11-8): Hydrogens in a molecule whose replacement by some other group leads to different enantiomers.

3' End (Section 24-1): The end of a nucleic acid chain with a free hydroxyl group at C3'.

5' End (Section 24-1): The end of a nucleic acid chain with a free hydroxyl group at C5'.

Endergonic (Section 6-7): A reaction that has a positive free-energy change and is therefore nonspontaneous. In an energy diagram, the product of an endergonic reaction has a higher energy level than the reactants.

Endothermic (Section 6-7): A reaction that absorbs heat and therefore has a positive enthalpy change.

Energy diagram (Section 6-9): A representation of the course of a reaction, in which free energy is plotted as a function of reaction progress. Reactants, transition states, intermediates, and products are represented, and their appropriate energy levels are indicated.

Enol (Sections 8-15, 17-1): A vinylic alcohol that is in equilibrium with a carbonyl compound, $C=C-OH$.

Enolate ion (Section 17-1): The anion of an enol, $C=C-O^-$.

Enthalpy change, ΔH (Section 6-7): The heat of reaction. The enthalpy change that occurs during a reaction is a measure of the difference in total bond energy between reactants and products.

Entropy change, ΔS (Section 6-7): The change in amount of molecular randomness. The entropy change that occurs during a reaction is a measure of the difference in randomness between reactants and products.

Enzyme (Sections 6-11, 19-9): A biological catalyst. Enzymes are large proteins that catalyze specific biochemical reactions.

Epimers (Section 5-6): Diastereomers that differ in configuration at only one chirality center but are the same at all others.

Epoxyde (Section 8-6): A three-membered-ring ether functional group.

Equatorial bond (Section 4-6): A bond to cyclohexane that lies along the rough equator of the ring.

ESI (Section 10-4): Electrospray ionization; a soft ionization method used for mass spectrometry of biological samples of very high molecular weight.

Essential amino acid (Section 20-5): One of nine amino acids that are biosynthesized only in plants and microorganisms and must be obtained by humans in the diet.

Essential monosaccharide (Section 21-7): One of eight simple sugars that is best obtained in the diet rather than by biosynthesis.

Essential oil (Chapter 7 *Something Extra*): The volatile oil obtained by steam distillation of a plant extract.

Ester (Chapter 16 Introduction): A compound containing the $-\text{CO}_2\text{R}$ functional group.

Estrogen (Section 23-9): A female steroid sex hormone.

Ether (Chapter 13 Introduction): A compound that has two organic substituents bonded to the same oxygen atom, ROR' .

Exergonic (Section 6-7): A reaction that has a negative free-energy change and is therefore spontaneous. On an energy diagram, the product of an exergonic reaction has a lower energy level than that of the reactants.

Exon (Section 24-4): A section of DNA that contains genetic information.

Exothermic (Section 6-7): A reaction that releases heat and therefore has a negative enthalpy change.

Fat (Section 23-1): A solid triacylglycerol derived from an animal source.

Fatty acid (Section 23-1): A long, straight-chain carboxylic acid found in fats and oils.

Fatty acid-derived substance (Section 25-1): A natural product biosynthesized from simple acyl precursors such as acetyl CoA and propionyl CoA.

Fiber (Section 27-6): A thin thread produced by extruding a molten polymer through small holes in a die.

Fibrous protein (Section 19-8): A protein that consists of polypeptide chains arranged side by side in long threads. Such proteins are tough, insoluble in water, and used in nature for structural materials such as hair, hooves, and fingernails.

Fingerprint region (Section 10-7): The complex region of the infrared spectrum from 1500 to 400 cm^{-1} .

First-order reaction (Section 12-9): A reaction whose rate-limiting step is unimolecular and whose kinetics therefore depend on the concentration of only one reactant.

Fischer esterification reaction (Section 16-3): The acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol to yield an ester.

Fischer projection (Section 21-2): A means of depicting the absolute configuration of a chiral molecule on a flat page. A Fischer projection uses a cross to represent the chirality center. The horizontal arms of the cross represent bonds coming out of the plane of the page, and the

vertical arms of the cross represent bonds going back into the plane of the page.

Fmoc derivative (Section 19-7): A fluorenylmethyloxy-carbonyl N-protected amino acid.

Formal charge (Section 2-3): The difference in the number of electrons owned by an atom in a molecule and by the same atom in its elemental state.

Formyl group (Section 14-1): A $-\text{CHO}$ group.

Frequency, ν (Section 10-5): The number of electromagnetic wave cycles that travel past a fixed point in a given unit of time. Frequencies are expressed in units of cycles per second, or hertz.

Friedel–Crafts reaction (Section 9-7): An electrophilic aromatic substitution reaction to alkylate or acylate an aromatic ring.

Frontier orbitals (Section 26-1): The highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals.

FT-NMR (Section 11-4): Fourier-transform NMR; a rapid technique for recording NMR spectra in which all magnetic nuclei absorb at the same time.

Functional group (Section 3-1): An atom or group of atoms that is part of a larger molecule and has a characteristic chemical reactivity.

Functional RNA (Section 24-4): An alternative name for small RNAs.

Furanose (Section 21-5): The five-membered-ring form of a simple sugar.

Gauche conformation (Section 3-7): The conformation of butane in which the two methyl groups lie 60° apart as viewed in a Newman projection. This conformation has 3.8 kJ/mol steric strain.

Geminal (Section 14-5): Referring to two groups attached to the same carbon atom. For example, the hydrate formed by nucleophilic addition of water to an aldehyde or ketone is a geminal diol.

Gibbs free-energy change, ΔG (Section 6-7): The free-energy change that occurs during a reaction, given by the equation $\Delta G = \Delta H - T\Delta S$. A reaction with a negative free-energy change is spontaneous, and a reaction with a positive free-energy change is nonspontaneous.

Gilman reagent (Section 12-5): A diorganocopper reagent, R_2CuLi .

Glass transition temperature, T_g (Section 27-6): The temperature at which a hard, amorphous polymer becomes soft and flexible.

Globular protein (Section 19-8): A protein that is coiled into a compact, nearly spherical shape. Globular proteins, which are generally water-soluble and mobile within the cell, are the structural class to which enzymes belong.

Glucogenic amino acid (Section 20-4): An amino acid that is metabolized either to pyruvate or to an intermediate of the citric acid cycle.

Gluconeogenesis (Section 22-5): The anabolic pathway by which organisms make glucose from simple three-carbon precursors.

Glycal (Section 21-9): An unsaturated sugar with a C1–C2 double bond.

Glycal assembly method (Section 21-9): A method for linking monosaccharides together to synthesize polysaccharides.

Glycerophospholipid (Section 23-3): A lipid that contains a glycerol backbone linked to two fatty acids and a phosphoric acid.

Glycoconjugate (Section 21-6): A molecule in which a carbohydrate is linked through its anomeric center to another biological molecule such as a lipid or protein.

Glycol (Section 8-7): A diol, such as ethylene glycol, HOCH₂CH₂OH.

Glycolipid (Section 21-6): A biological molecule in which a carbohydrate is linked through a glycoside bond to a lipid.

Glycolysis (Section 22-2): A series of ten enzyme-catalyzed reactions that break down glucose into 2 equivalents of pyruvate, CH₃COC(=O)C(=O)⁻.

Glycoprotein (Section 21-6): A biological molecule in which a carbohydrate is linked through a glycoside bond to a protein.

Glycoside (Section 21-6): A cyclic acetal formed by reaction of a sugar with another alcohol.

Graft copolymer (Section 27-3): A copolymer in which homopolymer branches of one monomer unit are “grafted” onto a homopolymer chain of another monomer unit.

Green chemistry (Chapter 18 *Something Extra*): The design and implementation of chemical products and processes that reduce waste and attempt to eliminate the generation of hazardous substances.

Grignard reagent (Section 12-4): An organomagnesium halide, RMgX.

Ground state (Section 1-3): The most stable, lowest-energy electron configuration of a molecule or atom.

Halogenation (Sections 8-2, 9-6): The reaction of halogen with an alkene to yield a 1,2-dihalide addition product or with an aromatic compound to yield a substitution product.

Haloalcohol (Section 8-3): A 1,2-haloalcohol, such as that obtained on addition of HOBr to an alkene.

Hammond postulate (Section 7-9): A postulate stating that we can get a picture of what a given transition state looks like by looking at the structure of the nearest stable species. Exergonic reactions have transition states that resemble reactant; endergonic reactions have transition states that resemble product.

Heat of combustion (Section 4-3): The amount of heat released when a compound burns completely in oxygen.

Heat of hydrogenation (Section 7-5): The amount of heat released when a carbon–carbon double bond is hydrogenated.

Heat of reaction (Section 6-7): An alternative name for the enthalpy change in a reaction, ΔH .

Hell–Volhard–Zelinskii (HVZ) reaction (Section 17-3): The reaction of a carboxylic acid with Br₂ and phosphorus to give an α -bromo carboxylic acid.

Hemiacetal (Section 14-8): A functional group having one –OR and one –OH group bonded to the same carbon.

Hemithioacetal (Section 22-2): The sulfur analog of an acetal, resulting from nucleophilic addition of a thiol to a ketone or aldehyde.

Henderson–Hasselbalch equation (Sections 15-3, 18-5): An equation for determining the extent of dissociation of a weak acid at various pH values.

Hertz, Hz (Section 10-5): A unit of measure of electromagnetic frequency, the number of waves that pass by a fixed point per second.

Heterocycle (Sections 9-4, 18-8): A cyclic molecule whose ring contains more than one kind of atom. For example, pyridine is a heterocycle that contains five carbon atoms and one nitrogen atom in its ring.

Heterolytic bond breakage (Section 6-2): The kind of bond-breaking that occurs in polar reactions when one fragment leaves with both of the bonding electrons: $A:B \rightarrow A^+ + B:^-$.

High-energy compound (Section 6-8): A term used in biochemistry to describe substances such as ATP that undergo highly exothermic reactions.

Hofmann elimination reaction (Section 18-7): The elimination reaction of an amine to yield an alkene by reaction with iodomethane, followed by heating with Ag₂O.

HOMO (Sections 10-9, 26-1): The highest occupied molecular orbital.

Homolytic bond breakage (Section 6-2): The kind of bond-breaking that occurs in radical reactions when each fragment leaves with one bonding electron: $A:B \rightarrow A\cdot + B\cdot$.

Homopolymer (Section 27-3): A polymer made up of identical repeating units.

Homotopic (Section 11-8): Hydrogens in a molecule that give the identical structure on replacement by X and thus show identical NMR absorptions.

Hormone (Section 23-9): A chemical messenger that is secreted by an endocrine gland and carried through the bloodstream to a target tissue.

HPLC (Section 19-5): High-pressure liquid chromatography; a variant of column chromatography using high pressure to force solvent through very small absorbent particles.

Hückel's rule (Section 9-3): A rule stating that monocyclic conjugated molecules having $4n + 2 \pi$ electrons ($n =$ an integer) are aromatic.

Hund's rule (Section 1-3): If two or more empty orbitals of equal energy are available, one electron occupies each, with their spins parallel, until all are half-full.

Hybrid orbital (Section 1-6): An orbital derived from a combination of atomic orbitals. Hybrid orbitals, such as the sp^3 , sp^2 , and sp hybrids of carbon, are strongly directed and form stronger bonds than atomic orbitals do.

Hydration (Section 8-4): Addition of water to a molecule, such as occurs when alkenes are treated with aqueous sulfuric acid to give alcohols.

Hydride shift (Section 7-10): The shift of a hydrogen atom and its electron pair to a nearby cationic center.

Hydroboration (Section 8-4): Addition of borane (BH_3) or an alkylborane to an alkene. The resultant trialkylborane products can be oxidized to yield alcohols.

Hydrocarbon (Section 3-2): A compound that contains only carbon and hydrogen.

Hydrogen bond (Sections 2-12, 13-2): The weak attraction between a hydrogen atom bonded to an electronegative atom and an electron lone pair on another electronegative atom.

Hydrogenation (Section 8-5): Addition of hydrogen to a double or triple bond to yield a saturated product.

Hydrogenolysis (Section 19-7): Cleavage of a bond by reaction with hydrogen. Benzylic ethers and esters, for instance, are cleaved by hydrogenolysis.

Hydrophilic (Sections 2-12, 23-2): Water-loving; attracted to water.

Hydrophobic (Section 2-12, 23-2): Water-fearing; not attracted to water.

Hydroquinone (Section 13-5): A 1,4-dihydroxybenzene.

Hydroxylation (Section 8-7): Addition of two $-OH$ groups to a double bond.

Hyperconjugation (Section 7-5): An electronic interaction that results from overlap of a vacant p orbital on one atom with a neighboring $C-H \sigma$ bond. Hyperconjugation is important in stabilizing carbocations and substituted alkenes.

Imine (Section 14-7): A compound with the $R_2C=NR$ functional group; also called a Schiff base.

Inductive effect (Sections 2-1, 7-8, 9-8): The electron-attracting or electron-withdrawing effect transmitted through σ bonds. Electronegative elements have an electron-withdrawing inductive effect.

Infrared (IR) spectroscopy (Section 10-6): A kind of optical spectroscopy that uses infrared energy. IR spectroscopy is particularly useful in organic chemistry for determining the kinds of functional groups present in molecules.

Initiator (Section 6-3): A substance with an easily broken bond that is used to initiate a radical chain reaction. For example, radical chlorination of alkanes is initiated when light energy breaks the weak $Cl-Cl$ bond to form $Cl\cdot$ radicals.

Integration (Section 11-10): A technique for measuring the area under an NMR peak to determine the relative numbers of the kinds of proton in a molecule.

Intermediate (Section 6-10): A species that is formed during the course of a multistep reaction but is not the final product. Intermediates are more stable than transition states but may or may not be stable enough to isolate.

Intramolecular, intermolecular (Section 17-8): A reaction that occurs within the same molecule is intramolecular; a reaction that occurs between two molecules is intermolecular.

Intron (Section 24-4): A section of DNA that does not contain genetic information.

Ion pair (Section 12-9): A loose association between two ions in solution. Ion pairs are implicated as intermediates in S_N1 reactions to account for the partial retention of stereochemistry that is often observed.

Ionic bond (Section 1-4): The electrostatic attraction between ions of unlike charge.

Ionophore (Section 13-11): A fat-soluble molecule that binds to a specific ion and facilitates transport of the ion through biological membranes.

Isoelectric point, pI (Section 19-2): The pH at which the number of positive charges and the number of negative charges on a protein or an amino acid are equal.

Isomers (Sections 3-2, 5-9): Compounds that have the same molecular formula but different structures.

Isoprene rule (Chapter 7 *Something Extra*): An observation to the effect that terpenoids appear to be made up of isoprene (2-methylbuta-1,3-diene) units connected head-to-tail.

Isotactic (Section 27-2): A chain-growth polymer in which the stereochemistry of the substituents is oriented regularly along the backbone.

Isotopes (Section 1-1): Atoms of the same element that have different mass numbers.

IUPAC system of nomenclature (Section 3-4): Rules for naming compounds, devised by the International Union of Pure and Applied Chemistry.

Kekulé structure (Section 1-4): An alternative name for a line-bond structure, which represents a molecule by showing covalent bonds as lines between atoms.

Ketal (Section 14-8): An alternative name for an acetal that is derived from a ketone rather than an aldehyde and consisting of two –OR groups bonded to the same carbon, $R_2C(OR')_2$. Ketals are often used as protecting groups for ketones.

Keto-enol tautomerism (Sections 8-15, 17-1): The equilibrium between a carbonyl form and vinylic alcohol form of a molecule.

Ketogenic amino acid (Section 20-4): An amino acid that is metabolized into an intermediate that can enter fatty-acid biosynthesis.

Ketone (Chapter 14 Introduction): A compound with two organic substituents bonded to a carbonyl group, $R_2C=O$.

Ketone body (Section 20-4): One of the substances acetoacetate, β -hydroxybutyrate, or acetone resulting from amino acid catabolism.

Ketose (Section 21-1): A carbohydrate with a ketone functional group.

Kiliani-Fischer synthesis (Section 21-6): A method for lengthening the chain of an aldose sugar.

Kinetics (Section 12-7): Referring to reaction rates. Kinetic measurements are useful for helping to determine reaction mechanisms.

Krebs cycle (Section 22-4): An alternative name for the citric acid cycle, by which acetyl CoA is degraded to CO_2 .

L Sugar (Section 21-3): A sugar whose hydroxyl group at the chirality center farthest from the carbonyl group points to the left when drawn in Fischer projection.

Lactam (Section 16-7): A cyclic amide.

Lactone (Section 16-6): A cyclic ester.

Lagging strand (Section 24-3): The complement of the original $3' \rightarrow 5'$ DNA strand that is synthesized discontinuously in small pieces that are subsequently linked by DNA ligases.

LDA (Section 17-4): Lithium diisopropylamide, $LiN(i-C_3H_7)_2$, a strong base commonly used to convert carbonyl compounds into their enolate ions.

LD₅₀ (Chapter 1 *Something Extra*): The amount of a substance per kilogram body weight that is lethal to 50% of test animals.

Leading strand (Section 24-3): The complement of the original $5' \rightarrow 3'$ DNA strand that is synthesized continuously in a single piece.

Leaving group (Section 12-7) The group that is replaced in a substitution reaction.

Leverotatory (Section 5-3): An optically active substance that rotates the plane of polarization of plane-polarized light in a left-handed (counterclockwise) direction.

Lewis acid (Section 2-11): A substance with a vacant low-energy orbital that can accept an electron pair from a base. All electrophiles are Lewis acids.

Lewis base (Section 2-11): A substance that donates an electron lone pair to an acid. All nucleophiles are Lewis bases.

Lewis structure (Section 1-4): A representation of a molecule showing valence electrons as dots.

Lindlar catalyst (Section 8-15): A hydrogenation catalyst used to convert alkynes to cis alkenes.

Line-bond structure (Section 1-4): An alternative name for a Kekulé structure, which represents a molecule by showing covalent bonds as lines between atoms.

1 \rightarrow 4 Link (Section 21-8): A glycoside link between the C1 –OH group of one sugar and the C4 –OH group of another sugar.

Lipid (Chapter 23 Introduction): A naturally occurring substance isolated from cells and tissues by extraction with a nonpolar solvent. Lipids belong to many different structural classes, including fats, terpenoids, prostaglandins, and steroids.

Lipid bilayer (Section 23-3): The ordered lipid structure that forms a cell membrane.

Lone-pair electrons (Section 1-4): Nonbonding valence-shell electron pairs. Lone-pair electrons are used by nucleophiles in their reactions with electrophiles.

LUMO (Sections 10-9, 26-1): The lowest unoccupied molecular orbital. The symmetries of the LUMO and the HOMO are important in determining the stereochemistry of pericyclic reactions.

Magnetic resonance imaging, MRI (Chapter 11 *Something Extra*): A medical diagnostic technique based on nuclear magnetic resonance.

Major groove (Section 24-2): The larger of two grooves in the DNA double helix.

MALDI (Section 10-4): Matrix-assisted laser desorption ionization, a soft ionization method used for mass spectrometry of biological samples of very high molecular weight.

Malonic ester synthesis (Section 17-5): The synthesis of a carboxylic acid by alkylation of an alkyl halide with diethyl malonate, followed by hydrolysis and decarboxylation.

Markovnikov's rule (Section 7-7): A guide for determining the regiochemistry (orientation) of electrophilic addition reactions. In the addition of HX to an alkene, the hydrogen atom bonds to the alkene carbon that has fewer alkyl substituents.

Mass number, A (Section 1-1): The total of protons plus neutrons in an atom.

Mass spectrometry (Section 10-1): A technique for measuring the mass, and therefore the molecular weight (MW), of molecules.

McLafferty rearrangement (Section 10-3): A mass-spectral fragmentation pathway for carbonyl compounds.

Mechanism (Section 6-2): A complete description of how a reaction occurs. A mechanism accounts for all reactants and all products and describes the details of each individual step in the overall reaction process.

Meisenheimer complex (Section 9-9): The intermediate in a nucleophilic aromatic substitution reaction, formed by addition of a nucleophile to a halo-substituted aromatic ring.

Melt transition temperature, T_m (Section 27-6): The temperature at which crystalline regions of a polymer melt to give an amorphous material.

Mercapto group (Section 13-1): An alternative name for the thiol group, $-SH$.

Meso compound (Section 5-7): A compound that contains chirality centers but is nevertheless achiral because it contains a symmetry plane.

Messenger RNA (Section 24-4): A kind of RNA formed by transcription of DNA and used to carry genetic messages from DNA to ribosomes.

Meta, m - (Section 9-1): A naming prefix used for 1,3-disubstituted benzenes.

Metabolism (Section 20-1): A collective name for the many reactions that go on in the cells of living organisms.

Metallacycle (Section 27-5): A cyclic compound that contains a metal atom in its ring.

Methylene group (Section 7-2): A $-CH_2-$ or $=CH_2$ group.

Micelle (Section 23-2): A spherical cluster of soaplike molecules that aggregate in aqueous solution. The ionic heads of the molecules lie on the outside, where they are solvated by water, and the organic tails bunch together on the inside of the micelle.

Michael reaction (Section 17-11): The conjugate addition reaction of an enolate ion to an unsaturated carbonyl compound.

Minor groove (Section 24-2): The smaller of two grooves in the DNA double helix.

Molar absorptivity (Section 10-9): A quantitative measure of the amount of UV light absorbed by a sample.

Molecular ion (Section 10-1): The cation produced in a mass spectrometer by loss of an electron from the parent molecule. The mass of the molecular ion corresponds to the molecular weight of the sample.

Molecular mechanics (Chapter 4 *Something Extra*): A computer-based method for calculating the minimum-energy conformation of a molecule.

Molecular orbital (MO) theory (Sections 1-11, 26-1): A description of covalent bond formation as resulting from a mathematical combination of atomic orbitals (wave functions) to form molecular orbitals.

Molecule (Section 1-4): A neutral collection of atoms held together by covalent bonds.

Molozonide (Section 8-8): The initial addition product of ozone with an alkene.

Monomer (Section 8-10): The simple starting unit from which a polymer is made.

Monosaccharide (Section 21-1): A simple sugar.

Monoterpenoid (Chapter 7 *Something Extra*; Section 23-8): A 10-carbon lipid.

Multiplet (Section 11-11): A pattern of peaks in an NMR spectrum that arises by spin-spin splitting of a single absorption because of coupling between neighboring magnetic nuclei.

Mutarotation (Section 21-5): The change in optical rotation observed when a pure anomer of a sugar is dissolved in water. Mutarotation is caused by the reversible opening and closing of the hemiacetal linkage, which yields an equilibrium mixture of anomers.

$n + 1$ rule (Section 11-11): A hydrogen with n other hydrogens on neighboring carbons shows $n + 1$ peaks in its 1H NMR spectrum.

N-terminal amino acid (Section 19-4): The amino acid with a free $-NH_2$ group at the end of a protein chain.

Natural gas (Chapter 3 *Something Extra*): A naturally occurring hydrocarbon mixture consisting chiefly of methane, along with smaller amounts of ethane, propane, and butane.

Natural product (Chapter 6 *Something Extra*; Chapter 25): A catchall term generally taken to mean a secondary metabolite found in bacteria, plants, and other living organisms.

Neopentyl group (Section 3-4): The 2,2-dimethylpropyl group, $(\text{CH}_3)_3\text{CCH}_2-$.

Neuraminidase (Chapter 22 *Something Extra*): An enzyme present on the surface of viral particles that cleaves the bond holding the newly formed viral particles to host cells.

New molecular entity, NME (Chapter 6 *Something Extra*): A new biologically active chemical substance approved for sale as a drug by the U.S. Food and Drug Administration.

Newman projection (Section 3-6): A means of indicating stereochemical relationships between substituent groups on neighboring carbons. The carbon-carbon bond is viewed end-on, and the carbons are indicated by a circle. Bonds radiating from the center of the circle are attached to the front carbon, and bonds radiating from the edge of the circle are attached to the rear carbon.

Nitration (Section 9-6): The substitution of a nitro group onto an aromatic ring.

Nitrile (Chapter 15 Introduction): A compound containing the $\text{C}\equiv\text{N}$ functional group.

Nitrogen rule (Section 18-10): A compound with an odd number of nitrogen atoms has an odd-numbered molecular weight.

Node (Section 1-2): A surface of zero electron density within an orbital. For example, a p orbital has a nodal plane passing through the center of the nucleus, perpendicular to the axis of the orbital.

Nonbonding electrons (Section 1-4): Valence electrons that are not used in forming covalent bonds.

Noncoding strand (Section 24-4): An alternative name for the antisense strand of DNA.

Noncovalent interaction (Section 2-12): One of a variety of nonbonding interactions between molecules, such as dipole-dipole forces, dispersion forces, and hydrogen bonds.

Nonessential amino acid (Section 20-5): One of the 11 amino acids that are biosynthesized by humans.

Nonribosomal polypeptide (Section 25-1): A peptidic compound biosynthesized from an amino acid without direct RNA transcription. The penicillins are examples.

Normal alkane (Section 3-2): A straight-chain alkane, as opposed to a branched alkane. Normal alkanes are denoted by the suffix n , as in $n\text{-C}_4\text{H}_{10}$ (n -butane).

NSAID (Chapter 9 *Something Extra*): A nonsteroidal anti-inflammatory drug, such as aspirin or ibuprofen.

Nuclear magnetic resonance, NMR (Chapter 11): A spectroscopic technique that provides information about the carbon-hydrogen framework of a molecule. NMR works by detecting the energy absorption accompanying the transitions between nuclear spin states that occur when a molecule is placed in a strong magnetic field and irradiated with radiofrequency waves.

Nucleic acid (Section 24-1): Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); biological polymers made of nucleotides joined together to form long chains.

Nucleophile (Section 6-4): An electron-rich species that donates an electron pair to an electrophile in a polar bond-forming reaction. Nucleophiles are also Lewis bases.

Nucleophilic acyl substitution reaction (Section 16-2): A reaction in which a nucleophile attacks a carbonyl compound and substitutes for a leaving group bonded to the carbonyl carbon.

Nucleophilic addition reaction (Section 14-4): A reaction in which a nucleophile adds to the electrophilic carbonyl group of a ketone or aldehyde to give an alcohol.

Nucleophilic aromatic substitution reaction (Section 9-9): The substitution reaction of an aryl halide by a nucleophile.

Nucleophilic substitution reaction (Section 12-6): A reaction in which one nucleophile replaces another attached to a saturated carbon atom.

Nucleophilicity (Section 12-8): The ability of a substance to act as a nucleophile in an $\text{S}_{\text{N}}2$ reaction.

Nucleoside (Section 24-1): A nucleic acid constituent, consisting of a sugar residue bonded to a heterocyclic purine or pyrimidine base.

Nucleotide (Section 24-1): A nucleic acid constituent, consisting of a sugar residue bonded both to a heterocyclic purine or pyrimidine base and to a phosphoric acid. Nucleotides are the monomer units from which DNA and RNA are constructed.

Nylon (Section 16-9): A synthetic polyamide step-growth polymer.

Okazaki fragment (Section 24-3): A short segment of a DNA lagging strand that is biosynthesized discontinuously and then linked by DNA ligases.

Olefin (Chapter 7 Introduction): An alternative name for an alkene.

Olefin metathesis polymerization (Section 27-5): A method of polymer synthesis based on using an olefin metathesis reaction.

Olefin metathesis reaction (Section 27-5): A reaction in which two olefins (alkenes) exchange substituents on their double bonds.

Oligonucleotide (Section 24-7): A short segment of DNA.

Optical activity (Section 5-3): The rotation of the plane of polarization of plane-polarized light by a chiral substance in solution.

Optical isomers (Section 5-4): An older name for enantiomers. Optical isomers are isomers that have a mirror-image relationship.

Orbital (Section 1-2): A wave function, which describes the volume of space around a nucleus in which an electron is most likely to be found.

Organic chemistry (Chapter 1 Introduction): The study of carbon compounds.

Organohalide (Chapter 12 Introduction): A compound that contains one or more halogen atoms bonded to carbon.

Organometallic compound (Section 12-4): A compound that contains a carbon–metal bond. Grignard reagents, RMgX , are examples.

Organophosphate (Section 1-10): A compound that contains a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon.

Ortho, o- (Section 9-1): A naming prefix used for 1,2-disubstituted benzenes.

Oxidation (Section 8-6): A reaction that causes a decrease in electron ownership by carbon, either by bond formation between carbon and a more electronegative atom (usually oxygen, nitrogen, or a halogen) or by bond breaking between carbon and a less electronegative atom (usually hydrogen).

Oxidative deamination (Section 20-2): The conversion of a primary amine into a ketone by oxidation to an imine followed by hydrolysis.

Oxidative decarboxylation (Section 22-3): A decarboxylation reaction, usually of an α -keto acid, that is accompanied by a change in oxidation state of the carbonyl carbon from that of a ketone to that of a carboxylic acid or ester.

Oxirane (Section 8-6): An alternative name for an epoxide.

Oxymercuration–demercuration (Section 8-4): A method for double-bond hydration by reaction of an alkene with aqueous mercuric acetate followed by treatment with NaBH_4 .

Ozonide (Section 8-8): The product initially formed by addition of ozone to a carbon–carbon double bond.

Ozonides are usually treated with a reducing agent, such as zinc in acetic acid, to produce carbonyl compounds.

Para, p- (Section 9-1): A naming prefix used for 1,4-disubstituted benzenes.

Paraffin (Section 3-5): A common name for alkanes.

Parent peak (Section 10-1): The peak in a mass spectrum corresponding to the molecular ion. The mass of the parent peak therefore represents the molecular weight of the compound.

Pauli exclusion principle (Section 1-3): No more than two electrons can occupy the same orbital, and those two must have spins of opposite sign.

Peptide (Chapter 19 Introduction): A short amino acid polymer in which the individual amino acid residues are linked by amide bonds.

Peptide bond (Section 19-4): An amide bond in a peptide chain.

Pericyclic reaction (Section 8-14; Chapter 26): A reaction that takes place in a single step without intermediates by a cyclic redistribution of bonding electrons.

Periplanar (Section 12-13): A conformation in which bonds to neighboring atoms have a parallel arrangement. In an eclipsed conformation, the neighboring bonds are syn periplanar; in a staggered conformation, the bonds are anti periplanar.

Peroxyacid (Section 8-6): A compound with the $-\text{CO}_3\text{H}$ functional group.

Petroleum (Chapter 3 *Something Extra*): A complex mixture of naturally occurring hydrocarbons derived from the decomposition of plant and animal matter.

Phenol (Chapter 13 Introduction): A compound with an $-\text{OH}$ group directly bonded to an aromatic ring, ArOH .

Phenoxide ion (Section 13-2): The anion of a phenol, ArO^- .

Phenyl group (Section 9-1): The name for the $-\text{C}_6\text{H}_5$ unit when the benzene ring is considered as a substituent. A phenyl group is abbreviated as $-\text{Ph}$.

Phosphine (Section 5-10): A trivalent phosphorus compound, R_3P .

Phosphite (Section 24-7): A compound with the structure $\text{P}(\text{OR})_3$.

Phospholipid (Section 23-3): A lipid that contains a phosphate residue. For example, glycerophospholipids contain a glycerol backbone linked to two fatty acids and a phosphoric acid.

Phosphoramidite (Section 24-7): A compound with the structure $R_2NP(OR)_2$.

Phosphoric acid anhydride (Section 20-1): A substance that contains PO_2PO link, analogous to the CO_2CO link in carboxylic acid anhydrides.

Physiological pH (Section 15-3): The pH of 7.3 that exists inside cells.

Photochemical reaction (Section 26-2): A reaction carried out by irradiating the reactants with light.

Pi (π) bond (Section 1-8): The covalent bond formed by sideways overlap of atomic orbitals. For example, carbon-carbon double bonds contain a π bond formed by sideways overlap of two p orbitals.

PITC (Section 19-6): Phenylisothiocyanate, used in the Edman degradation of proteins.

pK_a (Section 2-8): The negative common logarithm of the K_a ; used to express acid strength.

Plane of symmetry (Section 5-2): A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Plane-polarized light (Section 5-3): Light that has its electromagnetic waves oscillating in a single plane rather than in random planes. The plane of polarization is rotated when the light is passed through a solution of a chiral substance.

Plasticizer (Sections 16-6, 27-6): A small organic molecule added to polymers to act as a lubricant between polymer chains.

Polar aprotic solvent (Section 12-8): A polar solvent that can't function as a hydrogen ion donor. Polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) are particularly useful in S_N2 reactions because of their ability to solvate cations.

Polar covalent bond (Section 2-1): A covalent bond in which the electron distribution between atoms is unsymmetrical.

Polar reaction (Section 6-4): A reaction in which bonds are made when a nucleophile donates two electrons to an electrophile and in which bonds are broken when one fragment leaves with both electrons from the bond.

Polarity (Section 2-1): The unsymmetrical distribution of electrons in a molecule that results when one atom attracts electrons more strongly than another.

Polarizability (Section 6-4): The measure of the change in a molecule's electron distribution in response to changing electrostatic interactions with solvents or ionic reagents.

Polycarbonate (Section 27-4): A polyester in which the carbonyl groups are linked to two $-OR$ groups, $[O=C(OR)_2]$.

Polycyclic aromatic compound (Section 9-5): A compound with two or more benzene-like aromatic rings fused together.

Polycyclic compound (Section 4-9): A compound that contains more than one ring.

Polyketide (Section 25-1): A natural product biosynthesized from simple acyl precursors such as acetyl CoA, propionyl CoA, and methylmalonyl CoA by a large multifunctional enzyme complex.

Polymer (Sections 8-10, 16-9; Chapter 27): A large molecule made up of repeating smaller units. For example, polyethylene is a synthetic polymer made from repeating ethylene units and DNA is a biopolymer made of repeating deoxyribonucleotide units.

Polymerase chain reaction, PCR (Section 24-8): A method for amplifying small amounts of DNA to produce larger amounts.

Polysaccharide (Section 21-9): A carbohydrate that is made of many simple sugars linked together by glycoside (acetal) bonds.

Polyunsaturated fatty acid (Section 23-1): A fatty acid containing two or more double bonds.

Polyurethane (Section 27-4): A step-growth polymer prepared by reaction between a diol and a diisocyanate.

Posttranslational modification (Section 24-6): A chemical modification of a protein that occurs after translation from DNA.

Primary, secondary, tertiary, quaternary (Section 3-3): Terms used to describe the substitution pattern at a specific site. A primary site has one organic substituent attached to it, a secondary site has two organic substituents, a tertiary site has three, and a quaternary site has four.

	Carbon	Carbo-cation	Hydrogen	Alcohol	Amine
Primary	RCH_3	RCH_2^+	RCH_3	RCH_2OH	RNH_2
Secondary	R_2CH_2	R_2CH^+	R_2CH_2	R_2CHOH	R_2NH
Tertiary	R_3CH	R_3C^+	R_3CH	R_3COH	R_3N
Quaternary	R_4C				

Primary structure (Section 19-8): The amino acid sequence in a protein.

Prochiral (Section 5-11): A molecule that can be converted from achiral to chiral in a single chemical step.

Prochirality center (Section 5-11): An atom in a compound that can be converted into a chirality center by changing one of its attached substituents.

Promotor sequence (Section 24-4): A short sequence on DNA located upstream of the transcription start site and recognized by RNA polymerase.

Propagation step (Section 6-3): A step in a radical chain reaction that carries on the chain. The propagation steps must yield both product and a reactive intermediate.

pro-R configuration (Section 5-11): One of two identical atoms or groups of atoms in a compound whose replacement leads to an *R* chirality center.

pro-S configuration (Section 5-11): One of two identical atoms or groups of atoms in a compound whose replacement leads to an *S* chirality center.

Prostaglandin (Section 23-7): A lipid derived from arachidonic acid. Prostaglandins are present in nearly all body tissues and fluids, where they serve many important hormonal functions.

Protecting group (Sections 13-6, 14-8, 19-7, 21-9, 24-7): A group that is introduced to protect a sensitive functional group toward reaction elsewhere in the molecule. After serving its protective function, the group is removed.

Protein (Chapter 19 Introduction): A large peptide containing 50 or more amino acid residues. Proteins serve both as structural materials and as enzymes that control an organism's chemistry.

Protein Data Bank (Chapter 19 *Something Extra*): A worldwide online repository of X-ray and NMR structural data for biological macromolecules. To access the Protein Data Bank, go to <http://www.rcsb.org/pdb/>.

Protic solvent (Section 12-8): A solvent such as water or alcohol that can act as a proton donor.

Pyramidal inversion (Section 18-2): The rapid inversion of configuration of an amine.

Pyranose (Section 21-5): The six-membered, cyclic hemiacetal form of a simple sugar.

Quartet (Section 11-11): A set of four peaks in an NMR spectrum, caused by spin–spin splitting of a signal by three adjacent nuclear spins.

Quaternary: *See* Primary.

Quaternary ammonium salt (Section 18-1): An ionic compound containing a positively charged nitrogen atom with four attached groups, $R_4N^+ X^-$.

Quaternary structure (Section 19-8): The highest level of protein structure, involving an ordered aggregation of individual proteins into a larger cluster.

Quinone (Section 13-5): A cyclohexa-2,5-diene-1,4-dione.

R configuration (Section 5-5): The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

R group (Section 3-3): A generalized abbreviation for an organic partial structure.

Racemic mixture (Section 5-8): A mixture consisting of equal parts (+) and (–) enantiomers of a chiral substance; also called a racemate.

Radical (Section 6-2): A species that has an odd number of electrons, such as the chlorine radical, $Cl\cdot$.

Radical reaction (Section 6-3): A reaction in which bonds are made by donation of one electron from each of two reactants and in which bonds are broken when each fragment leaves with one electron.

Rate constant (Section 12-7): The constant k in a rate equation.

Rate equation (Section 12-7): An equation that expresses the dependence of a reaction's rate on the concentration of reactants.

Rate-limiting step (Section 12-9): The slowest step in a multistep reaction sequence; also called the rate-determining step. The rate-limiting step acts as a kind of bottleneck in multistep reactions.

Re face (Section 5-11): One of two faces of a planar, sp^2 -hybridized atom.

Rearrangement reaction (Section 6-1): What occurs when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product.

Reducing sugar (Section 21-6): A sugar that reduces silver ion in the Tollens test or cupric ion in the Fehling or Benedict tests.

Reduction (Section 8-5): A reaction that causes an increase of electron ownership by carbon, either by bond breaking between carbon and a more electronegative atom or by bond formation between carbon and a less electronegative atom.

Reductive amination (Sections 18-6, 19-3): A method for preparing an amine by reaction of an aldehyde or ketone with ammonia and a reducing agent.

Refining (Chapter 3 *Something Extra*): The process by which petroleum is converted into gasoline and other useful products.

Regiospecific (Section 7-7): A term describing a reaction that occurs with only one of two possible orientations to give a single product rather than a mixture of products.

Replication (Section 24-3): The process by which double-stranded DNA uncoils and is replicated to produce two new copies.

Replication fork (Section 24-3): The point of unraveling in a DNA chain where replication occurs.

Residue (Section 19-4): An amino acid in a protein chain.

Resolution (Section 5-8): The process by which a racemate is separated into its two pure enantiomers.

Resonance effect (Section 9-8): The donation or withdrawal of electrons through orbital overlap with neighboring π bonds. For example, an oxygen or nitrogen substituent donates electrons to an aromatic ring by overlap of the O or N orbital with the aromatic ring p orbitals.

Resonance form (Section 2-4): An individual structural form of a resonance hybrid.

Resonance hybrid (Section 2-4): A molecule, such as benzene, that can't be represented adequately by a single Kekulé structure but must instead be considered as an average of two or more resonance forms. The resonance forms themselves differ only in the positions of their electrons, not their nuclei.

Restriction endonuclease (Section 24-6): An enzyme that is able to cleave a DNA molecule at points in the chain where a specific base sequence occurs.

Retrosynthetic (Section 9-11): Planning an organic synthesis by working backward from product to starting material.

Ribonucleic acid, RNA (Section 24-1): The biopolymer found in cells that serves to transcribe the genetic information found in DNA and uses that information to direct the synthesis of proteins.

Ribosomal RNA (Section 24-4): A kind of RNA used in the physical makeup of ribosomes.

Ring-flip (Section 4-6): A molecular motion that interconverts two chair conformations of cyclohexane. The effect of a ring-flip is to convert an axial substituent into an equatorial substituent.

Ring-opening metathesis polymerization (ROMP) (Section 27-5): A method of polymer synthesis that uses an olefin metathesis reaction of a cycloalkene.

RNA (Section 24-1): *See* Ribonucleic acid.

S configuration (Section 5-5): The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

s-Cis conformation (Section 8-14): Describing a conformation that is “cis-like” about a single bond.

Saccharide (Section 21-1): A sugar.

Salt bridge (Section 19-8): An ionic attraction between two oppositely charged groups in a protein chain.

Sanger dideoxy method (Section 24-6): A biochemical method for sequencing DNA strands.

Saponification (Section 16-6): An old term for the base-induced hydrolysis of an ester to yield a carboxylic acid salt.

Saturated (Section 3-2): A molecule that has only single bonds and thus can't undergo addition reactions. Alkanes are saturated, but alkenes are unsaturated.

Sawhorse structure (Section 3-6): A manner of representing stereochemistry that uses a stick drawing and gives a perspective view of the conformation around a single bond.

Schiff base (Sections 14-7, 22-2): An alternative name for an imine, $R_2C=NR'$, used primarily in biochemistry.

Second-order reaction (Section 12-7): A reaction whose rate-limiting step is bimolecular and whose kinetics are therefore dependent on the concentration of two reactants.

Secondary: *See* Primary.

Secondary metabolite (Chapter 25 Introduction): A small naturally occurring molecule that is not essential to the growth and development of the producing organism and is not classified by structure.

Secondary structure (Section 19-8): The level of protein substructure that involves organization of chain sections into ordered arrangements such as β -pleated sheets or α -helices.

Semiconservative replication (Section 24-3): The process by which DNA molecules are made containing one strand of old DNA and one strand of new DNA.

Sense strand (Section 24-4): The coding strand of double-helical DNA that contains the gene.

Sequence rules (Sections 5-5, 7-4): A series of rules for assigning relative rankings to substituent groups on a double-bond carbon atom or on a chirality center.

Sesquiterpenoid (Chapter 7 *Something Extra*; Section 23-8): A 15-carbon lipid.

Sharpless epoxidation (Chapter 14 *Something Extra*): A method for enantioselective synthesis of a chiral epoxide by treatment of an allylic alcohol with *tert*-butyl hydroperoxide, $(CH_3)_3C-OOH$, in the presence of titanium tetrakispropoxide and diethyl tartrate.

Shell (electron) (Section 1-2): A group of an atom's electrons with the same principal quantum number.

Shielding (Section 11-2): An effect observed in NMR that causes a nucleus to absorb toward the right (upfield) side of the chart. Shielding is caused by donation of electron density to the nucleus.

Si face (Section 5-11): One of two faces of a planar, sp^2 -hybridized atom.

Sialic acid (Section 21-7): One of a group of more than 300 carbohydrates based on acetylneuramic acid.

Side chain (Section 19-1): The substituent attached to the α carbon of an amino acid.

Sigma (σ) bond (Section 1-5): A covalent bond formed by head-on overlap of atomic orbitals.

Silyl ether (Section 13-6): A substance with the structure $R_3Si-O-R$. The silyl ether acts as a protecting group for alcohols.

Simple sugar (Section 21-1): A carbohydrate that cannot be broken down into smaller sugars by hydrolysis.

Single bond (Section 1-8): A covalent bond formed by sharing one electron pair between atoms.

Skeletal structure (Section 1-12): A shorthand way of writing structures in which carbon atoms are assumed to be at each intersection of two lines (bonds) and at the end of each line.

Small RNAs (Section 24-4): A type of RNA that has a variety of functions within the cell, including silencing transcription and catalyzing chemical modifications of other RNA molecules.

S_N1 reaction (Section 12-9): A unimolecular nucleophilic substitution reaction.

S_N2 reaction (Section 12-7): A bimolecular nucleophilic substitution reaction.

Solid-phase synthesis (Section 19-7): A technique of synthesis whereby the starting material is covalently bound to a solid polymer bead and reactions are carried out on the bound substrate. After the desired transformations have been effected, the product is cleaved from the polymer.

Solvation (Section 12-8): The clustering of solvent molecules around a solute particle to stabilize it.

sp Hybrid orbital (Section 1-9): A hybrid orbital derived from the combination of an s and a p atomic orbital. The two sp orbitals that result from hybridization are oriented at an angle of 180° to each other.

sp^2 Hybrid orbital (Section 1-8): A hybrid orbital derived by combination of an s atomic orbital with two p atomic orbitals. The three sp^2 hybrid orbitals that result lie in a plane at angles of 120° to each other.

sp^3 Hybrid orbital (Section 1-6): A hybrid orbital derived by combination of an s atomic orbital with three p atomic orbitals. The four sp^3 hybrid orbitals that result are directed toward the corners of a regular tetrahedron at angles of 109° to each other.

Specific rotation, $[\alpha]_D$ (Section 5-3): The optical rotation of a chiral compound under standard conditions.

Sphingomyelin (Section 23-3): A phospholipid that has sphingosine as its backbone rather than glycerol.

Spin-spin splitting (Section 11-11): The splitting of an NMR signal into a multiplet because of an interaction between nearby magnetic nuclei whose spins are coupled. The magnitude of spin-spin splitting is given by the coupling constant, J .

Staggered conformation (Section 3-6): The three-dimensional arrangement of atoms around a carbon-carbon single bond in which the bonds on one carbon bisect the bond angles on the second carbon as viewed end-on.

Statin (Chapter 1 Introduction; Chapter 23 *Something Extra*): A drug that controls cholesterol biosynthesis in the body by blocking the HMG-CoA reductase enzyme.

Step-growth polymer (Sections 16-9, 27-4): A polymer in which each bond is formed independently of the others. Polyesters and polyamides (nylons) are examples.

Stereocenter (Section 5-2): An alternative name for a chirality center.

Stereochemistry (Section 3-6; Chapters 4 and 5): The branch of chemistry concerned with the three-dimensional arrangement of atoms in molecules.

Stereoisomers (Section 4-2): Isomers that have their atoms connected in the same order but have different three-dimensional arrangements. The term *stereoisomer* includes both enantiomers and diastereomers.

Stereospecific (Section 8-9): Describing a reaction in which only a single stereoisomer is produced in a given reaction rather than a mixture.

Steric strain (Sections 3-7, 4-7): The strain imposed on a molecule when two groups are too close together and try to occupy the same space. Steric strain is responsible both for the greater stability of trans versus cis alkenes and for the greater stability of equatorially substituted versus axially substituted cyclohexanes.

Steroid (Section 23-9): A lipid whose structure is based on a tetracyclic carbon skeleton with three 6-membered and one 5-membered ring. Steroids occur in both plants and animals and have a variety of important hormonal functions.

Stork enamine reaction (Section 17-12): The conjugate addition of an enamine to an α,β -unsaturated carbonyl compound, followed by hydrolysis to yield a 1,5-dicarbonyl product.

STR loci (Chapter 24 *Something Extra*): Short tandem repeat sequences of noncoding DNA that are unique to every individual and allow DNA fingerprinting.

Straight-chain alkane (Section 3-2): An alkane whose carbon atoms are connected without branching.

Substitution reaction (Section 6-1): What occurs when two reactants exchange parts to give two new products. S_N1 and S_N2 reactions are examples.

Sulfide (Chapter 13 Introduction): A compound that has two organic substituents bonded to the same sulfur atom, RSR' .

Sulfonation (Section 9-6): The substitution of a sulfonic acid group ($-SO_3H$) onto an aromatic ring.

Sulfone (Section 13-12): A compound of the general structure RSO_2R' .

Sulfonium ion (Section 13-12): A species containing a positively charged, trivalent sulfur atom, R_3S^+ .

Sulfoxide (Section 13-12): A compound of the general structure $RSOR'$.

Suprafacial (Section 26-5): A word used to describe the geometry of pericyclic reactions. Suprafacial reactions take place on the same side of the two ends of a π electron system.

Suzuki–Miyaura reaction (Section 12-5): The palladium-catalyzed coupling reaction of an aromatic or vinylic halide with an aromatic or vinylic boronic acid.

Symmetry-allowed, symmetry-disallowed (Section 26-2): A symmetry-allowed reaction is a pericyclic process that has a favorable orbital symmetry for reaction through a concerted pathway. A symmetry-disallowed reaction is one that does not have favorable orbital symmetry for reaction through a concerted pathway.

Symmetry plane (Section 5-2): A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Syn periplanar (Section 12-13): Describing a stereochemical relationship in which two bonds on adjacent carbons lie in the same plane and are eclipsed.

Syn stereochemistry (Section 8-4): The opposite of anti. A syn addition reaction is one in which the two ends of the double bond react from the same side. A syn elimination is one in which the two groups leave from the same side of the molecule.

Syndiotactic (Section 27-2): A chain-growth polymer in which the stereochemistry of the substituents alternates regularly on opposite sides of the backbone.

Tautomers (Sections 8-15, 17-1): Isomers that interconvert spontaneously, usually with the change in position of a hydrogen.

Terpenoid (Chapter 7 *Something Extra*; Section 23-8): A lipid that is formally derived by head-to-tail polymerization of isoprene units.

Tertiary: See Primary.

Tertiary structure (Section 19-8): The level of protein structure that involves the manner in which the entire protein chain is folded into a specific three-dimensional arrangement.

Thermoplastic (Section 27-6): A polymer that has a high T_g and is hard at room temperature but becomes soft and viscous when heated.

Thermosetting resin (Section 27-6): A polymer that becomes highly cross-linked and solidifies into a hard, insoluble mass when heated.

Thioester (Chapter 16 Introduction): A compound with the $RCOSR'$ functional group.

Thiol (Chapter 13 Introduction): A compound containing the $-SH$ functional group.

Thiolate ion (Section 13-12): The anion of a thiol, RS^- .

TMS (Section 11-3): Tetramethylsilane, used as an NMR calibration standard.

TOF (Section 10-4): A time-of-flight mass spectrometer.

Tollens' reagent (Section 21-6): A solution of Ag_2O in aqueous ammonia; used to oxidize aldehydes to carboxylic acids.

Torsional strain (Section 3-6): The strain in a molecule caused by electron repulsion between eclipsed bonds. Torsional strain is also called eclipsing strain.

Tosylate (Section 12-6): A *p*-toluenesulfonate ester.

Transamination (Section 20-2): The exchange of an amino group and a keto group between reactants.

Transcription (Section 24-4): The process by which the genetic information encoded in DNA is read and used to synthesize RNA in the nucleus of the cell. A small portion of double-stranded DNA uncoils, and complementary ribonucleotides line up in the correct sequence for RNA synthesis.

Transfer RNA (Section 24-4): A kind of RNA that transports amino acids to the ribosomes, where they are joined together to make proteins.

Transimination (Section 20-2): The exchange of an amino group and an imine group between reactants.

Transition state (Section 6-9): An activated complex between reactants, representing the highest energy point on a reaction curve. Transition states are unstable complexes that can't be isolated.

Translation (Section 24-5): The process by which the genetic information transcribed from DNA onto mRNA is read by tRNA and used to direct protein synthesis.

Tree diagram (Section 11-12): A diagram used in NMR to sort out the complicated splitting patterns that can arise from multiple couplings.

Triacylglycerol (Section 23-1): A lipid, such as that found in animal fat and vegetable oil, that is a triester of glycerol with long-chain fatty acids.

Tricarboxylic acid cycle (Section 22-4): An alternative name for the citric acid cycle by which acetyl CoA is degraded to CO₂.

Triple bond (Section 1-9): A covalent bond formed by sharing three electron pairs between atoms.

Triplet (Section 11-11): A symmetrical three-line splitting pattern observed in the ¹H NMR spectrum when a proton has two equivalent neighbor protons.

Turnover number (Section 19-9): The number of substrate molecules acted on by an enzyme molecule per unit time.

Twist-boat conformation (Section 4-5): A conformation of cyclohexane that is somewhat more stable than a pure boat conformation.

Ultraviolet (UV) spectroscopy (Section 10-9): An optical spectroscopy employing ultraviolet irradiation. UV spectroscopy provides structural information about the extent of π electron conjugation in organic molecules.

Unimolecular reaction (Section 12-9): A reaction that occurs by spontaneous transformation of the starting material without the intervention of other reactants. For example, the dissociation of a tertiary alkyl halide in the S_N1 reaction is a unimolecular process.

Unsaturated (Section 7-1): A molecule that has one or more multiple bonds.

Upfield (Section 11-3): The right-hand portion of the NMR chart.

Urea cycle (Section 20-3): The metabolic pathway for converting ammonia into urea.

Urethane (Section 27-4): A functional group in which a carbonyl group is bonded to both an -OR and an -NR₂.

Uronic acid (Section 21-6): A monocarboxylic acid formed by oxidizing the -CH₂OH end of an aldose without affecting the -CHO end.

Valence bond theory (Section 1-5): A bonding theory that describes a covalent bond as resulting from the overlap of two atomic orbitals.

Valence shell (Section 1-4): The outermost electron shell of an atom.

van der Waals forces (Section 2-12): Intermolecular forces that are responsible for holding molecules together in the liquid and solid states.

Vegetable oil (Section 23-1): A liquid triacylglycerol derived from a plant source.

Vinyl group (Section 7-2): An H₂C=CH- substituent.

Vinyl monomer (Section 8-10): A substituted alkene monomer used to make a chain-growth polymer.

Vinyllic (Section 9-7): A term that refers to a substituent at a double-bond carbon atom. For example, chloroethylene is a vinyllic chloride.

Virion (Chapter 22 *Something Extra*): A viral particle.

Vitamin (Section 19-9): A small organic molecule that must be obtained in the diet and is required in trace amounts for proper growth and function.

Vulcanization (Chapter 8 *Something Extra*): A technique for cross-linking and hardening a diene polymer by heating with a few percent by weight of sulfur.

Walden inversion (Section 12-6): The inversion of configuration at a chirality center that accompanies an S_N2 reaction.

Wave equation (Section 1-2): A mathematical expression that defines the behavior of an electron in an atom.

Wave function (Section 1-2): A solution to the wave equation for defining the behavior of an electron in an atom. The square of the wave function defines the shape of an orbital.

Wavelength, λ (Section 10-5): The length of a wave from peak to peak. The wavelength of electromagnetic radiation is inversely proportional to frequency and inversely proportional to energy.

Wavenumber, $\tilde{\nu}$ (Section 10-6): The reciprocal of the wavelength in centimeters.

Wax (Section 23-1): A mixture of esters of long-chain carboxylic acids with long-chain alcohols.

Williamson ether synthesis (Section 13-9): A method for synthesizing ethers by S_N2 reaction of an alkyl halide with an alkoxide ion.

Wittig reaction (Section 14-9): The reaction of a phosphorus ylide with an aldehyde or ketone to yield an alkene.

Wohl degradation (Section 21-6): A method for shortening the chain of an aldose sugar by one carbon.

X-ray crystallography (Chapter 10 *Something Extra*): A technique that uses X rays to determine the structure of molecules.

Ylide (Sections 14-9, 22-3): A neutral species with adjacent + and – charges, such as the phosphoranes used in Wittig reactions.

Z geometry (Section 7-4): A term used to describe the stereochemistry of a carbon–carbon double bond. The two groups on each carbon are ranked according to the Cahn–Ingold–Prelog sequence rules, and the two carbons are compared. If the higher ranked groups on each

carbon are on the same side of the double bond, the bond has *Z* geometry.

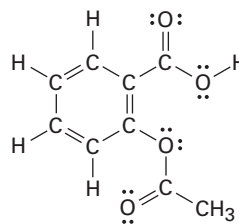
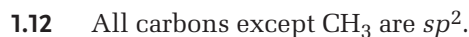
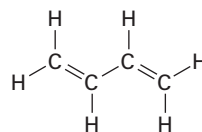
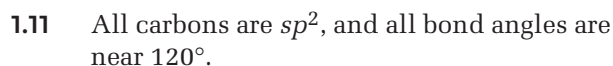
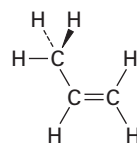
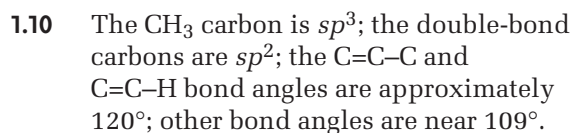
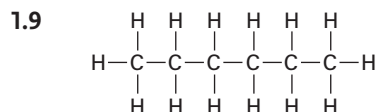
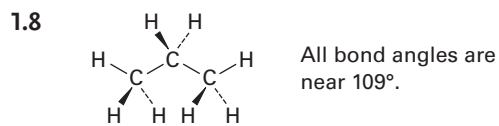
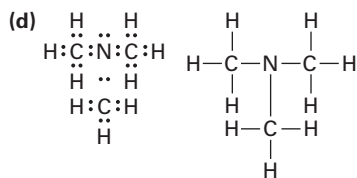
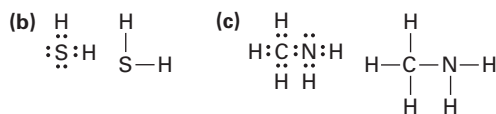
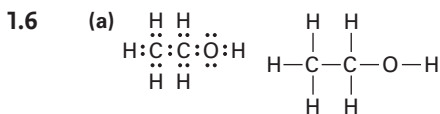
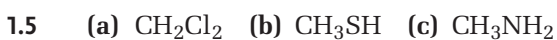
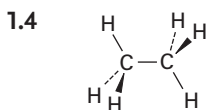
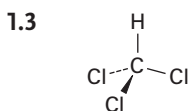
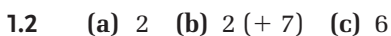
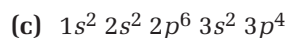
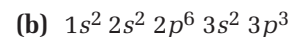
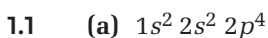
Zaitsev's rule (Section 12-12): A rule stating that E2 elimination reactions normally yield the more highly substituted alkene as major product.

Ziegler–Natta catalyst (Section 27-2): A catalyst of an alkylaluminum and a titanium compound used for preparing alkene polymers.

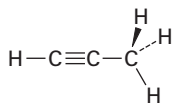
Zwitterion (Section 19-1): A neutral dipolar molecule in which the positive and negative charges are not adjacent. For example, amino acids exist as zwitterions, $\text{H}_3\text{N}^+ - \text{CHR} - \text{CO}_2^-$.

The following answers are meant only as a quick check while you study. Full answers for all problems are provided in the accompanying *Study Guide and Solutions Manual*.

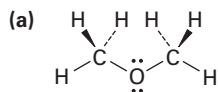
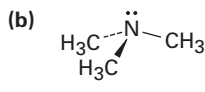
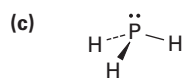
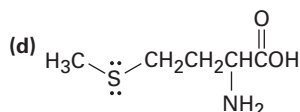
CHAPTER 1



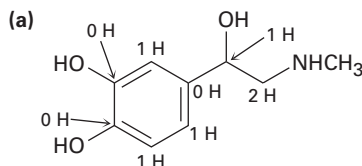
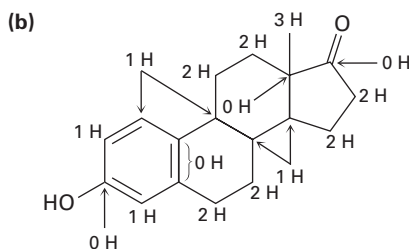
- 1.13 The CH_3 carbon is sp^3 ; the triple-bond carbons are sp ; the $\text{C}\equiv\text{C}-\text{C}$ and $\text{H}-\text{C}\equiv\text{C}$ bond angles are approximately 180° .



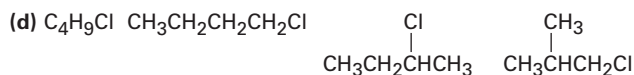
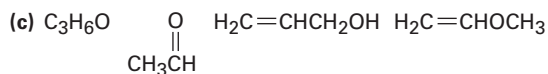
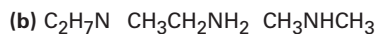
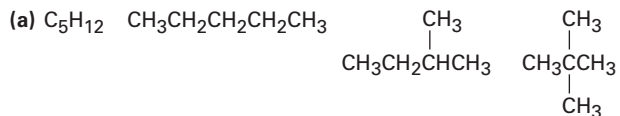
1.14

 sp^3 -tetrahedral sp^3 -tetrahedral sp^3 -tetrahedral sp^3 -tetrahedral

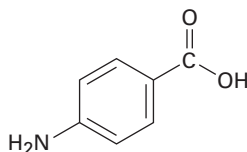
1.15

Adrenaline— $\text{C}_9\text{H}_{13}\text{NO}_3$ Estrone— $\text{C}_{18}\text{H}_{22}\text{O}_2$

- 1.16 There are numerous possibilities, such as:

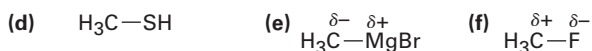
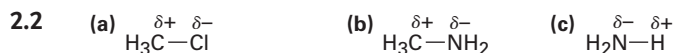


1.17



CHAPTER 2

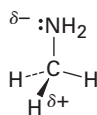
2.1 (a) H (b) Br (c) Cl (d) C



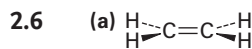
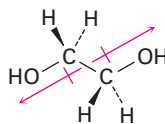
Carbon and sulfur have identical electronegativities.

2.3 $\text{H}_3\text{C}-\text{OH} < \text{H}_3\text{C}-\text{MgBr} < \text{H}_3\text{C}-\text{Li} = \text{H}_3\text{C}-\text{F} < \text{H}_3\text{C}-\text{K}$

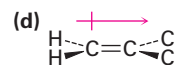
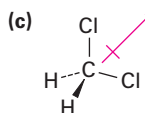
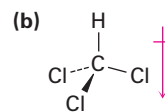
2.4 The nitrogen is electron-rich, and the carbon is electron-poor.



2.5 The two C–O dipoles cancel because of the symmetry of the molecule:

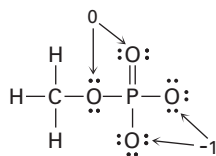


No dipole moment



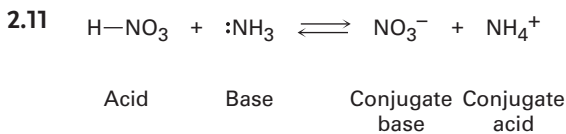
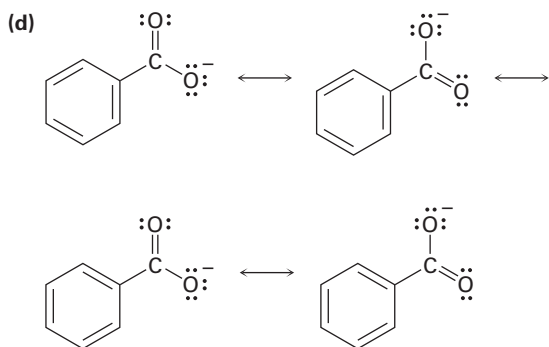
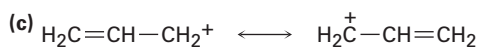
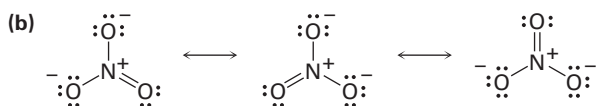
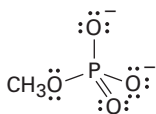
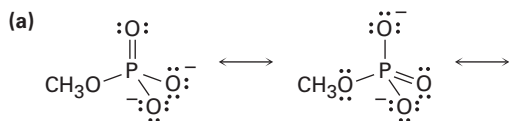
- 2.7 (a) For carbon: $\text{FC} = 4 - 8/2 - 0 = 0$;
for the middle nitrogen: $\text{FC} = 5 - 8/2 - 0 = +1$;
for the end nitrogen: $\text{FC} = 5 - 4/2 - 4 = -1$
- (b) For nitrogen: $\text{FC} = 5 - 8/2 - 0 = +1$;
for oxygen: $\text{FC} = 6 - 2/2 - 6 = -1$
- (c) For nitrogen: $\text{FC} = 5 - 8/2 - 0 = +1$;
for the end carbon: $\text{FC} = 4 - 6/2 - 2 = -1$

2.8



2.9 The structures in (a) are resonance forms.

2.10



2.12 Phenylalanine is stronger.

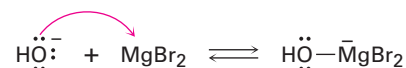
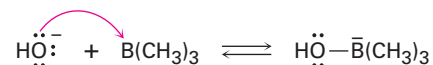
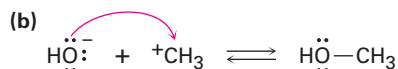
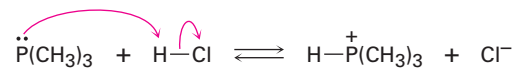
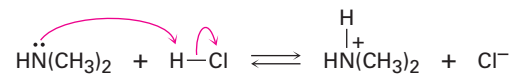
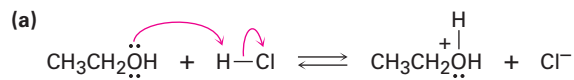
2.13 Water is a stronger acid.

2.14 Neither reaction will take place.

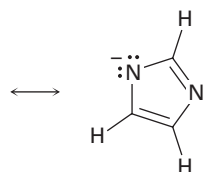
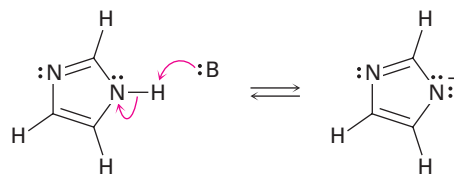
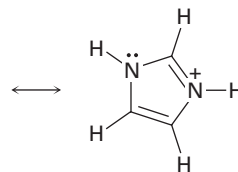
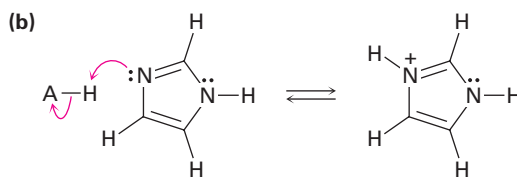
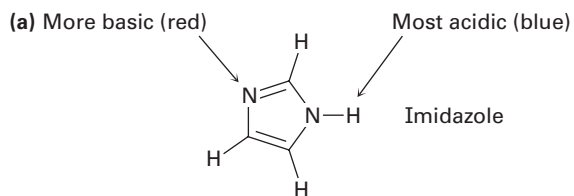
2.15 Reaction will take place.

2.16 $K_a = 4.9 \times 10^{-10}$

2.17



2.18



2.19 Vitamin C is water-soluble (hydrophilic); vitamin A is fat-soluble (hydrophobic).

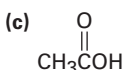
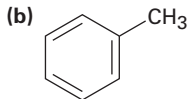
CHAPTER 3

3.1 (a) Sulfide, carboxylic acid, amine

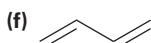
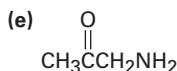
(b) Aromatic ring, carboxylic acid

(c) Ether, alcohol, aromatic ring, amide, C=C bond

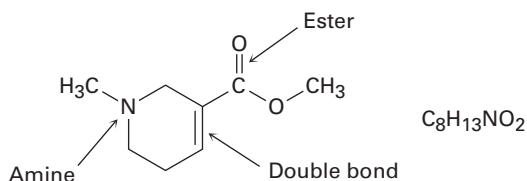
3.2 (a) CH₃OH



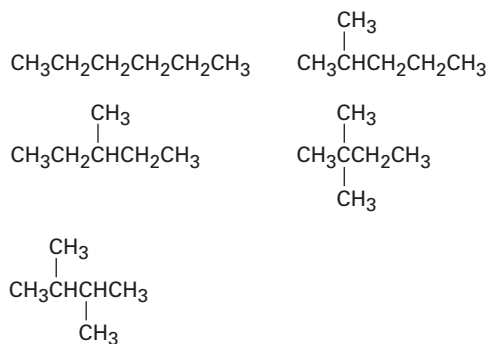
(d) CH₃NH₂



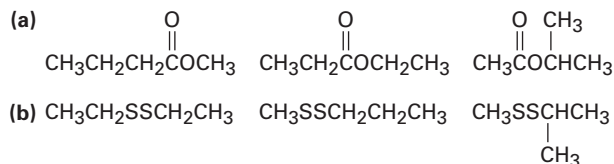
3.3



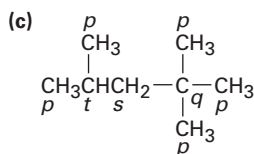
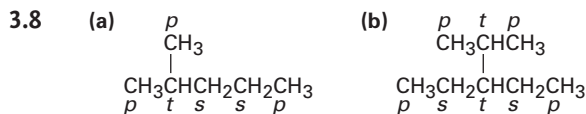
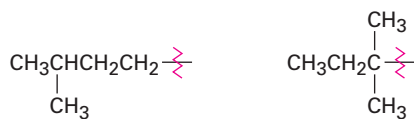
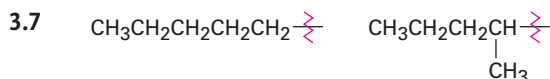
3.4



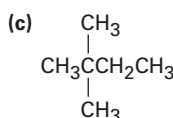
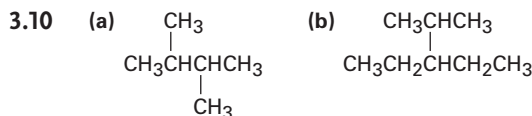
3.5 Part (a) has nine possible answers.



3.6 (a) Two (b) Four (c) Four



3.9 Primary carbons have primary hydrogens, secondary carbons have secondary hydrogens, and tertiary carbons have tertiary hydrogens.

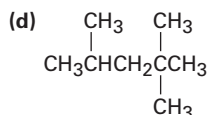
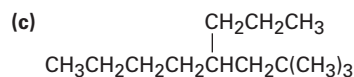
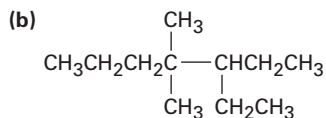
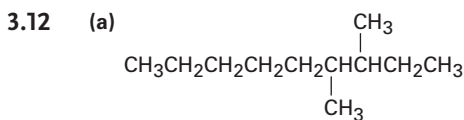


3.11 (a) Pentane, 2-methylbutane, 2,2-dimethylpropane

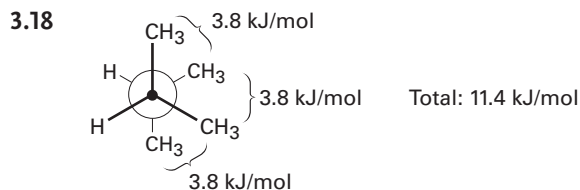
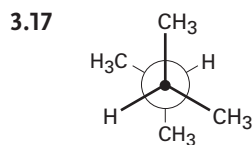
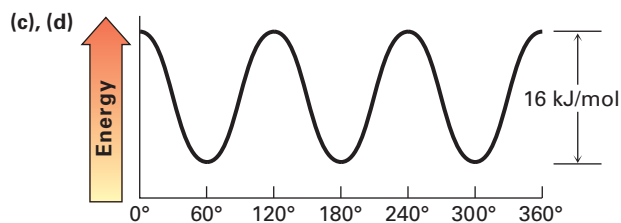
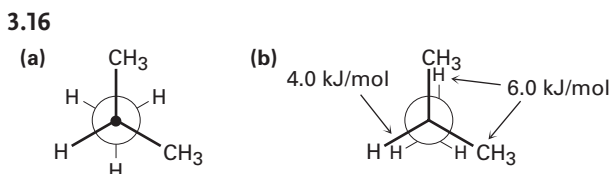
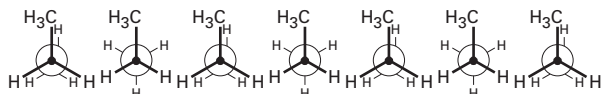
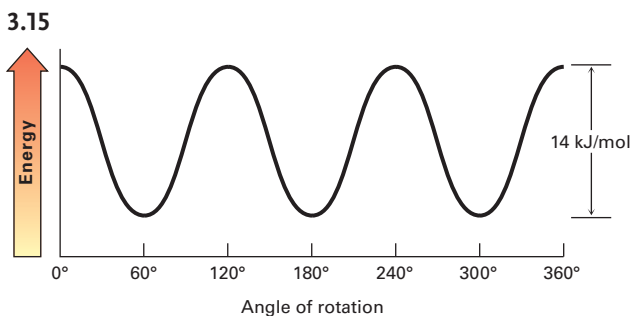
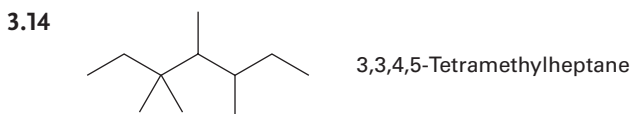
(b) 2,3-Dimethylpentane

(c) 2,4-Dimethylpentane

(d) 2,2,5-Trimethylhexane

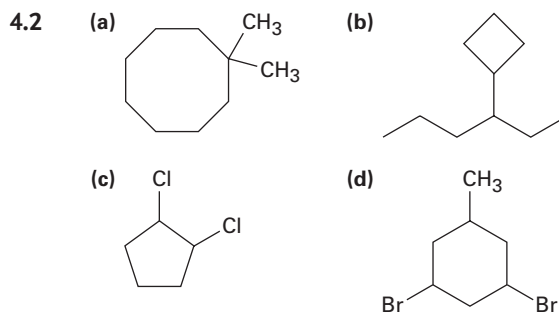


3.13 Pentyl, 1-methylbutyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl



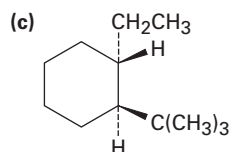
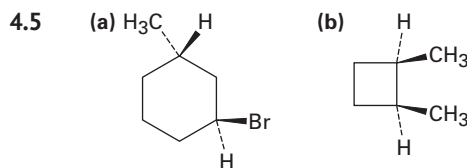
CHAPTER 4

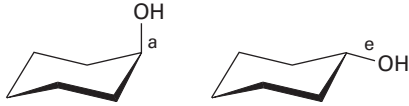
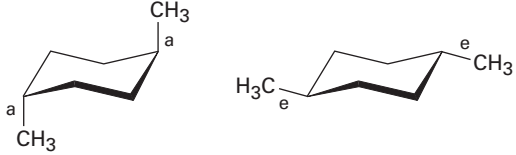
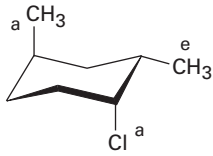
- 4.1 (a) 1,4-Dimethylcyclohexane
 (b) 1-Methyl-3-propylcyclopentane
 (c) 3-Cyclobutylpentane
 (d) 1-Bromo-4-ethylcyclodecane
 (e) 1-Isopropyl-2-methylcyclohexane
 (f) 4-Bromo-1-*tert*-butyl-2-methylcycloheptane



4.3 3-Ethyl-1,1-dimethylcyclopentane

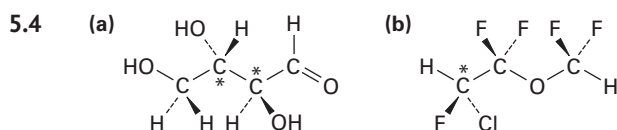
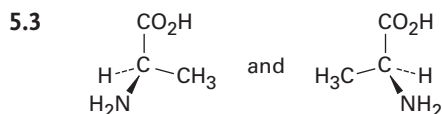
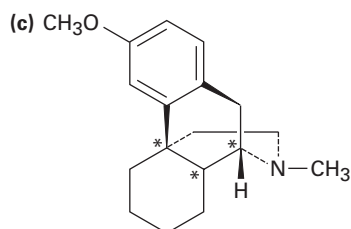
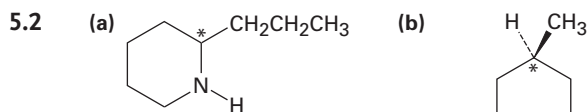
- 4.4 (a) *trans*-1-Chloro-4-methylcyclohexane
 (b) *cis*-1-Ethyl-3-methylcycloheptane



- 4.6 The two hydroxyl groups are cis. The two side chains are trans.
- 4.7 (a) *cis*-1,2-Dimethylcyclopentane
(b) *cis*-1-Bromo-3-methylcyclobutane
- 4.8 Six interactions; 21% of strain
- 4.9 The cis isomer is less stable because the methyl groups eclipse each other.
- 4.10 Ten eclipsing interactions; 40 kJ/mol; 35% is relieved.
- 4.11 Conformation (a) is more stable because the methyl groups are farther apart.
- 4.12 
- 4.13 
- 4.14 Before ring-flip, red and blue are equatorial and green is axial. After ring-flip, red and blue are axial and green is equatorial.
- 4.15 4.2 kJ/mol
- 4.16 The linear cyano group points straight up.
- 4.17 Equatorial is 70%; axial is 30%
- 4.18 (a) 2.0 kJ/mol (b) 11.4 kJ/mol
(c) 2.0 kJ/mol (d) 8.0 kJ/mol
- 4.19  Less stable chair form
- 4.20 *trans*-Decalin is more stable because it has no 1,3-diaxial interactions.
- 4.21 Both ring fusions are trans.

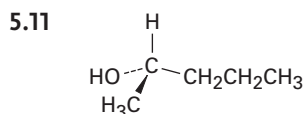
CHAPTER 5

5.1 Chiral: screw, shoe



5.5 Levorotatory

5.6 +16.1

5.7 (a) -Br (b) -Br (c) -CH₂CH₃(d) -OH (e) -CH₂OH (f) -CH=O5.8 (a) -OH, -CH₂CH₂OH, -CH₂CH₃, -H(b) -OH, -CO₂CH₃, -CO₂H, -CH₂OH(c) -NH₂, -CN, -CH₂NHCH₃, -CH₂NH₂(d) -SSCH₃, -SH, -CH₂SCH₃, -CH₃5.9 (a) *S* (b) *R* (c) *S*5.10 (a) *S* (b) *S* (c) *R*5.12 *S*

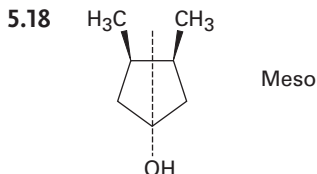
5.13 Compound (a) is D-erythrose 4-phosphate, (d) is its enantiomer, and (b) and (c) are diastereomers.

5.14 Five chirality centers; 32 stereoisomers

5.15 *S,S*

5.16 Compounds (a) and (d) are meso.

5.17 Compounds (a) and (c) have meso forms.



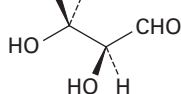
5.19 The product retains its *S* stereochemistry.

5.20 Two diastereomeric salts are formed: (*R*)-lactic acid plus (*S*)-1-phenylethylamine and (*S*)-lactic acid plus (*S*)-1-phenylethylamine.

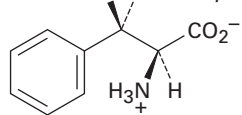
5.21 (a) Constitutional isomers

(b) Diastereomers

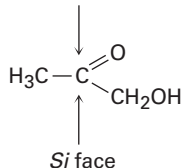
5.22 (a) *pro-S* → H H ← *pro-R*



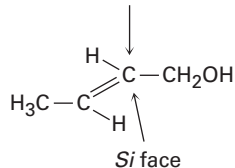
(b) *pro-R* → H H ← *pro-S*



5.23 (a) *Re* face



(b) *Re* face



5.24 (*S*)-Lactate

5.25 The -OH adds to the *Re* face of C2, and -H adds to the *Re* face of C3. The overall addition has anti stereochemistry.

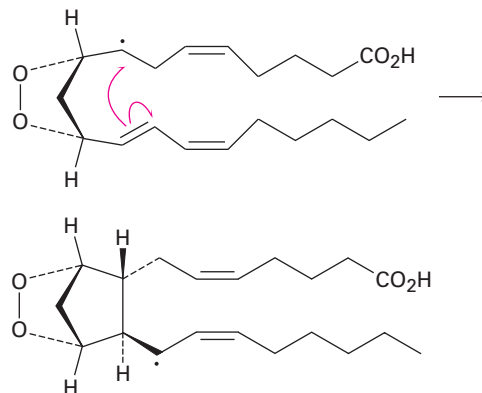
CHAPTER 6

6.1 (a) Substitution (b) Elimination

(c) Addition

6.2 1-Chloro-2-methylpentane, 2-chloro-2-methylpentane, 3-chloro-2-methylpentane, 2-chloro-4-methylpentane, 1-chloro-4-methylpentane

6.3 Radical addition reaction

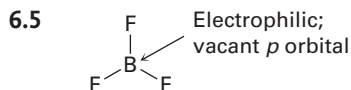


6.4 (a) Carbon is electrophilic.

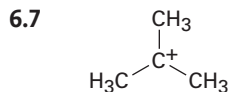
(b) Sulfur is nucleophilic.

(c) Nitrogens are nucleophilic.

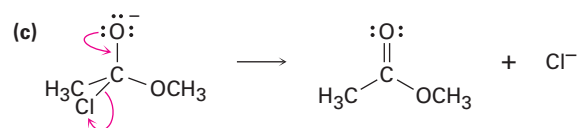
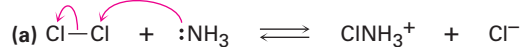
(d) Oxygen is nucleophilic; carbon is electrophilic.



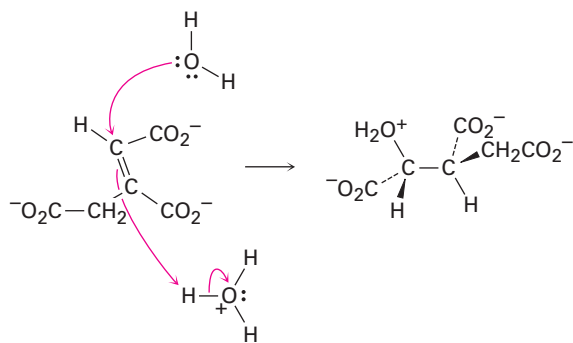
6.6 Cyclohexanol (hydroxycyclohexane)



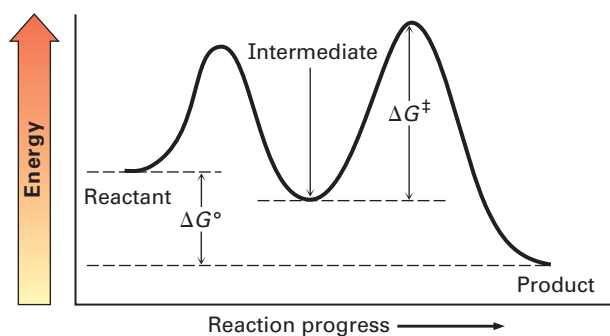
6.8



6.9

6.10 Negative ΔG° is more favored.6.11 Larger K_{eq} is more exergonic.6.12 Lower ΔG^\ddagger is faster.

6.13



CHAPTER 7

7.1 (a) 1 (b) 2 (c) 2

7.2 (a) 5 (b) 5 (c) 3 (d) 1 (e) 6 (f) 5

7.3 $C_{16}H_{13}ClN_2O$

7.4 (a) 3,4,4-Trimethylpent-1-ene

(b) 3-Methylhex-3-ene

(c) 4,7-Dimethylocta-2,5-diene

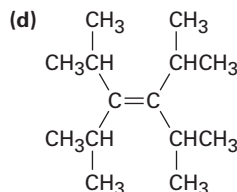
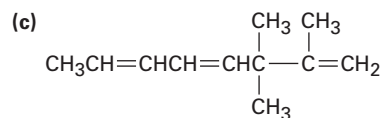
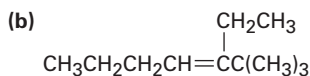
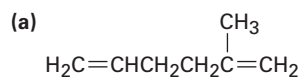
(d) 6-Ethyl-7-methylnon-4-ene

(e) 1,2-Dimethylcyclohexene

(f) 4,4-Dimethylcycloheptene

(g) 3-Isopropylcyclopentene

7.5



7.6 (a) 2,5-Dimethylhex-3-yne

(b) 3,3-Dimethylbut-1-yne

(c) 3,3-Dimethyloct-4-yne

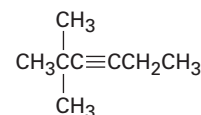
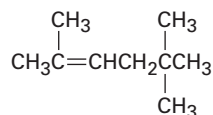
(d) 2,5,5-Trimethylhept-3-yne

(e) 6-Isopropylcyclodecyne

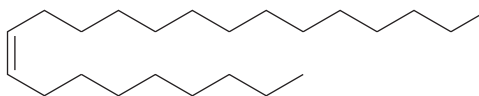
7.7

(a) 2,5,5-Trimethylhex-2-ene

(b) 2,2-Dimethylhex-3-yne



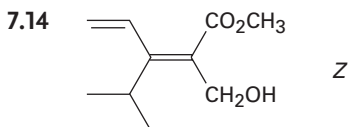
7.8



7.9 Compounds (c), (e), and (f) have cis-trans isomers.

7.10 (a) *cis*-4,5-Dimethylhex-2-ene(b) *trans*-6-Methylhept-3-ene7.11 (a) $-\text{CH}_3$ (b) $-\text{Cl}$ (c) $-\text{CH}=\text{CH}_2$ (d) $-\text{OCH}_3$ (e) $-\text{CH}=\text{O}$ (f) $-\text{CH}=\text{O}$ 7.12 (a) $-\text{Cl}$, $-\text{OH}$, $-\text{CH}_3$, $-\text{H}$ (b) $-\text{CH}_2\text{OH}$, $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_3$ (c) $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{OH}$, $-\text{C}\equiv\text{N}$, $-\text{CH}_2\text{NH}_2$ (d) $-\text{CH}_2\text{OCH}_3$, $-\text{C}\equiv\text{N}$, $-\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{CH}_3$

7.13 (a) *Z* (b) *E* (c) *Z* (d) *E*



7.15 (a) 2-Methylpropene is more stable than but-1-ene.

(b) *trans*-Hex-2-ene is more stable than *cis*-hex-2-ene.

(c) 1-Methylcyclohexene is more stable than 3-methylcyclohexene.

7.16 (a) Chlorocyclohexane

(b) 2-Bromo-2-methylpentane

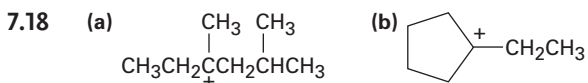
(c) 2-Hydroxy-4-methylpentane

(d) 1-Bromo-1-methylcyclohexane

7.17 (a) Cyclopentene

(b) 1-Ethylcyclohexene or ethylidenecyclohexane

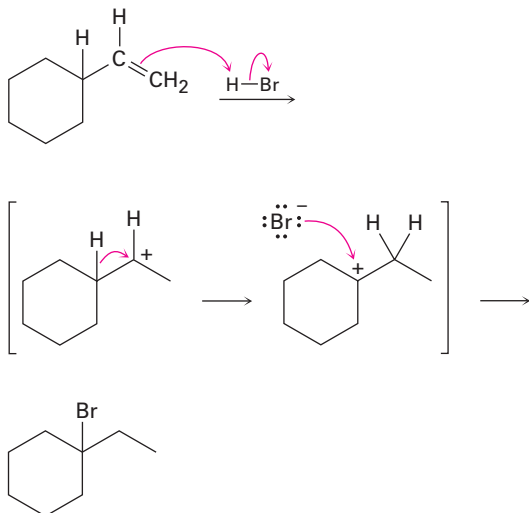
(c) Hex-3-ene (d) Cyclohexylethylene



7.19 In the conformation shown, only the methyl-group C–H that is parallel to the carbocation *p* orbital can show hyperconjugation.

7.20 The second step is exergonic; the transition state resembles the carbocation.

7.21

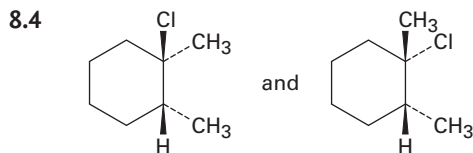


CHAPTER 8

8.1 2-Methylbut-2-ene and 2-methylbut-1-ene

8.2 Five

8.3 *trans*-1,2-Dichloro-1,2-dimethylcyclohexane



8.5 *trans*-2-Bromocyclopentanol

8.6 Markovnikov orientation

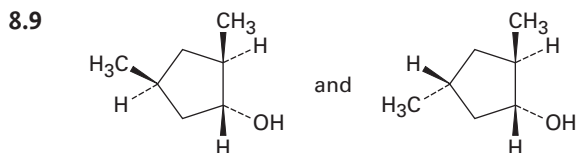
8.7 (a) Oxymercuration: 2-methylpentan-2-ol; hydroboration: 2-methylpentan-3-ol

(b) Oxymercuration: 1-ethylcyclohexanol; hydroboration: 1-cyclohexylethanol

8.8 (a) From 3-methylbut-1-ene by hydroboration

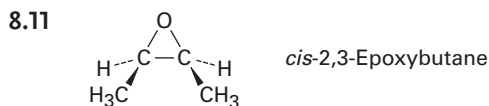
(b) From 2-methylbut-2-ene by hydroboration or from 3-methylbut-1-ene by oxymercuration

(c) From methylenecyclohexane by hydroboration



8.10 (a) 2-Methylpentane

(b) 1,1-Dimethylcyclopentane



8.12 (a) 1-Methylcyclohexene

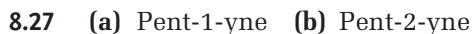
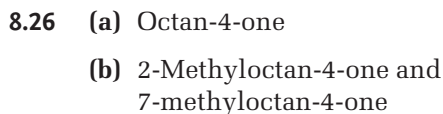
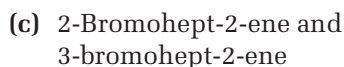
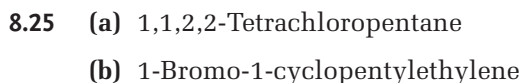
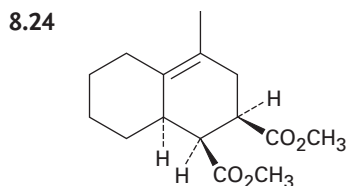
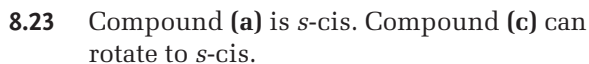
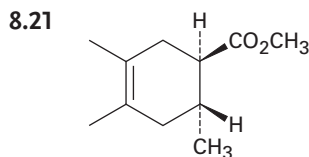
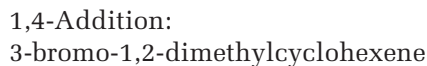
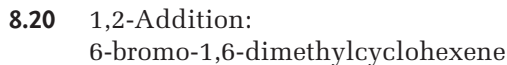
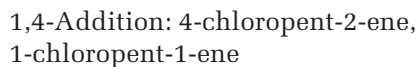
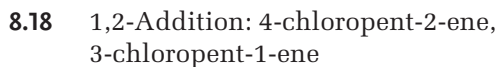
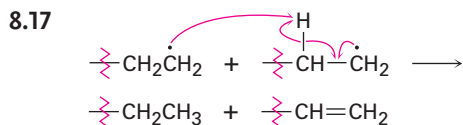
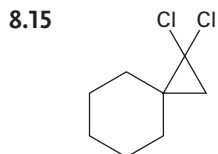
(b) 2-Methylpent-2-ene

(c) Buta-1,3-diene

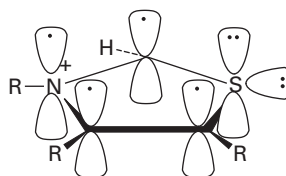
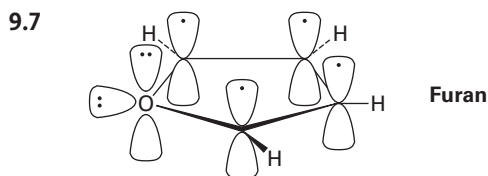
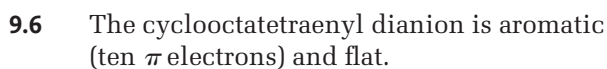
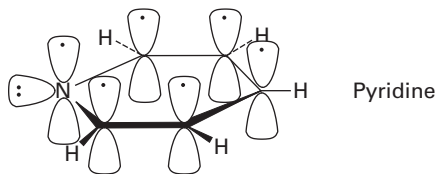
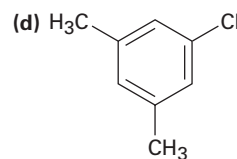
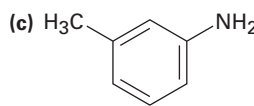
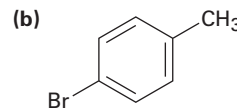
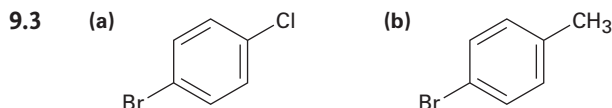
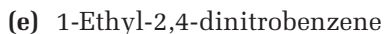
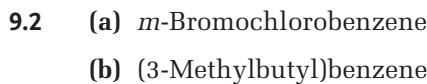
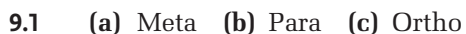
8.13 (a) $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$

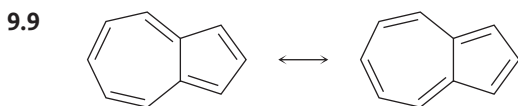
(b) $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$

8.14 (a) 2-Methylpropene (b) Hex-3-ene

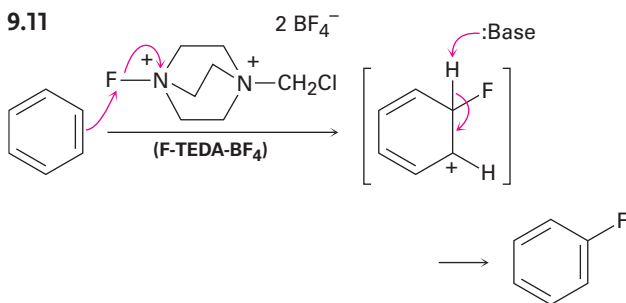


CHAPTER 9





9.10 The three nitrogens in double bonds each contribute one; the remaining nitrogen contributes two.



9.12 *o*-, *m*-, and *p*-Bromotoluene

9.13 *o*-Xylene: 2; *m*-xylene: 3; *p*-xylene: 1

9.14 No rearrangement: (a), (b), (e)

9.15 *tert*-Butylbenzene

9.16 (a) $(\text{CH}_3)_2\text{CHCOCl}$ (b) PhCOCl

9.17 (a) Phenol > Toluene > Benzene > Nitrobenzene

(b) Phenol > Benzene > Chlorobenzene > Benzoic acid

(c) Aniline > Benzene > Bromobenzene > Benzaldehyde

9.18 The initial alkylation product is more reactive than the starting material, but the initial acylation product is less reactive.

9.19 Toluene is more reactive; the trifluoromethyl group is electron-withdrawing.

9.20 (a) Methyl *m*-nitrobenzoate

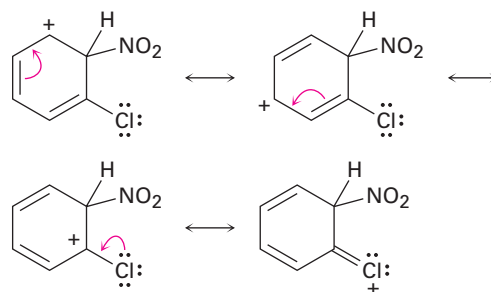
(b) *m*-Bromonitrobenzene

(c) *o*- and *p*-Chlorophenol

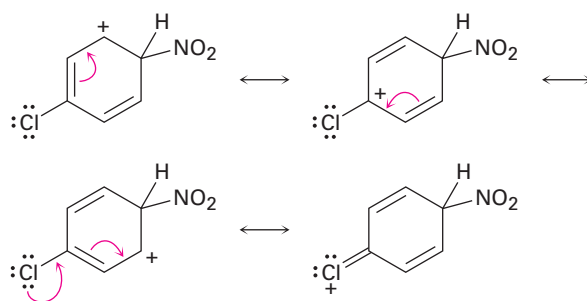
(d) *o*- and *p*-Bromoaniline

9.21

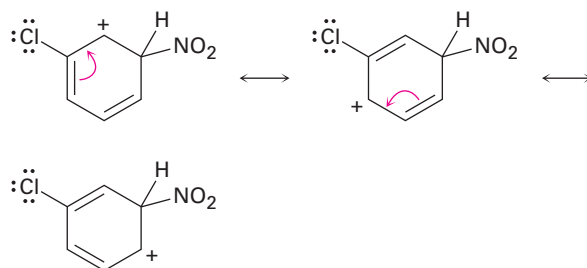
Ortho intermediate:



Para intermediate:



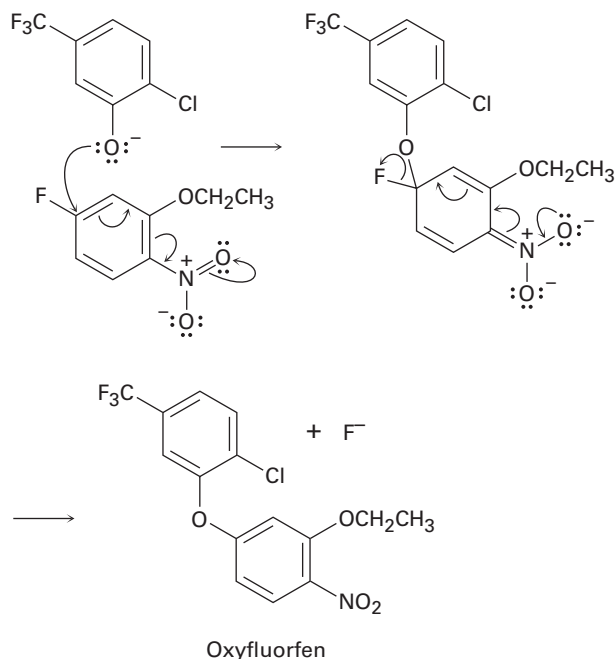
Meta intermediate:



9.22 (a) *m*-Chlorobenzonitrile

(b) *o*- and *p*-Bromochlorobenzene

9.23



- 9.24 (a) *m*-Nitrobenzoic acid
(b) *p*-*tert*-Butylbenzoic acid
- 9.25 1. PhCOCl, AlCl₃; 2. H₂/Pd
- 9.26 (a) 1. HNO₃, H₂SO₄; 2. Cl₂, FeCl₃
(b) 1. CH₃COCl, AlCl₃; 2. Cl₂, FeCl₃; 3. H₂, Pd
(c) 1. CH₃CH₂COCl, AlCl₃; 2. H₂, Pd; 3. Cl₂, FeCl₃
(d) 1. CH₃Cl, AlCl₃; 2. SO₃, H₂SO₄; 3. Br₂, FeBr₃
- 9.27 (a) The Friedel–Crafts reaction in step 1 will not take place on a cyano-substituted benzene.
(b) The Friedel–Crafts reaction will occur with a carbocation rearrangement, and the wrong isomer will be obtained on chlorination.

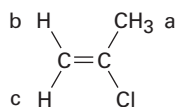
CHAPTER 10

- 10.1 C₁₉H₂₈O₂
- 10.2 (a) 2-Methylpent-2-ene (b) Hex-2-ene
- 10.3 (a) 43, 71 (b) 82 (c) 58 (d) 86
- 10.4 102 (M⁺), 84 (dehydration), 87 (alpha cleavage), 59 (alpha cleavage)
- 10.5 X-ray energy is higher. $\lambda = 9.0 \times 10^{-6}$ m is higher in energy.
- 10.6 (a) 2.4×10^6 kJ/mol (b) 4.0×10^4 kJ/mol
(c) 2.4×10^3 kJ/mol (d) 2.8×10^2 kJ/mol
(e) 6.0 kJ/mol (f) 4.0×10^{-2} kJ/mol
- 10.7 (a) Ketone or aldehyde
(b) Nitro compound
(c) Carboxylic acid
- 10.8 (a) CH₃CH₂OH has an –OH absorption.
(b) Hex-1-ene has a double-bond absorption.
(c) CH₃CH₂CO₂H has a very broad –OH absorption.
- 10.9 1450–1600 cm⁻¹: aromatic ring;
2100 cm⁻¹: C≡C; 3300 cm⁻¹: C≡C–H
- 10.10 (a) 1715 cm⁻¹ (b) 1730, 2100, 3300 cm⁻¹
(c) 1720, 2500–3100 cm⁻¹, 3400–3650 cm⁻¹
- 10.11 1690, 1650, 2230 cm⁻¹
- 10.12 300–600 kJ/mol; UV energy is greater than IR energy.
- 10.13 1.46×10^{-5} M
- 10.14 All except (a) have UV absorptions.

CHAPTER 11

- 11.1 7.5×10^{-5} kJ/mol for ¹⁹F;
 8.0×10^{-5} kJ/mol for ¹H
- 11.2 1.2×10^{-4} kJ/mol; energy increases

11.3 The vinylic C–H protons are nonequivalent.



11.4 (a) 7.27 δ (b) 3.05 δ (c) 3.46 δ (d) 5.30 δ

11.5 (a) 420 Hz (b) 2.1 δ (c) 1050 Hz

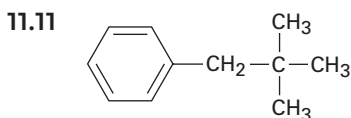
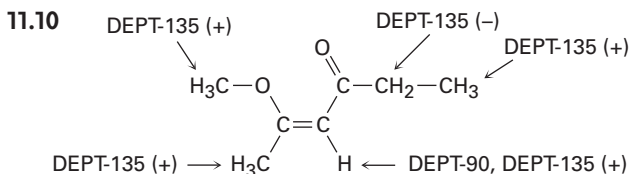
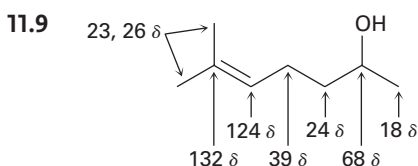
11.6 (a) 4 (b) 7 (c) 4 (d) 5 (e) 5 (f) 7

11.7 (a) 1,3-Dimethylcyclopentene

(b) 2-Methylpentane

(c) 1-Chloro-2-methylpropane

11.8 $-\text{CH}_3$, 9.3 δ ; $-\text{CH}_2-$, 27.6 δ ; C=O, 174.6 δ ;
 $-\text{OCH}_3$, 51.4 δ



11.12 A DEPT-90 spectrum would show two absorptions for the non-Markovnikov product ($\text{RCH}=\text{CHBr}$) but no absorptions for the Markovnikov product ($\text{RBrC}=\text{CH}_2$).

11.13 (a) Enantiotopic (b) Diastereotopic

(c) Diastereotopic (d) Diastereotopic

(e) Diastereotopic (f) Homotopic

11.14 (a) 2 (b) 4 (c) 3 (d) 4 (e) 5 (f) 3

11.15 4

11.16 (a) 1.43 δ (b) 2.17 δ (c) 7.37 δ

(d) 5.30 δ (e) 9.70 δ (f) 2.12 δ

11.17 Seven kinds of protons

11.18 Two peaks; 3 : 2 ratio

11.19 (a) $-\text{CHBr}_2$, quartet; $-\text{CH}_3$, doublet

(b) $\text{CH}_3\text{O}-$, singlet; $-\text{OCH}_2-$, triplet;
 $-\text{CH}_2\text{Br}$, triplet

(c) ClCH_2- , triplet; $-\text{CH}_2-$, quintet

(d) CH_3- , triplet; $-\text{CH}_2-$, quartet;
 $-\text{CH}-$, septet; $(\text{CH}_3)_2$, doublet

(e) CH_3- , triplet; $-\text{CH}_2-$, quartet;
 $-\text{CH}-$, septet; $(\text{CH}_3)_2$, doublet

(f) $=\text{CH}$, triplet, $-\text{CH}_2-$, doublet,
aromatic C–H, two multiplets

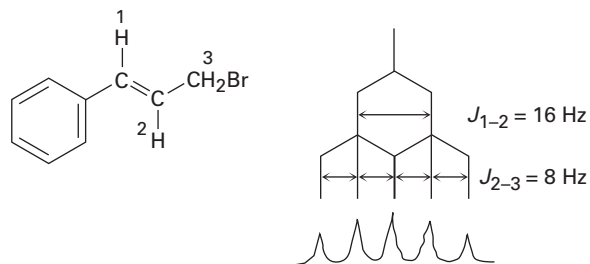
11.20 (a) CH_3OCH_3 (b) $\text{CH}_3\text{CH}(\text{Cl})\text{CH}_3$

(c) $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$

(d) $\text{CH}_3\text{CH}_2\text{CO}_2\text{CH}_3$ or $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$

11.21 $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$

11.22 $J_{1-2} = 16 \text{ Hz}$; $J_{2-3} = 8 \text{ Hz}$



11.23 1-Chloro-1-methylcyclohexane has a singlet methyl absorption; 1-chloro-2-methylcyclohexane has a doublet.

CHAPTER 12

12.1 (a) 1-Iodobutane

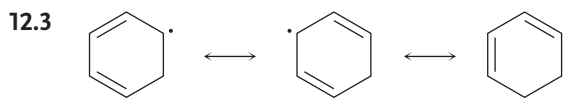
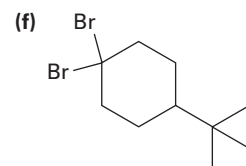
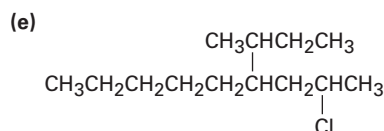
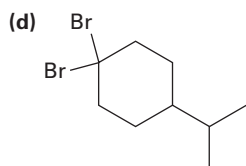
(b) 1-Chloro-3-methylbutane

(c) 1,5-Dibromo-2,2-dimethylpentane

(d) 1,3-Dichloro-3-methylbutane

(e) 1-Chloro-3-ethyl-4-iodopentane

(f) 2-Bromo-5-chlorohexane



12.4 The intermediate allylic radical reacts at the more accessible site and gives the more highly substituted double bond.

12.5 (a) 3-Bromo-5-methylcycloheptene and 3-bromo-6-methylcycloheptene

(b) Four products

12.6 (a) 2-Methylpropan-2-ol + HCl

(b) 4-Methylpentan-2-ol + PBr_3

(c) 5-Methylpentan-1-ol + PBr_3

(d) 3,3-Dimethylcyclopentanol + HF, pyridine

12.7 Both reactions occur.

12.8 React Grignard reagent with D_2O .

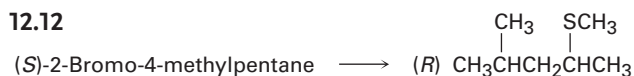
12.9 (a) 1. NBS; 2. $(\text{CH}_3)_2\text{CuLi}$

(b) 1. Li; 2. CuI; 3. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$

(c) 1. BH_3 ; 2. H_2O_2 , NaOH; 3. PBr_3 ; 4. Li, then CuI; 5. $\text{CH}_3(\text{CH}_2)_4\text{Br}$

12.10 (*R*)-1-Methylpentyl acetate,
 $\text{CH}_3\text{CO}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

12.11 (*S*)-Butan-2-ol



12.13 (a) 1-Iodobutane

(b) Butan-1-ol

(c) Hex-1-yne

(d) Butylammonium bromide

12.14 (a) $(\text{CH}_3)_2\text{N}^-$ (b) $(\text{CH}_3)_3\text{N}$ (c) H_2S

12.15 $\text{CH}_3\text{OTos} > \text{CH}_3\text{Cl} > (\text{CH}_3)_2\text{CHCl} > \text{CH}_3\text{NH}_2$

12.16 Similar rate to protic solvents because the transition state is not stabilized

12.17 Racemic 1-ethyl-1-methylhexyl acetate

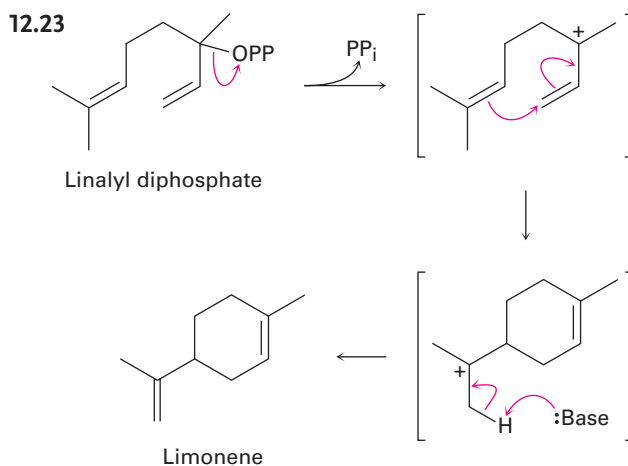
12.18 90.1% racemization and 9.9% inversion

12.19 Racemic 2-phenylbutan-2-ol

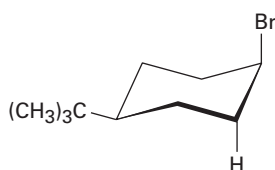
12.20 $\text{H}_2\text{C}=\text{CHCH}(\text{Br})\text{CH}_3 > \text{CH}_3\text{CH}(\text{Br})\text{CH}_3 > \text{CH}_3\text{CH}_2\text{Br} > \text{H}_2\text{C}=\text{CHBr}$

12.21 The same allylic carbocation intermediate is formed in both reactions.

12.22 (a) $\text{S}_{\text{N}}1$ (b) $\text{S}_{\text{N}}2$



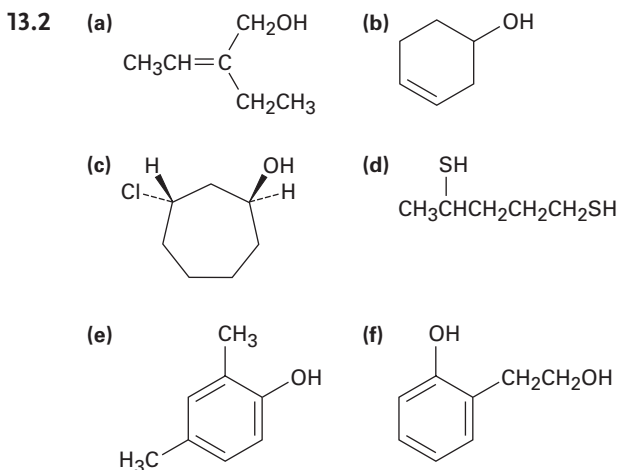
- 12.24** (a) Major: 2-methylpent-2-ene;
minor: 4-methylpent-2-ene
(b) Major: 2,3,5-trimethylhex-2-ene;
minor: 2,3,5-trimethylhex-3-ene
and 2-isopropyl-4-methylpent-1-ene
(c) Major: ethylidenecyclohexane;
minor: cyclohexylethylene
- 12.25** (a) 1-Bromo-3,6-dimethylheptane
(b) 4-Bromo-1,2-dimethylcyclopentane
- 12.26** (*Z*)-1-Bromo-1,2-diphenylethylene
- 12.27** (*Z*)-3-Methylpent-2-ene
- 12.28** The *cis* isomer reacts faster because the bromine is axial.



- 12.29** (a) S_N2 (b) $E2$ (c) S_N1 (d) $E1cB$

CHAPTER 13

- 13.1** (a) 5-Methylhexane-2,4-diol
(b) 2-Methyl-4-phenylbutan-2-ol
(c) 4,4-Dimethylcyclohexanol
(d) *trans*-2-Bromocyclopentanol
(e) 2-Methylheptane-4-thiol
(f) Cyclopent-2-ene-1-thiol



- 13.3** (a) *p*-Methylphenol < Phenol < *p*-(Trifluoromethyl)phenol
(b) Benzyl alcohol < Phenol < *p*-Hydroxybenzoic acid
- 13.4** The electron-withdrawing nitro group stabilizes an alkoxide ion, but the electron-donating methoxyl group destabilizes the anion.
- 13.5** Thiophenol is more acidic because the anion is resonance-stabilized.
- 13.6** (a) 2-Methylpentan-3-ol
(b) 2-Methyl-4-phenylbutan-2-ol
(c) *meso*-Decane-5,6-diol
- 13.7** (a) $NaBH_4$ (b) $LiAlH_4$ (c) $LiAlH_4$
- 13.8** (a) Benzaldehyde or benzoic acid (or ester)
(b) Acetophenone (c) Cyclohexanone
(d) 2-Methylpropanal or 2-methylpropanoic acid (or ester)
- 13.9** (a) 1-Methylcyclopentanol
(b) 3-Methylhexan-3-ol
- 13.10** (a) Acetone + CH_3MgBr ,
or ethyl acetate + 2 CH_3MgBr
(b) Cyclohexanone + CH_3MgBr
(c) Butan-2-one + $PhMgBr$,
or ethyl phenyl ketone + CH_3MgBr ,
or acetophenone + CH_3CH_2MgBr
(d) Formaldehyde + $PhMgBr$
- 13.11** Cyclohexanone + CH_3CH_2MgBr
- 13.12** (a) 2-Methylpent-2-ene
(b) 3-Methylcyclohexene
(c) 1-Methylcyclohexene
- 13.13** (a) 1-Phenylethanol
(b) 2-Methylpropan-1-ol
(c) Cyclopentanol
- 13.14** (a) Hexanoic acid, hexanal
(b) Hexan-2-one
(c) Hexanoic acid, no reaction

13.15 S_N2 displacement of alkoxide ion by F^- ion

13.16 1. $LiAlH_4$; 2. PBr_3 ; 3. $(H_2N)_2C=S$;
4. H_2O , $NaOH$

13.17 (a) Diisopropyl ether

(b) Cyclopentyl propyl ether

(c) *p*-Bromoanisole or
4-bromo-1-methoxybenzene

(d) 1-Methoxycyclohexene

(e) Benzyl methyl sulfide (f) Allyl methyl sulfide

13.18 A mixture of diethyl ether, dipropyl ether, and ethyl propyl ether is formed in a 1:1:2 ratio.

13.19 (a) $CH_3CH_2CH_2O^- + CH_3Br$

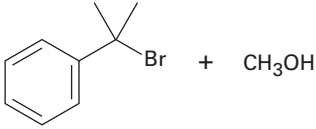
(b) $PhO^- + CH_3Br$


(c) $(CH_3)_2CHO^- + PhCH_2Br$

(d) $(CH_3)_3CCH_2O^- + CH_3CH_2Br$

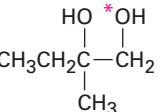
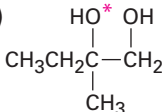
13.20 (a) Bromoethane > 2-Bromopropane >> Bromobenzene

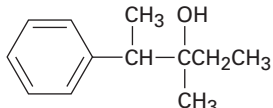
(b) Bromoethane > Chloroethane >> 1-Iodopropene

13.21 (a) 

(b) 

13.22 Protonation of the oxygen atom, followed by $E1$ reaction

13.23 (a)  (b) 

(c) 

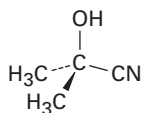
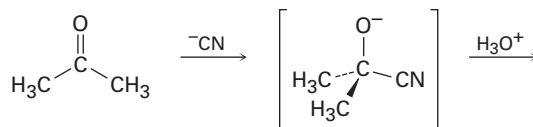
13.24 *o*-(1-Methylallyl)phenol

PREVIEW OF CARBONYL CHEMISTRY

1. Acetyl chloride is more electrophilic than acetone.

2. (a) Amide (b) Aldehyde, ester

3.



4. (a) Nucleophilic acyl substitution

(b) Nucleophilic addition

(c) Carbonyl condensation

CHAPTER 14

14.1 (a) 2-Methylpentan-3-one

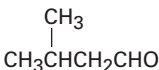
(b) 3-Phenylpropanal

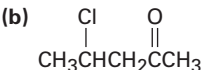
(c) Octane-2,6-dione

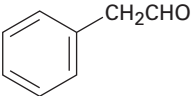
(d) *trans*-2-Methylcyclohexanecarbaldehyde

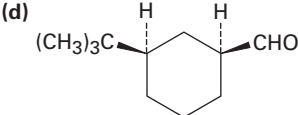
(e) Hex-4-enal

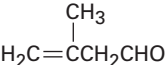
(f) *cis*-2,5-Dimethylcyclohexanone

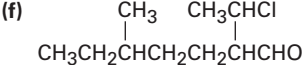
14.2 (a) 

(b) 

(c) 

(d) 

(e) 

(f) 

14.3 (a) Dess–Martin periodinane

(b) 1. O_3 ; 2. Zn

(c) DIBAL

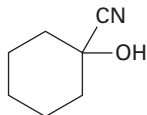
(d) 1. BH_3 , then H_2O_2 , $NaOH$;
2. Dess–Martin periodinane

14.4 (a) 1. CH_3COCl , AlCl_3 ; 2. Br_2 , FeBr_3

(b) 1. Mg ; 2. CH_3CHO , then H_3O^+ ;
3. Dess–Martin

(c) 1. BH_3 , then H_2O_2 , NaOH ;
2. Dess–Martin

14.5

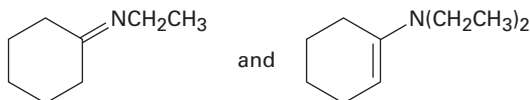


14.6 The electron-withdrawing nitro group in *p*-nitrobenzaldehyde polarizes the carbonyl group.

14.7 $\text{CCl}_3\text{CH}(\text{OH})_2$

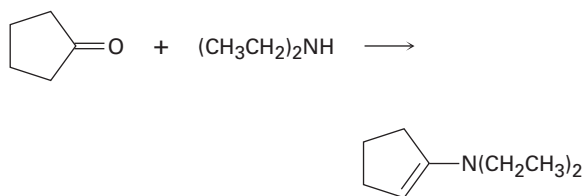
14.8 Labeled water adds reversibly to the carbonyl group.

14.9



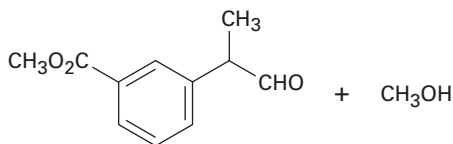
14.10 The steps are the exact reverse of the forward reaction, shown in Figure 14.6.

14.11



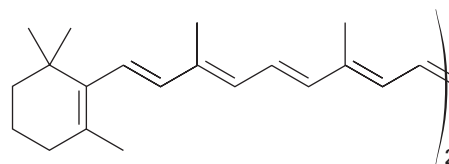
14.12 The mechanism is identical to that between a ketone and 2 equivalents of a monoalcohol, shown in Figure 14.8.

14.13



- 14.14 (a) Cyclohexanone + $\text{CH}_3\text{CH}=\text{P}(\text{Ph})_3$
 (b) Cyclohexanecarbaldehyde + $\text{H}_2\text{C}=\text{P}(\text{Ph})_3$
 (c) Acetone + $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{P}(\text{Ph})_3$
 (d) Acetone + $\text{PhCH}=\text{P}(\text{Ph})_3$
 (e) Acetophenone + $\text{PhCH}=\text{P}(\text{Ph})_3$
 (f) Cyclohex-2-enone + $\text{H}_2\text{C}=\text{P}(\text{Ph})_3$

14.15

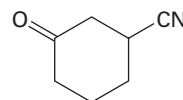


14.16 Intramolecular Cannizzaro reaction

14.17 Addition of the *pro-R* hydrogen of NADH takes place on the *Re* face of pyruvate.

14.18 The $-\text{OH}$ group adds to the *Re* face at C2, and $-\text{H}$ adds to the *Re* face at C3, to yield (2*R*,3*S*)-isocitrate.

14.19



14.20 (a) But-3-en-2-one + $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CuLi}$

(b) 3-Methylcyclohex-2-enone + $(\text{CH}_3)_2\text{CuLi}$

(c) 4-*tert*-Butylcyclohex-2-enone + $(\text{CH}_3\text{CH}_2)_2\text{CuLi}$

(d) Unsaturated ketone + $(\text{H}_2\text{C}=\text{CH})_2\text{CuLi}$

14.21 Look for the presence or absence of a saturated ketone absorption in the product.

14.22 (a) 1715 cm^{-1} (b) 1685 cm^{-1}

(c) 1750 cm^{-1} (d) 1705 cm^{-1}

(e) 1715 cm^{-1} (f) 1705 cm^{-1}

14.23 (a) Different peaks due to McLafferty rearrangement

(b) Different peaks due to α cleavage and McLafferty rearrangement

(c) Different peaks due to McLafferty rearrangement

14.24 IR: 1750 cm^{-1} ; MS: 140, 84

CHAPTER 15

15.1 (a) 3-Methylbutanoic acid

(b) 4-Bromopentanoic acid

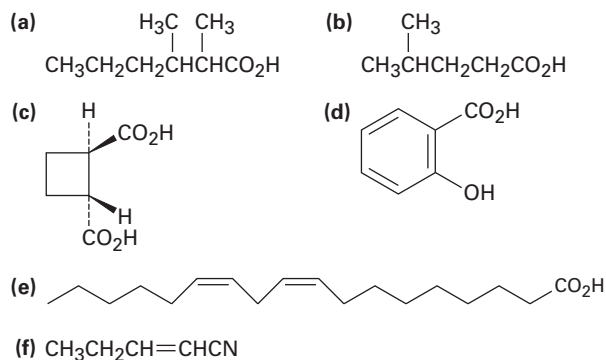
(c) 2-Ethylpentanoic acid

(d) *cis*-Hex-4-enoic acid

(e) 2,4-Dimethylpentanenitrile

(f) *cis*-Cyclopentane-1,3-dicarboxylic acid

15.2



15.3 Dissolve the mixture in ether, extract with aqueous NaOH, separate and acidify the aqueous layer, and extract with ether.

15.4 43%

15.5 (a) 82% dissociation (b) 73% dissociation

15.6 Lactic acid is stronger because of the inductive effect of the $-\text{OH}$ group.

15.7 The dianion is destabilized by repulsion between charges.

15.8 More reactive

15.9 (a) *p*-Methylbenzoic acid < Benzoic acid < *p*-Chlorobenzoic acid

(b) Acetic acid < Benzoic acid < *p*-Nitrobenzoic acid

15.10 (a) 1. Mg; 2. CO_2 , then H_3O^+

(b) 1. Mg; 2. CO_2 , then H_3O^+ ,
or 1. NaCN; 2. H_3O^+ with heat

15.11 1. NaCN; 2. H_3O^+ ; 3. LiAlH_4 ,
or Grignard carboxylation, then LiAlH_4

15.12 (a) Propanenitrile + $\text{CH}_3\text{CH}_2\text{MgBr}$,
then H_3O^+

(b) *p*-Nitrobenzotrile + CH_3MgBr ,
then H_3O^+

15.13 1. Heat 4-methylpentanenitrile with H_3O^+ ;
2. LiAlH_4

15.14 Cyclopentanecarboxylic acid has a broad $-\text{OH}$ absorption at $2500\text{--}3300\text{ cm}^{-1}$.

15.15 4-Hydroxycyclohexanone: $\text{H}-\text{C}-\text{O}$ absorption near $4\ \delta$ in ^1H spectrum and $\text{C}=\text{O}$ absorption near $210\ \delta$ in ^{13}C spectrum. Cyclopentanecarboxylic acid: $-\text{CO}_2\text{H}$ absorption near $12\ \delta$ in ^1H spectrum and $-\text{CO}_2\text{H}$ absorption near $170\ \delta$ in ^{13}C spectrum.

CHAPTER 16

16.1 (a) 4-Methylpentanoyl chloride

(b) Cyclohexylacetamide

(c) Isopropyl 2-methylpropanoate

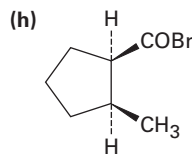
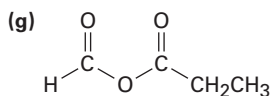
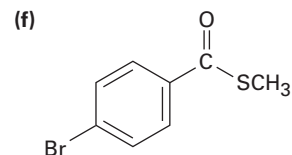
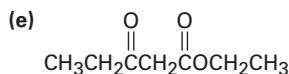
(d) Benzoic anhydride

(e) Isopropyl cyclopentanecarboxylate

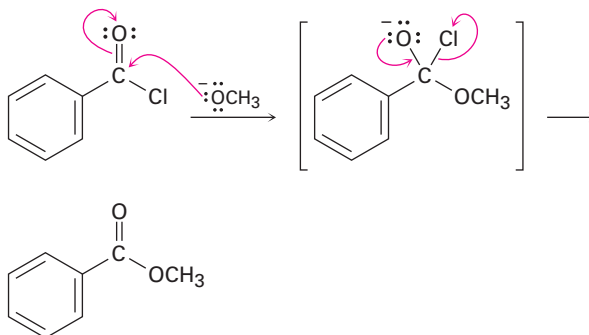
(f) Cyclopentyl 2-methylpropanoate

(g) *N*-Methylpent-4-enamide(h) (*R*)-2-Hydroxypropanoyl phosphate

(i) Ethyl 2,3-dimethylbut-2-enethioate

16.2 (a) $\text{C}_6\text{H}_5\text{CO}_2\text{C}_6\text{H}_5$ (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CON}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (c) $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{CH}_3)\text{COCl}$ (d) 

16.3



16.4 (a) Acetyl chloride > Methyl acetate > Acetamide

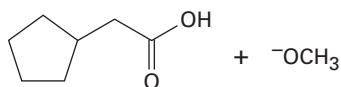
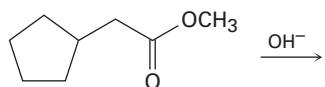
(b) Hexafluoroisopropyl acetate > 2,2,2-Trichloroethyl acetate > Ethyl acetate

16.5 (a) $\text{CH}_3\text{CO}_2^- \text{Na}^+$ (b) CH_3CONH_2

(c) $\text{CH}_3\text{CO}_2\text{CH}_3 + \text{CH}_3\text{CO}_2^- \text{Na}^+$

(d) $\text{CH}_3\text{CONHCH}_3$

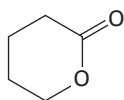
16.6



16.7 (a) Acetic acid + butan-1-ol

(b) Butanoic acid + methanol

16.8



16.9 (a) Propanoyl chloride + methanol

(b) Acetyl chloride + ethanol

(c) Benzoyl chloride + ethanol

16.10 Benzoyl chloride + cyclohexanol

16.11 (a) Propanoyl chloride + methylamine

(b) Benzoyl chloride + diethylamine

(c) Propanoyl chloride + ammonia

16.12 This is a typical nucleophilic acyl substitution reaction, with morpholine as the nucleophile and chloride as the leaving group.

16.13 (a) Benzoyl chloride + $[(\text{CH}_3)_2\text{CH}]_2\text{CuLi}$, or 2-methylpropanoyl chloride + Ph_2CuLi

(b) Prop-2-enoyl chloride + $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CuLi}$, or butanoyl chloride + $(\text{H}_2\text{C}=\text{CH})_2\text{CuLi}$

16.14 This is a typical nucleophilic acyl substitution reaction, with *p*-hydroxyaniline as the nucleophile and acetate ion as the leaving group.

16.15 Monomethyl ester of benzene-1,2-dicarboxylic acid

16.16 Reaction of a carboxylic acid with an alkoxide ion gives the carboxylate ion.

16.17 $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CHO}$

16.18 (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$

(b) $\text{PhOH} + \text{PhCH}_2\text{OH}$

16.19 (a) Ethyl benzoate + 2 CH_3MgBr

(b) Ethyl acetate + 2 PhMgBr

(c) Ethyl pentanoate + 2 $\text{CH}_3\text{CH}_2\text{MgBr}$

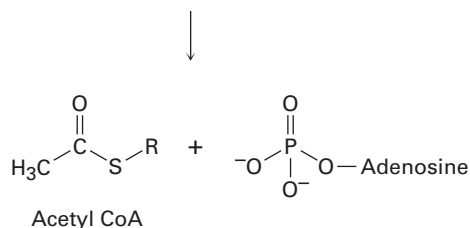
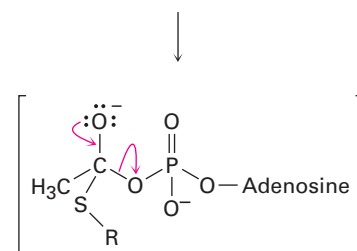
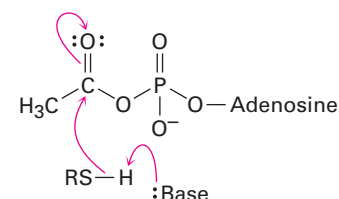
16.20 (a) H_2O , NaOH

(b) Product of (a), then LiAlH_4

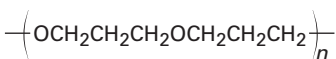
(c) LiAlH_4

16.21 1. Mg ; 2. CO_2 , then H_3O^+ ; 3. SOCl_2 ; 4. $(\text{CH}_3)_2\text{NH}$; 5. LiAlH_4

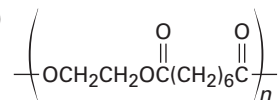
16.22



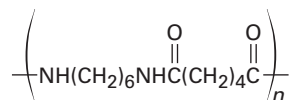
16.23 (a)



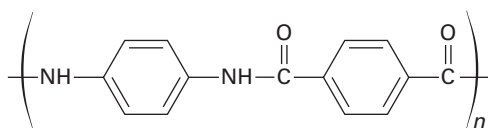
(b)



(c)



16.24



16.25 (a) Ester

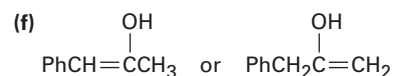
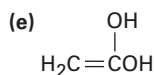
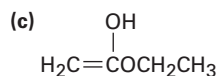
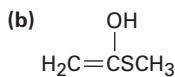
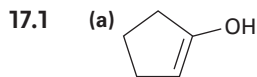
(b) Acid chloride

(c) Carboxylic acid

(d) Aliphatic ketone or cyclohexanone

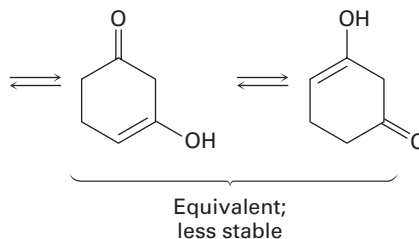
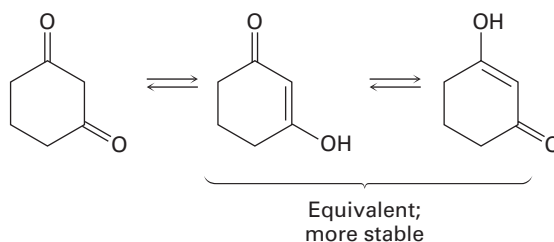
16.26 (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ and other possibilities(b) $\text{CH}_3\text{CON}(\text{CH}_3)_2$ (c) $\text{CH}_3\text{CH}=\text{CHCOCl}$ or $\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{COCl}$

CHAPTER 17



17.2 (a) 4 (b) 3 (c) 3 (d) 2 (e) 4 (f) 5

17.3

17.4 1. Br_2 ; 2. Pyridine, heat17.5 The intermediate α -bromo acid bromide undergoes a nucleophilic acyl substitution reaction with methanol to give an α -bromo ester.17.6 (a) $\text{CH}_3\text{CH}_2\text{CHO}$ (b) $(\text{CH}_3)_3\text{CCOCH}_3$ (c) $\text{CH}_3\text{CO}_2\text{H}$ (d) PhCONH_2 (e) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$ (f) $\text{CH}_3\text{CON}(\text{CH}_3)_2$ 17.7 $\text{CH}_2\text{C}\equiv\text{N}^- \longleftrightarrow \text{H}_2\text{C}=\text{C}=\ddot{\text{N}}^-$ 17.8 (a) 1. $\text{Na}^+ \text{OEt}^-$; 2. PhCH_2Br ; 3. H_3O^+ (b) 1. $\text{Na}^+ \text{OEt}^-$; 2. $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$;
3. $\text{Na}^+ \text{OEt}^-$; 4. CH_3Br ; 5. H_3O^+ (c) 1. $\text{Na}^+ \text{OEt}^-$; 2. $(\text{CH}_3)_2\text{CHCH}_2\text{Br}$;
3. H_3O^+

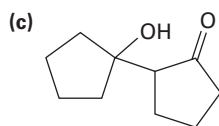
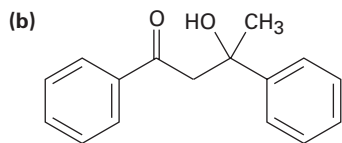
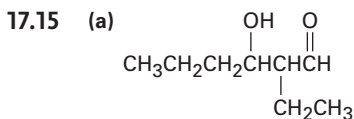
17.9 Malonic ester has only two acidic hydrogens to be replaced.

17.10 1. $\text{Na}^+ \text{OEt}^-$; 2. $(\text{CH}_3)_2\text{CHCH}_2\text{Br}$;
3. $\text{Na}^+ \text{OEt}^-$; 4. CH_3Br ; 5. H_3O^+ 17.11 (a) $(\text{CH}_3)_2\text{CHCH}_2\text{Br}$ (b) $\text{PhCH}_2\text{CH}_2\text{Br}$

17.12 None can be prepared.

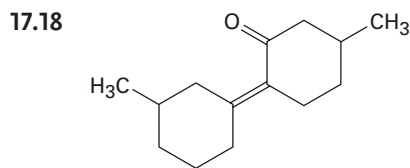
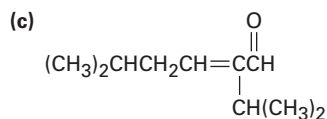
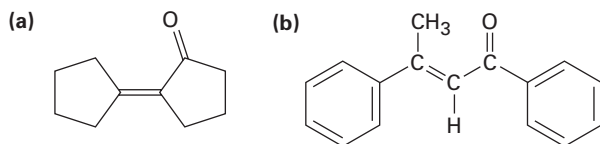
17.13 1. 2 $\text{Na}^+ \text{OEt}^-$; 2. $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$;
3. H_3O^+

- 17.14 (a) Alkylate phenylacetone with CH_3I
 (b) Alkylate pentanenitrile with $\text{CH}_3\text{CH}_2\text{I}$
 (c) Alkylate cyclohexanone with $\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$
 (d) Alkylate cyclohexanone with excess CH_3I
 (e) Alkylate $\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_3$ with CH_3I
 (f) Alkylate methyl 3-methylbutanoate with $\text{CH}_3\text{CH}_2\text{I}$

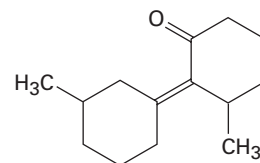


17.16 The reverse reaction is the exact opposite of the forward reaction, shown in Figure 17.7.

17.17



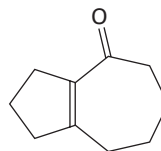
and



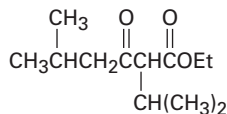
17.19 (a) Not an aldol product (b) Pentan-3-one

17.20 The CH_2 position between the two carbonyl groups is so acidic that it is completely deprotonated to give a stable enolate ion.

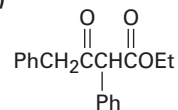
17.21



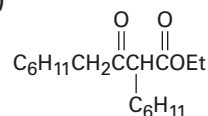
17.22 (a)



(b)

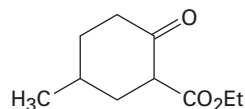


(c)

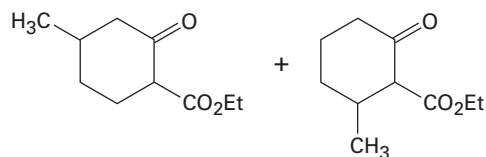


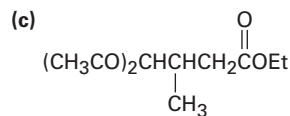
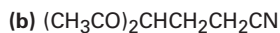
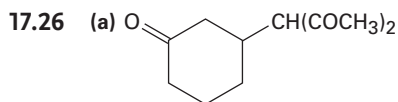
17.23 The cleavage reaction is the exact reverse of the forward reaction, shown in Figure 17.10.

17.24

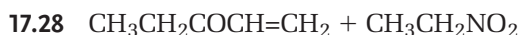
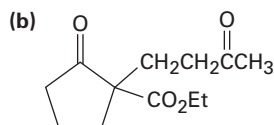
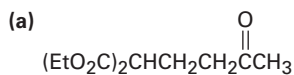


17.25

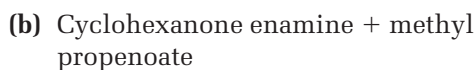
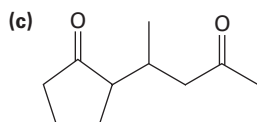
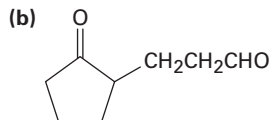
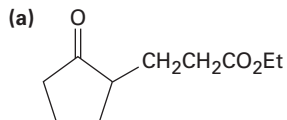




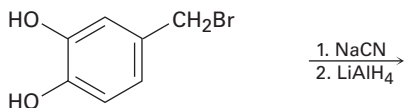
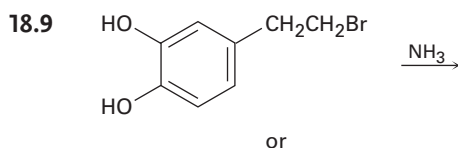
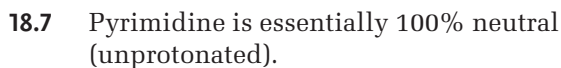
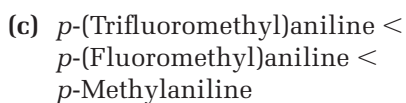
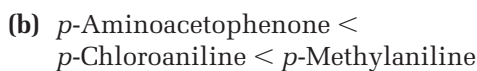
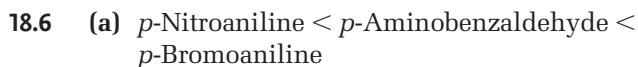
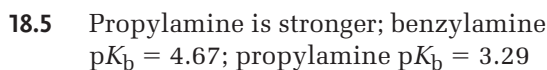
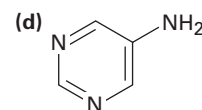
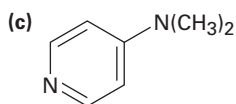
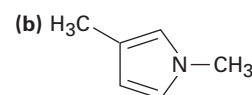
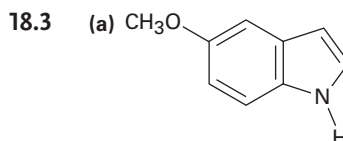
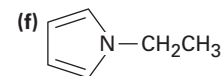
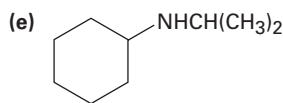
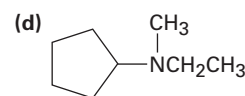
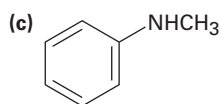
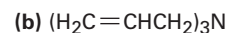
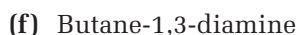
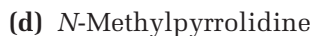
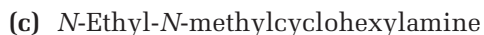
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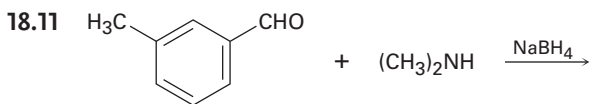
17.29



CHAPTER 18



- 18.10 (a) Ethylamine + acetone, or isopropylamine + acetaldehyde
 (b) Aniline + acetaldehyde
 (c) Cyclopentylamine + formaldehyde, or methylamine + cyclopentanone



- 18.12 (a) Oct-3-ene and oct-4-ene
 (b) Cyclohexene
 (c) Hept-3-ene
 (d) Ethylene and cyclohexene



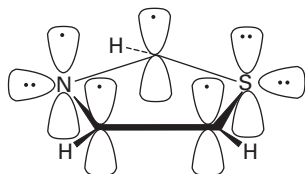
- 18.14 1. HNO_3 , H_2SO_4 ; 2. H_2/PtO_2 ;
 3. $(\text{CH}_3\text{CO})_2\text{O}$; 4. HOSO_2Cl ;
 5. aminothiazole; 6. H_2O , NaOH

- 18.15 (a) 1. HNO_3 , H_2SO_4 ; 2. H_2/PtO_2 ; 3. 2 CH_3Br

- (b) 1. HNO_3 , H_2SO_4 ; 2. H_2/PtO_2 ;
 3. $(\text{CH}_3\text{CO})_2\text{O}$; 4. Cl_2 ; 5. H_2O , NaOH

- (c) 1. HNO_3 , H_2SO_4 ; 2. Cl_2 , FeCl_3 ; 3. Sn

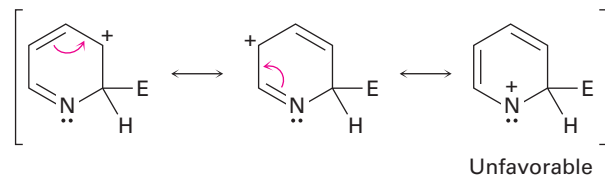
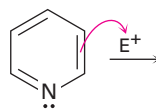
18.16



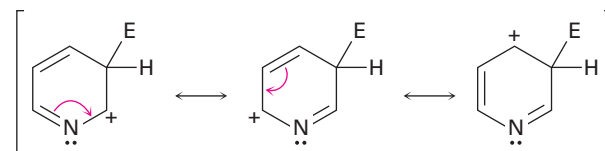
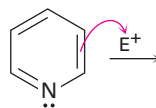
18.17 4.1% protonated

18.18

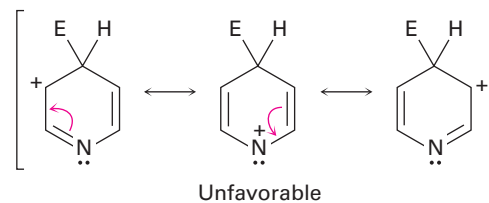
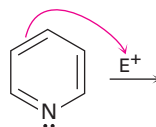
Attack at C2:



Attack at C3:

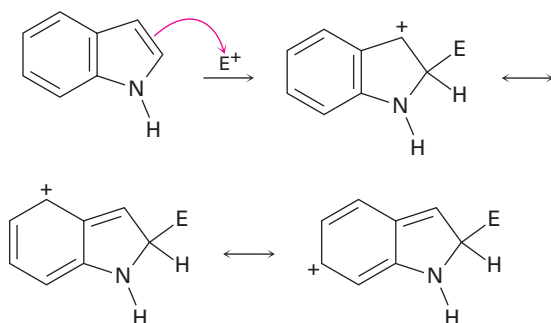


Attack at C4:



18.19 The side-chain nitrogen is more basic than the ring nitrogen.

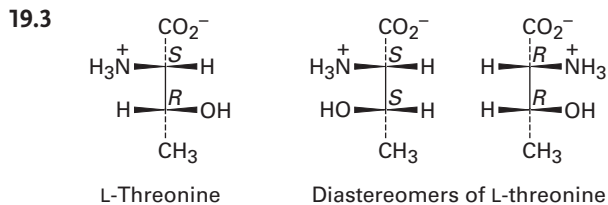
- 18.20** Reaction at C2 is disfavored because the aromaticity of the benzene ring is lost.



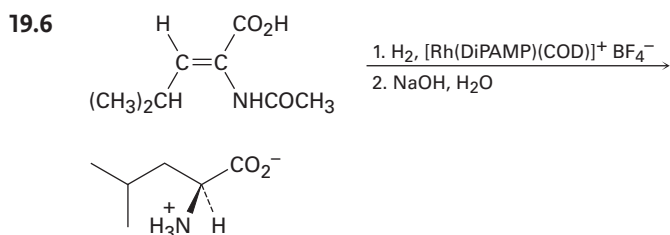
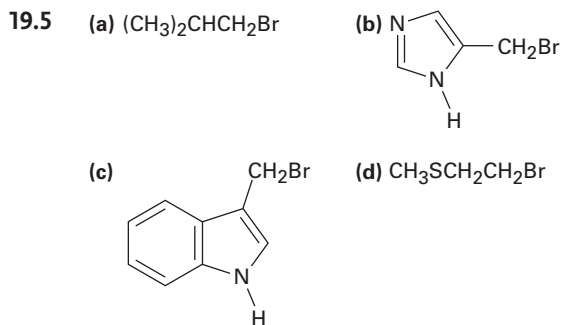
CHAPTER 19

- 19.1** Aromatic: Phe, Tyr, Trp, His;
sulfur-containing: Cys, Met; alcohols: Ser,
Thr; hydrocarbon side chains: Ala, Ile, Leu,
Val, Phe

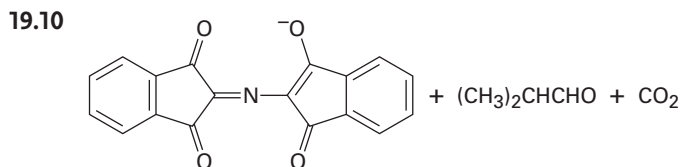
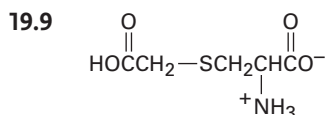
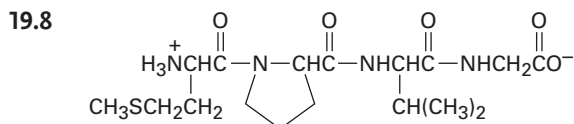
- 19.2** The sulfur atom in the $-CH_2SH$ group of
cysteine makes the side chain higher in
priority than the $-CO_2H$ group.



- 19.4** Net positive at pH = 5.3; net negative at
pH = 7.3

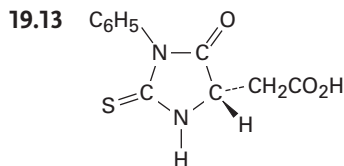


- 19.7** Val-Tyr-Gly (VYG), Tyr-Gly-Val (YGV),
Gly-Val-Tyr (GVY), Val-Gly-Tyr (VGY),
Tyr-Val-Gly (YVG), Gly-Tyr-Val (GYV)



- 19.11** Trypsin: Asp-Arg + Val-Tyr-Ile-His-Pro-Phe
Chymotrypsin: Asp-Arg-Val-Tyr
+ Ile-His-Pro-Phe

- 19.12** Methionine

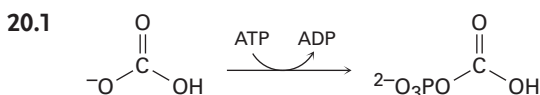


- 19.14** (a) Arg-Pro-Leu-Gly-Ile-Val
(b) Val-Met-Trp-Asp-Val-Leu (VMWNVL)

- 19.15** This is a typical nucleophilic acyl
substitution reaction, with the amine of the
amino acid as the nucleophile and *tert*-
butyl carbonate as the leaving group. The *tert*-
butyl carbonate then loses CO_2 and gives
tert-butoxide, which is protonated.

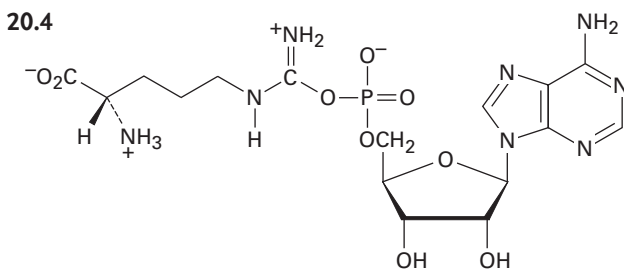
- 19.16** (1) Protect the amino group of leucine.
 (2) Protect the carboxylic acid group of alanine.
 (3) Couple the protected amino acids with DCC.
 (4) Remove the leucine protecting group.
 (5) Remove the alanine protecting group.
- 19.17** (a) Lyase (b) Hydrolase
 (c) Oxidoreductase

CHAPTER 20

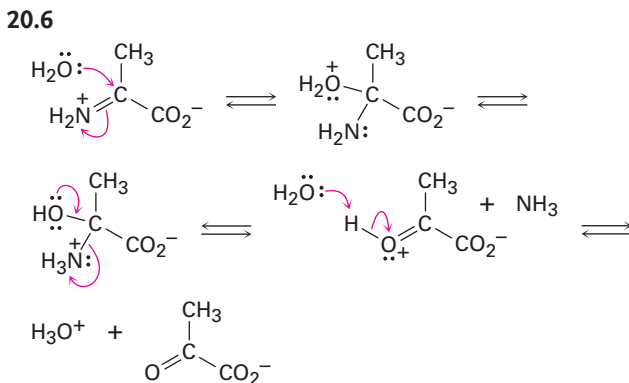


20.2 The mechanism is the exact reverse of that shown in Figure 20.2.

20.3 The *Re* face

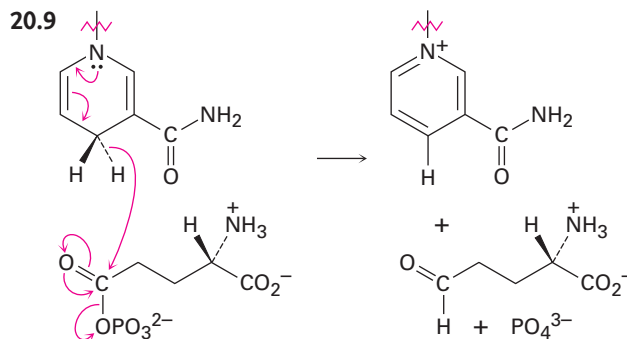


20.5 The mechanism is the same as that shown in Figure 20.2.

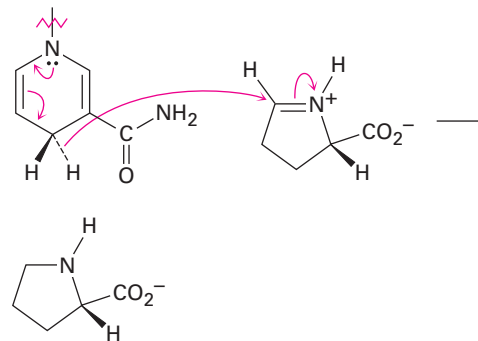


20.7 The mechanism is given in Figure 20.2.

20.8 The mechanism involves formation of a tetrahedral intermediate, followed by expulsion of ammonia.



20.10 The nonenzymatic cyclization is an internal imine formation that occurs by nucleophilic addition of the amine to the carbonyl group followed by loss of water. The enzymatic reduction is a nucleophilic addition to the iminium ion:

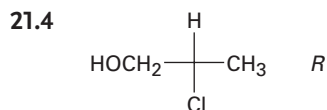


CHAPTER 21

21.1 (a) Aldotetrose (b) Ketopentose
 (c) Ketohehexose (d) Aldopentose

21.2 (a) *S* (b) *R* (c) *S*

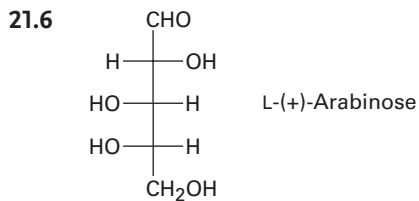
21.3 A, B, and C are the same.



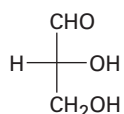
21.5 (a) L-Erythrose; 2*S*,3*S*

(b) D-Xylose; 2*R*,3*S*,4*R*

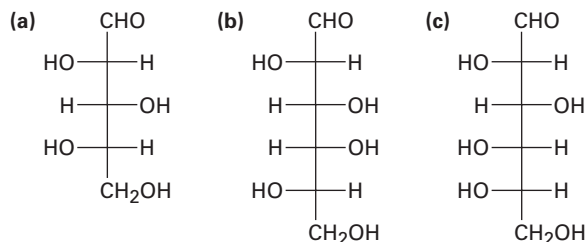
(c) D-Xylulose; 3*S*,4*R*



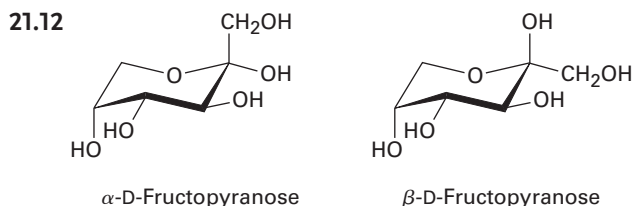
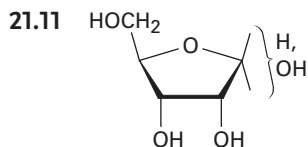
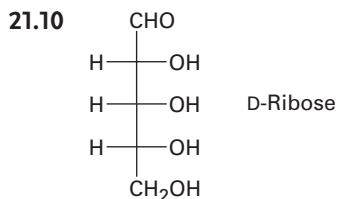
21.7 D-Glyceraldehyde



21.8

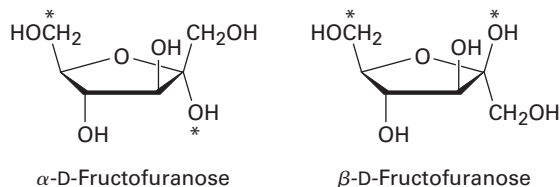


21.9 16 D and 16 L aldoheptoses

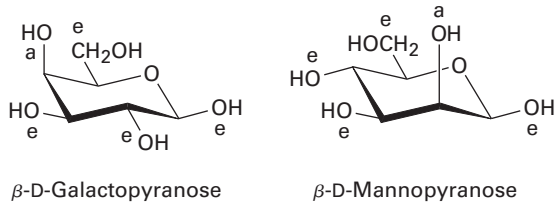


trans

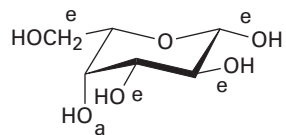
cis



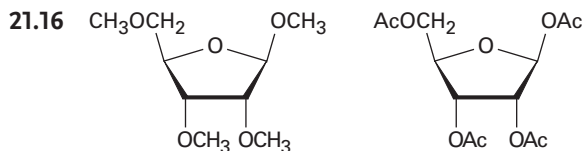
21.13



21.14



21.15 α -D-Allopyranose (see Figure 21.3)



21.17 D-Galactitol has a plane of symmetry and is a meso compound, whereas D-glucitol is chiral.

21.18 The -CHO end of L-gulose corresponds to the -CH₂OH end of D-glucose after reduction.

21.19 D-Allaric acid has a symmetry plane and is a meso compound, but D-glucaric acid is chiral.

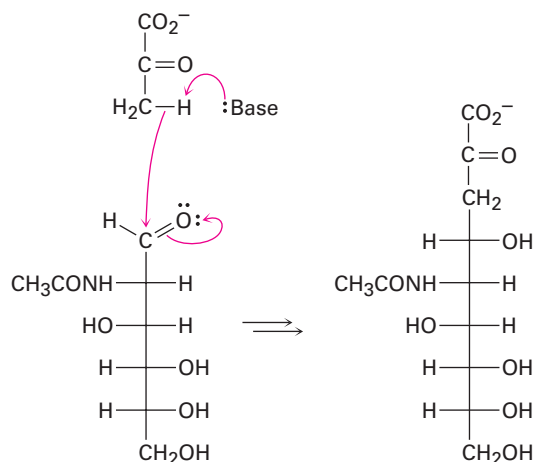
21.20 D-Allose and D-galactose yield meso aldaric acids; the others yield optically active aldaric acids.

21.21 D-Allose + D-altrose

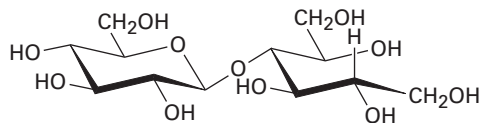
21.22 L-Xylose

21.23 D-Xylose and D-lyxose

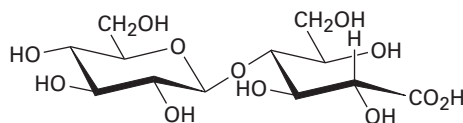
21.24



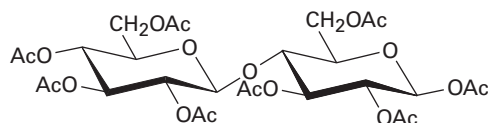
21.25 (a) Cellobiose $\xrightarrow[2. \text{H}_2\text{O}]{1. \text{NaBH}_4}$



(b) Cellobiose $\xrightarrow[\text{H}_2\text{O}]{\text{Br}_2}$



(c) Cellobiose $\xrightarrow[\text{pyridine}]{\text{CH}_3\text{COCl}}$



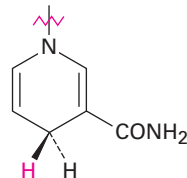
CHAPTER 22

22.1 Steps 7 and 10

22.2 Steps 1, 3: nucleophilic acyl substitutions at phosphorus; steps 2, 5, 7, 8, 10: isomerizations; step 4: retro-aldol reaction; step 6: oxidation and nucleophilic acyl substitution by phosphate; step 9: E1cB dehydration

22.3 *pro-R*

22.4



22.5 C1 and C6 of glucose become -CH₃ groups; C3 and C4 become CO₂.

22.6 Citrate and isocitrate

22.7 E1cB elimination of water, followed by conjugate addition

22.8 *pro-R*; anti geometry

22.9 *Re* face; anti geometry

22.10 The reaction occurs by two sequential nucleophilic acyl substitutions, the first by a cysteine residue in the enzyme, with phosphate as leaving group, and the second by hydride donation from NADH, with the cysteine residue as leaving group.

CHAPTER 23

23.1 CH₃(CH₂)₁₈CO₂CH₂(CH₂)₃₀CH₃

23.2 Glyceroyl tripalmitate is higher melting.

23.3 [CH₃(CH₂)₇CH=CH(CH₂)₇CO₂⁻]₂ Mg²⁺

23.4 Glyceroyl dioleate monopalmitate \rightarrow
Glycerol + 2 Sodium oleate + Sodium
palmitate

23.5 Capryloyl CoA \rightarrow Hexanoyl CoA \rightarrow
Butyroyl CoA \rightarrow 2 Acetyl CoA

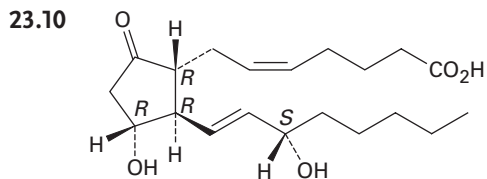
23.6 (a) 8 acetyl CoA; 7 passages

(b) 10 acetyl CoA; 9 passages

23.7 The dehydration is an E1cB reaction.

23.8 At C2, C4, C6, C8, and so forth

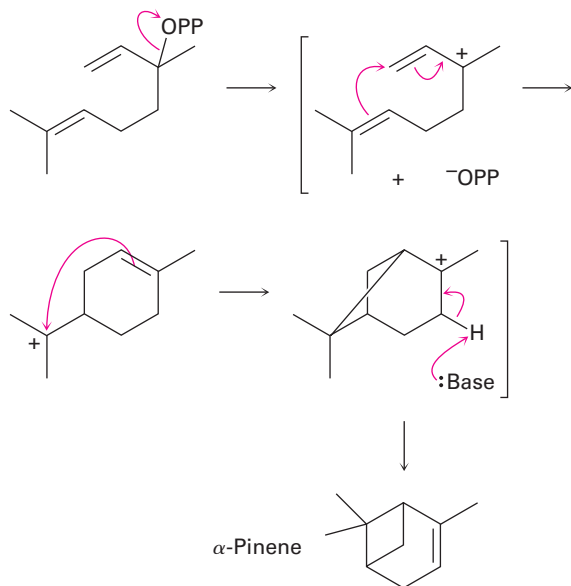
23.9 The *Si* face



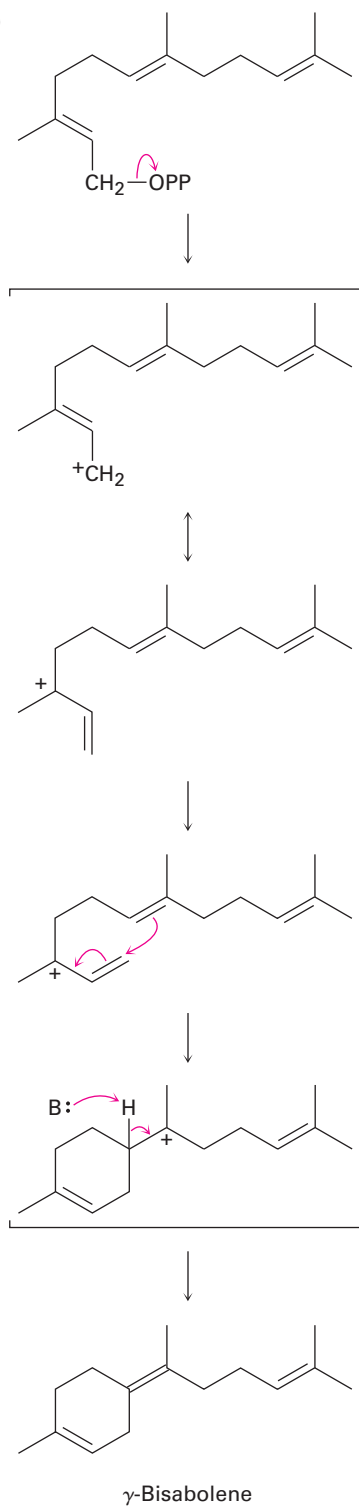
23.11 The *pro-S* hydrogen is cis to the $-\text{CH}_3$ group;
the *pro-R* hydrogen is trans.

23.12

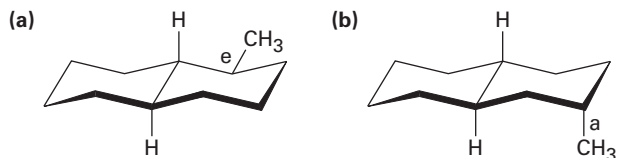
(a)



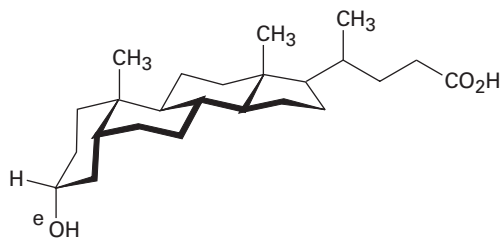
(b)



23.13



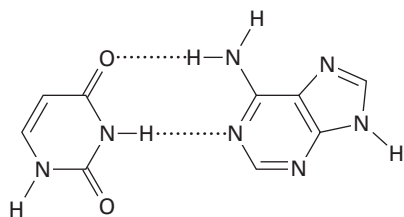
23.14



CHAPTER 24

24.3 (5') ACGGATTAGCC (3')

24.4



24.5 (3') CUA AUGGAU (5')

24.6 (5') ACTCTGCGAA (3')

24.7 (a) GCU, GCC, GCA, GCG (b) UUU, UUC

(c) UUA, UUG, CUU, CUC, CUA, CUG

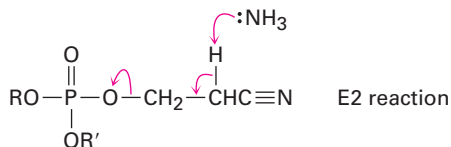
(d) UAU, UAC

24.8 Leu-Met-Ala-Trp-Pro-Stop

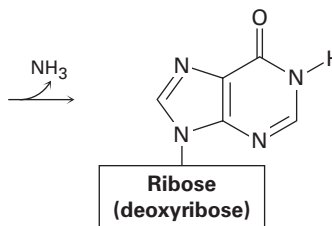
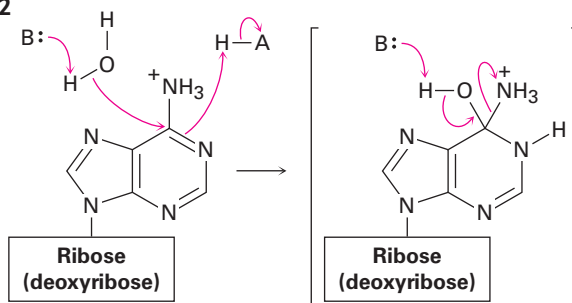
24.9 (5') TTA-GGG-CCA-AGC-CAT-AAG (3')

24.10 The cleavage is an S_N1 reaction that occurs by protonation of the oxygen atom followed by loss of the stable triarylmethyl carbocation.

24.11



24.12



24.13 The mechanism occurs by (1) phosphorylation of inosine monophosphate by reaction with GTP, (2) acid-catalyzed nucleophilic addition of aspartate to an imine, and (3) loss of phosphate by an $E1cB$ reaction.

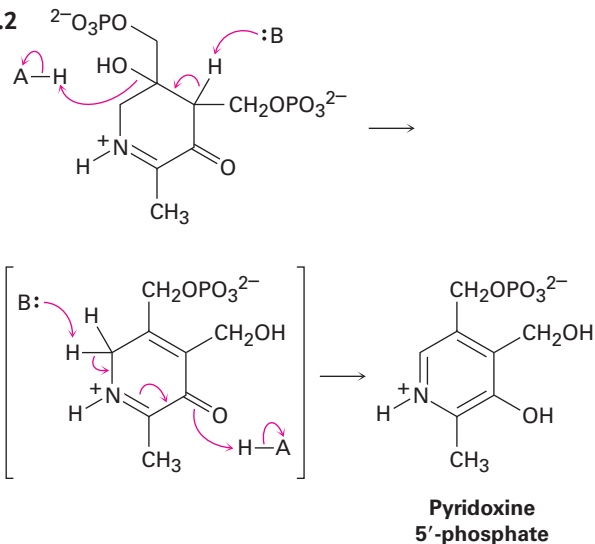
24.14 The reaction is an $E1cB$ elimination.

Chapters 25–27 are online-only chapters. To access them, enter ISBN 978-1-285-84291-2 at www.cengagebrain.com and visit this book's companion website.

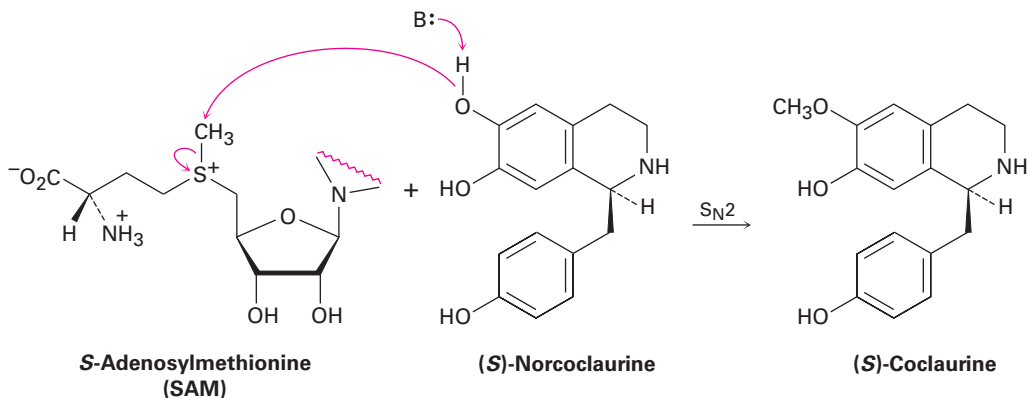
CHAPTER 25

25.1 *Si* face

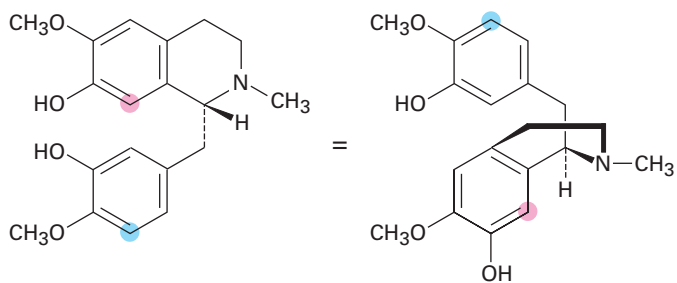
25.2



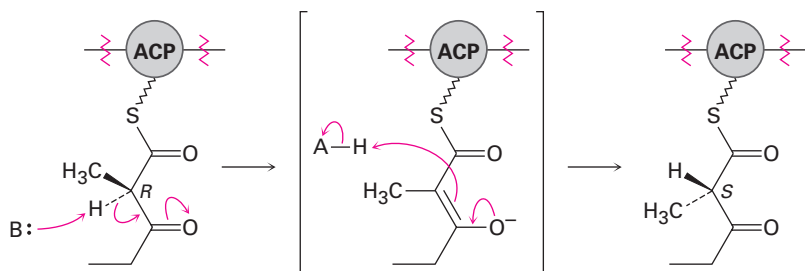
25.3



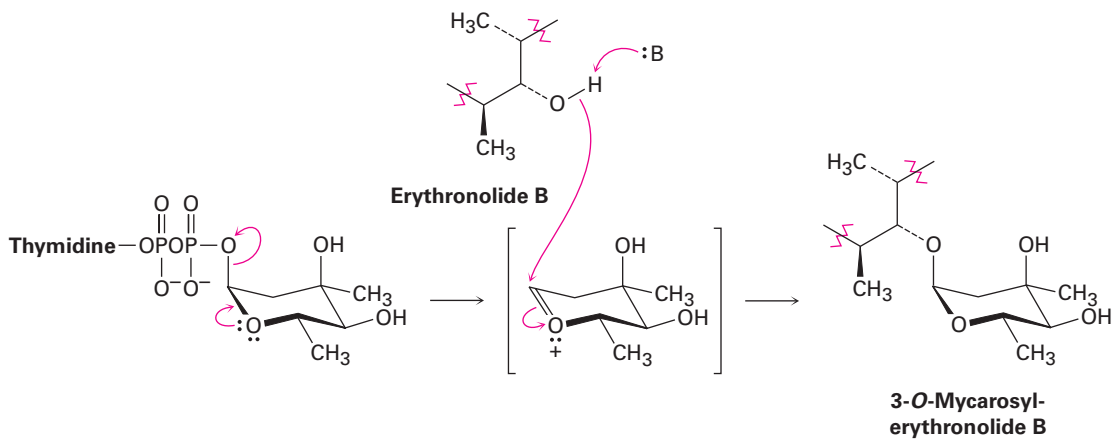
25.4



25.5



25.6

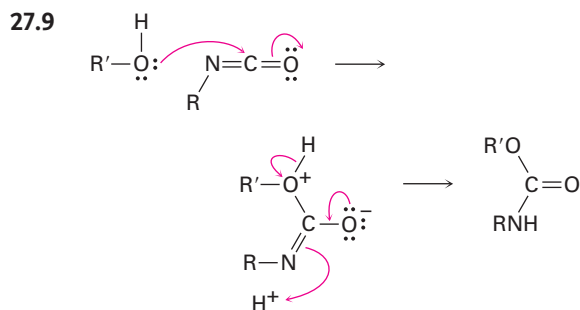
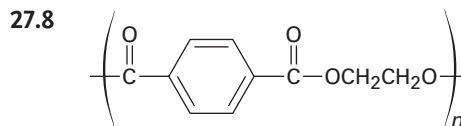
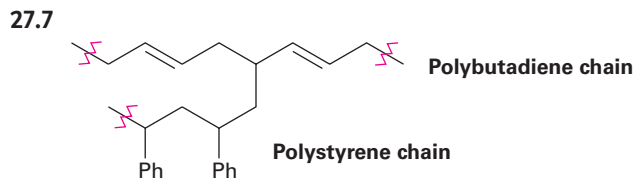
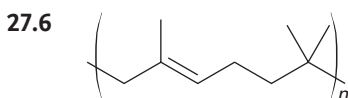


CHAPTER 26

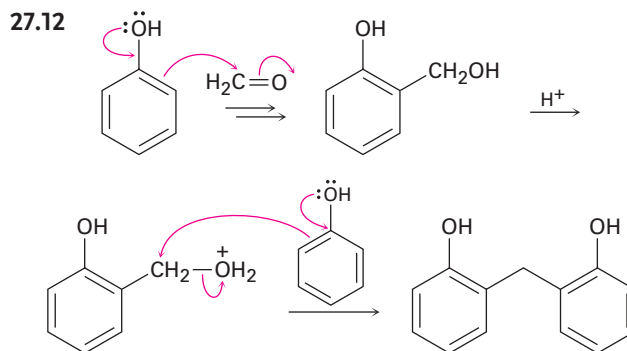
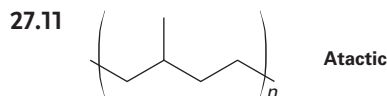
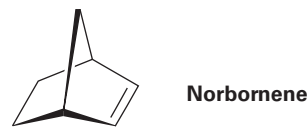
- 26.1 Ethylene: ψ_1 is the HOMO and ψ_2^* is the LUMO in the ground state; ψ_2^* is the HOMO and there is no LUMO in the excited state. Buta-1,3-diene: ψ_2 is the HOMO and ψ_3^* is the LUMO in the ground state; ψ_3^* is the HOMO and ψ_4^* is the LUMO in the excited state.
- 26.2 Disrotatory: *cis*-5,6-dimethylcyclohexa-1,3-diene; conrotatory: *trans*-5,6-dimethylcyclohexa-1,3-diene. Disrotatory closure occurs.
- 26.3 The more stable of two allowed products is formed.
- 26.4 *trans*-5,6-Dimethylcyclohexa-1,3-diene; *cis*-5,6-dimethylcyclohexa-1,3-diene
- 26.5 *cis*-3,6-Dimethylcyclohexene; *trans*-3,6-dimethylcyclohexene
- 26.6 A [6 + 4] suprafacial cycloaddition
- 26.7 An antarafacial [1,7] sigmatropic rearrangement
- 26.8 A series of [1,5] hydrogen shifts occur.
- 26.9 Claisen rearrangement is followed by a Cope rearrangement.
- 26.10 (a) Conrotatory (b) Disrotatory
(c) Suprafacial (d) Antarafacial
(e) Suprafacial

CHAPTER 27

- 27.1 $\text{H}_2\text{C}=\text{CHCO}_2\text{CH}_3 < \text{H}_2\text{C}=\text{CHCl} < \text{H}_2\text{C}=\text{CHCH}_3 < \text{H}_2\text{C}=\text{CH}-\text{C}_6\text{H}_5 < \text{H}_2\text{C}=\text{CHC}\equiv\text{N}$
- 27.2 $\text{H}_2\text{C}=\text{CHCH}_3 < \text{H}_2\text{C}=\text{CHC}_6\text{H}_5 < \text{H}_2\text{C}=\text{CHC}\equiv\text{N}$
- 27.3 The intermediate is a resonance-stabilized benzylic carbanion, $\text{Ph}-\ddot{\text{C}}\text{HR}$.
- 27.4 The polymer has no chirality centers.
- 27.5 The polymers are racemic and have no optical rotation.



- 27.10 Vestenamer: ADMET polymerization of deca-1,9-diene or ROMP of cyclooctene; Norsorex: ROMP of norbornene.



Index

Boldface references refer to pages where terms are defined.

α , *see* Alpha

Abbreviated mechanism, nucleophilic acyl substitution reactions, 733

ABS polymer, structure and uses of, 931

Absolute configuration, **124**

Absorbance, **343**

Absorption spectrum, **331**

Acesulfame-K, structure and sweetness of, 770

Acetal, **509**

aldehyde protecting group, 511

cyclic, 511

from aldehydes, 509–511

from ketones, 509–511

hydrolysis of, 511

ketone protecting group, 511

mechanism of formation of, 509–510

Acetaldehyde, aldol reaction of, 620–621

bond angles in, 485

bond lengths in, 485

electrostatic potential map of, 485

^{13}C NMR absorptions of, 524

^1H NMR spectrum of, 524

$\text{p}K_{\text{a}}$ of, 608

Acetamide, electrostatic potential map of, 561, 598b, 651

Acetaminophen, molecular model of, 27a
synthesis of, 577

Acetanilide, electrophilic aromatic substitution of, 663–664

Acetate ion, electrostatic potential map of, 36, 46, 49, 536

resonance in, 36–37

annual worldwide production of, 531

Acetic acid, dipole moment of, 32

dimer of, 534

electrostatic potential map of, 46, 48

industrial synthesis of, 531

$\text{p}K_{\text{a}}$ of, 45, 534

protonation of, 52–53

uses of, 531

Acetic acid dimer, electrostatic potential map of, 534

Acetic anhydride, electrostatic potential map of, 561

reaction with alcohols, 577

reaction with amines, 577

synthesis of, 565

Acetoacetic ester, alkylation of, 614–615
ketones from, 614–615

Acetoacetic ester synthesis, **614–615**

Acetone, annual worldwide production of, 493

electrostatic potential map of, 48, 49, 64, 491

enol content of, 601

hydrate of, 501

$\text{p}K_{\text{a}}$ of, 607

uses of, 493

Acetone anion, electrostatic potential map of, 49

Acetonitrile, electrostatic potential map of, 545

$\text{p}K_{\text{a}}$ of, 608

Acetophenone, ^{13}C NMR absorptions of, 524

structure of, 494

Acetyl adenylate, acetyl CoA from, 587–588

Acetyl azide, electrostatic potential map of, 598b

Acetyl chloride, electrostatic potential map of, 491, 561

$\text{p}K_{\text{a}}$ of, 608

reaction with alcohols, 572–573

reaction with amines, 573–574

Acetyl CoA, biological Claisen

condensation of, 830

biosynthesis of, 587–588

carboxylation of, 823

catabolism of, 787–792

Claisen condensation reaction of, 638–639

fat catabolism and, 815–820

fatty acids from, 820–825

from acetyl dihydroloipoamide, 786–787

from pyruvate, 783–787

function of, 588

glycolysis and, 776–782

reaction with glucosamine, 588

reaction with oxaloacetate, 789

structure of, 716

thioester group in, 588

Acetyl CoA anion, resonance in, 38–39

Acetyl CoA carboxylase, function of, 530
molecular model of, 530

Acetyl coenzyme A, *see* Acetyl CoA

Acetyl dihydroloipoamide, acetyl CoA from, 786–787

Acetyl group, **494**

N-Acetyl-D-neuraminic acid, structure and function of, 761

Acetylene, bond angles in, 17

bond lengths in, 17

bond strengths in, 17

molecular model of, 17

$\text{p}K_{\text{a}}$ of, 257

sp hybrid orbitals in, 16–17

structure of, 17

N-Acetylglucosamine, biosynthesis of, 588
structure and function of, 761

Acetylide anion, **256**

alkylation of, 258

electrostatic potential map of, 257

formation of, 256

N-Acetylmannosamine, structure and function of, 761

Achiral, **116**

Acid, Brønsted–Lowry, **42**

Lewis, **50**

organic, 48–49

strengths of, 44–45

Acid anhydride(s), **555**

amides from, 577

electrostatic potential map of, 561

esters from, 577

from acid chlorides, 572

from carboxylic acids, 565

IR spectroscopy of, 592–593

naming, 556

NMR spectroscopy of, 593–594

nucleophilic acyl substitution reactions of, 576–578

reaction summary of, 598

reaction with alcohols, 577

reaction with amines, 577

Acid chloride(s), acid anhydrides from, 572

alcohols from, 575

alcoholysis of, 572–573

amides from, 573–574

aminolysis of, 573–574

carboxylic acids from, 570–572

electrostatic potential map of, 561

esters from, 572–573

from carboxylic acids, 564

hydrolysis of, 570–572

IR spectroscopy of, 592–593

ketones from, 496, 575–576

naming, 556

- Acid chloride(s) (*continued*)
 NMR spectroscopy of, 593–594
 nucleophilic acyl substitution reactions of, 570–576
 pK_a of, 608
 polarity of, 64
 reaction summary of, 597
 reaction with alcohols, 572–573
 reaction with amines, 573–574
 reaction with ammonia, 573–574
 reaction with carboxylate ions, 572
 reaction with $LiAlH_4$, 575
 reaction with lithium diorganocopper reagents, 496, 575–576
 reaction with water, 570–572
 reduction of, 575
- Acid halide(s), **555**
 naming, 556
 nucleophilic acyl substitution reactions of, 570–576
see also Acid chloride
- Acidity, alcohols and, 439–441
 amines, 651
 carbonyl compounds and, 607–608
 carboxylic acids and, 534–535
 phenols and, 439–442
 thiols and, 441
- Acid–base reactions, prediction of, 46
- Acidity constant (K_a), **44**
 table of, 45
- Aclame, *see* Alitame, 770
- ACP, *see* Acyl carrier protein, 821
- Acrolein, structure of, 493
- Acrylic acid, pK_a of, 535
 structure of, 532
- Activating group (aromatic substitution), **296**
 acidity and, 539
 explanation of, 297–298
- Activation energy, **169**
 magnitude of, **169**
 reaction rate and, **169**
- Active site (enzyme), **173–174**
 citrate synthase and, 708
 hexokinase and, 174
 urocanase and, 736
- Acyclic diene metathesis polymerization (ADMET), **936**
 mechanism of, 936
- Acyl adenosyl phosphate, asparagine
 biosynthesis and, 733
 biological reactions of, 570–571
 structure of, 558
- Acyl adenylate, **570**
 biological reactions of, 570–571
 fatty acyl CoA biosynthesis and, 570–571
- Acyl carrier protein, 214
 structure and function of, 821
- Acyl carrier protein (ACP) domain,
 polyketide synthase and, 895
- Acyl cation, electrostatic potential map of, 292
 Friedel–Crafts acylation reaction and, 292
 resonance in, 292
- Acyl CoA dehydrogenase, function of, 179
 molecular model of, 179
- Acyl group, **292**, **483**, **494**
 name ending for, 532
 naming, 532
- Acyl phosphate, **555**
 biological reactivity of, 587–588
 naming, 557
- Acyl transfer (AT) domain, polyketide
 synthase and, 895
- Acylation (aromatic), *see* Friedel–Crafts
 acylation reaction
- Adams, Roger, 223
- Adams catalyst, hydrogenation with, 223
- 1,2-Addition (conjugated carbonyl), **518**
- 1,2-Addition (conjugated diene), **245**
- 1,4-Addition (conjugated carbonyl), **518**
- 1,4-Addition (conjugated diene), **245**
- Addition reaction, **147**
- Adenine, aromaticity of, 280
 electrostatic potential map of, 856
 molecular model of, 58b
 protection of, 867
 structure of, 853
- Adenosine, biosynthesis of, 873–874
 catabolism of, 873
- Adenosine diphosphate, structure of, 167
- Adenosine triphosphate, coupled reactions
 and, 718
 energy rich bonds in, 167
 function of, 706, 716–718
 hydrolysis of, 167
 reaction with alcohols, 716–718
 reaction with glucose, 718
 reaction with methionine, 474
 structure of, 167
- S-Adenosylhomocysteine, from
 S-adenosylmethionine, 418–419
 metabolism of, 434i
- S-Adenosylmethionine, biological
 methylation with, 418–419
 biological S_N2 reactions of, 418–419
 from methionine, 474
 stereochemistry of, 138
 structure and function of, 707
- Adipic acid, structure of, 532
- ADMET (acyclic diene metathesis
 polymerization), 936
- ADP, *see* Adenosine diphosphate
- Adrenaline, biosynthesis of, 418–419
 molecular model of, 145a
 structure of, 24
- Adrenocortical hormone, **841**
- al, aldehyde name ending, 493
- Alanine, biosynthesis of, 731
 catabolism of, 728
 configuration of, 125
 electrostatic potential map of, 679
 molecular model of, 27, 678
 pyruvate from, 728
 structure and properties of, 680
 titration curve of, 684–685
- Alanylserine, molecular model of, 689
- Alcohol(s), **435**
 acetals from, 509–511
 acidity of, 439–441
 aldehydes from, 456–458
 alkenes from, 213–214, 452–455
 alkoxide ions from, 440–441
 alkyl halides from, 390–391, 405,
 414–415, 452
 alpha cleavage of in mass spectrometry,
 326
 biological dehydration of, 454–455
 biological oxidation of, 458
 carbonyl compounds from, 456–458
 carboxylic acids from, 456–458
 common names of, 438
 dehydration of, 213–214, 452–455
 Dess–Martin oxidation of, 457–458
 electrostatic potential map of, 61
 esters from, 455–456
 ethers from, 466–467
 from acid chlorides, 575
 from aldehydes, 445–446, 449–451,
 504–505
 from alkenes, 218–221, 443–444
 from carbonyl compounds, 445–451
 from carboxylic acids, 447, 569
 from epoxides, 444
 from esters, 447, 449–451, 582–583
 from ethers, 468
 from ketones, 445–446, 449–451, 504–505
 hydrogen bonds in, 439
 IR spectroscopy of, 339, 475
 ketones from, 456–458
 mass spectrometry of, 326, 477
 mechanism of dehydration of, 453
 mechanism of oxidation of, 457–458
 naming, 437–438
 NMR spectroscopy of, 476–477
 oxidation of, 456–458
 polarity of, 61
 primary, **437**
 properties of, 439–442
 protection of, 460–462
 reaction summary of, 480–482
 reaction with acid, 453
 reaction with acid anhydrides, 577
 reaction with acid chlorides, 572–573
 reaction with aldehydes, 509–511
 reaction with alkyl halides, 466–467
 reaction with ATP, 716–718
 reaction with carboxylic acids, 565–567
 reaction with chlorotrimethylsilane,
 461–462
 reaction with CrO_3 , 456–458
 reaction with HF, 391
 reaction with HX, 390–391, 414–415, 452
 reaction with ketones, 509–511
 reaction with $Na_2Cr_2O_7$, 456–458
 reaction with NaH, 441
 reaction with $NaNH_2$, 441
 reaction with PBr_3 , 390–391, 405, 452
 reaction with $POCl_3$, 454
 reaction with potassium, 441
 reaction with $SOCl_2$, 390–391, 405, 452

- secondary, **437**
- synthesis of, 443–451
- tertiary, **437**
- tosylate from, 405
- Alcoholysis (nucleophilic acyl substitution reaction), **561**
- Aldaric acid, **758**
 - from aldoses, 758
- Aldehyde(s), **492**
 - α bromination of, 604–605
 - acetals from, 509–511
 - alcohols from, 445–446, 449–451, 504–505
 - aldol reaction of, 621
 - alkenes from, 513–514
 - amines from, 657–658
 - biological halogenation of, 604
 - biological reduction of, 446–447, 517
 - Cannizzaro reaction of, 516–517
 - carbonyl condensation reactions of, 620–621
 - carboxylic acids from, 497
 - common names of, 493
 - conjugate addition reactions of, 518–521
 - enamines from, 507
 - from alcohols, 456–458
 - from alkenes, 231–232
 - from esters, 495, 583
 - hydrates of, 501–502
 - imines from, 506
 - IR spectroscopy of, 340, 522–523
 - mass spectrometry of, 326–327, 524–525
 - McLafferty rearrangement of, 326
 - mechanism of hydration of, 501–502
 - mechanism of reduction of, 504
 - naming, 493
 - NMR spectroscopy of, 523–524
 - oxidation of, 497
 - pK_a of, 608
 - polarity of, 64
 - protection of, 511
 - reaction summary of, 528–529
 - reaction with alcohols, 509–511
 - reaction with amines, 505–508
 - reaction with Br_2 , 604–605
 - reaction with CrO_3 , 497
 - reaction with Grignard reagents, 449–451, 504–505
 - reaction with $LiAlH_4$, 446, 504
 - reaction with $NaBH_4$, 445, 504
 - reactivity of versus ketones, 499–500
 - reduction of, 445–446, 504
 - reductive amination of, 657–658
 - Wittig reaction of, 513–514
- Alditol, **756**
 - from monosaccharides, 756–757
- Aldol reaction, **620–621**
 - biological example of, 637–638
 - cyclohexenones from, 626–627
 - cyclopentenones from, 626–627
 - dehydration in, 623–625
 - equilibrium in, 621
 - glucose biosynthesis and, 637–638
 - intramolecular, 626–627
 - mechanism of, 621
 - mechanism of dehydration in, 623–624
 - mixed, 638
 - requirements for, 620–621
 - reversibility of, 621
 - steric hindrance to, 621
- Aldolase, class I, 637–638, 779
 - class II, 637–638, 779
 - function of, 778–779
 - types of, 637–638
- Aldonic acid(s), **757**
 - from aldoses, 757–758
- Aldose(s), **740**
 - aldaric acids from, 758
 - alditols from, 756–757
 - aldonic acids from, 757–758
 - Benedict's test on, 758
 - chain-extension of, 759–760
 - chain-shortening of, 760–760
 - configurations of, 746–747
 - esters from, 754
 - ethers from, 754
 - Fehling's test on, 758
 - glycosides of, 755
 - Kiliani–Fischer synthesis and, 759–760
 - names of, 747–748
 - oxidation of, 757–759
 - reaction with Br_2 , 757
 - reaction with HNO_3 , 758
 - reduction of, 756–757
 - see also Carbohydrate, Monosaccharide table of, 747
 - Tollens test on, 758
 - uronic acids from, 758–759
 - Wohl degradation of, 760
- Aldosterone, structure and function of, 841
- Aleve, see Naproxen
- Alicyclic, **88**
- Aliphatic compound, **66**
- Alitame, structure of, 770
 - sweetness of, 770
- Alkaloid, **56–57, 879**
 - number of, 56, 879
- Alkane(s), **66**
 - boiling points of, 79
 - branched-chain, **67**
 - combustion of, 78
 - conformations of, 84
 - dispersion forces in, 54, 79
 - from alkyl halides, 392
 - from Grignard reagents, 392
 - general formula of, 66
 - IR spectroscopy of, 337
 - isomers of, 67–68
 - mass spectrometry of, 322–323
 - melting points of, 79
 - naming, 68–69, 72–76
 - Newman projections of, 80
 - normal (*n*), **67**
 - pK_a of, 257
 - properties of, 78–79
 - reaction with chlorine, 78
 - sawhorse representations of, 80
 - straight-chain, **67**
- Alkene(s), **179**
 - alcohols from, 218–221, 443–444
 - aldehydes from, 231–232
 - allylic bromides from, 386–388
 - biological addition of radicals to, 240–241
 - biological epoxidation of, 228
 - biological hydration of, 218–219
 - biological reduction of, 226, 824–825
 - bond rotation in, 186–187
 - bromohydrins from, 217–218
 - bromonium ion from, 215
 - carbonyl compounds from, 231–232
 - carboxylic acids from, 232
 - cis–trans isomerism in, 187
 - cleavage of, 231–232
 - common names of, 184
 - cyclopropanes from, 233–235
 - 1,2-dihalides from, 214–216
 - 1,2-diols from, 229–230
 - electrophilic addition reactions of, 195–196
 - electrostatic potential map of, 61, 157
 - epoxides from, 227–228
 - E,Z* configuration of, 188–189
 - from alcohols, 213–214, 452–455
 - from aldehydes, 513–514
 - from alkyl halides, 213
 - from alkynes, 253
 - from amines, 660–661
 - from ketones, 513–514
 - general formula of, 180
 - halohydrins from, 217–218
 - heat of hydrogenation of, 193
 - hydration of, 218–221
 - hydroboration–oxidation of, 220–221
 - hydrogenation of, 223–226
 - hydroxylation of, 229–230
 - hyperconjugation in, 194
 - IR spectroscopy of, 338
 - ketones from, 231–232
 - Markovnikov's rule and, 198–199
 - naming, 183–184
 - nucleophilicity of, 157
 - organoboranes from, 220
 - oxymercuration–demercuration of, 219–220
 - pK_a of, 257
 - polymerization of, 236–238
 - reaction summary of, 212, 261–263
 - reaction with borane, 220
 - reaction with Br_2 , 214–216
 - reaction with carbenes, 233–235
 - reaction with Cl_2 , 214
 - reaction with dichlorocarbene, 233–235
 - reaction with H_3O^+ , 156–158, 196–197
 - reaction with HBr , 196
 - reaction with HCl , 196
 - reaction with HI , 196
 - reaction with hydrogen, 223–226
 - reaction with $KMnO_4$, 232
 - reaction with mercuric ion, 219
 - reaction with *N*-bromosuccinimide, 386–388
 - reaction with OsO_4 , 230

- Alkene(s) (*continued*)
 reaction with ozone, 231–232
 reaction with peroxyacids, 227
 reaction with radicals, 237–238
 reduction of, 223–226
 Sharpless epoxidation of, 527
 stability of, 191–194
 steric strain in *cis* isomer, 191–192
- Alkene polymer, table of, 239
- Alkenyl group, 185
- Alkoxide ion, **440**
- Alkoxy group, **465**
- Alkyl azide, amines from, 656
 reduction of, 656
- Alkyl group(s), **69–72**
 directing effect of, 297–298
 inductive effect of, 297
 naming, 70–71, 75–76
 orienting effect of, 299–300
- Alkyl halide(s), **383**
 alkenes from, 213
 amines from, 656
 amino acids from, 687
 bond lengths of, 384
 bond strengths of, 384
 carboxylic acids from, 541
 coupling reactions of, 393–395
 dehydrohalogenation of, 213
 dipole moments of, 384
 electrostatic potential map of, 61, 385
 ethers from, 466–467
 from alcohols, 390–391, 405, 414–415, 452
 from ethers, 468
 Grignard reagents from, 391
 malonic ester synthesis with, 611–613
 naming, 383–384
 phosphonium salts from, 513–514
 polarity of, 61
 polarizability of, 154
 reaction summary of, 433–434
 reaction with alcohols, 466–467
 reaction with amines, 656
 reaction with carboxylate ions, 565
 reaction with Gilman reagents, 393–394
 reaction with HS[−], 463
 reaction with magnesium, 391
 reaction with sulfides, 474
 reaction with thiols, 474
 reaction with thiourea, 463
 reaction with triphenylphosphine, 513–514
 synthesis of, 385–388
 thiols from, 463
 uses of, 382–383
- Alkyl shift, **207–208**
 carbocation rearrangements and, 207–208
- Alkylamine, **645**
 basicity of, 650
- Alkylation, **289**
 acetoacetic ester, 614–615
 acetylde anions and, 258
 aromatic compounds, 289–291
 biological example of, 619
 carbonyl compounds and, 610–619
 ester, 617
 ketone, 617–618
 lactone, 617
 malonic ester, 611–613
 nitrile, 618
- Alkylation (aromatic), 289–291
see also Friedel–Crafts reaction
- Alkylbenzene(s), from aryl alkyl ketones, 308
 side-chain oxidation of, 306
- Alkylthio group, **465**
- Alkyne(s), **179**
 acetylde anions from, 256–257
 acidity of, 256–258
 addition reactions of, 253
 alkenes from, 253
 electrophilic addition reactions of, 196
 electrostatic potential map of, 61
 hydration of, 254–256
 hydrogenation of, 253
 IR spectroscopy of, 338
 ketones from, 254–256
 mechanism of hydration of, 255
 naming, 185
 p*K*_a of, 257
 reaction with Br₂, 253
 reaction with Cl₂, 253
 reaction with HBr, 196, 253
 reaction with HCl, 253
 reaction with mercuric ion, 254–256
 reduction of, 253
 synthesis of, 258
 vinylic halides from, 253
- Alkynyl group, 185
- Allinger, Norman Louis, 111
- Allose, configuration of, 747
- Allyl aryl ether, Claisen rearrangement of, 471–472
- Allyl carbocation, electrostatic potential map of, 413
- Allyl group, **184**
- Allylic, **245**
 Allylic bromide, from alkenes, 386–388
 Allylic bromination, mechanism of, 386–388
 Allylic carbocation, electrostatic potential map of, 246
 resonance in, 245–246
 S_N1 reaction and, 413–414
 stability of, 245–246
- Allylic halide, S_N1 reaction and, 413
 S_N2 reaction and, 414
- Allylic radical, resonance in, 387
 stability of, 386–387
- Alpha amino acid, **682**
see also Amino acid
- Alpha anomer, **751**
- Alpha cleavage, alcohol mass spectrum and, 326, 477
 aldehyde mass spectrum and, 327, 525
 amine mass spectrum and, 326, 673
 ketone mass spectrum and, 327, 525
- Alpha helix (protein), molecular model of, 701
 secondary protein structure and, 700–701
- Alpha pinene, structure of, 179
- Alpha position (carbonyl compounds), **599**
 acidity of, 601
- Alpha-keto acid, amino acids from, 688
 reductive amination of, 688
 transamination of, 719–722
- Alpha-substitution reaction, **489, 599**
 alkylation and, 610–619
 carbonyl condensation reactions and, 622–623
 enolate ions and, 610–619
 enols and, 603
 mechanism of, 603
 summary of, 642–643
- Altrose, configuration of, 747
- Aluminum chloride, Friedel–Crafts reaction and, 292
- Amantadine, structure of, 112f
- Amide(s), **555**
 amines from, 586
 basicity of, 651
 carboxylic acids from, 584–585
 DCC in formation of, 568–569
 electrostatic potential map of, 561
 from acid anhydrides, 577
 from acid chlorides, 573–574
 from carboxylic acids, 568–569
 from esters, 582
 from nitriles, 545–546
 hydrolysis of, 584–585
 IR spectroscopy of, 592–593
 mechanism of hydrolysis of, 546, 584–585
 mechanism of reduction of, 586
 naming, 557
 natural occurrence of, 584
 nitriles from, 544–545
 NMR spectroscopy of, 593–594
 nucleophilic acyl substitution reactions of, 584–586
 peptide bond and, 690
 p*K*_a of, 608
 polarity of, 64
 reaction summary of, 598
 reaction with LiAlH₄, 586
 reaction with SOCl₂, 544–545
 reduction of, 586
 resonance in, 651
 restricted rotation in, 690
- Amidomalate synthesis (amino acids), **687**
- amine*, name ending for amines, 645
- Amine(s), **644**
 acidity of, 651
 acylation of, 659–660
 alkenes from, 660–661
 alpha cleavage of in mass spectrometry, 326
 azide synthesis of, 656
 basicity of, 649–653
 biological, 653–654
 carbonyl nucleophilic addition reactions of, 505–508
 chirality of, 137, 647–648
 conjugate addition reactions to enones, 519

- electrostatic potential map of, 64
 from aldehydes, 657–658
 from alkyl azides, 656
 from alkyl halides, 656
 from amides, 586
 from ketones, 657–658
 from lactams, 586
 from nitriles, 547
 Henderson–Hasselbalch equation and, 653–654
 heterocyclic, 646, 665–669
 Hofmann elimination of, 660–661
 hydrogen bonding in, 648
 IR spectroscopy of, 339, 672
 mass spectrometry of, 326, 673–674
 naming, 645–646
 occurrence of, 644
 odor of, 649
 polarity of, 61
 primary, **645**
 properties of, 648–649
 pyramidal inversion in, 647–648
 reaction summary of, 676–677
 reaction with acid anhydrides, 577
 reaction with acid chlorides, 573–574
 reaction with aldehydes, 505–508
 reaction with alkyl halides, 656
 reaction with carboxylic acids and DCC, 568–569
 reaction with enones, 519
 reaction with epoxides, 470
 reaction with esters, 582
 reaction with ketones, 505–508
 secondary, **645**
 S_N2 reactions of, 656
 structure of, 647
 synthesis of, 654–658
 tertiary, **645**
 uses of, 648
- Amino acid(s), 678**
 α -ketoglutarate from, 729
 abbreviations for, 680–681
 acetoacetate from, 729
 acetyl CoA from, 729
 acidic, 681
 amidomalonate synthesis of, 687
 amphiprotic behavior of, 679
 basic, 681
 biological precursors of, 732
 biosynthesis of, 731–734
 Boc protecting group for, 697
 C-terminal, **690**
 catabolism of, 719–723, 728–731
 catabolism of carbon chains in, 728–731
 chromatography of, 691–692
 configuration of, 683
 deamination of, 719–723
 electrophoresis of, 687
 enantioselective synthesis of, 688–689
 essential, **683**, 731–732
 esters of, 696
 from α -keto acids, 688
 from alkyl halides, 687
 fumarate from, 729
 glucogenic, 728–729
 Henderson–Hasselbalch equation and, 654, 684–685
 isoelectric points of, 680–681
 ketogenic, 728–729
 L configuration of, 683
 molecular weights of, 680–681
 N-terminal, **690**
 neutral, 680–681
 nonessential, **683**, 731–732
 nonprotein, 682
 oxaloacetate from, 729
 pK_a 's of, 680–681
 protecting groups for, 696–697
 pyruvate from, 729
 reaction summary of, 712–713
 reaction with di-*tert*-butyl dicarbonate, 697
 reaction with ninhydrin, 692
 succinyl CoA from, 729
 synthesis of, 687–689
 table of, 680–681
 titration curve of, 684–685
 transamination of, 719–722
 transimination of, 721
 zwitterion form of, 50, 679
- D-Amino-acid aminotransferase, function of, 714
 molecular model of, 714
- Amino acid analysis, 691–692
- Amino acid analyzer, **691**
- Amino group, **646**
 directing effect of, 297–298
 inductive effect of, 297
 orienting effect of, 300
 resonance effect of, 298
- Amino sugar, **762**
- p*-Aminobenzoic acid, molecular model of, 24
- Aminolysis (nucleophilic acyl substitution reaction), **561**
- Aminotransferase, function of, 719
- Ammonia, carbamoyl phosphate from, 724
 dipole moment of, 32
 electrostatic potential map of, 155
 elimination of in animals, 723
 hydrogen bond in, 54–55
 reaction with acid chlorides, 573–574
 reaction with carboxy phosphate, 724
 reaction with carboxylic acids and DCC, 568–569
 urea cycle and, 724
- Amobarbital, synthesis of, 640
- Amphetamine, synthesis of, 657
- Amphotericin B, structure and function of, 894
- Amplitude, **330**
- Amylase, specificity of, 703
 starch hydrolysis and, 774–775
- Amylopectin, structure of, 766
- Amylose, structure of, 766
- Anabolism, **715**
- Androgen, **840**
 function of, 840
- Androstenedione, structure and function of, 840
- Androsterone, structure and function of, 840
- ane, alkane name ending, 68–69
- Anesthetic, dental, 56–57
- Anethole, 1H NMR spectrum of, 482g
- Angle strain, **93**
- Angstrom, **4**
- Anhydride, *see* Acid anhydride
- Aniline, basicity of, 652–653
 electrostatic potential map of, 652
 from nitrobenzene, 287
 synthesis of, 287
- Anilinium ion, electrostatic potential map of, 652
- Anilinothiazolinone, Edman degradation and, 693–694
- Animal fat, **806**
- Anionic polymerization, 927
- Anisole, electrostatic potential map of, 554a
 molecular model of, 437
- Anomer, 750–751
 alpha, **751**
 beta, **751**
- Anomeric center, **751**
- Antarafacial geometry, **914**
- Anthracene, structure of, 279
- Anti conformation, **82**
- Anti periplanar geometry, **423**
 molecular model of, 424
- Anti stereochemistry, **215**
- Antiaromaticity, **272**
- Antibiotic, β -lactam, **594–595**
 cephalosporins, 595
 penicillins, 594–595
 sulfonamide, 287
- Antibonding molecular orbital, **20–21**
- Anticodon (tRNA), **862**
- Antigenic determinants, blood groups and, 769
- Antisense strand (DNA), **861**
- Arabinose, configuration of, 747
- Arachidic acid, structure of, 807
- Arachidonic acid, eicosanoids from, 827–828
 prostaglandins from, 240–241, 827–828
 radical reaction of, 151
 structure of, 807
- Arecoline, molecular model of, 65
- Arene(s), **267**
- Arene, electrostatic potential map of, 61
see also Aromatic compound
- Arginine, biosynthesis of, 727, 734
 from glutamate, 734
 ornithine from, 727
 structure and properties of, 681
 urea cycle and, 726–727
- Argininosuccinate, arginine from 727
 from citrulline, 726–727
 metabolism of, 434j
 urea cycle and, 726–727
- epi*-Aristolochene, biosynthesis of, 211i

- Aromatic compound(s), **265**
 alkylation of, 3 289–291
 biological hydroxylation of, 288–289
 bromination of, 282–284
 characteristics of, 272–273
 chlorination of, 285
 common names for, 266
 fluorination of, 284–285
 Friedel–Crafts acylation of, 292
 Friedel–Crafts alkylation of, 289–291
 halogenation of, 282–286
 hydrogenation of, 307
 iodination of, 285
 IR spectroscopy of, 338–339
 naming, 266–268
 nitration of, 286
 oxidation of, 306
 reaction summary of, 317–318
see also Aromaticity
 sulfonation of, 287
 trisubstituted, 308–313
- Aromatic electrophilic aromatic substitution reaction, mechanism of, 282–283
- Aromaticity, heterocycles and, 276–277
 Hückel $4n + 2$ rule and, 272–273
 imidazole and, 277
 ions and, 274–275
 naphthalene and, 279–280
 pyridine and, 276
 pyrimidine and, 276
 pyrrole and, 276–277
 requirements for, 272–273
- Arrow, fishhook, 148
see also Curved arrow
- Arsenic trioxide, LD₅₀ of, 25
- Aryl alkyl ketone, reduction of, 307–308
- Aryl allyl ether, Claisen rearrangement of, 471–472
- Aryl boronic acid, Suzuki–Miyaura reaction of, 394
- Aryl halide, S_N2 reaction and, 402–403
 Suzuki–Miyaura reaction of, 394
- Arylamine(s), **645**
 basicity of, 652–653
 electrophilic aromatic substitution of, 663–664
 from nitroarenes, 655
 resonance in, 652
 synthesis of, 287
- Ascorbic acid, *see* Vitamin C
- ase, enzyme name ending, 173, 704
- Asparagine, aspartate from, 730–731
 biosynthesis of, 733
 catabolism of, 730–731
 from aspartate, 733
 fumarate from, 730–731
 oxaloacetate from, 730–731
 structure and properties of, 680
- Aspartame, molecular model of, 27a
 structure of, 770
 sweetness of, 770
- Aspartate, asparagine from, 733
 biosynthesis of, 731
 catabolism of, 730–731
- from oxaloacetate, 724
 fumarate from, 730–731
 oxaloacetate from, 730–731
 reaction with citrulline, 726–727
- Aspartic acid, structure and properties of, 681
- Aspergillus terreus*, lovastatin from, 251
- Asphalt, composition of, 85
- Aspirin, history of, 314
 LD₅₀ of, 25
 molecular model of, 16
 synthesis of, 577
 toxicity of, 315
- Asymmetric center, **116**
- Atactic polymer, **928**
- ate, ester name ending, 556
- Atom, atomic number of, 4
 isotopes of, 4
 mass number of, 4
 orbitals in, 4–6
 quantum mechanical model of, 4–6
 size of, 4
 structure of, 3–4
- Atomic number (*Z*), **4**
- Atomic weight, **4**
- Atorvastatin, cholesterol levels and, 1–2, 849–850
 mechanism of action of, 2, 849–850
 molecular model of, 2, 849–850
 structure of, 2, 849–850
- ATP, *see* Adenosine triphosphate
- Atrazine, structure of, 25
 toxicity of, 25
- Atropine, structure proof of, 677h
- ATZ, *see* Anilinothiazolinone, 693–694
- Avian flu, 802
- Avian H5N1 virus, 802
- Axial bonds (cyclohexane), **99**
 drawing, 100
- Azulene, electrostatic potential map of, 318a
- β , *see* Beta
- Backbone (protein), **690**
- Backside displacement, S_N2 reaction and, 399–400
- Bacteriorhodopsin, function of, 319
 molecular model of, 319
- von Baeyer, Adolf, 93
- Baeyer strain theory, 93
- Bakelite, structure of, 939–940
- Banana, esters in, 578
- Barbiturates, history of, 639
 synthesis of, 640
- Base, Brønsted–Lowry, **42**
 Lewis, **50**
 organic, 49–50
 strengths of, 44–45
- Base pair (DNA), 855–856
 electrostatic potential maps of, 856
 hydrogen bonding in, 855–856
- Base peak (mass spectrum), **321**
- Basicity, alkylamines, 650
 amides, 651
 amines, 649–653
- arylamines, 652–653
 heterocyclic amines, 650
 nucleophilicity and, 403–404
- Basicity constant (*K_b*), **649**
- Beeswax, structure of, 806
- Benedict's test, 758
- Bent bond, cyclopropane, 95
- Benzaldehyde, electrophilic aromatic substitution of, 297, 300–301, 500
 IR spectrum of, 523
¹³C NMR absorptions of, 524
- Benzene, alkylation of, 289–291
 bond lengths in, 269
 bromination of, 282–284
 chlorination of, 285
 discovery of, 267
 electrostatic potential map of, 37, 270, 297
 fluorination of, 284–285
 Friedel–Crafts reactions of, 289–291
 heat of hydrogenation of, 269
 Hückel $4n + 2$ rule and, 272
 iodination of, 285
 molecular orbitals of, 271
 nitration of, 286
 reaction with Br₂, 282–284
 reaction with Cl₂, 285
 reaction with HNO₃, 286
 reaction with I₂, 285
 resonance in, 37, 270
 stability of, 269
 structure of, 268–271
 sulfonation of, 287
 toxicity of, 265
 UV absorption of, 345
- Benzenesulfonic acid, synthesis of, 287
- Benzilic acid rearrangement, 529g
- Benzoic acid, ¹³C NMR absorptions in, 549
 p*K_a* of, 535
 substituent effects on acidity of, 538–539
- Benzophenone, structure of, 494
- Benzoquinone, electrostatic potential map of, 459
- Benzoyl group, **494**
- Benzoyl peroxide, ethylene polymerization and, 237
- Benzo[a]pyrene, metabolism of, 230
 structure of, 279
- Benzyl ester, hydrogenolysis of, 696
- Benzyl group, **267**
- Benzylic carbocation, electrostatic potential map of, 413
 resonance in, 413
 S_N1 reaction and, 413–414
- Benzylic halide, S_N1 reaction and, 413
 S_N2 reaction and, 414
- Benzylic oxidation, biological example of, 306
- Benzylic radical, resonance in, 306
- Benzylic penicillin, discovery of, 594
 structure of, 878
- Berbamunine, biosynthesis of, 904, 904a
- Beta anomer, **751**
- Beta-blocker, function of, 470

- Beta carotene, structure of, 179, 829
UV spectrum of, 346
- Beta-diketone, Michael reactions and, 633
- Beta-keto acid, decarboxylation of, 612
- Beta-keto ester, alkylation of, 614–615
cyclic, 629–631
decarboxylation of, 630
Michael reactions and, 632–633
 pK_a of, 608
synthesis of, 627–631
- Beta lactam antibiotics, **594**–595
- Beta oxidation pathway, **815**–820
mechanism of, 815–820
steps in, 816
- Beta-pleated sheet (protein), molecular model of, 702
secondary protein structure and, 701–702
- Betaine, **513**
- Bextra, structure of, 318g
- Bicycloalkane, **109**
- Bimolecular, **399**
- Biodegradable polymers, 940–941
- Biological amine Henderson–Hasselbalch equation and, 653–654
protonation of, 653–654
- Biological carboxylic acid, dissociation of, 537–538
Henderson–Hasselbalch equation and, 537–538
- Biological epoxidation, mechanism of, 228
- Biological hydrolysis, thioester, 598j
- Biological mass spectrometry, 328–329
- Biological methylation reactions, 418–419
- Biological polymers, 235–236
- Biological reaction, alcohol dehydration, 214, 454–455
alcohol oxidation with NAD^+ , 458
aldehyde reduction, 446–447, 517
aldol reaction, 637–638
alkene epoxidation, 228
alkene halogenation, 216
alkene hydration, 218–219
alkene radical additions, 240–241
alkene reduction, 226, 824–825
amide formation, 588
amide hydrolysis, 585
aromatic hydroxylation, 288–289, 886–887, 890
aromatic iodination, 286
benzylic oxidation, 306
carbonyl condensation reactions, 637–639
carboxylation, 542
characteristics of, 173–175
Claisen condensation reaction, 638–639
Claisen rearrangement reaction, 472
comparison with laboratory reactions, 173–175
conjugate nucleophilic addition, 520
conventions for writing, 174, 197
Diels–Alder reaction, 251
E1cB reaction, 428, 782, 789
electrophilic aromatic substitution, 286
elimination reactions, 428
energy diagram of, 172
epoxidation, 842–843
epoxide opening, 230
ester hydrolysis, 581–582
fat hydrolysis, 581–582
Friedel–Crafts reaction, 292–293
halohydrin formation, 218
Hofmann elimination reaction, 661
ketone alkylation, 619
ketone halogenation, 604
ketone reduction, 446–447, 517
nucleophilic acyl substitution, 570–571
nucleophilic substitutions, 418–419
oxidation with FAD, 817–818
oxidation with NAD^+ , 458
protein hydrolysis, 585
radical addition, 151
reductive amination, 658
sigmatropic rearrangement, 922–923
 S_N1 reaction, 418–419
 S_N2 reaction, 418–419
thioester partial reduction, 588–589
- Bioprospecting, natural products and, 903
- Biosynthesis, acetyl CoA, 587–588
N-acetylglucosamine, 588
adenosine, 873–874
adrenaline, 418–419
alanine, 731
arginine, 727
asparagine, 733
aspartate, 731
carbamoyl phosphate, 724
cholesterol, 842–847
citrate, 708–709
clavulanic acid, 904b
D-galactose, 804b
D-mannose, 804b
1-deoxyxylulose 5-phosphate, 882
dopamine, 886–887
epinephrine, 418–419
erythromycin, 896–902
farnesyl diphosphate, 835–836
fatty acids, 820–825
geraniol, 418–419
geranyl diphosphate, 835–836
glucose, 794–800
glutamate, 731
glutamine, 733
indolmycin, 619
inosine, 874
isopentenyl diphosphate, 830–833
L-fucose, 804e
lanosterol, 842–847
leucine, 643j
limonene, 211i
linalyl diphosphate, 836
lovastatin, 251
methionine, 529g
mevaldehyde, 588–589
mevalonate, 830–833
morphine, 884–892
norcoclaurine, 888–889
norepinephrine, 306
nucleotides, 873–874
p-hydroxyphenylacetaldehyde, 888
phyloquinone, 293
polyketides, 894–895
porphobilinogen, 677h
proline, 658
prostaglandin H_2 , 151, 240–241
proteins, 861–863
pyridoxal phosphate, 879–884
reticuline, 889
ribonucleic acid, 859–861
salutaridine, 890–891
steroids, 842–847
terpenoids, 829–836
tetrapyrroles, 904a
thebaine, 892
thyroxine, 286
tyrosine, 454–455
vitamin K_1 , 293
- Biot, Jean Baptiste, 119
- Biotin, carboxylations with, 796–797, 823
function of, 796–797
mechanism of carboxylation with, 823
structure and function of, 707, 823
- bis*, name prefix, 587
- 1,3-Bisphosphoglycerate, from glyceraldehyde 3-phosphate, 780
- Block copolymer, **930**–931
synthesis of, 931
- Blood groups, antigenic determinants in, 769
compatibility of, 768
types of, 768
- Boc (*tert*-butoxycarbonyl amide), 697
amino acid protection with, 697
- Bond, covalent, **10**
 π , **15**
 σ , **11**
- Bond angle, **13**
- Bond dissociation energy (*D*), **166**
table of, 166
- Bond length, **11**
- Bond strength, **11**
- Bonding molecular orbital, **20**–21
- Borane, electrophilicity of, 220
reaction with alkenes, 220
- Boron trifluoride, electrostatic potential map of, 51, 156
- Branched-chain alkane, **67**
- Breathalyzer test, 478
- BRENDA enzyme database, 710
- Bridgehead atom, **108**
- Broadband-decoupled NMR, **361**
- Bromination (aromatic), 282–284
- Bromine, reaction with alkenes, 214–216
reaction with aromatic compounds, 282–284
reaction with carboxylic acids, 606
reaction with ketones, 604–605
- Bromo group, directing effect of, 297–298
- p*-Bromoacetophenone, molecular model of, 360
 ^{13}C NMR spectrum of, 359
symmetry plane in, 359–360
- Bromocyclohexane, molecular model of, 101
- Bromoethane, spin–spin splitting in, 371–372
 1H NMR spectrum of, 371

- Bromohydrin, **217**
 from alkenes, 217–218
 mechanism of formation of, 217
- Bromomethane, bond length of, 384
 bond strength of, 384
 dipole moment of, 384
 electrostatic potential map of, 155
- Bronium ion, **215**
 electrostatic potential map of, 216
 from alkenes, 215
- 2-Bromopropane, ¹H NMR spectrum of, 373
 spin–spin splitting in, 372–373
- N-Bromosuccinimide, reaction with alkenes, 386–388
- Brønsted–Lowry acid, **42**
 conjugate base of, **43**
 strengths of, 44–45
- Brønsted–Lowry base, **42**
 conjugate acid of, **43**
 strengths of, 44–45
- Bupivacaine, structure of, 57
- cis-But-2-ene, heat of hydrogenation of, 193
 molecular model of, 187, 192
 steric strain in, 191–192
- trans-But-2-ene, heat of hydrogenation of, 193
 molecular model of, 187, 192
- But-3-en-2-one, electrostatic potential map of, 519
 UV absorption of, 345
- Buta-1,3-diene, 1,2 addition reactions of, 245–246
 1,4 addition reactions of, 245–246
 electrophilic addition reactions of, 245–246
 electrostatic potential map of, 244
 heat of hydrogenation of, 242
 molecular orbitals of, 243–244, 906
 reaction with HBr, 245–246
 stability of, 242–245
 UV spectrum of, 344
- Butan-1-ol, mass spectrum of, 477
- Butan-2-one, ¹³C NMR absorptions of, 359, 524
- Butane, anti conformation of, 82
 bond rotation in, 82–83
 conformations of, 82–83
 gauche conformation of, 82
 molecular model of, 67
- Butanoic acid, IR spectrum of, 549
- tert-Butoxycarbonyl amide, amino acid derivatives with, 697
- Butter, composition of, 807
- tert-Butyl alcohol, pK_a of, 440
- tert-Butyl carbocation, molecular model of, 201
- Butyl group, 71
- tert-Butyl group, 71
- Butyl rubber polymer, structure and uses of, 931
- Butyllithium, electrostatic potential map of, 393
 reaction with alkyltriphenylphosphonium salts, 514
 reaction with diisopropylamine, 608
- c (Speed of light), 330
- C-terminal amino acid, **690**
- C-terminal domain of spider dragline silk protein, molecular model of, 925
- Cadaverine, odor of, 649
- Caffeine, structure of, 27f
- Cahn–Ingold–Prelog sequence rules, **122–125**
 alkenes and, 188–189
 enantiomers and, 122–125
- Camphor, molecular model of, 110
 specific rotation of, 120
 structure of, 110, 829
- Cannizzaro reaction, **516–517**
 mechanism of, 517
- Caprolactam, nylon 6 from, 932
- Capsaicin, structure of, 65
- carbaldehyde, aldehyde name ending, 493
- Carbamic acid, 934
- Carbamoyl phosphate, biosynthesis of, 724
- Carbanion, **392**
 stability of, 257
- Carbene, **233**
 reaction with alkenes, 233–235
- Carbinolamine, **506**
- Carbocaine, structure of, 57
- Carbocation, **158**
 alkyl shift in, 207–208
 aromatic substitution and, 282–283
 E1 reaction and, 427
 electronic structure of, 201
 electrophilic addition reactions and, 158, 195–199
 electrostatic potential maps of, 202
 Friedel–Crafts reaction and, 291
 Hammond postulate and, 204–206
 hydride shift in, 206–208
 hyperconjugation in, 202–203
 Markovnikov's rule and, 198–199
 molecular orbital of, 203
 rearrangements of, 206–208, 291
 solvation of, 416
 stability of, 201–203, 413
 steroid biosynthesis and, 843–847
- Carbohydrate, **738**
 anomers of, 750–751
 catabolism of, 776–782
 classification of, 740
 complex, **739**
 Fischer projection of, 743, 747
 glycosides of, 755
 1→4-links in, 763
 origin of name, 738
 photosynthesis of, 739
 reaction summary of, 772
see also Aldose, Monosaccharide
- carbonitrile, nitrile name ending, 533
- Carbonyl chemistry, overview of, 483–491
- Carbonyl compound(s), acidity of, 607–608
 alcohols from, 445–451
 alkylation of, 610–619
 classification of, 484
 electrophilicity of, 485
 electrostatic potential map of, 64, 155
 from alcohols, 456–458
 general reactions of, 485–490
 IR spectroscopy of, 339–340
 kinds of, 64, 483–484
 mass spectrometry of, 326–327
 name endings for, 484
 polarity of, 64
- Carbonyl condensation reaction, **490, 599**
 α-substitution reactions and, 622–623
 biological examples of, 637–639
 mechanism of, 620
- Carbonyl group, **483**
 directing effect of, 297–298
 inductive effect of, 297
 orienting effect of, 300–301
 resonance effect of, 298
- carbothioate, thioester name ending, 557
- carboxamide, amide name ending, 557
- Carboxy phosphate, reaction with ammonia, 724
- Carboxyl group, **532**
- Carboxylate ion, reaction with acid chlorides, 572
 reaction with alkyl halides, 565
 resonance in, 535–536
- Carboxylation, **541**
 biological example of, 542
- carboxylic acid, name ending for carboxylic acids, 531
- Carboxylic acid(s), **530**
 α bromination of, 606
 acid anhydrides from, 565
 acid chlorides from, 564
 acidity of, 534–535
 alcohols from, 447, 569
 amides from, 568–569
 biological, 537–538
 biological nucleophilic acyl substitutions of, 570–571
 common names of, 532
 dimers of, 534
 dissociation of, 534
 esters from, 565–567
 from acid halides, 570–572
 from alcohols, 456–458
 from aldehydes, 497
 from alkenes, 232
 from alkyl halides, 541, 611–613
 from amides, 584–585
 from esters, 579–582
 from Grignard reagents, 541
 from malonic ester synthesis, 611–613
 from nitriles, 541, 545–546
 Henderson–Hasselbalch equation and, 537–538
 hydrogen bonding in, 533–534
 inductive effects in, 538
 IR spectroscopy of, 548–549
 naming, 531–532
 NMR spectroscopy of, 549
 nucleophilic acyl substitution reactions of, 564–570
 occurrence of, 530–531
 pK_a table of, 535

- polarity of, 64
 properties of, 533–536
 reaction summary of, 553, 596–597
 reaction with alcohols, 565–567
 reaction with amines and DCC, 568–569
 reaction with ammonia and DCC, 568–569
 reaction with Br₂, 606
 reaction with diazomethane, 598h
 reaction with Grignard reagents, 450
 reaction with LiAlH₄, 447, 569
 reaction with SOCl₂, 564
 reduction of, 447, 569
 substituent effects on acidity of, 538–539
 synthesis of, 540–541
- Carboxylic acid derivative(s), **555**
 electrostatic potential maps of, 561
 interconversions of, 561
 IR spectroscopy of, 592–593
 kinds of, 555
 naming, 556–558
 NMR spectroscopy of, 593–594
 nucleophilic acyl substitution reactions of, 561–562
 polarity of, 561
 relative reactivity of, 560–561
- Cardiolipin, structure of, 851b
- Carvone, structure of, 23
- Catabolism, **715**
 acetyl CoA, 787–792
 amino acids, 719–723, 728–731
 carbohydrates, 776–782
 fats, 813–820
 fatty acids, 815–820
 glucose, 776–782
 glycerol, 815
 guanosine, 871–873
 nucleic acids, 871–873
 pyruvate, 783–787
 stages of, 715–716
 triacylglycerols, 813–820
- Catalytic cracking, 86
- Catalytic hydrogenation, *see* Hydrogenation
- Cation radical, mass spectrometry 320
- Cationic polymerization, 926
- Celebrex, *see* Celecoxib
- Celecoxib, structure of, 315
- Cell membrane, lipid bilayer in, 812
- Cellobiose, molecular model of, 763
 mutarotation of, 763
- Cellulose, function of, 765
 structure of, 765
 uses of, 765
- Cellulose nitrate, 765
- Cephalexin, structure of, 145g, 595
- Cephalosporin, mechanism of action of, 595
 structure of, 595
- Chain, Ernst, 594
- Chain-growth polymer, **237, 926–927**
- Chain reaction (radical reaction), **150**
- Chair conformation (cyclohexane), **97–98**
 drawing, 98
 molecular model of, 98
see also Cyclohexane
- Chemical Abstracts*, 59
- Chemical equations, conventions for writing, 196
- Chemical shift (NMR), **356**
 factors determining, 358–359
¹³C NMR spectroscopy and, 358–359
¹H NMR spectroscopy and, 368–369
- Chemical structure, drawing, 21–22
- Chiral, **115**
- Chiral drugs, 143–144
- Chiral environment, **143**
- Chiral methyl group, 434k
- Chirality, amines and, 137, 647–648
 amino acids and, 683
 carbohydrates and, 746–747
 cause of, 116–117
 naturally occurring molecules and, 141–143
 phosphines and, 137, 689
 sulfonium salts and, 137–138
- Chirality center, **116**
 detection of, 116–117
R,S configuration of, 122–125
- Chloramphenicol, structure of, 145h
- Chlorination (aromatic), 285
- Chlorine, reaction with alkanes, 78
 reaction with alkenes, 214
 reaction with aromatic compounds, 285
 reaction with methane, 149–150
- Chloro group, directing effect of, 297–298
- Chlorobenzene, electrostatic potential map of, 297
- Chloroform, LD₅₀ of, 25
- Chloromethane, bond length of, 384
 bond strength of, 384
 dipole moment of, 32, 384
 electrostatic potential map of, 152
 natural sources of, 382
- Chloronium ion, **215**
p-Chlorophenol, pK_a of, 440
- Chlorosulfite, leaving group ability of, 405
- Chlorotrimethylsilane, alcohol protection with, 461–462
 molecular model of, 462
- Cholecalciferol, structure of, 923
- Cholesterol, structure of, 129
- Cholesterol, amount of in body, 1
 biosynthesis of, 842–847
 coronary heart disease and, 1–2, 849–850
 molecular model of, 839
 specific rotation of, 120
- Cholic acid, molecular model of, 531
 structure of, 851
 synthesis of, 677g
- Chorismate mutase, function of, 905
 molecular model of, 905
- Chromatography, ion-exchange, 691–692
- Chrysanthemic acid, structure of, 87
- Chymotrypsin, peptide cleavage with, 695
- trans*-Cinnamaldehyde, ¹H NMR spectrum of, 377
 tree diagram for, 378
- cis–trans isomers, **92**
 alkenes and, 187
 cycloalkanes and, 91–92
 requirements for, 187
- Citaneast, structure of, 57
 biosynthesis of, 708–709, 789
 isocitrate from, 789
- Citrate synthase, active site in, 708
 function of, 678, 707–708
 mechanism of, 708–709
 molecular model of, 678, 708
- Citric acid, molecular model of, 27
- Citric acid cycle, **787–792**
 requirements for, 787
 result of, 792
 steps in, 788
- Citrulline, argininosuccinate from, 726–727
 from ornithine, 725–726
 reaction with aspartate, 726–727
- Claisen condensation reaction, **627–629**
 acetyl CoA and, 830
 β-oxidation and, 819
 biological example of, 638–639
 fatty acid biosynthesis and, 638–639, 824
 intramolecular, 629–631
 mechanism of, 627–628
- Claisen rearrangement reaction, **471–472, 920–921**
 biological example of, 472
 mechanism of, 471–472
 suprafacial geometry of, 920–921
- Claritin, structure of, 211b
- Clavulanic acid, biosynthesis of, 904b
- Clomiphene, structure of, 211e
- Clopidogrel, structure of, 27f
- Coca-Cola, cocaine in, 57
- Cocaine, specific rotation of, 120
 structure of, 57, 120, 644
 synthesis of, 643l
- Coconut oil, composition of, 807
- Codeine, structure of, 885
- Coding strand (DNA), **861**
- CODIS DNA registry, 875
- Codon (mRNA), **861**
 table of, 862
- Coenzyme, **175, 705–707**
 function of, 705–707
 table of, 706–707
- Coenzyme A, *see* Acetyl CoA
 structure and function of, 588, 706
- Coenzyme Q, **460**
- Cofactor (enzyme), **705–707**
- Color, perception of, 346–347
 UV spectroscopy and, 346–347
- Common cold, vitamin C and, 551
- Complex carbohydrate, **739**
 biological hydrolysis of, 774–775
- Concanavalin A, β sheet in, 702
 ribbon model of, 702
- Concerted reaction, **905**
- Condensed structure, **21–22**
 rules for drawing, 22
- Cone cells, vision and, 347

- Configuration, **122**
 assignment of, 123–124
 chirality centers and, 122–125
 Fischer projections and, 742
 inversion of, 396–397
R, **123**
S, **123**
- Conformation, **80**
 calculating energy of, 111
- Conformational analysis (cyclohexane),
 105–106
- Conformational isomers, **80**
- Conformer, **80**
- Coniine, molecular model of, 27
 structure of, 118
- Conjugate acid, **43**
- Conjugate base, **43**
- Conjugate nucleophilic addition reaction,
518–521
 biological, 520
 mechanism of, 518–519
 Michael reactions and, 632–633
- Conjugated diene, 1,2 addition reactions of,
 245–246
 1,4 addition reactions of, 245–246
 allylic carbocations from, 245
 Diels–Alder reactions of, 247–251
 electrocyclic reactions of, 908–909
 electrophilic addition reactions of,
 245–246
 electrostatic potential map of, 244
 heats of hydrogenation of, 242
 molecular orbitals in, 243–244
 polymers of, 259
 reaction with HBr, 245–246
s-cis conformation of, 249–250
 stability of, 242–245
- Conjugated polyene, electrocyclic reactions
 of, 908–909
 molecular orbitals of, 906–907
- Conjugated triene, electrocyclic reactions of,
 908–909
- Conjugation, **241**
 ultraviolet spectroscopy and, 345
- Conrotatory motion, **909**
- Consensus sequence (DNA), 860
- Constitutional isomers, **67**
 kinds of, 67–68
- Contraceptive, steroid, 841
- Cope rearrangement, **920–921**
 suprafacial geometry of, 920–921
- Copolymer, **930–932**
 block, **930–931**
 graft, **930–932**
 table of, 931
- Copper(II) chloride, aromatic iodination
 and, 285
- Coprostanol, structure of, 129
- Corn oil, composition of, 807
- Coronary heart disease, atorvastatin and, 2,
 849–850
 cholesterol and, 1–2, 849–850
- Coronene, structure of, 279
- Cortisone, structure of, 88
- Coupled reactions, ATP and, 718
 explanation of, 717–718
- Coupling (NMR), **371–373**
see also Spin–spin splitting
- Coupling constant (NMR), **373**
 size of, 373
 use of, 373
- Covalent bond, molecular orbital theory of,
 20–21
 polar, **28–29**
 valence bond theory of, 10–19
- COX enzymes, eicosanoid biosynthesis and,
 827
- COX-2 Inhibitors, 315
- Crestor, mechanism of action of, 2, 849–850
- Crick, Francis, 855
- Crotonaldehyde, structure of, 493
- Crotonic acid, ¹³C NMR absorptions in, 549
- Crown ether, **472–473**
 electrostatic potential map of, 473
 metal-ion complexation by, 473
 naming, 472
 S_N2 reactions and, 473
- Crystallite (polymer), **937**
- Curved arrow, electron movement and, 38,
 50–51, 154, 159–161
 guidelines for using, 159–161
 Lewis acids and, 50–51
 polar reactions and, 154, 159–161
- Cyanocobalamin, structure of, 848
- Cyanocycline A, structure of, 544
- Cyanogenic glycoside, **544**
 function of, 544
- Cyclic metabolic pathways, reasons for,
 792–793
- Cycloaddition reaction, **247, 913–914**
 antarafacial geometry of, 914–916
 cyclobutane synthesis and, 915–916
 photochemical, 915–916
see also Diels–Alder reaction
 stereochemical rules for, 916
 stereochemistry of, 914–916
 suprafacial geometry of, 914–916
 thermal, 915–916
- Cycloalkane(s), **88**
 angle strain in, 93–94
 Baeyer strain theory and, 93
 cis–trans isomerism in, 91–92
 naming, 88–90
 representation of, 88
 strain energies of, 94
- Cycloalkene, naming, 184
- Cyclobutadiene, antiaromaticity of, 272
 electrostatic potential map of, 272
 Hückel 4*n* + 2 rule and, 272
- Cyclobutane, angle strain in, 96
 conformation of, 96
 molecular model of, 96
 photochemical synthesis of, 915–916
 strain energy of, 94
 torsional strain in, 96
- Cyclobutanone, IR absorption of, 522
- Cyclodecane, strain energy of, 94
- Cyclodecapentaene, molecular model of, 273
- Cycloheptane, strain energy of, 94
- Cycloheptatrienyl cation, aromaticity of,
 274–275
 electrostatic potential map of, 275
- Cyclohexa-1,3-diene, heat of hydrogenation
 of, 269
 UV absorption of, 345
- Cyclohexane, axial bonds in, 99–101
 barrier to ring flip in, 101, 354–355
 chair conformation of, 97–98
 conformational analysis of, 105–106
 1,3-diaxial interactions in, 103–104
 drawing chair form of, 98
 E2 reactions and, 425
 equatorial bonds in, 99–101
 IR spectrum of, 349d
 ring-flip in, 101
 strain energy of, 94
 twist-boat conformation of, **98–99**
- Cyclohexanol, IR spectrum of, 475
¹³C NMR spectrum of, 476
- Cyclohexanone, aldol reaction of, 621
 enol content of, 600–601
 enolate ion of, 608
 IR spectrum of, 523
¹³C NMR absorptions of, 524
- Cyclohexene, heat of hydrogenation of, 269
 IR spectrum of, 349d
- Cyclohexenones, from 1,5-diketones,
 626–627
- Cyclohexylamine, IR spectrum of, 672
- Cyclohexylmethanol, ¹H NMR spectrum of,
 379
- Cyclononane, strain energy of, 94
- Cyclooctane, strain energy of, 94
- Cyclooctatetraene, electrostatic potential
 map of, 273
 Hückel 4*n* + 2 rule and, 273
 reactivity of, 273
- Cyclooctatetraene dianion, aromaticity of,
 276
- Cycloooxygenases, eicosanoid biosynthesis
 and, 827
- Cyclopenta-1,3-diene, electrostatic potential
 map of, 666
- Cyclopentadienyl anion, aromaticity of,
 274–275
 electrostatic potential map of, 275
- Cyclopentane, angle strain in, 96
 conformation of, 96
 molecular model of, 96
 strain energy of, 94
 torsional strain in, 96
- Cyclopentanone, IR absorption of, 522
- Cyclopentenones, from 1,4-diketones,
 626–627
- Cyclopropane, angle strain in, 95
 bent bonds in, 95
 bond strength in, 95
 from alkenes, 233–235
 molecular model of, 91, 95
 strain energy of, 94
 torsional strain in, 95
- Cystathionine, cysteine from, 737b

- Cysteine, biosynthesis of, 737b
 disulfide bridges from, 691
 structure and properties of, 680
- Cytochrome P450, function of, 890
- Cytosine, electrostatic potential map of, 856
 molecular model of, 58b
 protection of, 867
 structure of, 853
- D* (Bond dissociation energy), **166**
- D* (Debye), **31**
- D* configuration, **745**
- Dacron, structure of, 591
- Dalton, unit for atomic mass, 329
- Darzens reaction, 6431
- DCC, peptide synthesis with, 696
see also Dicyclohexylcarbodiimide
- Deactivating group (aromatic substitution), **296**
 acidity and, 539
 explanation of, 297–298
- Deamination, **719**
 amino acids and, 719–723
 mechanism of, 719–722
 pyridoxal phosphate and, 719–721
- Debye (*D*), **31**
- cis*-Decalin, conformation of, 108–109
 molecular model of, 109, 838
- trans*-Decalin, conformation of, 108–109
 molecular model of, 109, 838
- Decane, molecular model of, 84
- Decarboxylation, **612**
 acetoacetic ester synthesis and, 615
 malonic ester synthesis and, 612
 oxidative, 784–787, 790
 thiamin diphosphate and, 785–786
- DEET, structure of, 598h
- Degenerate orbitals, **271**
- Degree of unsaturation, **181**
 calculation of, 181–182
- Dehydratase domain (DH), polyketide synthase and, 895
- Dehydration, **213**
 alcohol mass spectrum and, 477
 alcohols and, 213–214, 452–455
 aldol reaction and, 623–625
 biological example of, 214, 454–455
- 7-Dehydrocholesterol, vitamin D from, 923
- Dehydrohalogenation, **213**
- Delocalization (electron), 244–245
- Delta scale (NMR), **356**
- Denature (protein), **702**
- Deoxy sugar, **762**
- 6-Deoxyerythronolide B, biosynthesis of, 898–901
- 6-Deoxyerythronolide B synthase (DEBS), domains in, 897
 domains in, 895
 modules in, 895
 size of, 895
- Deoxyribonucleic acid (DNA), **852–855**
 antisense strand of, 861
 base-pairing in, 855–856
 bases in, 853
 cleavage of, 864
 coding strand of, 861
 consensus sequences in, 860
 double helix in, 855–856
 3' end of, 855
 5' end of, 855
 exons in, 861
 fingerprinting with, 875–876
 hydrogen bonds in, 55
 introns in, 861
 major groove in, 856–857
 minor groove in, 856–857
 molecular model of, 857
 noncoding strand of, 861
 polymerase chain reaction and, 869–870
 promotor sequences in, 860
 replication fork in, 858
 replication of, 858–859
 sense strand of, 861
 sequencing of, 864–866
 size of, 854
 structure(s) of, 854–855
 synthesis of, 866–869
 transcription of, 859–861
 Watson–Crick model of, 855–856
- 2'-Deoxyribose, structure of, 853
- 1-Deoxyxylulose 5-phosphate, biosynthesis of, 882
 isopentenyl diphosphate from, 830
- DEPT-NMR, **361–363**
 uses of, 361–362
- DEPT-NMR spectrum, 6-methylhept-5-en-2-ol, 362
- Dermabond, structure of, 927
- Dess–Martin periodinane, alcohol oxidation with, 457–458
- Detergent, structure of, 811
- Deuterium isotope effect, **423**
 E1 reaction and, 428
 E2 reaction and, 423
- Dewar benzene, 924d
- Dextromethorphan, structure of, 118
- Dextrorotatory, **119**
- Dialkyl phthalates, as plasticizers, 579
- Dialkylamine, pK_a of, 608
- Diastereomers, **128**
 kinds of, 135–136
- Diastereotopic (NMR), **367**
 1,3-Diaxial interactions, **103–104**
 table of, 104
- Diazepam, structure of, 182
- Diazomethane, reaction with carboxylic acids, 598h
- DIBAH, *see* Diisobutylaluminum hydride
- Dibromophosphite, leaving group ability of, 405
- Dichlorocarbene, electrostatic potential map of, 234
 formation of, 234
 reaction with alkenes, 233–235
- cis*-1,2-Dichloroethylene, electrostatic potential map of, 58a
- trans*-1,2-Dichloroethylene, electrostatic potential map of, 58a
- Dicyclohexylcarbodiimide (DCC), amide bond formation with, 568–569
 peptide bond formation with, 696
- Dideoxy DNA sequencing, **865–866**
- 2',3'-Dideoxyribonucleotide, 865
- Dieckmann cyclization, **629–631**
 mechanism of, 630–631
- Diels–Alder cycloaddition reaction, **247**
 biological example of, 251
 dienophiles in, 248–249
 HOMO in, 915–916
 LUMO in, 915–916
 mechanism of, 248
s-cis diene conformation in, 249–250
 stereochemistry of, 249, 915–916
 suprafacial geometry of, 915–916
- Diene, electrophilic addition reactions of, 245–246
 polymers of, 259
- Dienophile, **248**
 electrostatic potential maps of, 249
 requirements of, 248–249
- Diethyl ether, molecular model of, 437
 synthesis of, 466
 uses of, 436
- Diethyl malonate, alkylation of, 611–613
 carboxylic acids from, 611–613
 Michael reactions and, 633
 pK_a of, 608
see also Malonic ester synthesis
- Diethyl propanedioate, *see* Diethyl malonate
- Diffraction limit, light waves and, 348
- Digestion, **716**
 carbohydrates, 766–767, 774–775
 fats, 813–815
 starch, 766–767
- Digitoxin, structure of, 755
- Dihedral angle, **81**
- Dihydrogen phosphate ion, pK_a of, 45
- Dihydroliipoamide, oxidation by FAD, 786–787
- Dihydroxyacetone phosphate, from glycerol, 815
 fructose 1,6-bisphosphate from, 798–799
 isomerization of, 780
- Diisobutylaluminum hydride, reaction with esters, 583
 structure of, 495
- Diisopropylamine, pK_a of, 608, 651
 reaction with butyllithium, 608
- 1,3-Diketone, pK_a of, 608
- Dimethyl ether, electrostatic potential map of, 51, 465
- Dimethyl sulfide, bond angle in, 19
 molecular model of, 19
 sp^3 hybrid orbitals in, 19
 structure of, 19
- Dimethyl sulfoxide (DMSO), electrostatic potential map of, 34
 formal charges in, 33–35
 skin penetration by, 475
 S_N2 reaction and, 407

- Dimethylallyl diphosphate, from isopentenyl diphosphate, 834
terpenoids from, 834–836
- Dimethylamine, electrostatic potential map of, 648
- cis*-1,2-Dimethylcyclohexane, conformational analysis of, 105–106
- trans*-1,2-Dimethylcyclohexane, conformational analysis of, 105–106
- cis*-1,2-Dimethylcyclopropane, molecular model of, 91
- trans*-1,2-Dimethylcyclopropane, molecular model of, 91
- Dimethylformamide (DMF), S_N2 reaction and, 407
- 2,2-Dimethylpropane, mass spectrum of, 322
molecular model of, 67
- N,N*-Dimethyltryptamine, electrostatic potential map, 671
- 1,2-Diol, **229**
cleavage of with HIO₄, 232
from alkenes, 229–230
from epoxides, 229
- Diovan, synthesis of, 394
- DIPAMP ligand, amino acid synthesis and, 689
- Dipole moment (μ), **31**
polar covalent bonds and, 31–32
table of, 32
- Dipole–dipole forces, **54**
- Disaccharide, **762–765**
1→4-link in, 763
synthesis of, 767–768
- Dispersion forces, **54**
alkanes and, 79
- Disrotatory motion, **909**
- Distortionless enhancement by polarization transfer, *see* DEPT-NMR
- Disulfide, **463**
electrostatic potential map of, 64
from thiols, 463
polarity of, 61
reduction of, 463
thiols from, 463
- Disulfide bridge, peptides and, 691
- Diterpene, **210**
- Diterpenoid, **829**
- DMAPP, *see* Dimethylallyl diphosphate
- DMF, *see* Dimethylformamide
- DMSO, *see* Dimethyl sulfoxide
- DMT protecting group (dimethoxytrityl ether), 867
- DNA fingerprinting, 875–876
reliability of, 875–876
STR loci and, 875–876
- DNA polymerase, function of, 865
- DNA, *see* Deoxyribonucleic acid
- Dopamine, benzylic oxidation of, 306
biosynthesis of, 886–887
molecular model of, 656
norepinephrine from, 306
- Double bond, electronic structure of, 15
length of, 15
molecular orbitals in, 21
see also Alkene
strength of, 15
- Double helix (DNA), **855–856**
- Doublet (NMR), 373
- Downfield (NMR), **355**
- Doxorubicin, structure and function of, 894
- Drugs, approval procedure for, 176–177
chiral, 143–144
origin of, 176
- E* configuration, **189**
assignment of, 188–189
- E1 reaction, **421**, 427–428
deuterium isotope effect and, 428
kinetics of, 427
mechanism of, 427–428
rate-limiting step in, 427
stereochemistry of, 428
- E1cB reaction, **421**, 428
biological example of, 428
carbanion intermediate in, 428
mechanism of, 428
rate-limiting step in, 428
requirements for, 428
- E2 reaction, **421**, 422–425
alcohol oxidation and, 457–458
cyclohexane conformation and, 425
deuterium isotope effect and, 423
kinetics of, 422–423
mechanism of, 422–423
periplanar geometry of, 423–424
rate law for, 422
rate-limiting step in, 423
stereochemistry of, 424–425
- E90 automobile fuel, 436, 478
- Ebonite, structure of, 259
- Eclipsed conformation, **80**
molecular model of, 80
- Edman degradation, **693–695**
mechanism of, 693–694
- Eicosanoid, **827–828**
biosynthesis of, 827–828
naming, 827
- Elaidic acid, structure of, 809
- Elastomer, **939**
characteristics of, 939
cross links in, 939
*T*_g of, 939
- Electrocyclic reaction, **908–909**
conrotatory motion in, 909
disrotatory motion in, 909
examples of, 908–909
HOMO and, 910–912
photochemical, 912
stereochemical rules for, 912
stereochemistry of, 910–912
thermal, 910–911
- Electromagnetic radiation, **329**
amplitude of, 330
characteristics of, 330
energy of, 331
frequency of, 330
kinds of, 330
speed of, 330
wavelength of, 330
- Electromagnetic spectrum, **329**
regions in, 330
- Electron, delocalization of, 244–245
lone-pair, **9**
nonbonding, **9**
orbitals and, 4–6
- Electron-impact mass spectrometry, 320–321
- Electron movement, curved arrows and, 38, 50–51, 154, 159–161
- Electron-transport chain, **716**
- Electronegativity, **29**
inductive effects and, 30
polar covalent bonds and, 29–30
table of, 29
- Electrophile, **154–155**
characteristics of, 159–160
curved arrows and, 154, 159–161
electrostatic potential maps of, 155
examples of, 155
- Electrophilic addition reaction, **195–196**
carbocation rearrangements in, 206–208
energy diagram of, 168–169
Hammond postulate and, 204–206
intermediate in, 170–171
Markovnikov's rule and, 198–199
mechanism of, 157–158, 195–196
regiospecificity of, 198–199
- Electrophilic aromatic substitution reaction, **281–282**
arylamines and, 663–664
biological example of, 286
inductive effects in, 297–298
kinds of, 282
pyridine and, 668
pyrrole and, 667
resonance effects in, 298
substituent effects in, 295–302
- Electrophoresis, **687**
DNA sequencing and, 866
- Electrospray ionization mass spectrometry, *see* ESI mass spectrometry
- Electrostatic potential map, **30**
acetaldehyde, 485
acetamide, 561, 598b, 651
acetate ion, 36, 46, 49, 536
acetic acid, 46, 48
acetic acid dimer, 534
acetic anhydride, 561
acetone, 48, 49, 64, 491
acetone anion, 49
acetonitrile, 545
acetyl azide, 598b
acetyl chloride, 491, 561
acetylidene anion, 257
acid anhydride, 561
acid chloride, 561
acyl cation, 292
adenine, 856
alanine, 679
alcohol, 61
alkene, 61, 157

- alkyl halide, 61, 385
 alkyne, 61
 allylic carbocation, 246, 413
 amide, 561
 amine, 64
 ammonia, 155
 aniline, 652
 anilinium ion, 652
 anisole, 554a
 arene, 61
 azulene, 318a
 benzaldehyde, 297, 500
 benzene, 37, 270, 297
 benzoquinone, 459
 benzyl carbocation, 413
 boron trifluoride, 51, 156
 bromomethane, 155
 bromonium ion, 216
 but-3-en-2-one, 519
 buta-1,3-diene, 244
 butyllithium, 393
 carbocations, 202
 carbonyl compound, 64, 155
 carboxylic acid derivatives, 561
 chlorobenzene, 297
 chloromethane, 152
 conjugated diene, 244
 crown ether, 473
 cyclobutadiene, 272
 cycloheptatrienyl cation, 275
 cyclooctatetraene, 273
 cyclopenta-1,3-diene, 666
 cyclopentadienyl anion, 275
 cytosine, 856
 dichlorocarbene, 234
cis-1,2-dichloroethylene, 58a
trans-1,2-dichloroethylene, 58a
 dienophiles, 249
 dimethyl ether, 51, 465
 dimethyl sulfoxide, 34
 dimethylamine, 648
N,N-dimethyltryptamine, 671
 disulfide, 64
 DNA base pairs, 856
 electrophiles, 155
 enamine, 635
 enol, 600, 603
 enolate ion, 607, 610
 ester, 561
 ethane, 157
 ether, 61
 ethoxide ion, 536
 ethylene, 60, 157, 249
 formaldehyde, 178a, 500
 formate ion, 536
 Grignard reagent, 392
 guanine, 856
 histidine, 683
 HOSO₂⁺, 287
 hydrogen bond, 55, 439
 hydronium ion, 155
 hydroxide ion, 46, 155
 imidazole, 53, 277
 menthene, 60
 methanethiol, 178a
 methanol, 30, 48, 49, 153, 439
 methoxide ion, 49, 442
 methyl acetate, 561
 methyl anion, 257
 methyl thioacetate, 561
 9-methyladenine, 876a
 methylamine, 31, 49, 651
 9-methylguanine, 876a
 methyllithium, 30, 152
 methylmagnesium iodide, 392
 naphthalene, 280
 nitronium ion, 286
 nucleophiles, 155
 organophosphate, 61
 penta-1,4-diene, 244
 phenol, 297
 phenoxide ion, 442
 polar covalent bonds and, 30
 propenal, 249
 propenenitrile, 249
 protonated methanol, 153
 purine, 671
 pyridine, 276
 pyrimidine, 276
 pyrrole, 277, 666
 pyrrolidine, 666
 S_N2 reaction, 400
 sulfide, 64
 thioanisole, 554a
 thioester, 561
 thiol, 64
 thymine, 856
 toluene, 299
 (trifluoromethyl)benzene, 299
 trimethylamine, 649
 2,4,6-trinitrochlorobenzene, 303
 vinylic anion, 257
 water, 46, 155
 zwitterion, 679
- Elimination reaction, **147**
 biological example of, 428, 782, 789
 mechanisms of, 420–421
 summary of, 429
 Zaitsev's rule and, 420
- Emden–Meyerhof pathway, **776–782**
see also Glycolysis
- Enamido acid, amino acids from, 688
- Enamine, **505**
 conjugate addition reactions of, 635–636
 electrostatic potential map of, 635
 from aldehydes, 507
 from ketones, 507
 mechanism of formation of, 507
 Michael reactions of, 635–636
 nucleophilicity of, 635
 pH dependence of formation, 507–508
 reaction with enones, 635–636
- Enantiomeric excess, **527**
- Enantiomers, **114–115**
 discovery of, 121
 resolution of, 133–134
- Enantioselective synthesis, **526–527**
- Enantiotopic (NMR), **366**
- Endergonic reaction, **163**
 Hammond postulate and, 204–205
- Endothermic reaction, **164**
 -ene, alkene name ending, 183
- Energy diagram, *see* Reaction energy diagram, **168–170**
- Energy-rich bonds, explanation of, 167
- Enethiol, **435**
- Enflurane, molecular model of, 118
- Enol, **254, 435, 600**
 α-substitution reaction and, 603
 acid-catalyzed formation of, 601–602
 base-catalyzed formation of, 601–602
 electrostatic potential map of, 600, 603
 from ketones, 600–601
 reactivity of, 603
- Enolase, function of, 782
- Enolate ion, **489, 601**
 alkylation of, 610–619
 electrostatic potential map of, 607, 610
 reactivity of, 610
 resonance in, 607
- Enone, conjugate addition reaction with
 lithium diorganocopper reagents,
 520–521
 conjugate addition reactions of amines,
 519
 conjugate addition reactions of water, 520
 from aldol reaction, 623–624
 IR absorption of, 522
 molecular orbitals of, 624
 reaction with amines, 519
 reaction with water, 520
 stability of, 624
 synthesis of, 604–605
- Enoyl CoA hydratase, function of, 212
 molecular model of, 212
- Enoyl reductase (ER) domain, polyketide
 synthase and, 895
- Entgegen (*E* configuration), **189**
- Enthalpy change (ΔH), **164**
 explanation of, 164
- Entner–Doudoroff pathway, 804a
- Entropy change (ΔS), **164**
 explanation of, 164–165
- Enzyme, **173–175, 703–705**
 active site in, 173–174
 classification of, 704–705
 naming, 704
 rate enhancements by, 703
 specificity of, 703
 transition state stabilization by, 704
 turnover number of, 704
 visualization of, 735–736
- Ephedrine, structure of, 57
- Epimers, **129**
- Epinephrine, biosynthesis of, 418–419
- Epoxide(s), **227**
 acid-catalyzed cleavage of, 229, 469
 alcohols from, 444
 base-catalyzed cleavage of, 470
 1,2-diols from, 229
 from alkenes, 227–228
 from halohydrins, 228

- Epoxide(s) (*continued*)
 mechanism of cleavage of, 229
 reaction with acid, 229, 469
 reaction with amines, 470
 reaction with base, 470
 reaction with HCl, 405–406
 S_N2 reactions of, 405–406
 synthesis of, 227–228
- Equatorial bonds (cyclohexane), **99**
 drawing, 100
- Equilibrium constant (K_{eq}), **162–163**
 free-energy change and, 164
- Ergocalciferol, structure of, 923
- Ergosterol, UV absorption of, 349f
 vitamin D from, 923
- Erythromycin, biosynthesis of, 896–902
- Erythromycin A biosynthesis, overview of, 896
 structure of, 878, 902
- Erythromycin C, structure of, 902
- Erythromycin D, structure of, 902
- Erythronolide B, biosynthesis of, 898–901
 structure of, 145b
- Erythrose, configuration of, 747
- D-Erythrose 4-phosphate, oxidation of, 879–881
- ESI mass spectrometry, 328
- Essential amino acid, **683**, 731–732
 biological precursors of, 732
- Essential monosaccharide, 761–762
 biosynthesis of, 762
- Essential oil, **209**
- Ester(s), **555**
 acid-catalyzed hydrolysis of, 580–581
 alcohols from, 447, 449–451, 582–583
 aldehydes from, 495, 583
 alkylation of, 617
 amides from, 582
 aminolysis of, 582
 base-catalyzed hydrolysis of, 579–580
 carbonyl condensation reactions of, 627–629
 carboxylic acids from, 579–582
 electrostatic potential map of, 561
 from acid anhydrides, 577
 from acid chlorides, 572–573
 from alcohols, 455–456
 from carboxylic acids, 565–567
 Grignard reaction of, 583
 hydrolysis of, 579–582
 IR spectroscopy of, 340, 592–593
 mechanism of Grignard addition to, 583
 mechanism of reduction of, 582–583
 naming, 556
 NMR spectroscopy of, 593–594
 nucleophilic acyl substitution reactions of, 579–583
 occurrence of, 578
 partial reduction of, 495, 583
 pK_a of, 608
 polarity of, 64
 reaction summary of, 598
 reaction with amines, 582
 reaction with DIBAH, 495, 583
 reaction with Grignard reagents, 449–451
 reaction with LDA, 617
 reaction with $LiAlH_4$, 447
 reduction of, 447, 582–583
 saponification of, 579–580
 uses of, 578–579
- Estradiol, structure and function of, 841
- Estrogen, **840**
 function of, 840
- Estrone, conformation of, 110
 structure and function of, 841
 synthesis of, 924e
- Et, abbreviation for ethyl, 627
- Ethane, bond angles in, 13
 bond lengths in, 13
 bond rotation in, 79–81
 bond strengths in, 13
 conformations of, 80
 eclipsed conformation of, 80
 electrostatic potential map of, 157
 molecular model of, 10, 13, 67
 rotational barrier in, 81
 sp^3 hybrid orbitals in, 13
 staggered conformation of, 80
 structure of, 13
 torsional strain in, 81
- Ethanol, annual U.S. production of, 218, 478
 annual worldwide production of, 436
 E90 fuel from, 436, 478
 history of, 478
 industrial synthesis of, 218, 436
 IR spectrum of, 331
 LD_{50} of, 25, 478
 metabolism of, 478
 molecular model of, 436
 physiological effects of, 478
 pK_a of, 45, 440
 toxicity of, 478
- Ether(s), **435**
 alcohols from, 468
 alkyl halides from, 468
 bond angles in, 465
 cleavage of with HBr, 468
 cleavage of with HI, 468
 cleavage of with trifluoroacetic acid, 468
 electrostatic potential map of, 61
 from alcohols, 466–467
 from alkyl halides, 466–467
 IR spectroscopy of, 476
 naming, 464–465
 NMR spectroscopy of, 477
 polarity of, 61
 properties of, 465
 reaction summary of, 482
 reaction with HBr, 468
 reaction with HI, 468
 uses of, 436
- Ethoxide ion, electrostatic potential map of, 536
- Ethyl acetate, ethyl acetoacetate from, 627–628
 1H NMR spectrum of, 593
- Ethyl acetoacetate, *see* Acetoacetic ester
- Ethyl acrylate, ^{13}C NMR absorptions in, 360
- Ethyl alcohol, *see* Ethanol
- Ethyl benzoate, ^{13}C NMR spectrum of, 381f
- Ethyl carbocation, molecular orbital of, 203
- Ethyl group, **70**
- Ethylcyclopentane, mass spectrum of, 324
- Ethylene, annual worldwide production of, 180
 bond angles in, 15
 bond lengths in, 15
 bond strengths in, 15
 electrostatic potential map of, 60, 157, 249
 ethanol from, 218
 heat of hydrogenation of, 193
 hormonal activity of, 179
 industrial uses of, 180
 molecular model of, 15
 molecular orbitals of, 21, 906
 pK_a of, 257
 polymerization of, 236–238
 reaction with H_2O , 156–158
 sp^2 hybrid orbitals in, 14–15
 structure of, 14–15
- Ethylene dichloride, annual worldwide production of, 214
 synthesis of, 214
- Ethylene glycol, acetals from, 511
 manufacture of, 229
 uses of, 229
- N-Ethylpropylamine, mass spectrum of, 674
- Ethynylestradiol, structure and function of, 841
- Etoricoxib, structure of, 315
- Exergonic reaction, **163**
 Hammond postulate and, 204–205
- Exon (DNA), **861**
- Exothermic reaction, **164**
- FAD, *see* Flavin adenine dinucleotide
- $FADH_2$, *see* Flavin adenine dinucleotide (reduced)
- Faraday, Michael, 267
- Farnesyl diphosphate, biosynthesis of, 835–836
 squalene from, 835, 842
- Fat, animal, **806**
 biological hydrolysis of, 581–582, 813–815
 catabolism of, 813–820
 digestion of, 813–815
 energy content of, 806
 hydrolysis of, 806
 saponification of, 809
 table of, 807
- Fatty acid, **806**
 acetyl CoA from, 815–820
 β -oxidation of, 815–820
 biosynthesis of, 820–825
 catabolism of, 815–820
 fatty acyl CoAs from, 815–820
 mechanism of biosynthesis, 821–825
 melting point trends in, 808
 omega-3, 808

- polyunsaturated, **807**
table of, 807
trans, 225–226, 808–809
- Fatty acid biosynthesis, loading reaction in, 823
overall result of, 825
priming reactions in, 821
steps in, 822
- Fatty-acid derived substance, **879**
number of, 879
- Fatty acid synthase, function of, 821
- Fatty acyl CoA, mechanism of biosynthesis, 570–571
- Favorskii reaction, 554h
- Fehling's test, 758
- Fiber, **938**
crystallites in, 938
manufacture of, 938
- Fibrous protein, **700**
- Fingerprint region (IR), **334**
- First-order reaction, **409**
- Fischer, Emil, 740, 759
- Fischer esterification reaction, **565–567**
limitations of, 565
mechanism of, 565–567
- Fischer projection, **740–743**
carbohydrates, 743, 747
conventions for, 741
D sugars, 745
L sugars, 745
rotation of, 741–742
R,S configuration of, 742
- Fishhook arrow, radical reactions and, 148
- Flavin adenine dinucleotide, aromatic hydroxylation with, 288
mechanism of oxidation with, 817–818
structure and function of, 288, 706, 817–818
- Flavin adenine dinucleotide (reduced), structure of, 817
- Flavin hydroperoxide, alkene epoxidation with, 228
biological epoxidations and, 842–843
- Fleming, Alexander, 594
- Florey, Howard, 594
- Fluorination (aromatic), 284
- Fluoromethane, bond length of, 384
bond strength of, 384
dipole moment of, 384
- (*S*)-Fluoxetine, molecular model of, 142
stereochemistry of, 142
structure of, 285
synthesis of, 434h
- Fmoc, amino acid protection with, 697
- Fmoc protecting group, cleavage of, 713e
- Food and Drug Administration (FDA), 176
- Food, catabolism of, 715–716
- Formal charge, **33–35**
calculation of, 35
table of, 35
- Formaldehyde, annual worldwide production of, 492
dipole moment of, 32
electrostatic potential map of, 178a, 500
hydrate of, 501
reaction with Grignard reagents, 449–451
uses of, 492–493
- Formate ion, bond lengths in, 535
electrostatic potential map of, 536
- Formic acid, bond lengths in, 535
 pK_a of, 535
- Formyl group, **494**
- Fourier-transform NMR spectroscopy (FT-NMR), **357–358**
- Free radical, **149**
- Free-energy change (ΔG), **163**
- Frequency (ν), 329–**330**
- Friedel–Crafts acylation reaction, **292**
acyl cations in, 292
arylamines and, 663–664
mechanism of, 292
- Friedel–Crafts alkylation reaction, **289–291**
arylamines and, 663–664
carbocation rearrangements in, 291
limitations of, 289–290
mechanism of, 289–290
polyalkylation in, 290–291
biological example of, 292–293
- Frontier orbitals, **907**
- Fructose, anomers of, 751
furanose form of, 751
pyranose form of, 751
sweetness of, 770
- Fructose 1,6-bisphosphate, cleavage of, 777–778
hydrolysis of, 799–800
- Fructose-1,6-bisphosphate aldolase, crystal structure of, 348
- Fructose 6-phosphate, phosphorylation of, 777–778
- FT-NMR, **357–358**
- L-Fucose, biosynthesis of, 804e
structure and function of, 761
- Fukui, Kenichi, 907
- Fumarate, from succinate, 791
malate from, 791
- Fumaric acid, structure of, 532
- Functional group, **59**
carbonyl compounds and, 64
electronegative atoms in, 61, 64
importance of, 59–60
IR spectroscopy of, 334–336
multiple bonds in, 60–61
polarity patterns of, 153
table of, 62–63
- Functional RNAs, **860**
- Furan, industrial synthesis of, 666
- Furanose, **751**
- Fused-ring heterocycle, **669–671**
- GABA, *see* Gamma-aminobutyric acid, 682
- D-Galactose, biosynthesis of, 804b
configuration of, 747
metabolism of, 482k
- Gamma rays, electromagnetic spectrum and, 330
- Gamma-aminobutyric acid, structure of, 682
- Gasoline, composition of, 85
octane number of, 86
- Gatterman–Koch reaction, 318i
- Gauche conformation, **82**
steric strain in, 82–83
- Gel electrophoresis, DNA sequencing and, 866
- Gem, *see* Geminal, 501
- Geminal (gem) diol, **501**
- Gene, **860**
number of in humans, 1, 866
- Genome, size of in humans, 859
- Gentamicin, structure of, 769
- Geraniol, biosynthesis of, 418–419
- Geranyl diphosphate, biosynthesis of, 835–836
terpenoids from, 835–836
- Gibbs free-energy change (ΔG), **163**
equilibrium constant and, 164
- Gilman reagent, **393**
organometallic coupling reactions of, 393–394
reaction with alkyl halides, 393–394
- Glass transition temperature (polymers), **937**
- Globular protein, **700**
- Glucitol, structure of, 757
- Glucocorticoid, **841**
- Glucogenic amino acid, **727**
- Gluconeogenesis, **794–800**
comparison with glycolysis, 800–801
result of, 800
steps in, 795–796
- α -D-Glucopyranose, molecular model of, 750
- β -D-Glucopyranose, molecular model of, 750
- Glucosamine, biosynthesis of, 804b
- Glucose, aldol reactions in biosynthesis of, 637–638
anomers of, 750
biosynthesis of, 794–800
catabolism of, 776–782
chair conformation of, 99
configuration of, 747
ethers from, 466
from starch, 774
gluconeogenesis and, 794–800
glycolysis of, 776–782
glycosides of, 755
molecular model of, 99, 107
mutarotation of, 751–752
oxidation of, 757–759
pentaacetyl ester of, 754
pentamethyl ether of, 754
phosphorylation of, 777
pyranose form of, 750
reaction with acetic anhydride, 754
reaction with ATP, 718
reduction of, 757
sweetness of, 770
vitamin C from, 551
Williamson ether synthesis with, 754
- Glucose 6-phosphate, hydrolysis of, 800
isomerization of, 777–778

- Glutamate, arginine from, 734
 biosynthesis of, 731
 glutamine from, 733
 ornithine from, 734
 oxidative deamination of, 723
 partial reduction of, 734
 proline from, 734
- Glutamate 5-semialdehyde, from glutamate, 734
 proline from, 658
- Glutamic acid, structure and properties of, 681
- Glutamine, biosynthesis of, 733
 from glutamate, 733
 structure and properties of, 680
- Glutamine synthase, function of, 644
 molecular model of, 644
- Glutaric acid, structure of, 532
- Glutathione, function of, 464
 oxidation of, 464
 prostaglandin biosynthesis and, 828
 structure of, 464
- Glycal, **767**
- Glycal assembly method, **767–768**
- (–)-Glyceraldehyde, configuration of, 125
- (R)-Glyceraldehyde, Fischer projection of, 741–742
 molecular model of, 741–742
- Glyceraldehyde 3-phosphate, biological oxidation of, 780
 from dihydroxyacetone phosphate, 780
 fructose 1,6-bisphosphate from, 799
 phosphorylation of, 780
- Glyceric acid, structure of, 532
- Glycerol, catabolism of, 815
 phosphorylation of, 815
- sn*-Glycerol 3-phosphate, naming of, 815
- Glycerophospholipid, **811–812**
- Glycine, structure and properties of, 680
- Glycoconjugate, **756**
 biosynthesis of, 756
 mechanism of formation of, 756
- Glycogen, structure and function of, 767
- Glycogen synthase, function of, 113
 molecular model of, 113
- Glycol, **229**
- Glycolic acid, pK_a of, 535
 structure of, 532
- Glycolipid, **756**
- Glycolysis, **776–782**
 comparison with gluconeogenesis, 800–801
 result of, 782
 steps in, 776–777
- Glycoprotein, **756**
 biosynthesis of, 756
- α -Glycosidase, 766–767, 774–775
 mechanism of, 774–775
 rate acceleration by, 703
 starch hydrolysis and, 774–775
- Glycoside, **755**
 hydrolysis of, 755
 naming, 755
 occurrence of, 755
- Glyoxalate cycle, 804a
- Glyptal, structure of, 942b
- GPP, *see* Geranyl diphosphate
- Graft copolymer, **930–932**
 synthesis of, 931–932
- Green chemistry, **674–675**
 example of, 675
 principles of, 674–675
- Grignard, Victor, 391
- Grignard reaction, **391**
 alkanes from, 392
 carboxylation of, 541
 carboxylic acids from, 541
 electrostatic potential map of, 392
 from alkyl halides, 391
 mechanism of, 504
 with acids, 392
 with aldehydes, 449–451, 504–505
 with carboxylic acids, 450
 with CO_2 , 541
 with esters, 449–451, 583
 with formaldehyde, 449–451
 with ketones, 449–451, 504–505
 with nitriles, 547
- Grubbs catalyst, olefin metathesis polymerization and, 934–935
- Guanidino group, 713f
- Guanine, aromaticity of, 280
 catabolism of, 871–873
 electrostatic potential map of, 856
 hydrolysis of, 872
 protection of, 867
 structure of, 853
 xanthine from, 872
- Guanosine, catabolism of, 871–873
 phosphorolysis of, 872
- Gulose, configuration of, 747
- Guncotton, 765
- ΔH_{hydrog} (heat of hydrogenation), **193**
- Halo group, directing effect of, 297–298
 inductive effect of, 297
 orienting effect of, 300
- Haloalkane, *see* Alkyl halide
- Halogen, inductive effect of, 297
 resonance effect of, 298
- Halogenation (aromatic), 282–286
- Halohydrin, **217**
 biological formation of, 218
 epoxides from, 228
 reaction with base, 228
- Halomon, anticancer activity of, 431
 biosynthesis of, 216
 molecular model of, 431
- Haloperoxidase, biological halogenations with, 216
 biological halohydrin formation with, 218
- Hammond postulate, **204–205**
 Markovnikov's rule and, 204–205
 S_N1 reaction and, 412–413
- Handedness, molecular, 114–117
see also Chirality
- Heart disease, cholesterol and, 849–850
 control of, 849–850
 HMG-CoA reductase and, 849–850
 statin drugs and, 849–850
- Heat of hydrogenation, 192–193
 table of, 193
- Heat of reaction, **164**
- Helicase, DNA replication and, 858
- Hell–Volhard–Zelinskii reaction, 606
- Helminthogermacrene, structure of, 851a
- Heme, structure of, 665
- Hemiacetal, **509**
- Hemithioacetal, **780**
- Hemoglobin, function of, 265
 molecular model of, 265
- Henderson–Hasselbalch equation, **537–538**
 amines and, 653–654
 amino acids and, 684–685
 carboxylic acids and, 537–538
- Heroin, structure of, 885
- Hertz (Hz), **330**
- Heterocycle, **276**
 aromatic, 276–277
 fused-ring, **669–671**
- Heterocyclic amine, **646**, 665–669
 basicity of, 650
 names for, 646
- Heterolytic bond cleavage, 148
- HETPP, *see* Hydroxyethylthiamin diphosphate
- Hevea brasiliensis*, rubber from, 258
- Hex-1-ene, IR spectrum of, 335
- Hex-2-ene, mass spectrum of, 325
- Hex-1-yne, IR spectrum of, 335
- Hexa-1,3,5-triene, UV absorption of, 345
 molecular orbitals of, 907
- Hexachlorophene, synthesis of, 318i
- Hexamethylphosphoramide (HMPA), S_N2 reaction and, 407
- Hexane, IR spectrum of, 335
 mass spectrum of, 323
 molecular model of, 14
- Hexokinase, active site in, 174
 function of, 174, 738
 glucose phosphorylation with, 777
 molecular model of, 174, 738
- HF, reaction with alcohols, 391
- High-molecular-weight polyethylene, synthesis of, 929
 uses of, 929
- Highest occupied molecular orbital (HOMO), **343**, **907**
 cycloaddition reactions and, 914–916
 electrocyclic reactions and, 910–912
 UV spectroscopy and, 343
- Histidine, basicity of, 667
 catabolism of, 737d
 electrostatic potential map of, 683
 side-chain basicity of, 683
 structure and properties of, 681
- HIV protease, function of, 28
 molecular model of, 28

- HMG-CoA, *see* 3-Hydroxy-3-methylglutaryl CoA, 831–832
- HMPA, *see* Hexamethylphosphoramide
- Hoffmann, Roald, 906
- Hoffmann-LaRoche Co., vitamin C synthesis and, 551
- Hofmann elimination reaction, **660–661**
biological example of, 661
mechanism of, 660
regiochemistry of, 661
Zaitsev's rule and, 661
- HOMO, *see* Highest occupied molecular orbital
- Homocysteine, structure of, 682
- Homolytic bond cleavage, 148
- Homopolymer, **930**
- Homotopic (NMR), **366**
- Honey, sugars in, 764
- Hormone, **840**
adrenocortical, 841
steroid, 840–841
- Hückel, Erich, 272
- Hückel $4n + 2$ rule, **272**
cyclobutadiene and, 272
cycloheptatrienyl cation and, 274–275
cyclooctatetraene and, 273
cyclopentadienyl anion and, 274–275
explanation of, 273
imidazole and, 277
molecular orbitals and, 273
pyridine and, 276
pyrimidine and, 276
pyrrole and, 276–277
- Hughes, Edward Davies, 399
- Human fat, composition of, 807
- Human genome, sequencing of, 864–866
size of, 859, 865
- Humulene, structure of, 209
- sp^3 Hybrid orbitals, **12**
- sp^2 Hybrid orbitals, **14**
- sp Hybrid orbitals, **16**
- Hydrate (carbonyl), **497**
from aldehydes, 501–502
from ketones, 501–502
- Hydration, alkene, 218–221
- Hydride shift, **207**
carbocation rearrangements and, 206–207
regiochemistry of, 379
- Hydroboration, mechanism of, 221
regiochemistry of, 379
- Hydroboration–oxidation, **220**
regiochemistry of, 220–221
stereochemistry of, 220–221
- Hydrocarbon, **66**
- Hydrochloric acid, pK_a of, 45
- Hydrocortisone, structure and function of, 112b, 492, 841
- Hydrocyanic acid, pK_a of, 45
- Hydrogen bond, **54**
alcohols and, 439
amines and, 648
ammonia and, 54–55
carboxylic acids and, 533–534
DNA and, 55
DNA base pairs and, 855–856
electrostatic potential map, 55, 439
phenols and, 439
thiols and, 439
water and, 54–55
- Hydrogen bromide, ether cleavage with, 468
- Hydrogen iodide, ether cleavage with, 468
- Hydrogen molecule, bond length in, 11
bond strength in, 11
molecular orbitals in, 20–21
- Hydrogen peroxide, reaction with organoboranes, 220
- [1,5] Hydrogen shift, 919
- Hydrogenation, **223**
alkenes and, 223–226
alkynes, 253
aromatic compounds, 307
catalysts for, 223
mechanism of, 223–224
stereochemistry of, 224–225
trans fatty acids and, 225–226, 808–809
vegetable oil, 808
- Hydrolase, **704–705**
- Hydrolysis, amides, 584–585
carbohydrates, 766–767, 774–775
esters, 579–582
fats, 581–582, 813–815
nitriles, 545–546
nucleophilic acyl substitution reactions and, **561**
proteins, 585
- Hydronium ion, electrostatic potential map of, 155
- Hydrophilic, **55**
- Hydrophobic, **55**
- Hydroquinone, **459**
from quinones, 459
- Hydroxide ion, electrostatic potential map of, 46, 155
- 3-Hydroxy-3-methylglutaryl-CoA, reduction of, 832
- 3-Hydroxy-3-methylglutaryl-CoA reductase, active site in, 2, 850
function of, 2
heart disease and, 849–850
molecular model of, 2
statin drugs and, 2, 849–850
- Hydroxyacetic acid, pK_a of, 535
- Hydroxyacyl-CoA dehydrogenase, function of, 805
molecular model of, 805
- Hydroxyethylthiamin diphosphate, from pyruvate, 785
pyridoxal phosphate biosynthesis and, 881–882
reaction with lipoamide, 786
- Hydroxyl group, directing effect of, 297–298
inductive effect of, 297
orienting effect of, 300–301
resonance effect of, 298
- Hydroxylation, alkene, **229**
aromatic, 288–289
biological examples of, 886–887, 890
- p*-Hydroxyphenylacetaldehyde, biosynthesis of, 888
- p*-Hydroxyphenylpyruvate, decarboxylation of, 888
- Hyperconjugation, **194**
alkenes and, 194
carbocation stability and, 202–203
- Ibuprofen, chirality and, 144
green synthesis of, 675
molecular model of, 144
stereochemistry of, 144
structure of, 315
synthesis of, 541
- Idose, configuration of, 747
- Imidazole, aromaticity of, 277
basicity of, 650, 667
electrostatic potential map of, 53, 277
Hückel $4n + 2$ rule and, 277
- Imine(s), **505**
from aldehydes, 506
from ketones, 506
mechanism of formation of, 506
pH dependence of formation, 507–508
Schiff base and, 779
- IND, *see* Investigational new drug, 176–177
- Indole, aromaticity of, 280
electrophilic substitution reaction of, 671
structure of, 670
- Indolmycin, biosynthesis of, 619
- Inductive effect, **30**
carboxylic acid strength and, 538
electronegativity and, 30
electrophilic aromatic substitution and, **297–298**
- Influenza pandemics, 802
- Influenza virus, spread of, 802
- Infrared radiation, electromagnetic spectrum and, 330
energy of, 333
frequencies of, 332
wavelengths of, 332
- Infrared spectroscopy, **332–334**
acid anhydrides, 592–593
acid chlorides, 592–593
alcohols, 339, 475
aldehydes, 340, 522–523
alkanes, 337
alkenes, 338
alkynes, 338
amides, 592–593
amines, 339, 672
aromatic compounds, 338–339
bond stretching in, 333
carbonyl compounds, 339–340
carboxylic acid derivatives, 592–593
carboxylic acids, 548–549
esters, 340, 592–593
ethers, 476
explanation of, 333–334
fingerprint region in, 334
ketones, 340, 522–523
molecular motions in, 333

- Infrared spectroscopy (*continued*)
 nitriles, 549
 phenols, 476
 regions in, 336
 table of absorptions in, 334
 vibrations in, 333
- Infrared spectrum, benzaldehyde, 523
 butanoic acid, 549
 cyclohexane, 349d
 cyclohexanol, 475
 cyclohexanone, 523
 cyclohexene, 349d
 cyclohexylamine, 672
 ethanol, 331
 hexane, 335
 hex-1-ene, 335
 hex-1-yne, 335
 interpretation of, 334–336
 phenol, 476
 phenylacetaldehyde, 341
 phenylacetylene, 342
 toluene, 339
- Ingold, Christopher, 399
- Initiation step, radical chain reaction and, **150**
- Inosine, biosynthesis of, 874
- Inosine monophosphate, oxidation of, 874
- Insulin, structure of, 713d
- Integration (^1H NMR), **370**
- Intermediate, *see* Reaction intermediate
- Intoxilyzer test, 478
- Intramolecular aldol reaction, 626–627
 mechanism of, 626–627
- Intramolecular Claisen reaction, 629–631
 mechanism of, 630–631
- Intron (DNA), **861**
- Invert sugar, 764
- Investigational new drug (IND), 176–177
- Iodination (aromatic), 285
 thyroxine biosynthesis and, 286
- Iodoform reaction, 598k
- Iodomethane, bond length of, 384
 bond strength of, 384
 dipole moment of, 384
- Ion exchange chromatography, amino acids and, 691–692
- Ion pair, **411**
 $\text{S}_{\text{N}}1$ reaction and, 411
- Ionization sources, mass spectrometry and, 320
- Ionophore, **473**
 function of, 473
- IPP, *see* Isopentenyl diphosphate, 830
- IR, *see* Infrared
- Iron, reaction with nitroarenes, 655
- Iron sulfate, LD_{50} of, 25
- Iron(III) bromide, aromatic bromination and, 282–283
- Iron–oxo complex, biological hydroxylation and, 886–887, 890
- Isoamyl group, **76**
- Isoborneol, rearrangement of, 851f
- Isobutane, molecular model of, 67
- Isobutyl group, 71
- Isobutylene, polymerization of, 926
- Isocitrate, from citrate, 789
 oxalosuccinate from, 790
 oxidation of, 790
- Isoelectric point (pI), **686–687**
 amino acids, 680–681
 calculation of, 686
- Isoleucine, molecular model of, 130
 structure and properties of, 680
- Isomerase, **704–705**
- Isomers, **67**
 alkanes and, 67–68
 alkenes and, 187
 cis–trans, **92**
 conformational, **80**
 constitutional, **67**
 cycloalkanes and, 91–92
 diastereomers, 127–128
 enantiomers, 114–115
 epimers, 129
 kinds of, 135–136
 review of, 135–136
 stereoisomers, **91**
- Isopenicillin N, epimerization of, 904a
- Isopentenyl diphosphate, biosynthesis of, 830–833
 dimethylallyl diphosphate from, 834
 mevalonate pathway for, 830–833
 terpenoids from, 834–836
- Isoprene, heat of hydrogenation of, 242
 polymers from, 259
 structure of, 184
- Isoprene rule, terpenes and, 209–210
- Isopropyl group, 71
- Isoquinoline, aromaticity of, 280
 electrophilic substitution reaction of, 670
- Isotactic polymer, **928**
- Isotope, **4**
- IUPAC system of nomenclature, **72**
- J*, *see* Coupling constant, 373
- Januvia, structure of, 285
- Jefferson, Thomas, DNA fingerprinting and, 875
- K_{a} (acidity constant), **44**
 calculation of from $\text{p}K_{\text{a}}$, 47
- K_{b} (basicity constant), 649
- K_{eq} (equilibrium constant), **162–163**
- KEGG biosynthesis database, 710
- Kerosene, composition of, 85
- Ketal, *see* Acetal, **509**
- α -Keto acid, hydrate of, 501
 transamination of, 719–722
- β -Ketoacyl-CoA thiolase, function of, 599
 mechanism of, 819
 molecular model of, 599
- Ketogenic amino acid, **727**
- α -Ketoglutarate, from glutamate, 723
 from oxalosuccinate, 790
 glutamate from, 731
 oxidative decarboxylation of, 790
 succinyl CoA from, 790
 transamination of, 719–722
- α -Ketoglutaric acid, hydrate of, 501
- Ketone(s), **492**
 α bromination of, 604–605
 acetals from, 509–511
 acidity of, 607–608
 alcohols from, 445–446, 449–451, 504–505
 aldol reaction of, 621
 alkenes from, 513–514
 alkylation of, 617–618
 amines from, 657–658
 biological halogenation of, 604
 biological reduction of, 446–447, 517
 carbonyl condensation reactions of, 620–621
 common names of, 494
 conjugate addition reactions of, 518–521
 enamines from, 507
 enols of, 600–601
 from acetoacetic ester synthesis, 614–615
 from acid chlorides, 496, 575–576
 from alcohols, 456–458
 from alkenes, 231–232
 from alkynes, 254–256
 from nitriles, 547
 hydrates of, 501–502
 imines from, 506
 IR spectroscopy of, 340, 522–523
 mass spectrometry of, 326–327, 524–525
 McLafferty rearrangement of, 326, 524
 mechanism of hydration of, 501–502
 mechanism of reduction of, 504
 naming, 494
 NMR spectroscopy of, 524
 $\text{p}K_{\text{a}}$ of, 608
 polarity of, 64
 protection of, 511
 reaction summary of, 528–529
 reaction with alcohols, 509–511
 reaction with amines, 505–508
 reaction with Br_2 , 604–605
 reaction with Grignard reagents, 449–451, 504–505
 reaction with LDA, 617–618
 reaction with LiAlH_4 , 446, 504
 reaction with NaBH_4 , 445, 504
 reactivity versus aldehydes, 499–500
 reduction of, 445–446, 504
 reductive amination of, 657–658
 Wittig reaction of, 513–514
- Ketone bodies, **727**
- Ketoreductase domain (KR), polyketide synthase and, 895
- Ketose, **740**
- Ketosynthase (KS) domain, polyketide synthase and, 895
- Keto–enol tautomerism, **254**, 600–602
 catalysis of, 601–602
- Kiliani, Heinrich, 759
- Kiliani–Fischer synthesis, 759–760
- Kilojoule (kJ), **11**
- Kinetics, **398**
 E1 reaction and, 427
 E2 reaction and, 422–423

- S_N1 reaction and, 409–410
 S_N2 reaction and, 398–400
 Knowles, William S., 526, 688
 Kodel, structure of, 942a
 Krebs, Hans, 787
 Krebs cycle, *see* Citric acid cycle
- L** configuration, **745**
 Labetalol, stereochemistry of, 648
 structure of, 648
 synthesis of, 648
 Laboratory reaction, comparison with
 biological reactions, 173–175
 Lactam, **586**
 cyclic amines from, 586
 reaction with LiAlH_4 , 586
 Lactic acid, configuration of (+) enantiomer,
 124
 configuration of (–) enantiomer, 124
 enantiomers of, 114–115
 molecular model of, 116
 resolution of, 133–134
 Lactone, **579**
 alkylation of, 617
 reaction with LDA, 617
 Lactose, molecular model of, 764
 occurrence of, 764
 structure of, 764
 sweetness of, 770
 Lagging strand, DNA replication and, 859
 Lanosterol, biosynthesis of, 842–847
 cholesterol from, 847
 structure of, 209
 Lard, composition of, 807
 Latex, rubber from, 259
 Lauric acid, structure of, 807
LD₅₀, **25**
 table of, 25
 LDA, *see* Lithium diisopropylamide
 Leading strand, DNA replication and,
 859
 Leaving group, **404**
 reactivity of, 404–405
 S_N1 reaction and, 414
 S_N2 reactions and, 404–406
 LeBlanc process, 809
 Leucine, biosynthesis of, 643j, 737e
 structure and properties of, 680
 Leukotriene E₄, structure of, 826
 Leuprolide, structure of, 713f
 Levorotatory, **119**
 Lewis acid, **50**
 examples of, 51
 reactions of, 50–51
 Lewis base, **50**
 examples of, 52
 reactions of, 52–53
 Lewis Y hexasaccharide, structure of, 768
 Lexan, structure and uses of, 933
 structure of, 591
 uses of, 591
 Lidocaine, molecular model of, 86a
 structure of, 57
 Ligase, **704–705**
- Light, plane-polarized, 119
 speed of, 330
 Limit dextrin, from starch, **774**
 Limonene, biosynthesis of, 211i, 836
 molecular model of (+) enantiomer, 141
 molecular model of (–) enantiomer, 141
 odor of, 141
 Linalyl diphosphate, biosynthesis of, 836
 Lindlar catalyst, **253**
 Line-bond structure, resonance and, 36–37
 Linear metabolic pathways, reasons for,
 792
1→4-Link, **763**
 Linoleic acid, structure of, 807
 Linolenic acid, molecular model of, 808
 structure of, 807
 Lipase, function of, 813
 mechanism of, 813–815, 581–582
 Lipid, **805**
 classification of, 805
 Lipid bilayer, **812**
 structure of, 812
 Lipitor, *see* Atorvastatin
 Lipoamide, structure and function of, 786
 Lipoic acid, structure and function of, 707,
 786
 Lithium aluminum hydride, danger of,
 446
 reaction with aldehydes, 446
 reaction with carboxylic acids, 447, 569
 reaction with esters, 447
 reaction with ketones, 446
 Lithium diisopropylamide, formation of,
 608
 properties of, 608
 reaction with cyclohexanone, 608
 reaction with esters, 617
 reaction with ketones, 617–618
 reaction with lactones, 617
 reaction with nitriles, 618
 Lithium diorganocopper reagent, conjugate
 addition reaction to enones, 520–521
 reaction with acid chlorides, 496,
 575–576
 reaction with enones, 520–521
 see also Gilman reagent
 synthesis of, 520
 Lithocholic acid, 554g
 structure of, 840
 Liver alcohol dehydrogenase, function of,
 435
 molecular model of, 435
 Loading reaction, fatty acid biosynthesis
 and, 823
 Locant (nomenclature), **73**
 position of in chemical names, 183–184
 Lone-pair electrons, **9**
 Loratadine, structure of, 211b, 285
 Lotaustralin, structure of, 544
 Lovastatin, biosynthesis of, 251
 mechanism of action of, 2, 849–850
 structure and function of, 894
 structure of, 251
 Low-density polyethylene, synthesis of, 929
- Lowest unoccupied molecular orbital
 (LUMO), **343, 907**
 cycloaddition reactions and, 914–916
 UV spectroscopy and, 343
 LUMO, *see* Lowest unoccupied molecular
 orbital
 Lyase, **704–705**
 Lysine, catabolism of, 737c
 saccharopine from, 737c
 structure and properties of, 681
 Lysozyme, isoelectric point of, 686
 MALDI–TOF mass spectrum of, 329
 Lyxose, configuration of, 747
- m*, *see* Meta, 267
 Magnetic field, NMR spectroscopy and,
 351–352
 Magnetic resonance imaging, **380**
 uses of, 380
 Major groove (DNA), 856–857
 (S)-Malate, molecular model of, 368
 oxaloacetate from, 792
 oxidation of, 792
 MALDI–TOF mass spectrometry, 328–329
 MALDI–TOF mass spectrum, lysozyme, 329
 Maleic acid, structure of, 532
 Malic acid, structure of, 532
 Walden inversion of, 396
 Malonic ester, pK_a of, 608
 Malonic ester synthesis, **611–613**
 decarboxylation in, 612
 intramolecular, 613
 Malonyl CoA, from acetyl CoA, 823
 Maltose, molecular model of, 763
 mutarotation of, 763
 Maltotriose, from starch, 774
 Manicone, synthesis of, 576
 Mannich reaction, 643l
 D-Mannose, biosynthesis of, 804b
 configuration of, 747
 molecular model of, 107
 Marcaine, structure of, 57
 Margarine, manufacture of, 808
 Markovnikov, Vladimir, 198
 Markovnikov's rule, **198–199**
 alkene additions and, 198–199
 alkyne additions and, 253
 carbocation stability and, 198–199
 hydroboration and, 220–221
 oxymercuration and, 219–220
 Mass analyzers, mass spectrometry and, 320
 Mass number (A), **4**
 Mass spectrometer, detectors in, 320
 double-focusing, 322
 exact mass measurement in, 322
 ionization sources in, 320
 kinds of, 320
 mass analyzers in, 320
 operation of, 320–321
 soft ionization in, 322, 328
 Mass spectrometry (MS), **320**
 alcohols, 326, 477
 aldehydes, 326–327, 524–525
 alkanes and, 322–323

- Mass spectrometry (MS) (*continued*)
 alpha cleavage of alcohols in, 326, 477
 alpha cleavage of aldehydes in, 327, 525
 alpha cleavage of amines in, 326, 673
 alpha cleavage of ketones in, 327, 525
 amines, 326, 673–674
 base peak in, 321
 biological, 328–329
 carbonyl compounds and, 326–327
 cation radicals in, 320
 dehydration of alcohols in, 326
 electron-impact, 320–321
 ESI source in, 328
 fragmentation in, 323–324
 ketones, 326–327, 524–525
 MALDI source in, 328
 McLafferty rearrangement in, 326, 524
 molecular ion in, 321
 nitrogen rule and, 349b, 673
 parent peak in, 321
 peptide sequencing with, 693
 time-of-flight, 328–329
- Mass spectrum, **321**
 butan-1-ol, 477
 2,2-dimethylpropane, 322
 ethylcyclopentane, 324
 N-ethylpropylamine, 674
 hexane, 323
 hex-2-ene, 325
 lysozyme, 329
 methylcyclohexane, 324
 5-methylhexan-2-one, 525
 2-methylpentane, 349c
 2-methylpentan-2-ol, 327
 2-methylpent-2-ene, 325
 propane, 321
- Matrix-assisted laser-desorption ionization
 mass spectrometry, *see* MALDI mass spectrometry
- McLafferty rearrangement, **326, 524**
- Mechanism (reaction), **148**
 acetal formation, 509–510
 acid-catalyzed enol formation, 601–602
 acid-catalyzed epoxide cleavage, 229
 acid-catalyzed ester hydrolysis, 580–581
 alcohol dehydration with acid, 453
 alcohol dehydration with POCl_3 , 454
 alcohol oxidation, 457–458
 aldehyde hydration, 501–502
 aldehyde oxidation, 497
 aldehyde reduction, 504
 aldol dehydration, 623–624
 aldol reaction, 621
 alkene bromination, 215–216
 alkene epoxidation, 227
 alkene oxymercuration, 219–220
 alkene ozonolysis, 231
 alkene polymerization, 237–238
 alkyne hydration, 255
 allylic bromination with NBS, 386–388
 amide dehydration, 545
 amide hydrolysis, 546, 584–585
 amide reduction, 586
 amide synthesis with DCC, 568–569
 argininosuccinate biosynthesis, 726
 aromatic bromination, 282–283
 aromatic chlorination, 285
 aromatic fluorination, 284
 aromatic iodination, 285
 aromatic nitration, 286
 aromatic sulfonation, 287
 base-catalyzed enol formation, 601–602
 base-catalyzed epoxide cleavage, 470
 base-catalyzed ester hydrolysis, 579–580
 biological alkene epoxidation, 228, 842–843
 biological alkene reductions with NADPH, 226
 biological aromatic hydroxylation, 288–289, 886–887, 890
 biological oxidation with FAD, 817–818
 biological oxidation with NAD^+ , 458
 biological reduction with NADH, 446–447
 biological reduction with NADPH, 446–447
 biotin-mediated carboxylation, 823
 α bromination of aldehydes, 604–605
 α bromination of carboxylic acids, 606
 α bromination of ketones, 604–605
 bromohydrin formation, 217
 bromonium ion formation, 215
 Cannizzaro reaction, 517
 carbonyl condensation reaction, 620
 carboxylic acid reduction, 569
 citrate synthase, 708–709
 citric acid cycle, 788–792
 Claisen condensation reaction, 627–628
 Claisen rearrangement, 471–472
 conjugate addition of lithium diorganocopper reagents, 521
 conjugate nucleophilic additions to enones, 518–519
 deamination, 719–722
 dichlorocarbene formation, 234
 Dieckmann cyclization reaction, 630–631
 Diels–Alder reaction, 248
 DNA replication, 858–859
 DNA transcription, 859–861
 E1 reaction, 427
 E1cB reaction, 428
 E2 reaction, 422–423
 Edman degradation, 693–694
 electrophilic addition reaction, 157–158, 195–196
 electrophilic aromatic substitution, 282–283
 enamine formation, 507
 ester reduction, 582–583
 ether cleavage with HI, 468
 FAD reactions, 817–818
 fat hydrolysis, 581–582, 813–815
 fatty acid biosynthesis, 821–825
 fatty acyl CoA biosynthesis, 570–571
 Fischer esterification reaction, 565–567
 Friedel–Crafts acylation reaction, 292
 Friedel–Crafts alkylation reaction, 289–290
 geranyl diphosphate biosynthesis, 835–836
 glycoconjugate biosynthesis, 756
 Grignard carboxylation, 541
 Grignard reaction, 504
 guanine hydrolysis, 872
 guanosine phosphorolysis, 872
 Hofmann elimination reaction, 660
 hydroboration, 221
 hydrogenation, 223–224
 L-3-hydroxyacyl-CoA dehydrogenase, 818
 imine formation, 506
 intramolecular aldol reaction, 626–627
 inverting glycosidase, 774–775
 isopentenyl diphosphate biosynthesis, 830–833
 β -ketoacyl-CoA thiolase, 819
 ketone hydration, 501–502
 ketone reduction, 504
 lipase, 813–815
 mevalonate decarboxylation, 832–833
 Michael reaction, 632
 mutarotation, 752
 nitrile hydrolysis, 545–546
 nucleophilic acyl substitution reaction, 559–560
 nucleophilic addition reaction, 497–498
 nucleophilic aromatic substitution reaction, 304
 olefin metathesis polymerization, 934–935
 organometallic coupling reaction, 394
 β -oxidation pathway, 815–820
 oxidative deamination, 723
 oxidative decarboxylation, 784–787
 oxymercuration, 219–220
 phosphorylation with ATP, 717
 pyruvate oxidative decarboxylation, 784–787
 reductive amination, 657
 retaining glycosidase, 774–775
 saponification, 579–580
 $\text{S}_{\text{N}}1$ reaction, 409–410, 414–415
 $\text{S}_{\text{N}}2$ reaction, 399–400
 starch hydrolysis, 774–775
 steroid biosynthesis, 842–847
 Stork enamine reaction, 635–636
 α -substitution reaction, 603
 Suzuki–Miyaura reaction, 395
 transamination, 719–720
 transimination, 721
 Williamson ether synthesis, 466
 Wittig reaction, 513
 xanthine oxidation, 872–873
 Meerwein–Ponndorf–Verley reaction, 529h
 Meisenheimer complex, **304**
 Melmac, structure of, 942b
 Melt transition temperature (polymers), **937**
 Membrane channel protein, function of, 59, 87
 molecular model of, 59, 87
 Menthene, electrostatic potential map of, 60
 Menthol, molecular model of, 97
 structure of, 118

- Meperidine, structure of, 885
- Mepivacaine, structure of, 57
- Mercapto group, **438**
- Mercurinium ion, **219**
- Merrifield, R. Bruce, 698
- Merrifield solid-phase synthesis, **698–700**
- Fmoc protecting group in, 699
 - PAM resin in, 699
 - steps in, 698–699
 - Wang resin in, 699
- Meso compound, **131**
- plane of symmetry in, 131
- Messenger RNA, **860**
- codons in, 861–862
 - translation of, 861–863
- Mestranol, structure of, 264g
- Meta (m)*, **267**
- Meta-directing group, **296**
- Metabolic pathways, cyclic, 792–793
- linear, 792
- Metabolism, **715**
- overview of, 715–716
- Methadone, structure of, 885
- Methandrostenolone, structure and function of, 841
- Methane, bond angles in, 13
- bond lengths in, 12
 - bond strengths in, 12
 - molecular model of, 13, 67
 - pK_a of, 257
 - reaction with Cl_2 , 149–150
 - sp^3 hybrid orbitals in, 12–13
 - structure of, 13
- Methanethiol, bond angle in, 19
- dipole moment of, 32
 - electrostatic potential map of, 178a
 - molecular model of, 19
 - pK_a of, 440
 - sp^3 hybrid orbitals in, 19
 - structure of, 19
- Methanol, annual worldwide production of, 435
- bond angle in, 19
 - dipole moment of, 32
 - electrostatic potential map of, 30, 48, 49, 153, 439
 - industrial synthesis of, 435–436
 - molecular model of, 19, 436
 - pK_a of, 440
 - polar covalent bond in, 29–30
 - sp^3 hybrid orbitals in, 19
 - structure of, 19
 - toxicity of, 436
 - uses of, 436
- Methionine, biosynthesis of, 529g
- molecular model of, 127
 - reaction with ATP, 474
 - S*-adenosylmethionine from, 474
 - structure and properties of, 680
- Methoxide ion, electrostatic potential map of, 49, 442
- p*-Methoxybenzoic acid, pK_a of, 539
 - p*-Methoxypropiphenone, 1H NMR spectrum of, 373
- Methyl acetate, electrostatic potential map of, 561
- ^{13}C NMR spectrum of, 353
 - 1H NMR spectrum of, 353
 - pK_a of, 608
- Methyl anion, electrostatic potential map of, 257
- Methyl α -cyanoacrylate, polymerization of, 927
- Methyl 2,2-dimethylpropanoate, 1H NMR spectrum of, 370
- Methyl group, **70**
- directing effect of, 297–298
 - inductive effect of, 297
 - orienting effect of, 299–300
- Methyl phosphate, bond angle in, 19
- molecular model of, 19
 - sp^3 hybrid orbitals in, 19
 - structure of, 19
- Methyl propanoate, ^{13}C NMR spectrum of, 361
- Methyl thioacetate, electrostatic potential map of, 561
- pK_a of, 608
- 9-Methyladenine, electrostatic potential map of, 876a
- Methylamine, bond angles in, 18
- dipole moment of, 32
 - electrostatic potential map of, 18, 31, 49, 651
 - sp^3 hybrid orbitals in, 18
 - structure of, 18
- 2-Methylbutane, molecular model of, 67
- Methylcyclohexane, 1,3-diaxial interactions in, 103–104
- conformations of, 103–104
 - mass spectrum of, 324
 - molecular model of, 117
- Methylcyclohex-1-ene, ^{13}C NMR spectrum of, 364
- 1-Methylcyclohexanol, 1H NMR spectrum of, 379
- 2-Methylcyclohexanone, chirality of, 117
- molecular model of, 117
- N*-Methylcyclohexylamine, ^{13}C NMR spectrum of, 673
- 1H NMR spectrum of, 673
- Methylene group, **184**
- 9-Methylguanine, electrostatic potential map of, 876a
- 6-Methylhept-5-en-2-ol, DEPT-NMR spectra of, 362
- 5-Methylhexan-2-one, mass spectrum of, 525
- Methyl lithium, electrostatic potential map of, 30, 152
- polar covalent bond in, 29–30
- Methylmagnesium iodide, electrostatic potential map of, 392
- N*-Methylmorpholine *N*-oxide, alkene hydroxylation with OsO_4 and, 230
- 2-Methylpentane, mass spectrum of, 349c
- 2-Methylpentan-3-ol, mass spectrum of, 327
- 2-Methylpent-2-ene, mass spectrum of, 325
- p*-Methylphenol, pK_a of, 440
- 2-Methylpropane, molecular model of, 67
- 2-Methylpropene, heat of hydrogenation of, 193
- Metoprolol, synthesis of, 470
- Mevacor, mechanism of action of, 2, 849–850
- Mevaldehyde, biosynthesis of, 588–589
- Mevalonate, biosynthesis of, 830–833
- decarboxylation of, 832–833
 - isopentenyl diphosphate from, 830–833
 - phosphorylation of, 832–833
- Micelle (soap), **810**
- Michael reaction, **632–633**
- acceptors in, 633
 - donors in, 633
 - mechanism of, 632
 - Stork enamine reaction and, 635–636
- Microwaves, electromagnetic spectrum and, 330
- Mineralocorticoid, **841**
- Minor groove (DNA), 856–857
- Mitomycin C, structure of, 677j
- Molar absorptivity, **344**
- Molecular ion (M^+), **321**
- Molecular mechanics, 111
- Molecular model, acetaminophen, 27a
- acetyl CoA carboxylase, 530
 - acetylene, 17
 - acyl CoA dehydrogenase, 179
 - adenine, 58b
 - N*6-adenine methyltransferase, 382
 - adrenaline, 145a
 - alanine, 27, 678
 - alanylserine, 689
 - α helix (protein), 701
 - D*-amino-acid aminotransferase 714
 - p*-aminobenzoic acid, 24
 - anisole, 437
 - anti periplanar geometry, 424
 - arecoline, 65
 - aspartame, 27a
 - aspirin, 16
 - bacteriorhodopsin, 319
 - p*-bromoacetophenone, 360
 - bromocyclohexane, 101
 - butane, 67
 - tert*-butyl carbocation, 201
 - cis*-but-2-ene, 187, 192
 - trans*-but-2-ene, 187, 192
 - C-terminal domain of spider dragline silk protein, 925
 - camphor, 110
 - cellulose, 763
 - chair cyclohexane, 98
 - chlorotrimethylsilane, 462
 - cholesterol, 839
 - cholic acid, 531
 - chorismate mutase, 905
 - citrate synthase, 678, 708
 - citric acid, 27
 - coniine, 27
 - cyclobutane, 96
 - cyclodecapentaene, 273

- Molecular model (*continued*)
 cyclohexane ring flip, 101
 cyclopentane, 96
 cyclopropane, 91, 95
 cytosine, 58b
cis-decalin, 109, 838
trans-decalin, 109, 838
 decane, 84
 diethyl ether, 437
 dimethyl sulfide, 19
cis-1,2-dimethylcyclopropane, 91
trans-1,2-dimethylcyclopropane, 91
 2,2-dimethylpropane, 67
 DNA, 857
 dopamine, 656
 eclipsed ethane conformation, 80
 enflurane, 118
 enoyl CoA hydratase, 212
 ethane, 10, 13, 67
 ethanol, 436
 ethylene, 15
 (*S*)-fluoxetine, 142
 fructose-1,6-bisphosphate aldolase, 348
 α -D-glucopyranose, 750
 β -D-glucopyranose, 750
 glucose, 99, 107
 glutamine synthase, 644
 glycogen synthase, 113
 halomon, 431
 hemoglobin, 265
 hexane, 14
 hexokinase, 174, 738
 HIV protease, 28
 HMG-CoA reductase, 2
 hydroxyacyl-CoA dehydrogenase, 805
 (*S*)-ibuprofen, 144
 isobutane, 67
 isoleucine, 130
 β -ketoacyl-CoA thiolase, 599
 lactic acid, 116
 lactose, 764
 lidocaine, 86a
 (–)-limonene, 141
 (+)-limonene, 141
 linolenic acid, 808
 liver alcohol dehydrogenase, 435
 maltose, 763
 mannose, 107
 membrane channel protein, 59, 87
 menthol, 97
meso-tartaric acid, 131
 methane, 13, 67
 methanethiol, 19
 methanol, 19, 436
 methionine, 127
 methyl phosphate, 19
 methylamine, 18
 2-methylbutane, 67
 methylcyclohexane, 117
 2-methylcyclohexanone, 117
 2-methylpropane, 67
 naphthalene, 58a
 Newman projections, 80
 norbornane, 110
 norcoclaurine synthase, 877
 oseltamivir, 111
 pancreatic lipase, 555
 pentane, 67
 phenylalanine, 86a
 phosphoglucosyltransferase, 492
 phosphoribosyl-diphosphate synthetase, 852
 piperidine, 662
 β -pleated sheet (protein), 702
 propane, 67, 81
 protein kinase A, 146
 pseudoephedrine, 145a
R-glyceraldehyde, 741–742
 serine, 145a
 serylalanine, 690
S-malate, 368
 staggered ethane conformation, 80
 stearic acid, 808
 steroid, 838
 sucrose, 765
 syn periplanar geometry, 424
 tamiflu, 111
 testosterone, 109
 tetrahydrofuran, 437
 threose, 118
 trimethylamine, 647
 triose-phosphate isomerase, 773
 tRNA, 863
 twist-boat cyclohexane, 99
 ubiquinone–cytochrome *c* reductase, 350
 urocanase, 735
 vitamin C, 551
 Molecular orbital (MO) theory, 20–21
 Molecular orbital, **20**
 algebraic signs of lobes in, 20–21, 186
 antibonding, **20–21**
 benzene and, 271
 bonding, **20–21**
 buta-1,3-diene, 243–244, 906
 conjugated dienes and, 243–244
 ethylene, 906
 1,3,5-hexatriene, 907
 Hückel $4n + 2$ rule and, 273
 Molecular weight, determination of, 322
 Molecule, electron-dot structures of, 8–9
 lone-pair electrons in, 9
 Molozonide, **231**
 Monomer, **235**
 Monosaccharide(s), **739**
 aldaric acids from, 758
 alditols from, 756–757
 aldonic acids from, 758
 anomers of, 750–751
 configurations of, 746–747
 cyclic forms of, 750–751
 essential, 761–762
 esters from, 754
 ethers from, 754
 glycosides of, 755
 hemiacetal forms of, 750–751
 osazones from, 772f
 oxidation of, 757–759
 phosphorylation of, 756
 reaction with acetic anhydride, 754
 reaction with NaBH₄, 756–757
 reduction of, 756–757
 see also Aldose
 uronic acids from, 758–759
 Monoterpene, **210**
 Monoterpenoid, **829**
 Morphine, biosynthesis of, 884–892
 from opium, 884
 from thebaine, 892–893
 mechanism of action of, 885
 specific rotation of, 120
 structure of, 57
 Morphine rule, **885**
 MRI, *see* Magnetic resonance imaging, 380
 mRNA, *see* Messenger RNA
 MS, *see* Mass spectrometry
 Mullis, Kary, 869
 Multiplet (NMR), **371–373**
 table of, 373
 Mutarotation, **751**
 glucose and, 751–752
 mechanism of, 752
 L-Mycarose, structure of, 901
 3-*O*-Mycarosylerythronolide B, structure of, 901
 Mycomycin, structure of, 145h
 Mylar, structure of, 591
 Myoglobin, α helix in, 701
 ribbon model of, 701
 Myrcene, structure of, 209
 Myristic acid, catabolism of, 819–820
 structure of, 807

n (normal), 67
n + 1 rule (NMR), **372**
 N-terminal amino acid, **690**
 N6-Adenine methyltransferase, function of, 382
 molecular model of, 382
 NAD⁺, *see* Nicotinamide adenine dinucleotide
 NADH, *see* Nicotinamide adenine dinucleotide (reduced)
 NADPH, *see* Nicotinamide adenine dinucleotide phosphate (reduced)
 Naming, acid anhydrides, 556
 acid chlorides, 556
 acid halides, 556
 acyl groups, 532
 acyl phosphates, 557
 alcohols, 437–438
 aldehydes, 493
 aldoses, 747–748
 alkanes, 68–69, 72–76
 alkenes, 183–184
 alkyl groups, 70–71, 75–76
 alkyl halides, 383–384
 alkynes, 185
 alphabetization and, 75–76
 amides, 557
 amines, 645–646
 aromatic compounds, 266–268
 carboxylic acid derivatives, 556–558

- carboxylic acids, 531–532
 crown ethers, 472
 cycloalkanes, 88–90
 cycloalkenes, 184
 eicosanoids, 827
 enzymes, 704
 esters, 556
 ethers, 464–465
 heterocyclic amines, 646
 ketones, 494
 nitriles, 533
 phenols, 438
 prostaglandins, 827
 sulfides, 465
 thioesters, 557
 thiols, 438
- Naphthalene, aromaticity of, 279–280
 electrostatic potential map of, 280
 Hückel $4n + 2$ rule and, 279
 molecular model of, 58a
 reaction with Br_2 , 279
 resonance in, 279
- Naproxen, structure of, 315
- Natural gas, composition of, 85
 thiols in, 463
- Natural product, **877**
 alkaloids, 879
 bioprospecting for, 903
 classification of, 878–879
 drugs from, 176
 enzyme cofactors, 879
 fatty-acid derived substances, 879
 nonribosomal polypeptides, 879
 polyketides, 879
 terpenoids and steroids, 878
- Natural rubber, structure of, 258
- NBS, *see* *N*-Bromosuccinimide
- NDA, *see* New drug application, 176–177
- Neopentyl group, **76**
 $\text{S}_{\text{N}}2$ reaction and, 402
- Neuraminic acid, biosynthesis of, 762
 influenza virus and, 762
- Neuraminidase, influenza virus and, 802
- New drug application (NDA), 176–177
- New molecular entity (NME), number of, 176
- Newman projection, **80**
 molecular model of, 80
- Nicotinamide adenine dinucleotide,
 biological oxidations and, 458, 706
 biological reductions with, 517
 mechanism of, 517
 oxidative deamination and, 723
 structure and function of, 706
 yeast alcohol dehydrogenase and,
 139–140
- Nicotinamide adenine dinucleotide
 (reduced), mechanism of reduction
 with, 446–447
 structure of, 175
- Nicotinamide adenine dinucleotide
 phosphate (reduced), biological
 reductions with, 226
 mechanism of reduction with, 446–447
- Nicotine, structure of, 27b, 644
- Ninhydrin, reaction with amino acids, 692
- Nitration (aromatic), 286
- Nitric acid, $\text{p}K_{\text{a}}$ of, 45
- Nitrile(s), **532**
 alkylation of, 618
 amides from, 545–546
 amines from, 547
 carboxylic acids from, 541, 545–546
 from alkyl halides, 541
 from amides, 544–545
 Grignard reaction of, 547
 hydrolysis of, 541, 545–546
 IR spectroscopy of, 549
 ketones from, 547
 mechanism of hydrolysis of, 545–546
 naming, 533
 naturally occurring, 544
 NMR spectroscopy of, 549
 nucleophilic additions to, 545
 $\text{p}K_{\text{a}}$ of, 608
 reaction summary of, 553–554
 reaction with LDA, 618
 reaction with LiAlH_4 , 547
 reduction of, 547
 synthesis of, 544–545
- Nitrile group, directing effect of, 297–298
 inductive effect of, 297
 orienting effect of, 300
 resonance effect of, 298
- Nitrile rubber polymer, structure and uses
 of, 931
- Nitro group, directing effect of, 297–298
 inductive effect of, 297
 orienting effect of, 300
 resonance effect of, 298
- Nitroarene, arylamines from, 655
 reaction with iron, 655
 reaction with tin, 655
 reduction of, 655
- Nitrobenzene, aniline from, 287
 reduction of, 287
 synthesis of, 286
- p*-Nitrobenzoic acid, $\text{p}K_{\text{a}}$ of, 539
- Nitrogen rule (mass spectrometry), **673**
- Nitronium ion, 286
 electrostatic potential map of, 286
- p*-Nitrophenol, $\text{p}K_{\text{a}}$ of, 440
- p*-Nitrophenoxide ion, resonance in, 442
- NME, *see* New molecular entity, 176
- NMR, *see* Nuclear magnetic resonance
- Nomenclature, *see* Naming
- Nomex, structure of, 942a
- Nonbonding electrons, **9**
- Noncoding strand (DNA), **861**
- Noncovalent interaction(s), **54**
 kinds of, 54–55
 dipole–dipole forces and, 54
 dispersion forces and, 54
 hydrogen bonds and, 54–55
 van der Waals forces and, 54
- Nonequivalent protons, spin–spin splitting
 and, 377–378
 tree diagram in NMR of, 378
- Nonessential amino acid, **683**, 731–732
 biological precursors of, 732
- Nonribosomal polypeptide, **879**
- Norbornane, molecular model of, 110
 structure of, 110
- (*S*)-Norcoclaurine, biosynthesis of, 888–889
- Norcoclaurine synthase, function of, 877
 molecular model of, 877
- Norepinephrine, biosynthesis of, 306
- Norethindrone, structure and function of,
 841
- Normal (*n*) alkane, **67**
- Norsorex, synthesis of, 936
- Novocain, structure of, 57
- Noyori, Ryoji, 526
- NSAID, **314–315**
- Nuclear magnetic resonance spectrometer,
 operation of, 354
- Nuclear magnetic resonance spectroscopy
 (NMR), **350**
 acid anhydrides, 593–594
 acid chlorides, 593–594
 alcohols, 476–477
 aldehydes, 523–524
 amides, 593–594
 amines, 672–673
 ^{13}C chemical shifts in, 358–359
 calibration peak for, 355–356
 carboxylic acid derivatives, 593–594
 carboxylic acids, 549
 chart for, 355
 coupling constants in, 373
 delta scale for, 356
 DEPT-NMR and, 361–363
 diastereotopic protons and, 367
 enantiotopic protons and, 366
 energy levels in, 352
 esters, 593–594
 ethers, 477
 field strength and, 351–352
 FT-NMR and, 357–358
 ^1H chemical shifts in, 368–369
 homotopic protons and, 366
 integration of ^1H spectra, 370
 ketones, 524
 multiplets in, 373
 $n + 1$ rule and, 372
 nitriles, 549
 overlapping signals in, 376–377
 peak assigning in ^{13}C spectra, 359,
 361–362
 peak size in ^{13}C spectra, 360
 peak size in ^1H spectra, 370
 phenols, 477
 principle of, 350–352
 proton equivalence and, 365–367
 radiofrequency energy and, 351–352
 shielding in, 352–353
 signal averaging in, 357–358
 spin-flips in, 351
 spin–spin splitting in, 371–373
 time scale of, 354
 uses of ^{13}C spectra in, 363–364
 uses of ^1H spectra in, 379

- ¹³C Nuclear magnetic resonance spectrum,
acetaldehyde, 524
acetophenone, 524
benzaldehyde, 524
benzoic acid, 549
p-bromoacetophenone, 359
butan-2-one, 359e, 524
crotonic acid, 549
cyclohexanol, 476
cyclohexanone, 524
ethyl benzoate, 381f
methyl acetate, 353
methyl propanoate, 361
1-methylcyclohexene, 364
N-methylcyclohexylamine, 673
pentan-1-ol, 358
propanenitrile, 549
propanoic acid, 549
- ¹H Nuclear magnetic resonance spectrum,
acetaldehyde, 524
anethole, 482g
bromoethane, 371
2-bromopropane, 373
trans-cinnamaldehyde, 377
cyclohexylmethanol, 379
ethyl acetate, 593
p-methoxypropiofenone, 373
methyl acetate, 353
1-methylcyclohexanol, 379
N-methylcyclohexylamine, 673
phenacetin, 677f
phenylacetic acid, 550
propan-1-ol, 477
toluene, 377
- Nuclear spin, common nuclei and, 352
NMR and, 350–351
- Nuclease, function of, 871
- Nucleic acid, **852–855**
biosynthesis of, 873–874
catabolism of, 871–873
hydrolysis of, 871
phosphodiester bonds in, 855
see also Deoxyribonucleic acid,
Ribonucleic acid
structure of, 855
synthesis of, 866–869
- Nucleophile, **154–155**
characteristics of, 159–160
curved arrows and, 154, 159–161
electrostatic potential maps of, 155
examples of, 155
S_N1 reaction and, 415
S_N2 reaction and, 403–404
- Nucleophilic acyl substitution reaction,
488, 559–562
abbreviated mechanism for, 733
acid anhydrides, 576–578
acid chlorides, 570–576
acid halides, 570–576
amides, 584–586
biological example of, 570–571
carboxylic acids and, 564–570
esters, 579–583
kinds of, 561–562
mechanism of, 559–560
reactivity in, 560–561
- Nucleophilic addition reaction, **486–487, 497–500**
acid catalysis of, 501–502
base catalysis of, 501–502
kinds of, 499
mechanism of, 497–498
steric hindrance in, 499
trajectory of, 497–499
- Nucleophilic aromatic substitution reaction,
303–305
characteristics of, 304–305
mechanism of, 304
- Nucleophilic substitution reaction, **396**
biological examples of, 418–419
see also S_N1 reaction, S_N2 reaction
- Nucleophilicity, **403**
basicity and, 403–404
table of, 404
trends in, 403–404
- Nucleosidase, function of, 871
- Nucleoside, **852–855**
- Nucleotidase, function of, 871
- Nucleotide, **852–855**
biosynthesis of, 873–874
catabolism of, 871–873
3' end of, **855**
5' end of, **855**
- Nucleus, size of, 4
- Nylon, **590**
naming, 590
uses of, 591
- Nylon 6, synthesis of, 932
- Nylon 66, structure of, 591
synthesis of, 932
- o*, *see* Ortho, 267
- Octane number (fuel), 86
- oic acid*, name ending for carboxylic acids,
531
- Okazaki fragment, DNA replication and,
859
- ol*, alcohol name ending, 437
- Olefin, **179**
- Olefin metathesis polymerization, **934–936**
Grubbs catalyst for, 934–935
kinds of, 935–936
mechanism of, 934–935
- Oleic acid, structure of, 807
- Oligonucleotide, **866**
synthesis of, 866–869
- Olive oil, composition of, 807
- Omega-3 fatty acid, 808
- one*, ketone name ending, 494
- onitrile*, nitrile name ending, 533
- Opium, **884**
- Optical activity, measurement of, **119–120**
- Optical isomers, **121**
- Orbital, **4**
hybridization of, 12–19
- Organic acids, **48–49**
Organic bases, 49–50
Organic chemicals, elements found in, 3
number of, 59
risk evaluation of, 25
toxicity of, 25
- Organic chemistry, **3**
- Organic reactions, conventions for writing,
196
kinds of, 147
- Organic synthesis, enantioselective, 526–527
strategy for, 308–313
- Organoborane, from alkenes, 220
reaction with H₂O₂, 220
- Organodiphosphate, biological S_N1
reactions and, 418–419
Friedel-Crafts reactions and, 292–293
- Organohalide, biological uses of, 431
naturally occurring, 430–431
number of, 430
reaction with Gilman reagents, 393–394
- Organomagnesium halide, *see* Grignard
reagent
- Organometallic compound, **391**
polarity of, 152
- Organometallic coupling reaction, 393–395
mechanism of, 394
- Organopalladium compound,
Suzuki–Miyaura reaction of, 394
- Organophosphate, electrostatic potential
map of, 61
polarity of, 61
*sp*³ hybrid orbitals in, 19
structure of, 19
- Ornithine
biosynthesis of, 734
citrulline from, 725–726
from arginine, 727
reaction with carbamoyl phosphate,
725–726
urea cycle and, 725–726
- Ortho (*o*), **267**
- Ortho- and para-directing group, **296**
- Osazone, 772f
- ose*, carbohydrate name ending, 740
- Oseltamivir, molecular model of, 111
mechanism of, 802–803
- oside*, glycoside name ending, 755
- Osmium tetroxide, reaction with alkenes, 230
toxicity of, 230
- Oxalic acid, structure of, 532
- Oxaloacetate, aspartate from, 724, 731
decarboxylation of, 797–798
from malate, 792
from pyruvate, 796–797
phosphoenolpyruvate from, 797–798
reaction with acetyl CoA, 789
- Oxaloacetic acid, structure of, 532
- Oxalosuccinate, decarboxylation of, 790
from isocitrate, 790
- Oxaphosphetane, **513**
- Oxidation, alcohols and, 456–458
aldehydes, 497
Dess–Martin periodinane and, 457–458

- FAD and, 817–818
 NAD⁺ and, 458
 organic, **227**
 phenols, 459
 Oxidative deamination, **723**
 mechanism of, 723
 Oxidative decarboxylation, **783**
 α -ketoglutarate and, 790
 mechanism of, 784–787
 pyruvate and, 783–787
 thiamin diphosphate and, 785–786
 Oxidoreductase, **704–705**
 Oxime, 760
 Oxirane, **227**
see also Epoxide
 Oxo group, **494**
 Oxyfluorfen, synthesis of, 305
 Oxymercuration, mechanism of, 219–220
 Oxymercuration–demercuration, **219**
 regiochemistry of, 219–220
 -*oyl*, name ending for acyl groups, 532
 Ozone, laboratory preparation of, 231
 reaction with alkenes, 231–232
 Ozonide, **231**
 dangers of, 231
 reduction of with zinc, 231

p-, *see* Para, 267
p Orbital, algebraic signs of lobes in, 20–21, 186
 Paclitaxel, origin of, 903
 structure and function of, 903
 Palmitic acid, fatty acid biosynthesis and, 825
 structure of, 807
 Palmitoleic acid, structure of, 807
 PAM resin, peptide synthesis and, 699
 Pancreatic lipase, function of, 555
 molecular model of, 555
Papaver somniferum, morphine from, 884
Para (*p*), **267**
 Paraffin, **78**
 Parent (nomenclature), **73**
 Parent peak (mass spectrum), **321**
 Partial charge, 29–30
 Pasteur, Louis, 121
 Pasteur, enantiomers and, 121
 Patchouli alcohol, structure of, 829
 Pauling, Linus, 12
 PCR, *see* Polymerase chain reaction, 869–870
 PDB, *see* Protein Data Bank
 Peanut oil, composition of, 807
 Penicillin, discovery of, 594
 mechanism of action of, 595
 Penicillin G, structure of, 584
 Penicillin V, specific rotation of, 120
 stereochemistry of, 143
 Penta-1,4-diene, electrostatic potential map of, 244
 Pentadienyl radical, resonance forms of, 41
 Pentane, molecular model of, 67
 Pentane-2,4-dione anion, resonance forms of, 40
 enol content of, 601
 pK_a of, 609
 Pentan-1-ol, ¹³C NMR spectrum of, 358
 Pentobarbital, synthesis of, 640
 Pentose phosphate pathway, 804c, 804d
 PEP, *see* Phosphoenolpyruvate
 Pepsin, isoelectric point of, 686
 Peptide, **679**
 amino acid analysis of, 691–692
 backbone of, 690
 covalent bonding in, 690
 disulfide bonds in, 691
 Edman degradation of, 693–695
 hydrolysis of, 691
 partial hydrolysis of, 695
 reaction with phenylisothiocyanate, 693–694
 sequencing of, 693–695
 solid-phase synthesis of, 698–700
 synthesis of, 696–700
 Peptide bond, **689**
 DCC formation of, 696
 restricted rotation in, 690
 Pericyclic reaction, **247, 905**
 Claisen rearrangement and, 471–472
 cycloaddition reactions and, 913–916
 Diels–Alder reaction and, 247–251
 electrocyclic reactions and, 908–912
 frontier orbitals and, 907
 kinds of, 905
 sigmatropic reactions and, 917–921
 stereochemical rules for, 922
 Woodward–Hoffmann rules for, 906–907
 Periodic acid, diol cleavage with, 232
 Periplanar geometry **423**
 E2 reactions and, 423–424
 Peroxyacid, **227**
 reaction with alkenes, 227
 Petroleum, catalytic cracking of, 86
 composition of, 85
 gasoline from, 85–86
 refining of, 85–86
Pfu DNA polymerase, 870
 Pharmaceuticals, approval procedure for, 176–177
 fluorine-containing, 284–285
 origin of, 176
 Phenacetin, ¹H NMR spectrum of, 677f
 Phenol, **435**
 acidity of, 439–442
 Bakelite from, 939–940
 electrophilic aromatic substitution of, 300–301
 electrostatic potential map of, 297
 hydrogen bonds in, 439
 IR spectroscopy of, 476
 IR spectrum of, 476
 naming, 438
 NMR spectroscopy of, 477
 oxidation of, 459
 phenoxide ions from, 440–441
 pK_a of, 440
 properties of, 439–442
 quinones from, 459
 reaction summary of, 482
 uses of, 436
 Phenolic resin, 939–940
 Phenoxide ion, **440**
 electrostatic potential map of, 442
 resonance in, 441
 Phenyl group, **267**
 Phenylacetaldehyde, aldol reaction of, 621
 IR spectrum of, 341
 Phenylacetylene, IR spectrum of, 342
¹H NMR spectrum of, 550
 Phenylalanine, from chorismate, 472
 molecular model of, 86a
 structure and properties of, 680
 Phenylisothiocyanate, Edman degradation and, 693–694
 Phenylthiohydantoin, Edman degradation and, 693–694
 Phosphatidic acid, structure of, 812
 Phosphatidylcholine, structure of, 812
 Phosphatidylethanolamine, structure of, 812
 Phosphatidylserine, structure of, 812
 Phosphine(s), chirality of, 137, 689
 Phosphite, **868**
 oxidation of, 868
 Phosphodiester, nucleic acid and, 855
 Phosphoenolpyruvate, from oxaloacetate, 797–798
 from 2-phosphoglycerate, 782
 2-phosphoglycerate from, 798
 pyruvate from, 782
 function of, 492
 Phosphoglucoisomerase, molecular model of, 492
 2-Phosphoglycerate, from phosphoenolpyruvate, 798
 from 3-phosphoglycerate, 781
 3-Phosphoglycerate, from 1,3-bisphosphoglycerate, 781
 isomerization of, 781
 Phospholipid, **811–812**
 abundance of, 812
 classification of, 811
 function of, 812
 Phosphopantetheine, structure of, 588, 716
 Phosphoramidite, **868**
 Phosphorane, **513**
 Phosphoribosyl-diphosphate synthetase, function of, 852
 molecular model of, 852
 Phosphoric acid, pK_a of, 45
 Phosphoric acid anhydride, 716
 Phosphorus oxychloride, alcohol dehydration with, 454
 Phosphorus tribromide, reaction with alcohols, 390–391, 405, 452
 Phosphorylation, ATP and, 717
 mechanism of, 717
 Photochemical reaction, **908**

- Photon, **329**, 331
energy of, 331
- Photosynthesis, 739
- Phthalic acid, structure of, 532
- Phylloquinone, biosynthesis of, 293
- Physiological pH, **537**
- Phytyl diphosphate, vitamin K₁
biosynthesis and, 293
- Pi (π) bond, **15**
acetylene and, 17
ethylene and, 14–15
molecular orbitals in, 21
- Picometer, **4**
- Pinacol rearrangement, 482j
- Pineapple, esters in, 578
- Piperidine, molecular model of, 662
structure of, 646
- PITC, *see* Phenylisothiocyanate, 693–694
- pK_a, **44**
table of, 45
- PKS, *see* Polyketide synthase
- Planck equation, 331
- Plane of symmetry, **115**–116
meso compounds and, 131
- Plane-polarized light, **119**
- Plasmalogen, structure of, 851a
- Plastic, recyclable, 940–941
see also Polymer
- Plasticizer, **579**, **938**
structure and function of, 938
toxicity of, 938
- Plavix, structure of, 27f
- β -Pleated sheet (protein), 701–702
- PLP, *see* Pyridoxal phosphate
- PMP, *see* Pyridoxamine phosphate
- Poison ivy, urushiols in, 436
- Polar aprotic solvent, **406**
S_N1 reaction and, 416
S_N2 reaction and, 406–407
- Polar covalent bond, **28**–29
dipole moments and, 31–32
electronegativity and, 29–30
electrostatic potential maps and, 30
polar reactions and, 152–155
- Polar reaction, **149**, 152–155
characteristics of, 152–155
curved arrows in, 154, 159–161
electrophiles in, 154–155
nucleophiles in, 154–155
- Polarimeter, 119
- Polarizability, **153**
- Polyamide, **589**
- Polycarbonate, **933**
- Polycyclic aromatic compound, **279**
- Polycyclic compound, **108**
conformations of, 108–110
- Polyester, **589**
uses of, 591
annual worldwide production of, 237
- Polyethylene, crystallites in, 937
high-density, 929
high-molecular-weight, 929
kinds of, 929
low-density, 929
synthesis of, 237–238
ultrahigh-molecular-weight, 929
Ziegler–Natta catalysts and, 929
- Polyimide, structure of, 598
- Poly(ethylene terephthalate), structure of, 938
- Poly(glycolic acid), biodegradability of, 941
- Poly(hydroxybutyrate), biodegradability of, 941
- Poly(lactic acid), biodegradability of, 941
- Polyketide(s), **879**
number of, 879, 895
biosynthesis of, 894–895
examples of, 894
- Polyketide synthase (PKS), **895**
domains in, 895
modules in, 895
size of, 895
- Polymer(s), **235**
atactic, **928**
biodegradable, 940–941
biological, 235–236
chain-growth, **237**, **926**–927
classification of, 926
crystallites in, 937
elastomer, 939
fiber, 938
glass transition temperature of, 937
isotactic, **928**
kinds of, 937–940
melt transition temperature of, 937
plasticizers in, 938
recycling codes for, 941
step-growth, **589**, **932**–934
syndiotactic, **928**
thermoplastic, 937–938
thermosetting resin, 939–940
van der Waals forces in, 937
- Polymerase chain reaction (PCR), **869**–870
amplification factor in, 869
steps in, 870
taq DNA polymerase in, 870
- Polymerization,
anionic, 927
cationic, 926
mechanism of, 237–238
radical, 237–238
Ziegler–Natta catalysts for, 929
- Polypeptide, nonribosomal, 879
- Polypropylene, polymerization of, 928–929
stereochemical forms of, 928
- Polysaccharide, **765**–768
synthesis of, 767–768
- Polyunsaturated fatty acid, **807**
- Polyurethane, **933**
foam, 934
kinds of, 933–934
stretchable, 933–934
- Poly(vinyl butyral), uses of, 942b
- Poly(vinyl chloride), plasticizers in, 938
- Porphobilinogen, biosynthesis of, 677h
- Potassium permanganate, reaction with alkenes, 232
- Pravachol, mechanism of action of, 2, 849–850
structure of, 86f
- Pravastatin, mechanism of action of, 2, 849–850
structure of, 86f
- Prefix (nomenclature), **73**
- Priestley, Joseph, 258
- Prilocaine, structure of, 57
- Primary alcohol, **437**
- Primary amine, **645**
- Primary carbon, **70**–71
- Primary hydrogen, 71
- Primary protein structure, **700**
- Priming reaction, fatty acid biosynthesis and, 821
- pro-R* prochirality center, **139**
- pro-S* prochirality center, **139**
- Problems, how to work, 26–27
- Procaine, structure of, 27d, 57
- Prochirality, **138**–140
assignment of, 138–139
biological reactions and, 139–140
Re, 138
Si, 138
- Prochirality center, **139**
pro-R, 139
pro-S, 139
- Progesterone, structure and function of, 841
- Progesterin, **840**
function of, 840–841
- Proline, biosynthesis of, 658, 734
catabolism of, 737a
from glutamate, 734
structure and properties of, 680
- Promotor sequence (DNA), 860
- Propagation step (radical reaction), **150**
- Propane, bond rotation in, 81
conformations of, 81
mass spectrum of, 321
molecular model of, 67
- Propane conformation, molecular model of, 81
- Propanenitrile, ¹³C NMR absorptions in, 549
- Propanoic acid, ¹³C NMR absorptions in, 549
- Propan-1-ol, ¹H NMR spectrum of, 477
- Propenal, electrostatic potential maps of, 249
- Propenenitrile, electrostatic potential maps of, 249
- Propionyl CoA, catabolism of, 819–820
- Propyl group, 71
- Propylene, annual worldwide production of, 180
heat of hydrogenation of, 193
industrial uses of, 180
- Prostaglandin(s), **826**–828
biosynthesis of, 827–828
functions of, 150–151, 826
naming, 827
occurrence of, 826
- Prostaglandin E₁, structure of, 826
structure of, 87

- Prostaglandin E₂, biosynthesis of, 827–828
 Prostaglandin F_{2α}, structure of, 93
 Prostaglandin H₂, biosynthesis of, 151, 240–241, 827–828
 Prostaglandin I₂, structure of, 826
 Protease, mechanism of action of, 585
 Protecting group, **461**
 alcohols and, 460–462
 aldehydes and, 511
 amino acids, 696–697
 DNA synthesis and, 867
 ketones and, 511
 Protein, **679**
 α helix in, 700–701
 backbone of, 690
 biological hydrolysis of, 585
 biosynthesis of, 861–863
 classification of, 700
 denaturing, 702
 electrophoresis of, 687
 fibrous, **700**
 globular, **700**
 isoelectric point of, 686
 number of in humans, 866
 β-pleated sheet in, 701–702
 posttranslational modifications of, 866
 primary structure of, 700
 purification of, 687
 quaternary structure of, 700
 reaction with Sanger's reagent, 303
 secondary structure of, 700–702
 see also Peptide
 structure of, 700–703
 tertiary structure of, 700–702
 X-ray crystallography of, 348
 Protein Data Bank, **710–711**
 uses of, 710–711
 visualizing enzyme structures and, 735–736
 X-ray crystallographic structures in, 348
 Protein kinase A, function of, 146
 molecular model of, 146
 Protic solvent, S_N1 reaction and, 416
 S_N2 reaction and, 406
 Proton equivalence, ¹H NMR spectroscopy and, 365–367
 Protonated methanol, electrostatic potential map of, 153
 Protosteryl cation, steroid biosynthesis and, 846–847
 Prozac, see Fluoxetine
 Pseudoephedrine, molecular model of, 145a
 PTH, see Phenylthiohydantoin, 693–694
 Purine, aromaticity of, 280
 basicity of, 671
 catabolism of, 871–873
 electrostatic potential map of, 671
 Pyramidal inversion, amines and, 647–648
 energy barrier to, 648
 Pyran, structure of, 750
 Pyranose, **750**
 Pyridine, aromaticity of, 276, 668
 basicity of, 650
 bond lengths in, 668
 dipole moment of, 669
 electrophilic substitution reactions of, 668
 electrostatic potential map of, 276
 Hückel 4*n* + 2 rule and, 276
 p*K*_a of, 668
 Pyridoxal phosphate, alanine catabolism and, 728
 amino acid deamination and, 719–721
 amino acid transamination and, 719–721
 asparagine catabolism and, 730–731
 biosynthesis of, 879–884
 from pyridoxamine phosphate, 721–722
 imines of, 505, 721
 serine catabolism and, 729–730
 structure and function of, 707
 Pyridoxamine phosphate, structure of, 722
 transamination of, 721–722
 Pyridoxine, structure of, 719
 Pyridoxine 5' phosphate, from
 1-deoxyxylulose 5-phosphate, 883
 oxidation of, 884
 Pyrimidine, aromaticity of, 276
 basicity of, 650, 669
 electrostatic potential map of, 276
 Hückel 4*n* + 2 rule and, 276
 Pyrrole, aromaticity of, 276–277, 666
 basicity of, 650, 666
 electrophilic substitution reactions of, 667
 electrostatic potential map of, 276–277, 666
 Hückel 4*n* + 2 rule and, 276–277
 industrial synthesis of, 666
 Pyrrolidine, electrostatic potential map of, 666
 enamines from, 635
 structure of, 646
 Pyrrolysine, structure of, 682
 Pyruvate, acetyl CoA from, 783–787
 alanine from, 731
 carboxylation of, 796–797
 catabolism of, 783–787
 decarboxylation of, 783–787
 from alanine, 728
 from phosphoenolpyruvate, 782
 from serine, 729–730
 oxaloacetate from, 796–797
 reaction with thiamine diphosphate, 785
 Pyruvic acid, hydrate of, 501
 Qiana, structure of, 598d
 Quartet (NMR), 373
 Quaternary ammonium salt, **645**
 Hofmann elimination and, 660–661
 Quaternary carbon, **70–71**
 Quaternary protein structure, **700**
 Quetiapine, structure of, 27e
 Quinine, structure of, 280, 670
 Quinoline, aromaticity of, 280
 electrophilic substitution reaction of, 670
 Quinone, **459**
 from phenols, 459
 hydroquinones from, 459
 reduction of, 459
 R configuration, **123**
 assignment of, 123–124
 R group, **71**
 Racemate, **133**
 Racemic mixture, **133**
 Radical, **149**
 reactivity of, 149–151
 Radical reaction, **149–151**
 addition to alkenes, 237–238
 biological examples of, 150–151, 240–241
 characteristics of, 149–150
 fishhook arrows and, 148
 initiation steps in, 150
 polymerization, 237–238
 propagation steps in, 150
 prostaglandin biosynthesis and, 240–241
 termination steps in, 150
 Radio waves, electromagnetic spectrum and, 330
 Radiofrequency energy, NMR spectroscopy and, 351–352
 Rapa Nui, rapamycin from, 903
 Rapamycin, immunosuppressant activity of, 903
 structure and function of, 894
 Rate equation, **399**
 Rate-determining step, **409**
 Rate-limiting step, **409**
 Rayon, synthesis of, 765
 Re prochirality, **138**
 Reaction (polar), **149**, 152–155
 Reaction (radical), **149–151**
 Reaction coordinate, **168**
 Reaction energy diagram, **168–170**
 biological reactions and, 171–172
 electrophilic addition reactions and, 168–169
 endergonic reactions and, 169–170
 exergonic reactions and, 169–170
 intermediates and, 171
 Reaction intermediate, **170–171**
 Reaction mechanism, **148**
 Reaction rate, activation energy and, **169**
 Rearrangement reaction, **147**
 Red fox, scent marker in, 482g
 Reducing sugar, **758**
 Reduction, acid chlorides, 575
 aldehyde, 445–446, 504
 alkene, 223–226
 alkyne, 253
 amides, 586
 aromatic compounds and, 307
 biological with NADH and NADPH, 226
 carboxylic acids, 447
 ester, 447, 582–583
 ketone, 445–446, 504
 lactam, 586
 nitrile, 547
 organic, **223**
 quinone, 459
 Reductive amination, **657–658**
 biological example of, 658
 mechanism of, 657
 Refining (petroleum), 85–86

- Regiospecific, **197**
- Replication (DNA), **858–859**
error rate during, 859
- Replication fork (DNA), **858**
- Residue (protein), **689**
- Resolution (enantiomers), **133–134**
- Resonance, acetate ion and, 36–37
acetyl CoA anion and, 39
acyl cations and, 292
allylic carbocations and, 245–246
allylic radicals and, 387
amides and, 651
arylamines and, 652
benzene and, 37, 270
benzylic carbocation and, 413
benzylic radical and, 306
carboxylate ions and, 535–536
enolate ions and, 607
naphthalene and, 279
p-nitrophenoxide ion and, 442
pentadienyl radical and, 41
pentane-2,4-dione anion and, 40
phenoxide ion and, 441
- Resonance effect (electrophilic aromatic substitution), **298**
- Resonance form, 36–37
drawing, 39–40
electron movement and, 38–39
rules for, 37–39
three-atom groupings in, 39–40
stability of, 39
- Resonance hybrid, **37**
- Restriction endonuclease, **864**
- (*S*)-Reticuline, biosynthesis of, 889–890
epimerization of, 890–891
- Retinal, vision and, 347
- Reye's syndrome, aspirin and, 315
- Rhodopsin, isomerization of, 347
vision and, 347
- Ribavirin, structure of, 318g
- Ribonucleic acid (RNA), **852–855**
bases in, 853
biosynthesis of, 859–861
3' end of, 855
5' end of, 855
functional, **860**
kinds of, 860
messenger, **860**
ribosomal, **860**
size of, 854
small, **860**
structure of, 855
transfer, **860**
translation of, 861–863
- Ribonucleotide, biosynthesis of, 873–874
catabolism of, 871–873
structures of, 854
- Ribose, configuration of, 747
- Ribosomal RNA, **860**
function of, 861
- Ring-flip (cyclohexane), **101**
energy barrier to, 101
molecular model of, 101
- Ring-opening metathesis polymerization (ROMP), **935**
- Risk, chemicals and, 24–25
- RNA, *see* Ribonucleic acid
- Robinson, Robert, 885
- Rod cells, vision and, 347
- Rofecoxib, structure of, 315
- ROMP (ring-opening metathesis polymerization), **935**
- Rosuvastatin, mechanism of action of, 2, 849–850
- rRNA, *see* Ribosomal RNA
- Rubber, history of, 258–259
vulcanization of, 259
- S* configuration, **123**
assignment of, 123–124
- s*-Cis conformation, **249**
Diels–Alder dienes and, 249–250
- Saccharin, structure of, 770
sweetness of, 770
- SAH, *see* *S*-Adenosylhomocysteine
- Salt bridge (protein), **701**
- Salutaridine, biosynthesis of, 890–891
- SAM, *see* *S*-Adenosylmethionine
- Sanger, Frederick, 865
- Sanger dideoxy DNA sequencing, **865–866**
- Sanger's reagent, 303
uses of, 303
- Saponification, **579, 809**
mechanism of, 579–580
- Saran, structure and uses of, 930
- Saturated, **66**
- Sawhorse representation, **80**
- SBR polymer, structure and uses of, 931
- Schiff base, **505, 779**
see also Imine
- Scurvy, vitamin C and, 551
- sec*-Butyl group, 71
- Secobarbital, synthesis of 640
- Second-order reaction, **399**
- Secondary alcohol, **437**
- Secondary amine, **645**
- Secondary carbon, **70–71**
- Secondary hydrogen, 71
- Secondary metabolite, **877**
examples of, 877–878
function of, 877
number of, 877
- Secondary protein structure, **700–702**
 α helix in, 700–701
 β sheet in, 701–702
- Sedoheptulose, structure of, 740
- Selectfluor, aromatic fluorination with, 284
- Selenocysteine, structure of, 682
- Semiconservative replication (DNA), **858**
- Sense strand (DNA), **861**
- Sequence rules (Cahn–Ingold–Prelog), **122–125**
alkenes and, 188–189
enantiomers and, 122–125
- Serine, catabolism of, 729–730
molecular model of, 145a
pyruvate from, 729–730
structure and properties of, 681
- Seroquel, structure of, 27e
- Serylalanine, molecular model of, 690
- Sesquiterpene, **210**
- Sesquiterpenoid, **829**
- Sex hormone, **840–841**
- Sharpless, K. Barry, 526
- Sharpless epoxidation, 527
- Shielding (NMR), **352**
- Si* prochirality, **138**
- Sialic acid, **762**
- Side chain (amino acid), **682**
- Sigma (σ) bond, **11**
cylindrical symmetry of, 11
- Sigmatropic rearrangement, **917–918**
antarafacial geometry of, 918
biological example of, 922–923
examples of, 919–921
[1,5] hydrogen shift and, 919
notation for, 917–918
stereochemical rules for, 918
suprafacial geometry of, 918
vitamin D and, 922–923
- Signal averaging, FT-NMR spectroscopy and, 357–358
- Sildenafil, structure of, 665
- Silver oxide, Hofmann elimination reaction and, 660
- Silyl ether, alcohol protecting group, 461–462
- Simple sugar, **739**
- Simvastatin, mechanism of action of, 2, 849–850
structure of, 86f
- Single bond, electronic structure of, 13
- Sitagliptin, structure of, 285
- Skeletal structure, **22–23**
rules for drawing, 22–23
- Skunk scent, cause of, 463
- Small RNAs, **860**
- sn*-, naming prefix, 815
- S_N1 reaction, **409**
allylic halides in, 413
benzylic halides in, 413
biological example of, 418–419
carbocation in, 410–411
carbocation stability and, 413–414
characteristics of, 412–416
energy diagram for, 410
Hammond postulate and, 412–413
ion pairs in, 411
kinetics of, 409–410
leaving groups in, 414
mechanism of, 409–410, 414–415
nucleophiles and, 415
racemization in, 411
rate law for, 409
rate-limiting step in, 409–410
solvent effects on, 415–416
stereochemistry of, 410–411
substrate structure and, 413–414
summary of, 416–417
- S_N2 reaction, **399**
allylic halides in, 414
amines and, 656
benzylic halides in, 414
biological example of, 418–419
characteristics of, 401–408

- crown ethers and, 473
 electrostatic potential maps of, 400
 epoxide cleavage and, 469
 inversion of configuration in, 399–400
 kinetics of, 398–399
 leaving groups and, 404–406
 mechanism of, 399–400
 nucleophiles in, 403–404
 rate law for, 399
 solvent effects and, 406–407
 stereochemistry of, 399–400
 steric hindrance in, 401–402
 substrate structure and, 401–403
 summary of, 407
 table of, 404
 Williamson ether synthesis and, 467
- Soap, 809–810**
 history of, 809
 manufacture of, 809–810
 mechanism of action of, 810
 micelles of, 810
- Sodium amide, reaction with alcohols, 441**
- Sodium ammonium tartrate, optical activity of, 121**
- Sodium bisulfite, osmate reduction with, 230**
- Sodium borohydride, reaction with**
 aldehydes, 445
 reaction with ketones, 445
 reaction with organomercury compounds, 219–220
 reductive amination with, 657–658
- Sodium chloride, dipole moment of, 32**
- Sodium cyclamate, LD₅₀ of, 25**
- Sodium hydride, reaction with alcohols, 441**
- Solid-phase DNA synthesis, 866–869**
- Solid-phase peptide synthesis, 698–700**
see also Merrifield, 698–700
- Solvation, 406**
 carbocations and, 416
 S_N2 reaction and, 406
- Solvent, polar aprotic, 406**
 S_N1 reaction and, 415–416
 S_N2 reaction and, 406–407
- Soot, carcinogenic compounds in, 230**
- Sorbitol, structure of, 757**
- Spandex, synthesis of, 933–934**
- Specific rotation, 119–120**
 table of, 120
- Sphingomyelin, 812**
 function of, 812
 structure of, 812
- Spin-flip, NMR spectroscopy and, 351**
- Spin–spin splitting (NMR), 371–373**
 alcohols and, 477
 bromoethane and, 371–372
 2-bromopropane and, 372–373
n + 1 rule and, 372
¹³C NMR spectroscopy and, 374–375
¹H NMR spectroscopy and, 371–373
 nonequivalent protons and, 377–378
 origin of, 371–372
 rules for, 373–374
 tree diagrams and, 377–378
- Squalene, biological epoxidation of, 228, 842–843**
 from farnesyl diphosphate, 835, 842
 steroid biosynthesis and, 842–843
- Staggered conformation, 80**
 molecular model of, 80
- Standard state, biological, 164**
 thermodynamic, 164
- Starch, digestion of, 766–767, 774**
 glucose from, 774
 hydrolysis of, 774
 limit dextrin from, 774
 maltotriose from, 774
 structure of, 766
- Statins, heart disease and, 2, 849–850**
 mechanism of action of, 2, 849–850
- Stearic acid, molecular model of, 808**
 structure of, 807
- Step-growth polymer, 589, 932–934**
 table of, 590
- Stereochemistry, 79, 92**
 absolute configuration and, 124
 cis–trans alkene isomers and, 187
 cis–trans cycloalkane isomers and, 91–92
 diastereomers and, 127–128
 Diels–Alder reaction and, 249
E,Z alkene isomers and, 188–189
 E1 reaction and, 428
 E2 reactions and, 424–425
 enantiomers and, 114–115
 epimers and, 129
R,S configuration and, 123–124
 S_N1 reaction and, 410–411
 S_N2 reactions and, 399–400
- Stereogenic center, 116**
- Stereoisomers, 91**
 cis–trans isomers and, 91–92, 187
 diastereomers and, 127–128
 enantiomers and, 121
 epimers and, 129
 kinds of, 135–136
- Stereospecific, 235**
- Stereospecific numbering (*sn*-), 815**
- Steric hindrance, S_N2 reaction and, 401–402**
- Steric strain, 82**
 cis alkenes and, 191–192
 substituted cyclohexanes and, 103–104
- Steroid(s), 837–841**
 adrenocortical, 841
 anabolic, 841
 biosynthesis of, 842–847
 carbocation rearrangements in
 biosynthesis of, 843–847
 classification of, 840
 conformations of, 109, 838–839
 molecular model of, 838
 numbering of, 838
 synthetic, 841
- Steroid hormones, 840–841**
- Stork enamine reaction, 635–636**
 mechanism of, 635–636
- STR loci, DNA fingerprinting and, 875–876**
- Straight-chain alkane, 67**
- Structure, condensed, 21–22**
 electron-dot, 8
 Kekulé, 8
 Lewis, 8
 line-bond, 8
 skeletal, 22–23
- Strychnine, LD₅₀ of, 25**
- Styrene, anionic polymerization of, 927**
- Substituent effect, electrophilic aromatic substitution and, 295–302, 308–313**
- Substitution reaction, 147**
- Substrate (enzyme), 704–705**
- Succinate, dehydrogenation of, 791**
 from succinyl CoA, 790–791
 fumarate from, 791
- Succinic acid, structure of, 532**
- Succinyl CoA, from α -ketoglutarate, 790**
 succinate from, 790–791
- Sucralose, structure of, 770**
 sweetness of, 770
- Sucrose, molecular model of, 765**
 sources of, 764
 specific rotation of, 120
 structure of, 765
 sweetness of, 770
- Suffix (nomenclature), 73**
- Sugar, *see also* Aldose, Carbohydrate, Monosaccharide simple, 739**
- D Sugar, 745**
 Fischer projections of, 745
- L Sugar, 745**
 Fischer projections of, 745
- Sulfa drugs, 664**
 synthesis of, 287
- Sulfanilamide, structure of, 287**
 synthesis of, 664
- Sulfathiazole, structure of, 665**
- Sulfide(s), 435**
 electrostatic potential map of, 64
 from thiols, 474
 naming, 465
 occurrence of, 437
 oxidation of, 475
 polarity of, 61
 reaction with alkyl halides, 474
*sp*³ hybrid orbitals in, 19
 structure of, 19
 sulfoxides from, 475
- Sulfonamides, synthesis of, 287**
- Sulfonation (aromatic), 287**
- Sulfone(s), 475**
 from sulfoxides, 475
- Sulfonium ion, 137**
 chirality of, 137–138
- Sulfoxide(s), 475**
 from sulfides, 475
 oxidation of, 475
- Sunshine vitamin, 922**
- Superglue, structure of, 927**
- Suprafacial geometry, 914**
- Suzuki–Miyaura reaction, 394**
 mechanism of, 395
- Sweeteners, synthetic, 770**
- Swine flu, 802**

- Swine H1N1 virus, 802
 Symmetry plane, 115–116
 Symmetry-allowed reaction, 906
 Symmetry-disallowed reaction, 906
 Syn periplanar geometry, 423
 molecular model of, 424
 Syn stereochemistry, 220
 Syndiotactic polymer, 928
 Synthase, 821
 Synthesis, trisubstituted aromatic
 compounds, 308–313
- Table sugar, *see* Sucrose
 Talose, configuration of, 747
 Tamiflu, influenza virus and, 802–803
 mechanism of, 802–803
 molecular model of, 111
 Tamoxifen, structure of, 211e
 synthesis of, 529h
 Taq DNA polymerase, PCR and, 869–870
 Tartaric acid, stereoisomers of, 130–131
 meso-Tartaric acid, molecular model of,
 131
 Tautomer, 254, 600
 Tazobactam, structure of, 598k
 Termination step (radical reaction), 150
 Terpene, 209, 829
 number of, 209
 Terpenoid, 209, 829–836
 biosynthesis of, 829–836
 classification of, 829
 number of, 878
 occurrence of, 829
tert-Amyl group, 76
tert-Butyl group, 71
 Tertiary alcohol, 437
 Tertiary amine, 645
 Tertiary carbon, 70–71
 Tertiary hydrogen, 71
 Tertiary protein structure, 700–702
 hydrophilic interactions in, 701
 hydrophobic interactions in, 701
 noncovalent interactions in, 701
 salt bridges in, 701
 Testosterone, conformation of, 109
 molecular model of, 109
 structure and function of, 840
 Tetracycline, structure and function of,
 894
 Tetrahydrobiopterin, monooxygenase
 activity and, 886
 Tetrahydrofolate, structure and function of,
 707
 Tetrahydrofuran, as reaction solvent,
 213
 molecular model of, 437
 Tetramethylsilane, NMR spectroscopy and,
 355–356
 Tetrapyrroles, biosynthesis of, 904a
 Tetraterpenoid, 829
 Tetrazole, DNA synthesis and, 868
 Thebaine, biosynthesis of, 892
 morphine from 892–893
 Thermodynamic quantities, 164–165
 Thermodynamic standard state, 164
- Thermoplastic polymer, 937–938
 characteristics of, 937–938
 T_g of, 937
 uses of, 938
 Thermosetting resin, 939
 cross-linking in, 939–940
 uses of, 939
 Thiamin, aromaticity of, 278
 basicity of, 667
 Thiamin diphosphate, decarboxylations
 with, 785–786
 pK_a of, 785
 reaction with pyruvate, 785
 structure and function of, 707, 785
 ylide from, 785
 Thiazole, basicity of, 667
 Thiazolium ring, aromaticity of, 278
 pK_a of, 785
 Thioanion, electrostatic potential map of,
 554a
-thioate, thioester name ending, 557
 Thioester(s), 555
 biological hydrolysis of, 598j
 biological partial reduction of, 588–589
 biological reactivity of, 587–589
 electrostatic potential map of, 561
 naming, 557
 pK_a of, 608
 polarity of, 64
 Thioesterase domain (TE), polyketide
 synthase and, 895
 Thioglycolic acid, pK_a of, 554c
 Thiol(s), 435
 acidity of, 441
 disulfides from, 463
 electrostatic potential map of, 64
 from alkyl halides, 463
 hydrogen bonds in, 439
 naming, 438
 occurrence of, 437
 odor of, 463
 oxidation of, 463
 polarity of, 61
 polarizability of, 154
 reaction summary of, 482
 reaction with alkyl halides, 474
 reaction with Br_2 , 463
 reaction with NaH, 474
 sp^3 hybrid orbitals in, 19
 structure of, 19
 sulfides from, 474
 thiolate ions from, 474
-thiol, thiol name ending, 438
 Thionyl chloride, reaction with alcohols,
 390–391, 405, 452
 reaction with amides, 544–545
 reaction with carboxylic acids, 564
 Thiophene, aromaticity of, 278
 Thiophenol, 435
 Thiourea, reaction with alkyl halides, 463
 Threonine, catabolism of, 737e–737f
 stereoisomers of, 127–128
 structure and properties of, 681
 Threose, configuration of, 747
 molecular model of, 118
- Thromboxane B_2 , structure of, 826
 Thymine, electrostatic potential map of, 856
 structure of, 853
 Thyroxine, biosynthesis of, 286
 structure of, 682
 Time-of-flight (TOF) mass spectrometry,
 328–329
 sensitivity of, 329
 Tin, reaction with nitroarenes, 655
 Titration curve, amino acids and, 684–685
 TMS, *see* Tetramethylsilane, 355
 Tollens test, 758
 Toluene, electrostatic potential map of, 299
 IR spectrum of, 339
 1H NMR spectrum of, 377
 Toluene-2,4-diisocyanate, polyurethanes
 from, 933
 Torsional strain, 81
 Tosylate, 396–397
 from alcohols, 405
 S_N2 reactivity of, 405
 Toxicity, chemicals and, 25
 TPP, *see* Thiamin diphosphate
 Trans fatty acid, formation of, 225–226
 from hydrogenation of fats, 808–809
 Transamination, 719
 amino acids and, 719–722
 mechanism of, 719–720
 pyridoxamine phosphate and, 721–722
 Transcription (DNA), 859–861
 Transesterification, 581–582
 Transfer RNA, 860
 anticodons in, 862–863
 function of, 861–863
 molecular model of, 863
 shape of, 862–863
 Transferase, 704–705
 Transimination, 721
 amino acids and, 721
 mechanism of, 721
 Transition state, 169
 Hammond postulate and, 204–206
 Translation (RNA), 861–863
 Tree diagram (NMR), 378
 Triacylglycerol, 806
 catabolism of, 813–820
 Trialkylsulfonium ion, alkylations with, 475
 from sulfides, 474
 Tricarboxylic acid cycle, *see* Citric acid
 cycle
 Trifluoroacetic acid, ether cleavage with,
 468
 pK_a of, 535
 (Trifluoromethyl)benzene, electrostatic
 potential map of, 299
 Triglyceride, *see* Triacylglycerol, 806
 Trimethylamine, bond angles in, 647
 electrostatic potential map of, 649
 molecular model of, 647
 Trimetozine, synthesis of, 574
 2,4,6-Trinitrochlorobenzene, electrostatic
 potential map of, 303
 Triose-phosphate isomerase, function of,
 773
 molecular model of, 773

- Triphenylphosphine, reaction with alkyl halides, 513–514
- Triple bond, electronic structure of, 17
length of, 17
see also Alkyne
strength of, 17
- Triplet (NMR), 373
- Trisubstituted aromatic compound, synthesis of, 308–313
- Triterpenoid, **829**
- tRNA, *see* Transfer RNA
- Trypsin, peptide cleavage with, 695
- Tryptophan, structure and properties of, 681
- Turnover number (enzyme), **704**
- Twist-boat conformation, cyclohexane, 98–99
molecular model of, 99
- Tyrosine, aromatic hydroxylation of, 886–887
biological iodination of, 286
biosynthesis of, 454–455
catabolism of, 737b
structure and properties of, 681
- Ubiquinones, function of, 460
redox properties of, 460
structure of, 460
- Ubiquinone–cytochrome *c* reductase, function of, 350
molecular model of, 350
- Ultrahigh-molecular-weight polyethylene, uses of, 929
- Ultraviolet light, electromagnetic spectrum and, 330
wavelength of, 342
- Ultraviolet spectroscopy, **342–344**
absorbance and, 343
conjugation and, 345
explanation of, 342–343
HOMO–LUMO transition in, 343
interpretation of, 345
molar absorptivity and, 344
- Ultraviolet spectrum, benzene, 345
buta-1,3-diene, 344
but-3-en-2-one, 345
 β -carotene, 346
cyclohexa-1,3-diene, 345
ergosterol, 349f
hexa-1,3,5-triene, 345
- Unimolecular, **409**
- Unsaturated, **180**
- Unsaturated ketone, conjugate addition reactions of, 518–521
- Unsaturation, degree of, **181**
- Upfield (NMR), **355**
- Uracil, structure of, 853
- Urea, from ammonia, 724–727
- Urea cycle, **724–727**
steps in, 725
- Urethane, **933**
- Uric acid, from xanthine, 873
 pK_a of, 554c
structure of, 723
- Uridine triphosphate, glycoconjugate biosynthesis and, 756
- Urocanase, active site of, 736
ribbon model of, 735
- Uronic acid, **758**
from aldoses, 758–759
- Urushiols, structure of, 436
- UV, *see* Ultraviolet
- Valdecocix, structure of, 318g
- Valence bond theory, **10–19**
orbital hybridization and, 12–19
orbital overlap in, 10–11
- Valganciclovir, structure of, 876d
- Valine, structure and properties of, 681
- Valinomycin, structure of, 473
- Valsartan, synthesis of, 394
- Van der Waals forces, **54**
alkanes and, 79
polymers and, 937
- Vasopressin, structure of, 691
- Vegetable oil, **806**
hydrogenation of, 225–226, 808
table of, 807
- Vent DNA polymerase, 870
- Vestenamer, synthesis of, 936
- Viagra, structure of, 665
- Vinyl group, **184**
- Vinyl monomer, **238**
- Vinylcyclopropane, rearrangement of, 924c
- Vinyllic, **290**
- Vinyllic anion, electrostatic potential map of, 257
- Vinyllic carbocation, 290
- Vinyllic halide, S_N2 reaction and, 402–403
- Vioxx, *see* Rofecoxib
- Virion, **802**
- Visible light, electromagnetic spectrum and, 330
- Vision, chemistry of, 346–347
retinal and, 347
- Vitamin, **550, 705**
- Vitamin A acetate, industrial synthesis of, 515
- Vitamin B₆, structure of, 719
- Vitamin B₁₂, structure of, 848
- Vitamin C, from glucose, 551
history of, 550–551
industrial synthesis of, 551
molecular model of, 551
scurvy and, 551
uses of, 550
- Vitamin, coenzymes from, 705–707
- Vitamin D, sigmatropic rearrangements and, 922–923
- Vitamin K₁, biosynthesis of, 293
- Viton polymer, structure and uses of, 931
- Vulcanization, **259**
rubber and, 259
- Walden, Paul, 396
- Walden inversion, 396–398
- Wang resin, peptide synthesis and, 699
- Water, acid–base behavior of, 43
conjugate addition reactions to enones, 520
dipole moment of, 32
electrophilicity of, 155
electrostatic potential map of, 46, 155
hydrogen bond in, 54–55
nucleophilicity of, 155
 pK_a of, 45
reaction with enones, 520
- Watson, James, 855
- Watson–Crick DNA model, 855–856
- Wave equation, 4
- Wave function, molecular orbitals and, 20–21
- Wavelength (λ), **329**
- Wavenumber, **333**
- Wax, **806**
- Whale blubber, composition of, 807
- Williamson ether synthesis, **466–467**
Ag₂O in, 466
carbohydrates and, 754
mechanism of, 466
- Wittig reaction, **513–514**
mechanism of, 513
uses of, 514–515
ylides in 513–514
- Wohl degradation, 760
- Wood alcohol, 435
- Woodward, Robert Burns, 906
- Woodward–Hoffmann rules, pericyclic reactions and, 906–907
- X rays, electromagnetic spectrum and, 330
- X-Ray crystallography, 348
- X-Ray diffractometer, 348
- Xanthine, from guanine, 872
oxidation of, 872–873
- Xylocaine, structure of, 57
- Xylose, configuration of, 747
- Yeast alcohol dehydrogenase, stereochemistry of, 139–140
- yl, alkyl group name ending, 69–70
- Ylide, **513**
synthesis of, 514
Wittig reaction and, 513–514
- yne, alkyne name ending, 185
- Z configuration, **189**
assignment of, 188–189
- Zaitsev, Alexander, 420
- Zaitsev's rule, **420**
alcohol dehydration and, 452–453
Hofmann elimination and, 661
NMR proof for, 363–364
- Ziegler–Natta catalyst, **929**
- Zocor
mechanism of action of, 2, 849–850
structure of, 86f
- Zusammen (*Z* configuration), **189**
- Zwitterion, **50, 679**
amino acids and, 679
electrostatic potential map of, 679

Periodic Table of the Elements

Key

79	Atomic number	Metals
Au	Symbol	Semimetals
Gold	Name	Nonmetals
196.9665	Atomic weight	

An element

Group number,
U.S. system
IUPAC system

1A
(1)

Period
number

1																	2	8A (18)							
1	H Hydrogen 1.0079																	He Helium 4.0026	1						
2	Li Lithium 6.941	Be Beryllium 9.0122																	B Boron 10.811	C Carbon 12.011	N Nitrogen 14.0067	O Oxygen 15.9994	F Fluorine 18.9984	Ne Neon 20.1797	2
3	Na Sodium 22.9898	Mg Magnesium 24.3050	3B (3)	4B (4)	5B (5)	6B (6)	7B (7)	8B (8)	8B (9)	8B (10)	1B (11)	2B (12)	Al Aluminum 26.9815	Si Silicon 28.0855	P Phosphorus 30.9738	S Sulfur 32.066	Cl Chlorine 35.4527	Ar Argon 39.948	3						
4	K Potassium 39.0983	Ca Calcium 40.078	Sc Scandium 44.9559	Ti Titanium 47.88	V Vanadium 50.9415	Cr Chromium 51.9961	Mn Manganese 54.9380	Fe Iron 55.847	Co Cobalt 58.9332	Ni Nickel 58.693	Cu Copper 63.546	Zn Zinc 65.39	Ga Gallium 69.723	Ge Germanium 72.61	As Arsenic 74.9216	Se Selenium 78.96	Br Bromine 79.904	Kr Krypton 83.80	4						
5	Rb Rubidium 85.4678	Sr Strontium 87.62	Y Yttrium 88.9059	Zr Zirconium 91.224	Nb Niobium 92.9064	Mo Molybdenum 95.94	Tc Technetium (98)	Ru Ruthenium 101.07	Rh Rhodium 102.9055	Pd Palladium 106.42	Ag Silver 107.8682	Cd Cadmium 112.411	In Indium 114.82	Sn Tin 118.710	Sb Antimony 121.757	Te Tellurium 127.60	I Iodine 126.9045	Xe Xenon 131.29	5						
6	Cs Cesium 132.9054	Ba Barium 137.327	La Lanthanum 138.9055	Hf Hafnium 178.49	Ta Tantalum 180.9479	W Tungsten 183.85	Re Rhenium 186.207	Os Osmium 190.2	Ir Iridium 192.22	Pt Platinum 195.08	Au Gold 196.9665	Hg Mercury 200.59	Tl Thallium 204.3833	Pb Lead 207.2	Bi Bismuth 208.9804	Po Polonium (209)	At Astatine (210)	Rn Radon (222)	6						
7	Fr Francium (223)	Ra Radium (226)	Ac Actinium (227)	Rf Rutherfordium (265)	Db Dubnium (268)	Sg Seaborgium (271)	Bh Bohrium (270)	Hs Hassium (277)	Mt Meitnerium (276)	Ds Darmstadtium (281)	Rg Roentgenium (280)	Cn Copernicium (285)	Fl Flerovium (289)	Lv Livermorium (293)					7						
			Lanthanides	6	Ce Cerium 140.115	Pr Praseodymium 140.9076	Nd Neodymium 144.24	Pm Promethium (145)	Sm Samarium 150.36	Eu Europium 151.965	Gd Gadolinium 157.25	Tb Terbium 158.9253	Dy Dysprosium 162.50	Ho Holmium 164.9303	Er Erbium 167.26	Tm Thulium 168.9342	Yb Ytterbium 173.04	Lu Lutetium 174.967	6						
			Actinides	7	Th Thorium 232.0381	Pa Protactinium 231.0369	U Uranium 238.0289	Np Neptunium (237)	Pu Plutonium (244)	Am Americium (243)	Cm Curium (247)	Bk Berkelium (247)	Cf Californium (251)	Es Einsteinium (252)	Fm Fermium (257)	Md Mendelevium (258)	No Nobelium (259)	Lr Lawrencium (262)	7						

Numbers in parentheses
are mass numbers of
radioactive isotopes.

Structures of Some Common Functional Groups

Name	Structure	Name ending	Name	Structure	Name ending
Alkene (double bond)		-ene	Sulfide		sulfide
Alkyne (triple bond)		-yne	Disulfide		disulfide
Arene (aromatic ring)		None	Sulfoxide		sulfoxide
Halide	 (X = F, Cl, Br, I)	None	Aldehyde		-al
Alcohol		-ol	Ketone		-one
Ether		ether	Carboxylic acid		-oic acid
Monophosphate		phosphate	Ester		-oate
Amine		-amine	Thioester		-thioate
Imine (Schiff base)		None	Amide		-amide
Nitrile		-nitrile	Acid chloride		-oyl chloride
Thiol		-thiol			

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