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The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award

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The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award

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Foreword

The ACS Symposium Series was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from the ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previous published papers are not accepted.

ACS Books Department

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Preface

The symposium on which this book is based came about because one of us (Tom Strom) became increasingly concerned about the status of his chosen discipline, physical organic chemistry. With the recent flowering of organic synthesis, physical organic chemistry seemed to be shrinking or perhaps it was just being absorbed into the tool kit of the synthetic chemist. The only Nobel Prize that can be reasonably attributed to a physical organic chemist is the 1994 award to George Olah, although Jeffrey I. Seeman has recently made a strong case that R. B. Woodward was actually a physical organic chemist in disguise (*1*). However, it is clear that Woodward's 1965 Nobel Prize was awarded because of his prowess in synthetic chemistry.

Tom decided to arrange a symposium for the ACS History Division that examined the history and fundamentals of physical organic chemistry. He asked his friend Jeffrey Seeman to be co-organizer. In examining themes for such a symposium, Seeman noted that 2014 would see the awarding of the 50th James Flack Norris Award in Physical Organic Chemistry. It became clear that the research carried out by the winners of this award, sponsored by the ACS Northeastern Section, gave insight into the fundamentals of the discipline. Jeff and Tom decided on a two stage symposium: presentations by early winners of the award and a panel discussion by recent award winners on the topic, "Whither Physical Organic Chemistry." The symposium then came together rather quickly and was scheduled for the March, 2014, ACS National Meeting in Dallas, TX.

James Flack Norris was an early physical organic chemist, before the discipline received its name. His picture is on the cover of this book, and Arthur Greenberg led off the symposium with a talk on Norris. Then came talks from Norris Award winners Ned Arnett, Ronald Breslow, Andrew Streitwieser, John Brauman, Paul Schleyer, Kendall Houk, and Michael Wasielewski. The participants for the closing panel discussion were John Baldwin, Ned Porter, Matthew Platz, Hans Reich, John Roberts, and Michael Wasielewski.

ACS Books was very interested in issuing a volume on this historical symposium. Co-organizer Jeff Seeman was unable to continue as a co-editor because of the press of other activities. Tom asked his long-time friend and chemical historian Vera Mainz to co-edit the volume, and she graciously agreed to do so. Greenberg, Arnett, Breslow, Streitwieser, and Schleyer agreed to submit book chapters, but Brauman, Houk, and Wasielewski were unable to do so. However, Norris Award winners Ken Wiberg, Keith Ingold, and Wes Borden, who were unable to participate in the original symposium, agreed to submit chapters on their work.

The steady progress toward completion of this volume ended abruptly with the death of Paul Schleyer in November, 2014. In his last message to us on Nov. 19, he said he would try to finish his chapter the very next week. He died just two days later. Paul was 84 years old, but he was still strongly involved in quantum chemistry research and had a great deal left to give to chemistry and also to the history of chemistry. Your editors were faced with the problem of transforming his oral presentation, which we had on tape, into a written chapter. Also, we felt that this volume should not only contain a chapter by Paul, but a chapter **about** Paul. Eventually we were able to persuade Andy Streitwieser to provide such a chapter. Fortunately, Andy was able to obtain Paul's unfinished memoir, which he had started but never completed for Jeff Seeman's series of books by renowned organic chemists. We thank Paul's widow Inge for permission to use this material. Consequently, Paul Schleyer is represented in two chapters in this volume.

With the precedent of having a chapter about a deceased Norris Award winner in the volume, we asked ACS Books for permission to have two more chapters about deceased winners. This permission was given. Therefore, the book was completed with a chapter on William Doering written by Ron Magid and Maitland Jones and a chapter on Glen A. Russell written by Kathleen Trahanovsky and E. Thomas Strom.

Our first words of thanks must go to the authors of our book chapters. We are grateful for the sharing of their recollections and research with the readers of this book. For financial support of the original symposium, we want to thank the ACS History of Chemistry Division, ACS President Tom Barton, and the Northeastern ACS Section. The ACS Division of Organic Chemistry was also a sponsor of the original symposium. We also thank the HIST Program Chair Seth Rasmussen for his assistance in arranging the symposium. We appreciate the important work done by Jeff Seeman in obtaining the original group of speakers. We thank the many reviewers of these chapters for their comments and corrections. For their invaluable assistance in completing this volume, we thank Tim Marney, Bob Hauserman, Arlene Furman, Lindsey Watson, and Tara Urban of ACS Books.

Someday someone will write a history of physical organic chemistry. This volume, with its contributions by so many noted physical organic chemists, will be an invaluable starting point for such a history.

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Editors' Biographies

E. Thomas Strom

Dr. E. Thomas (Tom) Strom is an Adjunct Professor at the University of Texas at Arlington (UTA), where he teaches organic and polymer chemistry. He came to UTA after retiring from Mobil in Dallas, where he worked 32 years as a research chemist studying oil field chemistry. He was Chair of the ACS Division of the History of Chemistry in 2011-2012. His research interests are in the history of chemistry and the study of anion radicals by electron spin resonance spectroscopy. He was one of the initial ACS Fellows and is a past winner of the Dallas-Fort Worth ACS Section's Doherty Award. He received his B.S.Chem degree from the University of Iowa, his M.S.Chem degree in nuclear chemistry from UC-Berkeley, and his Ph.D. in physical organic chemistry from Iowa State University working under mentor Glen A. Russell. Previously he has co-edited two volumes in the ACS Symposium Series: "100+ Years of Plastics. Leo Baekeland and Beyond" (2011) and "Pioneers of Quantum Chemistry" (2013).

Vera V. Mainz

Dr. Vera Mainz is retired Director of the NMR Lab in the School of Chemical Sciences at the University of Illinois at Urbana-Champaign. She received a B.S. in Chemistry and Mathematics at Kansas Newman College (1976), a Ph.D. in Inorganic Chemistry at the University of California Berkeley (1981, with R. A. Andersen), spent 1-1/2 years working at Rohm and Haas in Springhouse, PA, and had a postdoctoral position at the University of Illinois at Urbana-Champaign (1983-1985) before becoming Director of the NMR Lab. She was elected to the position of Secretary-Treasurer of the History of Chemistry Division (HIST) of the ACS in 1995, and has served as Secretary-Treasurer since that time. Her interest in the HIST Division was kindled when she presented her work on the chemical genealogy of the University of Illinois (UI) Chemistry Department at a HIST symposium on chemical genealogies in 1994. She has continued her work in this area, posting her information to a website at http://www.scs.uiuc.edu/~mainzv/Web_Genealogy/, and plans to update this project when her schedule allows. Vera's interest in the history of chemistry led her and her husband, Gregory Girolami, to co-curate two exhibits at the Univ. of Illinois' Rare Book Room: 1) From Alchemy to Chemistry: Five Hundred Years of Rare and Interesting Books, http://www.scs.uiuc.edu/~mainzv/exhibit/; 2) Crystallography – Defining the Shape of Our Modern World, found online at URL http://www.scs.illinois.edu/xray_exhibit/. Vera was a member of the ACS Fellows Class of 2012, which

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honored her contributions to the ACS (HIST and local section service) and the many students she has helped while working in the NMR Lab.

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Chapter 1

James Flack Norris: His Early Contributions to Physical Organic Chemistry

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In honor of the fiftieth anniversary of the James Flack Norris Award in Physical Organic Chemistry, a brief biographical sketch of Norris is presented along with discussion of his research accomplishments in the contexts of the influence of his doctoral mentor Dr. Ira Remsen and the early development of physical organic chemistry. Dr. Norris had two distinct academic careers, researcher and teacher at Massachusetts Institute of Technology (MIT) and administrator and teacher at Simmons College. A third career, scientific leader and statesman, co-existed with these dual careers. This chapter will briefly describe Norris's researches in molecular addition compounds, the triphenylmethyl system, Friedel-Crafts chemistry as well as his twenty paper series on "The reactivity of atoms and groups in organic compounds" (from 1920 through 1940).

The Early Days of Physical Organic Chemistry and Some Modern Perspectives

The origins of the field recognized as "physical organic chemistry" may be dated close to the start of the twentieth century. In 1895 Paul Walden demonstrated (*1*) the stereochemical inversion that now bears his name. The concept of steric hindrance had been introduced by Victor Meyer (*2*) one year earlier. In 1899, Julius Stieglitz made a solid proposal for the existence of carbocations (*3*). In 1900 Moses Gomberg published his ground-breaking discovery of the triphenylmethyl free radical (*4*). Explicit recognition of the field dates to the

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period between 1920 and 1940 (*5*). Christopher K. Ingold published "Principles of an Electronic Theory of Organic Reactions" in *Chemical Reviews* in 1934 (*6*) and this was later expanded into his classic textbook, *Structure and Mechanism in Organic Chemistry*, published in 1953 (*7*). Louis P. Hammett formally anointed the field with his publication of the 1940 textbook *Physical Organic Chemistry* (*8*). Consistent with this early history, the American Chemical Society (ACS) presented the first James Flack Norris Award in Physical Organic Chemistry to Christopher Ingold in 1965 and the second award to Louis Hammett in 1966 (see the Appendix).

Hammett's Preface is brief and essentially defines physical organic chemistry as "…the investigation of the phenomena of organic chemistry by quantitative and mathematical methods (*8*)." The title of Ingold's book explicitly describes its theme and, whereas Hammett's 1940 textbook emphasizes kinetics and equilibria, the first 196 pages of Ingold's large tome emphasizes structural properties and includes resonance theory and Hückel molecular orbital theory (*7*). The late 1950s and early 1960s witnessed the widespread and fundamental introduction of physical organic chemistry into the undergraduate chemistry curriculum. Many from my own generation were first explicitly introduced to physical organic chemistry through Edwin S. Gould's *Mechanism and Structure in Organic Chemistry* (*9*) (note the permutation of Ingold's title). Other excellent text books, varying slightly in emphasis, soon followed (*10–13*).

The 1950s, 1960s and 1970s might well be considered to be a heyday of "classical" physical organic chemistry with the great non-classical carbonium ion controversy as its centerpiece. The sometimes thunderous arguments and disagreements during this period, among some of the most distinguished chemists of the era, led to refinements in the interpretation of substituent effects, solvent effects, steric effects and anchimeric assistance. Ultimately, the controversy was settled through spectroscopy experiments at temperatures approaching 0 K, coupled with increasingly reliable computational chemistry. During this period other "shoots" began to emerge including the beginnings of mechanistic biochemistry and nanotechnology. Indeed, even as its methodologies became widely employed in many fields of investigation, practitioners started to worry over whether physical organic chemistry, as a field, was still recognizable and even "viable" (read *fundable*) as such. This author recalls attending an evening talk in 1976 by a distinguished long-time physical organic chemist who pronounced chemistry "a dead field" and confidently laid out his new strategy which was to do only "useful" chemistry. Queried at the end of the talk about the totally counter-intuitive results derived from the emerging field of gas-phase organic ion chemistry (*e.g.* toluene a stronger acid in the gas phase than methanol), he described this and similar such observations as "artifacts." Still, the evolution of chemical science and changes in funding priorities and criteria have led to (useful) periods of self-doubt and self-examination. Such concerns provided impetus for an International Union of Pure and Applied Chemistry (IUPAC) Symposium in print concerning the past, present and future of physical organic chemistry (*14*). Reports of the demise of physical organic chemistry remain premature. This is readily appreciated by simply viewing the sheer scope of the table of contents of the 1100-page, folio-sized 2006 tome by Eric Anslyn and Dennis Dougherty (*15*).

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Early in the twenty-first century we find ourselves in a funding environment increasingly demanding practical solutions to the problems of the day such as "sustainability", a term so widely and indiscriminately used as to become almost as meaningless as it is highly fundable. Yet who would be so bold (or reckless) to assert that they can predict the future outcomes of fundamental research in physical organic chemistry? It was in 1959, that Richard Feynman first drew attention to the concept of nanoscience (*16*). A year later Edel Wasserman reported the first synthetic catenanes (*17*) and Gottfried Schill published *Catenanes, Rotaxanes and Knots* in 1971 (*18*). Who could have envisioned that a generation later such chemical exotica would play an important role in the design of nanodevices (*19*)? Similarly, Robert Bergman provided strong experimental and theoretical evidence for the esoteric, indeed evanescent, 1,4-benzyne (*20*). Some nineteen years later, naturally-occurring anti-cancer agents including calicheamicin were discovered. An enzyme "pulls a trigger" in this molecule, forming a 1,4-benzyne derivative that attacks DNA in the cancer cell (*21*). Thus, while the principles and methodologies of physical organic chemistry are widely adopted by many diverse scientific fields, physical organic chemistry itself remains vital, recognizable and will undoubtedly produce breakthroughs hard to anticipate today.

So where does the research of James Flack Norris fit into the development of physical organic chemistry? He was, in fact, "present at the creation", as Tidwell (*22*) references Norris's early preparation of carbocation salts (*23*). Norris's fundamental research was published even as he inveighed against tricoordinate carbon (*24*) and Gomberg's free radical. Moreover, his quantitative studies during the 1920s and 1930s of the dependence of rates of reaction on substituents and solvents certainly fit the Hammett definition of physical organic chemistry. In the remainder of this chapter we will briefly explore biographical details of Professor Norris's life, the influence of his research mentor Professor Ira Remsen, his contributions to the nascent field of physical organic chemistry, and the two different James Norris Flack awards: the chemical education award, presented by the Northeastern Section of the American Chemical Society (NESACS), starting in 1951, and the award in physical organic chemistry presented by the American Chemical Society at the national level starting in 1965.

Brief Biography of James Flack Norris

James Flack Norris (Figure 1) can be said to have had two nearly-distinct academic careers. Superimposed upon these was another career as a chemistry leader and scientist-statesman. His academic career started and finished at Massachusetts Institute of Technology (MIT) during which his synthetic and quantitative studies, very much congruent with Hammett's definition, added substantially to a burgeoning new field. This influence was recognized explicitly by the James Flack Norris Award in Physical Organic Chemistry celebrated in the present symposium. Norris spent a twelve-year hiatus period forming the chemistry program at Simmons College, with one year on sabbatical at Karlsruhe. This experience, complemented by important textbooks he authored, combined with his teaching accomplishments at MIT and Simmons provided impetus for the earlier endowed award, the James Flack Norris Award for Outstanding Achievement in Teaching of Chemistry.

Figure 1. Dr. James Flack Norris, Professor of Chemistry at MIT. (Courtesy Department of Chemistry, MIT)

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A number of sources provide details of the life and career of Professor James Flack Norris (*25–30*), the most extensive being the 1951 piece by Blake (*26*), reprinted in the special commemorative issue of *The NUCLEUS* in 1965 (*27*). While the 1974 National Academy of Sciences *Biographical Memoir* compiled and reformatted material from the earlier Tenney L. Davis article (*25*), its author John D. Roberts also contributed insights about the significance of Norris's research (*28*).

James Flack Norris was born in Baltimore, Maryland on January 20, 1871. He was the fifth of nine children born to Methodist Reverend Richard Norris (1835-1897) and Sarah Amanda (Baker) Norris (1849-1917). Young Norris graduated from Central High School in Washington, D.C. and attended Johns Hopkins University and received his A.B. degree in chemistry, coming under the influence of Professor Ira Remsen with whom he would complete his Ph.D. in 1895. His research involved study of "molecular addition compounds" including those formed between amines and molecular halogens His interest in the analytical chemistries of selenium and tellurium also developed during this period. Norris was appointed Instructor at MIT in 1895 and promoted to Assistant Professor in 1900 where he served until 1904. During 1904 Norris served as Chairman of the Northeastern Section of the ACS. Clearly, his leadership qualities were recognized early by his peers. On February 4, 1902 Norris married Anne Bent Chamberlin (1876-1948). She was a student at the Museum of Fine Arts in Boston and later became a pioneer in social work for the deaf. In 1903 Norris was honored with a lectureship at Simmons College in Boston and in 1904 was appointed the first Professor of Chemistry at Simmons. Simmons College was established in 1899 with the aspiration of becoming the "MIT for women." Norris would spend his next twelve years at Simmons organizing its course of chemistry instruction as well as the laboratories. From 1907 through 1910 he served as Director of the School of Science. Sensing the need to apply physical chemistry to his interests in organic chemistry, Norris spent part of the 1910-1911 period with Fritz Haber in Karlsruhe. (The irony in this association would become apparent almost a decade later following the end of World War I). Returning to Simmons, he was appointed Chairman of the Department of General Science. Norris was granted lectureships at Harvard during 1912 and 1913 where one of his students was Louis P. Hammett (*26*). He remained at Simmons until 1915, then spent one year as professor at Vanderbilt University before returning to MIT as professor in 1916. Upon leaving Vanderbilt he was presented a silver cigarette case with the inscription "Sunny Jim" (*31*), an apt nickname for this dapper, well-liked man and one that would remain with him for the rest of his life.

In 1906, James and Anne Norris built a summer house on Long Lake in Western Maine that they christened "Good Cheer." It was in this relaxing environment that Norris wrote the four books and subsequent editions that would eventually seed the Norris Fund after Anne Norris's passing. The first of these, titled *The Principles of Organic Chemistry*, was published in 1912. The second, *Experimental Organic Chemistry*, was published in 1915. By the time third editions of these books appeared in 1933, *each* had sold a total, in all editions, of over 70,000 copies (*26*).

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In October, 1917 MIT granted Norris a leave of absence to work for the U.S. Government on gas-related problems at the Bureau of Mines in Washington, D.C. He was subsequently placed in charge of "Offence Chemical Research" at the Bureau. In early 1918 he was commissioned a Lieutenant Colonel in the Chemical Warfare Service, based in London. After World War I (1919), Norris was placed in charge of investigating the German manufacture of poison gas including the frequency of illness and death among workers at Bayer Company and Höchst (*32*). It is not apparent from my brief perusal whether Norris had interviewed Haber in 1919. Haber's tragic contribution to the war effort, supervising the employment of 6000 steel cylinders filled with 160 tons of chlorine gas at Ypres in 1915, and his researches and applications of poison gas, are well known (*32*). A patriotic German, to the consternation of many, Haber was awarded the Nobel Prize in Chemistry in 1918 for his discovery of the fixation of atmospheric nitrogen to manufacture fertilizers that ultimately saved millions from starvation. Born Jewish he converted to Christianity. This did not mollify the Nazis and when they came to power in 1933, he lost his positions in Germany, fled to England and died in 1934.

In 1919 Norris was honorably discharged, returned to MIT and resumed a research career that focused initially on the Friedel-Crafts reaction. James Mason Crafts was on the MIT faculty from 1870 through 1874, spent the next seventeen years in Paris working with Charles Friedel, returning in 1892 as Professor. Crafts was President of MIT from 1897 to 1900 and continued his research for over a decade afterward. Thus, Norris had early access to Crafts as a faculty colleague as well as during Craft's later years in Boston. During the 1920s, Norris's research moved into areas easily recognized almost a century later as physical organic chemistry. These studies involved the effects of substituents and solvents upon reaction rates determined quantitatively and they will be very briefly outlined below.

In 1924, James Flack Norris was appointed Chair of the National Research Council Section on Chemistry and Technology. He was the last ACS President elected to serve multiple terms (1925, 1926; ten previous ACS presidents had served multiple terms consecutively or non-consecutively). On December 29, 1925, Norris gave the opening talk at the inaugural National Organic Chemistry Symposium (*33*). Titled "The Opportunities for Research in Organic Chemistry", Norris had originally planned a talk titled "Quantitative Measurement of Organic Reactivity of Organic Compounds (*33*)." This latter topic was, in all likelihood, the basis of his subsequent guest presentation, "Chemical Reactivity," delivered at Columbia University during summer, 1926 (*34*). During the period 1925-1928 Norris was Vice President of IUPAC. He had been elected an Honorary Member of the Royal Institution of Great Britain in 1925 and was a member of an educational delegation to the USSR in 1928. In 1937 Norris received the Gold Medal of the American Institute of Chemists honoring is accomplishments as "teacher and investigator." He served as Chairman of the Faculty of MIT during 1937-1939. James Flack Norris was elected to membership in various august groups including the American Academy of Arts and Sciences (serving as Vice President during 1936), the National Academy of Sciences (elected 1934), and as a fellow of the American Association for the Advancement of Science (Chairman, Chemistry Section in 1930). But it is almost irresistible to mention his membership in the

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rather lesser known “Ouroboros.” This club, founded in 1916 (*35*), evolved from the “Chemistry Round Table,” convened by members of NESACS in 1910. The ouroboros is a mythical alchemical legged serpent that regenerates itself even as it consumes its own tail. The membership of Ouroboros would include Theodore Richards, Charles James, James Conant, Arthur Noyes, Louis Fieser and Kenneth Wiberg among many luminaries. The first female member, Anna J. Harrison, Professor at Mount Holyoke, was admitted to Ouroboros in 1970, eight years before she became the first female President of ACS. Ouroboros seems to have become extinct during the first decade of the twenty-first century (*35*).

Over the course of a four-decade-long academic career, James Flack Norris authored roughly seventy publications (*28*) and mentored twenty-one Master degree students (including three women) and thirty-eight Ph.D. students (including three women) (*27*). It must be noted here that as a junior faculty member at MIT and during his period at Simmons, Norris had no graduate assistants. The first two Norris-trained graduates received masters (S.M.) degrees in 1920 and 1921 and his first Ph.D. student graduated in 1922 (*27*). One of his masters students, Charles J. Pederson (S.M. 1927) would spend his subsequent career at Du Pont and share the 1987 Nobel Prize in Chemistry with Donald J. Cram and Jean-Marie Lehn. The title page of the 1937 Ph.D. thesis of 1965 Nobel Laureate Robert Burns Woodward is signed by Norris as Chairman of the Department Committee of Graduate Students (*36*). Woodward famously completed his B.S. (1936) and Ph.D. (1937) degrees at MIT in a total of four years. Norris is revealingly quoted in the *Boston Globe* in 1937:

> *…we saw we had a person who possessed a very unusual mind and we wanted it to function at its best. If the red tape necessary for less brilliant minds had to be cut, we let it go. We did for Woodward what we have done for no other person like him in our department. We think he will make a name for himself in the scientific world (37).*

In his brief dissertation acknowledgement Woodward thanked “…Professors James F. Norris and Avery A. Morton, who have taken a particular interest in this work…” (*36*). Norris was also Morton’s research mentor at MIT (Ph.D. 1924) prior to the latter’s appointment to the MIT faculty.

During summer, 1940 successful cataract surgery in Norris’s right eye (June) was followed by phlebitis in July and hospitalization for blood transfusions some two weeks later. He died on August 4, 1940 survived by his wife Anne. The devoted couple had no children. Anne Bent (Chamberlin) Norris (born May 29, 1879) (*38*) passed away on May 29, 1948. She had been elected in 1933 the first female President of the American Society for the Hard of Hearing and continued to serve this and other related organizations for many years to come. In her will Mrs. Norris provided the Northeast Section of the ACS with a gift of $10,000, also sharing the remainder of the estate equally with MIT. The will stated:

> *It is my wish that the Directors of said Society shall use the money in any way they may see fit to perpetuate the memory of my said husband James F. Norris.*

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This fund would soon form the basis of the Norris award in teaching and over a decade later the Norris award in physical organic chemistry. These will be discussed later.

The Influence of Ira Remsen upon the Career of James Flack Norris

Although it might at first appear to be a routine academic exercise, the influence of Norris's Ph.D. advisor Ira Remsen (*39*) on his future career as scientist, scientific leader and statesman was quite profound and worth examining briefly. He left his mark on the education of American Ph.D. chemists from the late nineteenth century into modern times. Remsen saw no sharp dividing line between inorganic and organic chemistries and made noteworthy contributions in both fields (he lectured and authored important textbooks in both areas). Remsen explored structure-reactivity relationships in organic chemistry during the final quarter of the nineteenth century.

Ira Remsen (1846-1927) was born in New York City, received his undergraduate education at the Free Academy (now the City College of New York) and, obeying his father's wishes, obtained his M.D. degree in 1867 at the College of Physicians and Surgeons of Columbia University. However, Remsen developed an interest in chemistry and, exercising his free will, travelled to Munich hoping to work with Justus Liebig. Liebig was no longer taking students so young Remsen worked with *Privatdocent* Jacob Volhard, learning techniques in analytical chemistry. During this period, Friedrich Wöhler was an occasional visitor to the Munich laboratory and in fall 1868 he inspired Remsen to move to Göttingen. There Remsen pursued organic chemistry research under the direction of Rudolf Fittig, receiving his Ph.D. in 1870. The twenty-four year old Remsen followed Fittig to Tübingen where "he drank in the spirit of the German laboratories" (*39*). Returning to the United States in 1872 with a faculty appointment at the liberal arts institution Williams College, Remsen was severely disappointed by the lack of interest and support for teaching experimental chemistry (*39*). He did complete his masterful textbook *Theoretical Chemistry*, an extraordinarily useful work that made the principles and breakthroughs of the period widely accessible.

Despite the serious limitations at Williams, Remsen conducted experimental research including studies of the oxidation of carbon monoxide and reactions of phosphorus compounds. The concept of valence was still quite new and many chemists held the view that each element exhibits a single valence. Thus, reaction of PCl_3 with chlorine yields what was commonly regarded as the "molecular addition compound" $PCl_3{\cdot}Cl_2$. Remsen, aware of Wurtz's recent determination of vapor density consistent with the formula PCl_5, concluded that the reaction of PCl_3 and chlorine did in fact produce pentavalent phosphorus. Similarly, his studies of the reaction of ozone with PCl_3 led Remsen to interpret the product as containing pentavalent phosphorus: $O{=}PCl_3$ (*39*).

Ira Remsen was one of a galaxy of stars recruited to Johns Hopkins University in 1876 (*39*). There he established a Ph.D. program based upon the German

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model and revolutionized graduate education in chemistry in the United States. At Hopkins much of his research focused on organic chemistry. An early interest in structural organic chemistry led to "Remsen's Law"- *e.g.* a methyl group *ortho* to a sulfamido group (SO_2NH_2) is protected from certain oxidation reactions. Remsen's researches into what one might term "primordial physical organic chemistry" is exemplified by an 1884 paper in which he demonstrated that isopropyl bromide is less stable than n-propyl bromide in zinc and an acid but more stable in alcoholic sodium hydroxide (*39*). Remsen's student Norris would eventually make such structure-activity comparisons quantitative ("physical organic") rather than simply qualitative. In 1879 Remsen and Russian chemist Constantin Fahlberg, working in Remsen's laboratory, published the discovery of saccharin (*39*). Fahlberg would file patents in 1884 and 1886 claiming sole credit for the discovery and starting a business manufacturing and selling the first commercial synthetic sweetener.

Ira Remsen was a scientific and academic leader and scientific statesman, a path traversed by James Flack Norris decades later. Shortly after arriving at Johns Hopkins, Remsen inaugurated *The American Chemical Journal*. After publication of fifty volumes, Remsen agreed to incorporate it with *The Journal of the American Chemical Society* (JACS). Remsen was elected President of the American Chemical Society for 1902. He served as Acting President of Johns Hopkins (1889-90) and President from 1901 through 1913. In 1909 Ira Remsen was appointed by President Theodore Roosevelt to Chair a Board studying administration of the pure food law (*39*). Based upon this very brief biographical outline, it is reasonable to conclude that Ira Remsen exerted major influence upon James Flack Norris in both scientific and public venues.

Early Scientific Research on Selenium, Tellurium and Molecular Addition Compounds

The research of James Flack Norris under the mentorship of Ira Remsen at Johns Hopkins University included the chemistry, notably analytical chemistry, of selenium and tellurium. The earliest paper with Norris's name on it was co-authored with Remsen (*40*). Starting with a salt assigned the formula $SeBr_4.SeOBr_2 \cdot 2(CH_3)_3N \cdot HBr$, reaction with bromine formed $(CH_3)_3N \cdot Br_2$. The same product was obtained through reaction of trimethylamine with bromine. Similar chemistry was observed between trimethylamine and iodine. Such "molecular addition compounds" were poorly understood at the time. The physical methods for testing their nature were quite limited- formation of unique crystals upon reactions of molecular substances, new melting points, and percent composition of constituent elements were among relatively few experimental criteria. Theories about the bonding in these complexes included notions of "residual affinities" of atoms in the molecules.

Henry Fay would co-author Norris's next paper, which involved determination of selenious and selenic acids (*41*). These two young chemists first met as assistants at MIT. Three additional papers, also co-authored with Fay, would follow between 1898 and 1900 (*28*). In 1902, Fay was best man at Norris's wedding.

Although first investigated at MIT, a decade after Norris finished his doctoral studies at Johns Hopkins, it is worthwhile mentioning Norris's continued interest in selenium and tellurium. Among significant problems in the late nineteenth and very early twentieth century were the "anomalies" in the ordering in the periodic table of some elements according to atomic weight. One example involves tellurium, heavier than iodine, rather than lighter than iodine as would be expected by their placement:

As	Se	Br
$^{121.8}$Sb	$^{127.1}$Te	$^{126.9}$I

One simple explanation could be very minor contamination of tellurium samples with another, heavier chemical element. However, in 1906 Norris confirmed the purity and atomic weight of tellurium (*42*), so the apparent anomaly remained. Today, we understand that this "reversal" is due to the presence of heavy isotopes of tellurium (^{128}Te; ^{130}Te) in significant (each >30%) abundance. However, it was only in 1907 that Bertram Boltwood characterized "ionium", soon to be recognized as an isotope of thorium (the term coined by Frederick Soddy in 1913). Also in 1907, Joseph John ("J.J.") Thomson discovered canal rays associated with neon corresponding to atomic masses 20 and 22. These measurements were confirmed by Francis William Aston in 1919 using his early mass spectrograph.

Debating Tricoordinate Carbon with Moses Gomberg

Although the term "free radical" is in common (chemical) usage, the word "radical" is understood by most non-chemists as referring to "extreme" conditions (as in radical surgery) or in an "extreme" political context. However "radical" can be defined as "of or from the root" or "foundation or source of something." In the late eighteenth century, Louis Bernard Guyton de Morveau introduced the term "radical", later adopted by Antoine Laurent Lavoisier, to describe $RX + Y \rightarrow RY + X$. Here radical R is exchanged between X and Y. How R moved from X to Y was not imaginable. However, nineteenth-century chemists, especially organic chemists, did pose such questions and tried to obtain or at least infer the presence of the "free radical" (*e.g.* R). By the 1860s, the tetravalent nature of carbon was well accepted. During the latter part of the nineteenth century a number of excellent chemists claimed to have isolated free radicals but were quickly proven incorrect.

In 1900 Moses Gomberg reported his attempt to synthesize hexaphenylethane through reaction of triphenylmethyl chloride with zinc metal (Wurtz reaction) in a non-polar solvent free of oxygen (*4*). Zinc chloride precipitated leaving a yellow solution. This solution reacted instantly with added iodine to form triphenylmethyl iodide. The yellow solution also reacted instantly, when exposed to air, to form a peroxide:

$$2\ (C_6H_5)_3C\text{-}I \xleftarrow{I_2} 2\ (C_6H_5)_3C \xrightarrow{O_2} (C_6H_5)_3C\text{-}O\text{-}O\text{-}C(C_6H_5)_3$$

The observation of the stable triphenylmethyl free radical was indeed a radical claim but was well accepted within a few years. At the end of his paper Gomberg famously placed this injunction:

> *This work will be continued and I wish to reserve the field for myself.*

At this time, Norris was investigating the Friedel-Crafts reaction and the possibility of employing carbon tetrachloride and benzene to synthesize tetraphenylmethane. The reaction yielded triphenylmethyl chloride and therein did Norris collide with Gomberg (*23*) who had just reported the compound even as the Norris manuscript was ready for submission. Responding to Gomberg's expansive territorial claim, Norris countered (*23*):

> *He wishes to reserve this field for further work. As we have been working with triphenylchloromethane in this laboratory for about a year, with a view of preparing tetraphenylmethane from it, it seems advisable to give a preliminary account of the work that has been accomplished, and to describe briefly what is now in progress.*

When Norris combined triphenylmethyl chloride, benzene and aluminum trichloride in carbon disulfide solution, he failed to obtain tetraphenylmethane but found instead a solid that was insoluble in the non-polar solvents benzene, carbon disulfide, carbon tetrachloride and petroleum ether. The solid was soluble in nitrobenzene but decomposed in alcohol, ether, acetone, chloroform and acetic acid. The solid was reported as an addition compound of formula: $Al_2Cl_6 \cdot 2(C_6H_5)_3C \cdot Cl$ (*43*) [later modified to $(C_6H_5)_3CCl \cdot AlCl_3$)]. Norris realized that under typical Friedel-Crafts reaction conditions, after addition of the third benzene ring, a significant solubility change would occur resulting in precipitation and no further reaction. The Friedel-Crafts conditions employed by Norris were, of course, very different from the reaction conditions employed by Gomberg. Indeed, as intimated by Tidwell (*22*), Norris was in fact exploring the chemistry of the stable triphenylmethyl carbocation. Norris then reported reactions of triphenylmethyl chloride and benzene in the presence of sodium metal (*23*). This was, of course, uncomfortably close to Gomberg territory. In studying the chemistry of triphenylmethyl chloride in concentrated sulfuric acid, HCl was given off and the final product was triphenylcarbinol (*24*). Ironically, this paper (*24*) was titled by Norris "On the Non-Existence of Trivalent Carbon." He concluded that the highly-unsaturated hydrocarbon prepared by Gomberg was best represented as $(C_6H_5)_3C : C_6H_4$ and implied that the structure included the central carbon attached to two carbons on one of the benzene rings (*24*). Gomberg, however, sharply criticized Norris's studies on Wurtz-type chemistry and made a convincing case that experimental divergences from his own results were largely the result of incomplete purification by Norris of solvents (*43*).

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Gomberg was totally unconvinced by the hydrocarbon formula advanced by Norris. Indeed, he was irritated by Norris's very presence in the field (*43*):

> *It seems, therefore, strange that Norris should at this stage give up his original problem, the synthesis of tetraphenylmethane, and take up the study of the action of metals upon triphenylchlormethane. I have published only a preliminary paper upon this subject, asking that the field might be reserved for myself.*

Gomberg and Norris did agree on the experimental conversion of triphenylmethyl chloride to the alcohol in concentrated sulfuric acid (*43*). While Norris lost the triphenylmethyl radical debate to Gomberg, it is clear that he was an early contributor to stable carbocation chemistry. During the first decade of the twentieth century, conductivity studies in high dielectric constant solvents would demonstrate the reality of stable carbocation salts including triphenylmethyl carbocation.

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Contributions to Quantitative Organic Chemistry (1920s and 1930s)

In 1904 James Flack Norris left MIT to establish the chemistry program at Simmons College. He would return to MIT in 1916, with war assignments occupying his attention from 1917 through 1919. As a consequence, Norris published one research paper (*42*) in 1906 and one each in 1907, 1910 and 1916. Not until 1920 did Norris research papers reappear (three in the *Journal of the American Chemical Society*) (*27*). One series of papers (1907, 1916 and 1920) dealt with reactions of alcohols in aqueous solutions of HCl and HBr. Primary alcohols were found to be very unreactive whereas benzyl alcohol and allyl alcohol were highly reactive. The theme of exploring organic reactivities through kinetics became the major thrust of his research program at MIT starting in 1916 (*34*). This is one area in which Norris departed markedly from his doctoral mentor since Remsen was judged to be somewhat indifferent to physical chemistry (*44*). In his 1926 presentation at Columbia University (*34*), Norris nicely laid out his rationale for quantitative studies of organic reactions. In describing the understanding at that time of the chemical reactions of inorganic substances, Norris declared (*34*):

> *The modern conception of the changes involved in inorganic chemical reactions are based on the quantitative study of the energy changes of these reactions.*

and further (*34*):

> *The facts summed up in Faraday's law and in the electromotive series of the elements made possible the broadest generalizations in regard to the chemical behavior of the elements and their compounds.*

In other words, the reactions of inorganic substances were, in Norris's view, determined by thermodynamics. While the situation in organic chemistry was deemed far more complex (*34*):

> *Organic chemistry lacks such broad generalizations. The radicals in these compounds correspond to the elements in inorganic chemistry. Can these radicals be studied in some way to give results of a general nature that are applicable in this field of interpretations of reactions, as is the electromotive series of the elements in inorganic chemistry?*

When Norris resumed full-time faculty duties at MIT he entered a new landscape in which chemical theories of reactivity of organic molecules were being tested by experiment (*5*). Notably Arthur Lapworth had introduced a theory of "alternative polarities" as early as 1905. Robert Robinson became friendly with Lapworth in Manchester in 1909 and interested in the applications of Lapworth's theory. Combining Lapworth's views and Johannes Thiele's concept of "residual valencies", Robinson began developing a coherent theory of reactions of unsaturated molecules including substituted benzenes. In 1925, Robinson modified Thiele's 1899 representation of benzene to provide the structure we now commonly employ. Whereas residual valencies at the ends of 1,3-butadiene explained the reactivity of this molecule (as well as its 1,4-addition chemistry), in benzene, the ends meet in a cycle, neutralizing residual valencies and accounting for its stability. Robinson also introduced the "curvy arrow" to illustrate the movement of chemical bonds. He was an early supporter for applying electrons (Lewis pairs) toward understanding mechanisms, a position advocated by Thomas Martin Lowry (*5*).

An opposing school of thought grew in the early twenties around a theory of "affinity demand" proposed by Bernard Flürscheim, related to work by Thiele and Arthur Michael (*5*). Modifications, emphasizing electrical charges on atoms, were introduced by Daniel Vorländer. This view deemphasized the need for electron pairs. Christopher Ingold was, in fact, more in accord with this viewpoint.

The early differences in chemical theory between Robinson and Ingold intensified in 1923 and 1924 and reached a head in 1926 when Robinson came close to accusing Ingold of plagiarism. However, from 1926 onward, Ingold proceeded to define the developing field of mechanistic organic chemistry, introducing, for example, the terms "nucleophile" and "electrophile." The chemistry historian William H. Brock terms Ingold "…the great systematizer of twentieth-century organic chemistry who firmly established the importance of physical chemistry in understanding the subject" (*45*). Robinson's efforts would henceforth be increasingly directed to the studies of structure and synthesis of natural products that would eventually earn for him the 1947 Nobel Prize in Chemistry. Still, he made one large last effort in publishing in 1932 a pamphlet detailing his interpretation of organic reaction theory (*46*). However, this

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work was quickly overshadowed by Ingold's extensive 1934 review article (*6*). In 1930 one of the greatest partnerships in twentieth century chemistry began when Edward David Hughes was appointed by Ingold (initially) as a post-doctoral fellow at University College in London. Hughes was a master of experimental kinetics and, with Ingold, soon combined kinetics, stereochemistry and mechanism and developed the nomenclature of nucleophilic substitution. The Robinson-Ingold rivalry would continue for decades. As Brock notes (*47*): "For although the documentary evidence is lacking, Ingold and Hughes had seriously believed in the 1930s that Robinson, as Britain's most senior and respected chemist, lay behind the opposition that their views provoked."

A 1920 paper, co-authored with Dorothy M. Tibbetts (*48*), was built upon two earlier research areas: molecular addition compounds and the triphenylmethyl system. In this paper, the authors included a succinct statement characterizing the early philosophy of physical organic chemistry:

> *...especially in the field of organic chemistry...the chemist has it in his power to change by the use of the proper substituents the nature of the molecule and thus develop or reduce its ability to form addition products with other substances.*

Triphenylmethyl chloride was said by Norris to have an "active chlorine" which is readily hydrolyzed and its high "residual affinity" or "latent affinity" (*i.e.* high latent energy) is also manifested in its ability to form molecular addition compounds such as $(C_6H_5)_3CCl{\cdot}AlCl_3$. In contrast the "firmly-bound" chlorine in methyl chloride does not form molecular addition compounds. Diphenylmethyl chloride does not form analogous addition compounds although *p*-phenyldiphenylmethyl chloride does form a molecular addition compound (*48*). No mention was made in this paper of carbocation salts.

In 1925, the first of a series of twenty papers titled "The Reactivity of Atoms and Groups in Organic Compounds" was co-authored with Avery A. Ashdown and appeared in the *Journal of the American Chemical Society* (*49*). In it Norris explored the relationship between reactivity and structure. In reactions between *p*-nitrobenzoyl chloride and eleven alcohols, second-order rate constants varied by a factor of almost seventy [relative values for RO-H: $R = CH_3$, 100; $R = CH_3CH_2$, 45.7; $R = (CH_3)_2CH$, 5.4; $R = (CH_3)_3C$, 1.46].

In his presentation at Columbia University in summer, 1926 (*34*), Norris summarized his on-going research on the reactivities of alcohols, alkyl chlorides and acyl chlorides. In this presentation Norris emphasized the critical importance of the quantitative measurement of chemical reactivities. In describing the dependence of rates of reaction of derivatives of C_6H_5COCl with ethanol, he reported data for *o*-, *m*- and *p*-substituted compounds. Table 1 includes a small selection of data from this paper (acid chloride reactions were run at 0 °C and alkyl chloride reactions at 25 °C).

Table 1. Rates (relative to unsubstituted, X = H) of ethanolysis for a series of substituted benzoyl chlorides and diphenylmethyl chlorides selected from Table 1 in reference (*34*).

Substituent (X)	*C_6H_5COCl derivatives*	*$(C_6H_5)_2CHCl$ derivatives*
H	1 (assigned)	1 (assigned)
m-Cl	3.17	0.0451
p-Cl	1.74	0.421
p-CH_3	0.567	18.76
p-CH_3O	0.79	3200
p-NO_2	17.7	-------

In describing the inverse influences of these substituents on the rates of these two sets of reactions, Norris did not postulate an underlying explanation. At the time he considered the differentiation of acyl halides from alkyl halides, based upon the typically far greater reactivities of the former group, to be “an entirely arbitrary one” since suitable substitution could produce alkyl halides more reactive than acyl halides. Although different mechanisms were undoubtedly suspected, there was no discussion of mechanism nor was there specific discussion of the enormous rate enhancement noted for the *p*-methoxy substituent in Table 1. It is likely that thirty-two year old Louis P. Hammett, appointed to the Columbia faculty three years earlier, was present at this lecture and participated in discussions with Norris. Two years earlier, J.N. Brønsted had published the first example of a linear free energy relationship (*50*):

$$(1) \qquad \log k = \alpha \log (K_a) + C$$

This refers to the dependency of reaction rate (k) on ionization constant (K_a) in general acid-catalyzed reactions. Hammett would publish his famous linear free-energy relationship some thirteen years later (*51*):

$$(2) \qquad \log (K/K_o) = \sigma\rho$$

This relationship refers to the dependence of equilibrium (K) or rate (k) constants on the electronic nature of a substituent on a benzene ring (σ) and the sensitivity of a reaction type to electronic effects (ρ). This work would eventually systematize the types of kinetic findings published by Norris.

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The twentieth and final paper in the series "Reactivity of Atoms and Groups in Organic Compounds was co-authored with Arthur E. Bearse, and published in 1940 (*52*). This paper was received in January, 1940. Hammett's famous textbook was published later that year. Although Norris's paper considers both the acidities of substituted benzoic acids and their rates of conversion to the chlorides with $SOCl_2$, there is no reference to Hammett's earlier work. Three other papers authored by Norris, all focusing on Friedel-Crafts chemistry, were submitted and published in JACS early in 1940. Later that summer Norris died.

In his biographical sketch of James Flack Norris (*28*), John D. Roberts provided the follow summary of Norris's scientific career:

> *Norris was rather less successful in his work on reactivity than was his younger counterpart at Harvard, James B. Conant, who displayed an almost unerring instinct for choosing reactions for study of greater simplicity and involving wider ranges of reactivity, along with an excellent feel for the basic physical chemistry involved. Nonetheless, Norris had the prescience to be at the forefront of the still-developing area of making comparisons of organic reactivity under controlled conditions, and some of the reactions he was first to study are among the most important in preparative chemistry.*

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The James Flack Norris Awards

Anne Chamberlin Norris died in 1948, and her will provided a sizeable endowment, to be administered by the Northeastern Section of the American Chemical Society, to honor the memory of her late husband (*53*). A committee was established to decide how best to use the bequest. The decision was announced in January, 1950 to establish the James Flack Norris Award for Outstanding Achievement in Teaching of Chemistry. The first awardee (1951) was George Shannon Forbe, Professor Emeritus, Harvard University. Following retirement, Dr. Forbe was a lecturer at Northeastern University in Boston. Initially, awards were presented in alternate years (1951, 1953 and 1955), then one in 1956, spring and fall awards in 1957 and 1959 and a single annual award starting in 1960.

The initiative that led to the James Flack Norris Award in Physical Organic Chemistry came from Henry A. Hill, who was Chairman of NESACS in 1963 (*54*). Hill, a graduate of Johnson C. Smith University in Charlotte, North Carolina, would later become the first African American President of ACS (1977). He obtained his Ph.D. at MIT in 1942 and had overlapped briefly with Professor Norris. Hill learned that the Norris Fund had "…grown both in book value and income, and is now in excess of the fondest expectations of ten years ago" (*54*). An ad hoc committee was formed that included Avery A. Ashdown, a Norris Ph.D. graduate, and four other MIT alumni, met in February 1963. The decision was made to fund a physical organic chemistry award that would be administered by the American Chemical Society. The committee also authorized funding to assist in the furnishing of a James Flack Norris room in the new MIT chemistry building (*54*). The national ACS accepted responsibility in June of that year and the first award was presented to Christopher K. Ingold in 1965 (see the Appendix). A Symposium on Physical Organic Chemistry, to celebrate the first award, was held on September 14, 1965 at the National ACS Meeting in Atlantic City, New Jersey. Joseph F. Bunnett (Brown University) chaired the meeting. Other speakers in addition to the honoree, Christopher K. Ingold (University College, London), were Robert B. Woodward (Harvard University), Andrew Streitwieser, Jr. (University of California at Berkeley), C. Gardner Swain (Massachusetts Institute of Technology), Charles A. Bunton (University of California at Santa Barbara), Maurice M. Kreevoy (University of Minnesota), and Frederic P. Olsen (University of California at Riverside). Happily and most fittingly, Professor Emeritus Streitwieser made a presentation at the March 17, 2014 symposium celebrating the fiftieth anniversary of the award.

In 1972 ACS granted $10,000 to Simmons College to furnish a James Flack Norris room. It served as collegial interaction space for faculty, staff and students until 2000 when the building was totally renovated (*55*). A photograph of Dr. Norris hangs proudly in the Department of Chemistry and Physics main office. Indeed, a chemistry major was a member of the first graduating class of Simmons College (*55*). It is also worthwhile to mention the James Flack Norris and Theodore William Richards Undergraduate Summer Scholarships awarded by NESACS. Richards, a professor at Harvard, was the first American to win the Nobel Prize in Chemistry (1914).

There are some interesting and noteworthy points in revisiting the James Flack Award in Physical Organic Chemistry. Two awardees also received the Norris Award in Teaching: Louis P. Hammett (1960) and Paul D. Bartlett (1978). There is a single case in which parent (Christopher K. Ingold in 1965) and offspring (Keith U. Ingold in 1993) each received this award. None of the awardees were or subsequently became Nobel laureates. This explicitly raises a question my own Ph.D. advisor Pierre Laszlo rhetorically posed to me in the 1960s: Why had no Nobel Prize in Chemistry been yet awarded to a physical organic chemist? Far be it from me to plunge into the treacherous waters of controversy in which this question has often bobbed through the years. It is likewise interesting that Nobel laureates who have made important contributions to physical organic chemistry, such as Donald J. Cram (1987) and George A. Olah (1994), were not Norris awardees. Olah, in particular, discovered conditions for making transient carbocation intermediates relatively long-lived and observable by NMR. And for that matter, what about Robert Burns Woodward? In a paper titled "R.B. Woodward, A Great Physical Organic Chemist" (*56*), Jeffrey Seeman reminds readers of the 1965 Nobelist's impact well beyond organic synthesis. Here one also sees some parallels (and differences) between Woodward and Robert Robinson, who similarly received his Nobel Prize for work in synthetic organic chemistry but certainly left an early mark upon physical organic chemistry. In his paper (*56*), Seeman also notes that in April, 1957 B.S. Hutchinson, the Chairman of NESACS, informed Woodward that "…the committee has unanimously chosen you as the nominee" (i.e. for the James Flack Norris Award for Outstanding

Achievement in the Teaching of Chemistry). Seeman could locate no record of Woodward's response. Thus, for reasons not readily discernable, R.B. Woodward, received neither of the two Norris awards despite being a very strong case for the physical organic award and actually having been chosen unanimously for the teaching award.

Today physical organic chemistry remains recognizable as such even as it forms the foundation for research in very diverse fields. These contributions continue to be recognized by the James Flack Norris Award in Physical Organic Chemistry in areas diverse enough that predictions of the future (*14*) will almost certainly miss surprises that are unimaginable at the present time.

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Dedication

In memory of Dr. Paul von Ragué Schleyer (February 27, 1930 – November 21, 2014).

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The author is grateful to Thomas Strom who extended the invitation to make a presentation at the symposium in Dallas on March 17, 2014. For initiating my interest in physical organic chemistry, I wish to acknowledge my Ph.D. advisor Pierre Laszlo and three professors, each a physical organic Norris awardee, from whom I took classes in the 1960s: Kurt Mislow, Paul von Ragué Schleyer and Peter Stang. I was also very fortunate during this formative period to have been stimulated in seminars by Kenneth Wiberg, Michael Dewar and Ronald Breslow, all physical organic Norris awardees. I am grateful to Joel Liebman, Richard Johnson, Glen Miller and Gary Weisman who have been long time friends, colleagues, teachers and sounding boards. I also wish to express my gratitude to Jeffrey Seeman who provided me with ideas, critiques and early access to interesting archival materials. Special thanks to Susan J. Greenberg who helped me to organize the March 17, 2014 presentation.

Appendix

Winners of the James Flack Norris Award in Physical Organic Chemistry [For the list of winners of the James Flack Norris Award for College Chemistry Teaching visit the Northeast Section of the American Chemical Society (NESACS) site: www.nesacs.org/awards_norris.html]

1965 Christopher K. Ingold
1966 **Louis P. Hammett**
1967 Saul Winstein
1968 George S. Hammond
1969 **Paul D. Bartlett**
1970 Frank H. Westheimer
1971 Cheves Walling
1972 Stanley J. Cristol
1973 Kenneth B. Wiberg
1974 Gerhard L. Closs
1975 Kurt M. Mislow
1976 Howard E. Zimmerman
1977 Edward M. Arnett
1978 Jerome A. Berson
1979 John D. Roberts
1980 Ronald Breslow
1981 Jay K. Kochi
1982 Andrew Streitwieser, Jr.
1983 Glen A. Russell
1984 Michael S. Dewar
1985 Paul G. Gassman
1986 John I. Brauman
1987 Paul von Ragué Schleyer
1988 Nicholas J. Turro
1989 William von E. Doering
1990 Norman L. Allinger
1991 Kendall L. Houk
1992 Joseph F. Bunnett
1993 Keith U. Ingold
1994 George M. Whitesides
1995 William P. Jencks
1996 Thomas C. Bruice
1997 Julius Rebek, Jr.
1998 Peter J. Stang
1999 Barry K. Carpenter
2000 Martin E. Newcomb
2001 Josef Michl
2002 Charles H. Depuy
2003 Robert G. Bergman
2004 C. Dale Poulter
2005 Martin Saunders
2006 Michael Wasielewski
2007 Ben L. Feringa
2008 Dennis A. Dougherty
2009 Bernd Giese
2010 John E. Baldwin
2011 Weston Thatcher Borden
2012 Hans J. Reich
2013 Ned A. Porter
2014 Matthew S. Platz
2015 Charles Perrin

L.P. Hammett (1960) and P.D. Bartlett (1978) also received the James Flack Norris Award for College Chemistry Teaching

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in the United Kingdom. Its bit of advertising doggerel (just in case you were curious):

> Jim Dumps was a most unfriendly man,
> Who lived his life on the hermit plan;
> In his gloomy way he'd gone through life,
> And made the most of woe and strife,
> Till Force one day was served to him.
> Since then they've called him "Sunny Jim."

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Chapter 2

My Study of Optical Activity - From the Distant Past to the Present with Stops in-Between

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Physical organic studies encompass a variety of subjects. Our work included studies of small ring compounds where the higher energies lead to increased reactivity, studies of the mechanisms of reactions including oxidations, the application of ab initio theoretical calculations to studies of reactivity and properties, as well as spectroscopic studies. More recent work has concentrated on the relationship between structure and conformations on specific rotations.

Introduction

In the late 1940's when I was a graduate student at Columbia University working with Bill Doering, I was given the problem of looking at the stereochemistry of t-alkyl group migration in electron deficient molecular rearrangements. It was known that s-alkyl groups migrated in a seemingly concerted process, but t-alkyl was sufficiently different that it might involve bond cleavage to a t-alkyl cation followed by recombination. Starting with a chiral t-alkyl group this might lead to some loss of chirality. I proceeded to prepare methylethylisobutylacetic acid and to resolve it via a salt with brucine (*1*). A number of its reactions were studied and it appeared that chirality was normally conserved.

In the course of this work I became interested in the connection (if any) between structure and the sign and magnitude of the optical rotation. Not much was known about the subject at that time, and so my interest lay mainly dormant

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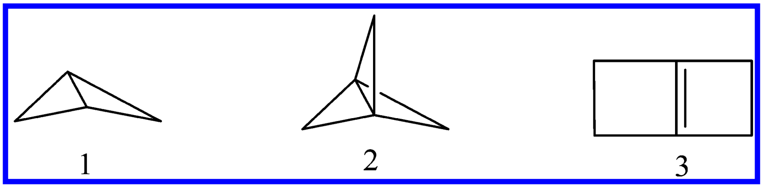
for the next 50 years, except for noting the development of the quadrant and octant rules (*2*), and Brewster's rules (*3*).

In the meantime, I carried out a number of studies that had a physical-organic context and I wrote a book (*4*) on the subject while enjoying a sabbatical leave (1962) in Rudolf Criegee's Institute at Karlsruhe, Germany.

Small Ring Compounds

Some of our work dealt with the synthesis and properties of small ring compounds such as the remarkably strained and reactive hydrocarbons, bicyclo[1.1.0]butane (**1**) (*5*), [1.1.1]propellane (**2**) (*6*), and $\Delta^{1,4}$-bicyclo[2.2.0]hexane (**3**) (*7*). They have calculated strain energies of 64, 98 and 87 kcal/mol respectively (*8*). These values are large considering that the C-C bond strength is 88 kcal/mol.



Despite its strain, **1** and its derivatives are readily formed via 1,3 elimination reactions (*5*). The central bond is easily cleaved. The propellane, **2**, also may be formed via a 1,3-elimination reaction of the bridgehead dihalides via reaction with t-butyllithium (*6*), and an elimination reaction from a tetrachloride provides a convenient way in which to prepare it in some quantity (*9*). The structure is interesting in that it has an "inverted" tetrahedral geometry at the bridgehead carbons (*10*). It adds iodine to form the diiodide, and reducing agents readily convert it back to **2**. It is very reactive toward free radicals and can lead to polymers (*6*). It's thermal stability is probably related to the high energy of any species formed by breaking a C-C bond. The alkene, **3**, can be prepared in dilute solutions, is a very reactive dienophile and these reactions lead to propellanes. It readily dimerizes to form a pentacyclic propellane that opens to form an interesting diene (*7*).

It was important to have experimental information about some of these small ring compounds. This led us to determine the heats of formation of cyclopropene, 1-methy-cyclopropene, methylenecyclopropane, bicyclobutane and cyclobutene using a flame calorimeter (*11*). The heat of formation of the "aromatic" cyclopropenyl cation could be derived from the heat of formation of cyclopropene and the results of a mass spectrometric study (*12*). Our interest in energies led us to make use of a precision solution calorimeter that we designed to be completely computer controlled including data collection and analysis (*13*). It was used to study steric interactions in the hydrolysis of orthoesters (*14*) and lactones (*15*). It was also used in determining the heats of hydration of alkenes (*16*), heats of reduction of ketones (*17*) as well as in a conformational study (*18*).

Solvolytic studies of exo and endo-5-bicyclo[2.1.0]pentyl tosylates (**4**,**5**) gave a 10^6:1 relative reactivity (*19*) (much greater than that for the

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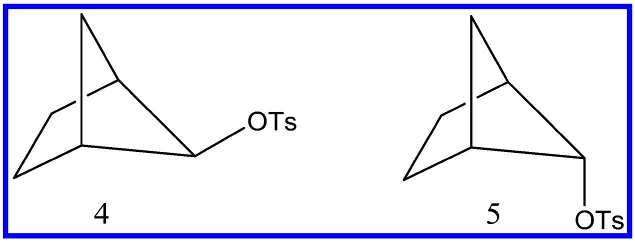
corresponding norbornyl derivatives), and related studies of cis- and trans-fused bicyclo[3.1.0]hexyl derivatives gave further information on the role of orbital interactions on reactivity (*20*). The interest in these and related compounds led to a study of what is now known as "molecular mechanics" and to develop the first general computer program for strain energy minimization (*21*).



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Mechanisms of Oxidation

Other studies dealt with the mechanisms of oxidation of organic compounds by hydrogen peroxide (*22*), potassium permanganate (*23*) and chromic acid (*24*). The reactions we studied included the oxidation of aldehydes, alkenes and alkanes. Both MnO_4^- and $HCrO_4^-$ usually undergo an initial two electron reduction in their reactions with organic compounds, commonly leading to a Mn(5) or Cr(4) intermediate. Using a stopped flow reactor and UV detection, it was possible to observe the formation and subsequent reaction of the inorganic intermediates, and to observe their rates of reaction (*25*). The studies of oxidation reactions led to an interest in deuterium kinetic isotope effects (*26*) and to writing a review on the subject (*27*).

Computational Studies

We became interested in using ab initio theory to supplement our experimental studies. A group equivalent scheme was developed to easily estimate heats of formation from the calculated total energies (*28*). One problem in making use of this theory results from the fact that the calculations are for the gas phase whereas most reactions are carried out in solution. We studied the use of Onsager's reaction field model (*29*) and methods derived from it (*30*) to estimate solvent effects, and applied it to several problems (*31*).

Chemists have often been interested in electron density distributions and assigning charges to atoms in molecules. We applied Bader's theory of atoms in molecules (*32*) and electron density difference maps to the question of why the energies of fluorinated methanes are linearly dependent with the number of fluorines, whereas this is not true with other substituents (*33*). We found that each fluorine in carbon tetrafluoride has the same electron distribution and charge as the fluorine in methyl fluoride. Thus, the carbon charge increases linearly with the number of fluorines resulting in increasing C^+-F^- Coulombic attraction (*34*). We have reviewed the differences in the charge that result from using the several available models (*35*), and we have examined the relationship between bond dipoles and the intensities of IR bands (*36*).

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As a result of a question from G. B. Ellison, we became interested in substituent effects on X-H bond dissociation energies (BDE). In the case of RO-H, experimental results showed that the BDE decreased from 119 in HOH to 105 in MeO-H and 87 kcal/mol in HOO-H (*37*). We found that it was possible to accurately reproduce these and other experimental results computationally using CBS-APNO (*38*). Structural effects, calculations of spin densities, and studies of electron density distributions showed that the main effect was a two center-three electron conjugative interaction that stabilized the radical center (*39*). A subsequent more extended study included second row elements and found in interesting difference between P and S in their ability to interact with a radical center (*40*). The differences between compounds with C=O and C=S also were examined (*41*).

Spectroscopic Studies

NMR spectroscopy has become the most important structural tool for organic chemists. It was known that hydrogen chemical shifts are normally upfield from a hydrogen nucleus, whereas carbon chemical shifts are normally downfield from a bare carbon nucleus (*42*). Thus, hydrogens experience a diamagnetic interaction that depends on the electron density about it, whereas carbons experience mainly a paramagnetic interaction that results from the coupling between the ground state and the excited states of the molecule in the presence of a magnetic field. We have examined the contribution of the excited states and the effect of their orientation and thereby gained a better understanding of the carbon chemical shifts (*43*).

Ultraviolet spectroscopy provides information about some electronically excited states of molecules. However, studies in solution lead to broadening of vibrational structure in the UV bands. We have made use of vacuum ultraviolet (VUV) spectroscopy for gas phase measurements including spectral regions where atmospheric oxygen absorbs. Bicyclobutane is an example where the vibrational structure of the bands could be observed, allowing the transitions to be assigned (*44*). Calculations clarified its photochemical transformation leading to butadiene and cyclobutene (*45*). Other studies made use of calculations to assist in gaining an understanding of the experimental results (*46*).

Infrared spectroscopy provides information on the inner workings of molecules. We have carried out extended studies of many molecules such as cyclopropene (*47*), cyclohexane (*36*), bicyclo[.1.10]pentane (*48*) and [1.1.1]propellane (*49*).

Back to Optical Activity

I "retired" in 1997 when I turned 70, and in that year Polavarapu published the first ab initio optical rotation calculation (*50*). It made use of the 1928 report by Rosenfeld (*51*) of his derivation for an equation for optical rotation based on the newly developed wave mechanics:

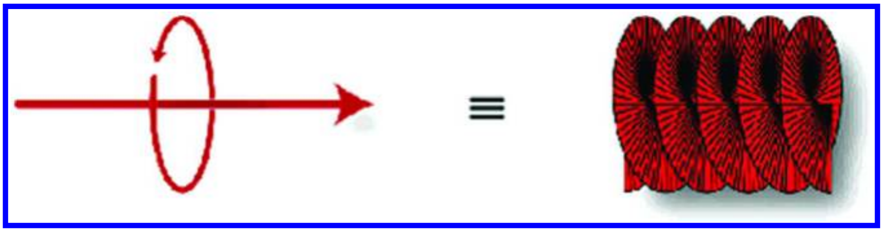
$$\boxed{[\alpha] = \frac{9143.03}{M}\sum_{b\neq a}^{\infty}\frac{\nu^2}{\nu_{ba\backslash}^2 - \nu^2}R_{ba}}$$

where M is the molar mass in g/mol, v is the energy of the polarized light, ν_{ba} is the transition energy to exited state b, and R_{ba} is the rotatory strength for the transition. The rotatory strength, R_{ba} is given by

$$R_{ba} = \mathrm{Im}\{\langle a \mid \mu^{\mathrm{El}} \left| b \right\rangle \cdot \langle b \mid \mu^{\mathrm{Ml}} \mid a \rangle\}$$

and couples the ground state *a* to excited state *b* under the simultaneous action of the electric (μ^{E1}) and magnetic (μ^{M1}) dipole transition operators. The summation is over all of the excited states of the molecule. Thus, the observed rotation depends on accurately calculating both the electric and magnetic transition moments for a given transition and taking the product of them for each excited state, followed by a summation. This becomes a formidable computational effort, and could not be done until there was both improvements in ab initio theory and the development of fast computers.

The electric transition moment, such as for the π→π* transition of an alkene lies along the bond coordinate, whereas a magnetic transition moment, such as for an n→π* transition of a ketone goes about the axis. A product of the two would describe a helix that can be either right or left handed. This in turn can lead to an interaction with polarized light leading to either positive or negative sign of rotation.



Rather than using Rosenfeld's equation given above, Polavarapu (*50*) recast it in a form in which one would not have to do a sum over excited states, and allowing a more direct calculation. This was followed by a number of related studies. One that caught my attention was by Stephens, Devlin, Cheeseman and Frisch (*52*) that made use of density functional theory (DFT) and showed that reasonably accuracy (±35°) could be achieved.

This reinvigorated my interest in optical activity, especially when the needed code became available in a development version of the Gaussian program (*53*), I returned to thinking about my old interest in the relationship between structure and optical rotation. In the following "optical rotations" (OR) will be used as a short hand for specific rotations that are defined as

$$[\alpha]_\lambda = \text{observed rotation/(cell length*concentration)}$$

where the cell length is given in dm (usually 1.0) and the concentration is given in g/ml or as the density with neat liquids. It has the units of deg. $dm^{-1}(g/mL)^{-1}$ The wavelength of the polarized light is given as λ.

Experimental Studies of Optical Activity

When the rotation for a compound is measured, one observes the weighted average over its possible conformations. Here was a place where calculations could provide information that could not be obtained by direct measurement, and the calculated values could be compared against experiments by applying the mole fractions of the conformers derived from the energy differences among conformers using the Boltzmann equation. Since for many compounds, these energies are not experimentally available, a calculation of the conformer energies allows the rotations to be estimated, providing a double check on the accuracy of the calculations.

In our first study, we examined one of the simplest of chiral compounds, 3-choro-1-butene (*54*). This was prepared in chiral form and the specific rotations were obtained in several solvents. This compound has three conformers resulting from rotation about the CH_2=CH-CH_2 single bond (Figure 1). The relative energies of the conformers were obtained from a scan of the energy as a function of torsion angle (Fig 2), and the rotation also was calculated as a function of the torsion angle (Figure 3) The relative free energies of the conformers were obtained using G2 (*55*) allowing them to be estimated at 298K giving 1.05 and 1.10 kcal/mol for the two gauche conformers. The calculated results are in good accord with experimental meaurements of the conformer energies (*56*).

It was surprising to find the wild swings of the rotation with a range of -526 at $\tau = 180'^\circ$ to +435 at $\tau = 320^\circ$ when the compound has a maximum rotation of only $[\alpha]_D = \pm 57.3^\circ$. Using the populations of the two conformers obtained from the G2 energy differences, and the calculated rotations shown in Figure 3, an estimated rotation is on the order of -99.7 whereas the observed rotation was $[\alpha]_D = -57.3$. Thus the rotation was estimated to be twice as large as observed. Since this was one of the earliest studies of its type and led to remarkably large changes in OR, it seemed important to obtain further information. It might be noted that a later study by Tam, Abrams and Crawford (*57*) found that density functional theory was not adequate for calculations for this compound, and that a coupled-cluster method (CCSD) was able to give a much more satisfactory result.

In order to see if the double bond were responsible for the deviation between calculated and observed rotations, we examined 2-substututed butanes where X = F, Cl, CN and C=CH (*58*). These substituents are convenient in that they do not add to the number of conformers. In addition they would be expected to lead to significant differences in electronic levels that are involved in the calculation of optical rotation, and this was confirmed by measurement of their VUV spectra. It is well known that compounds such as these have three conformations, trans and two gauche. The energies of the conformers were obtained by using G3.

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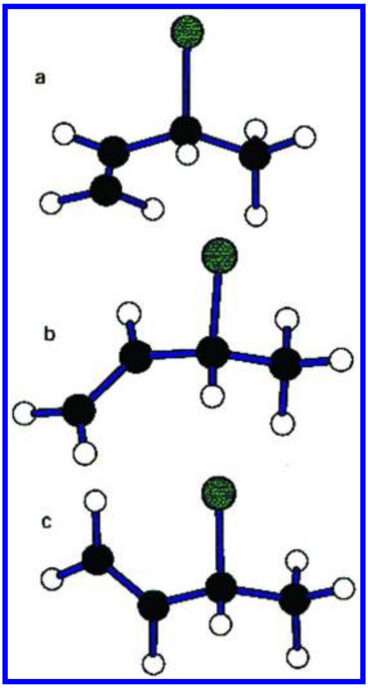

Figure 1. 3-Chloro-1-butene conformers

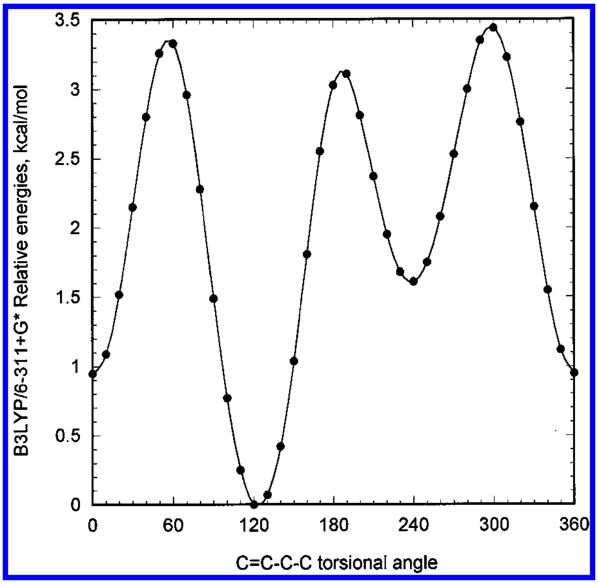

Figure 2. Calculated conformational energies

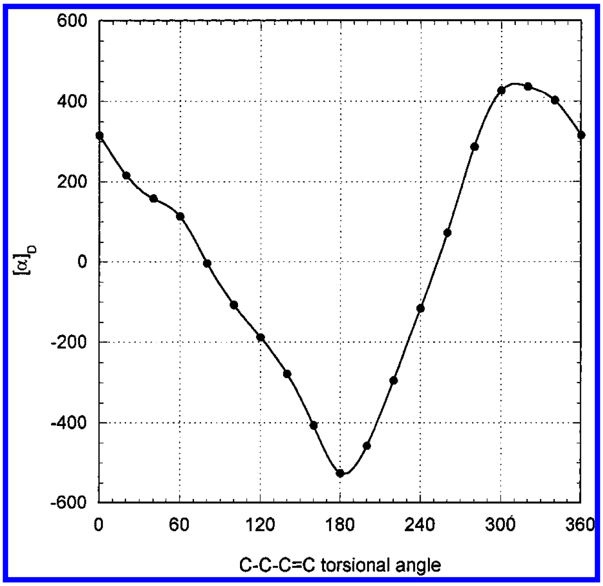

Figure 3. Calculated Optical rotation profile for 3-chloro-2-butene

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The OR of these compounds were calculated using B3LYP/aug-cc-pVDZ, and the results are summarized in Figure 4. Despite the obvious differences among the substituents there is remarkable similarity between the curves for the four compounds. This suggests that in this case, substituents have a small effect other than creating the chiral center. This was a surprising conclusion.

The observed specific rotation is the weighted average for the three conformers. The averaged rotations were calculated using G3 (*59*) calculated conformational energies allowing a comparison with the experimental rotations (Table 1).

With these compounds there is fairly good agreement between experiment and theory. Here, one must remember that the calculations refer to the gas phase whereas the observed values are for the condensed phase. In some cases these differences can become significant.

The agreement between observation and calculations could be fortuitous, and it remained to be seen if the calculated rotations for the individual conformers of 2-chlorobutane are in agreement with the calculated values. Some useful information may be obtained from the temperature dependence of the optical rotation that results from the effect of temperature on the conformer ratio. The conformational energies have been studied experimentally giving an average value of $\Delta G \approx 700$ cal/mol. The data from the temperature dependence study should be given by

$$\alpha_{obs} = (\alpha_A + 2\alpha'\exp(-\Delta G/RT)/(1 + 2\exp(\Delta G/RT))$$

where α_A is the rotation for the low energy conformer and α' is the average of that for the higher energy conformers. A least squares treatment gave a specific rotations of -77.4° for the low energy conformer and 37.4° for the average of the higher energy conformers. This may be compared with the calculated values of -77.6° and 34.6°. The remarkably good agreement is probably in part fortuitous, but the result confirm that the DFT-OR calculations for 2-chloro- butane are quite good. A similar study for 2-cyanobutane (2-methylbutyronitrile) found slightly poorer agreement with the calculated rotations about 25% larger than the experimental values.

These results suggest that the calculations for saturated compounds may be significantly more satisfactory than for their unsaturated analogs. This may be a result of the double bond π→π* transition not being treated well using DFT.

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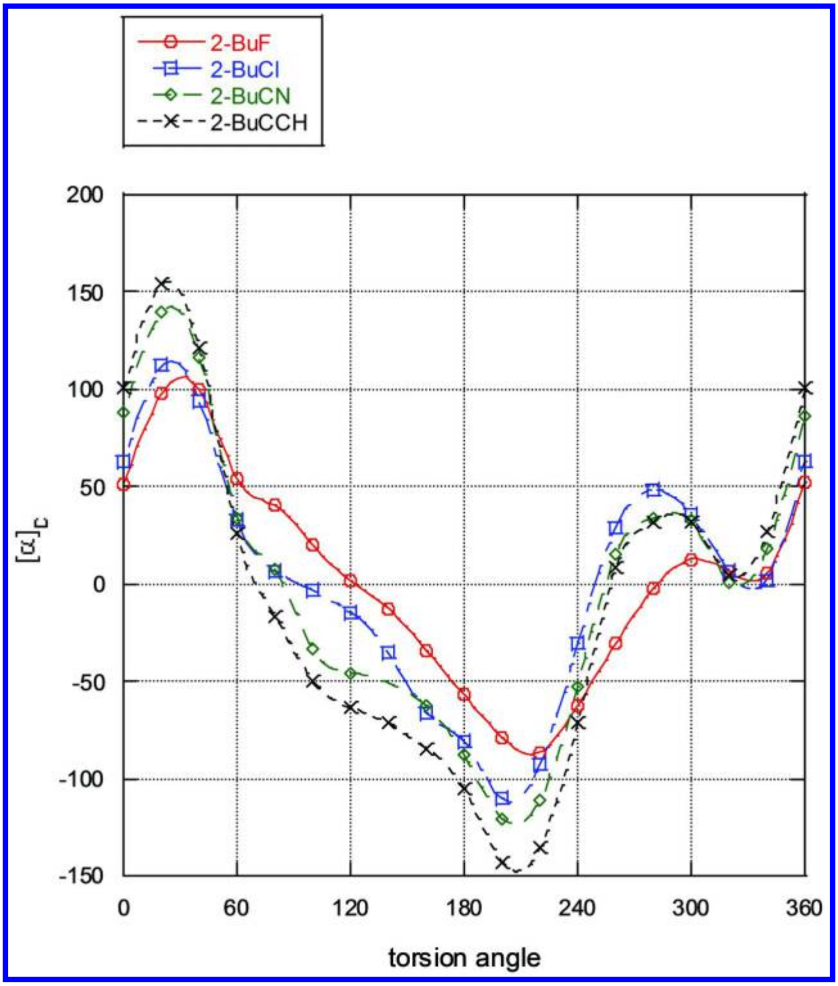

Figure 4. Relationship between calculated optical rotations and the C_2-C_3 torsion angle

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Table 1. Calculated and observed specific rotations at 589 nm for conformational mixtures at 25° C.

X	*Calculated*	*Observed,neat*	*Observed,soln*
F	-17.2	na	
Cl	-37.1	-33.8	-33.8
CN	-45.1	-36.3	-34.1
HCC	-57.8	-46.8	

Twisted Achiral Compounds

The large conformational effects suggest that achiral compounds may give significant optical rotations when twisted from planarity. This was examined for a number of hydrocarbons including 1-butene and n-butane (Figure 5) (*60*), and showed that these compounds can give large rotations in their twisted forms. However, there is a significant effect of theoretical method on the observed values.

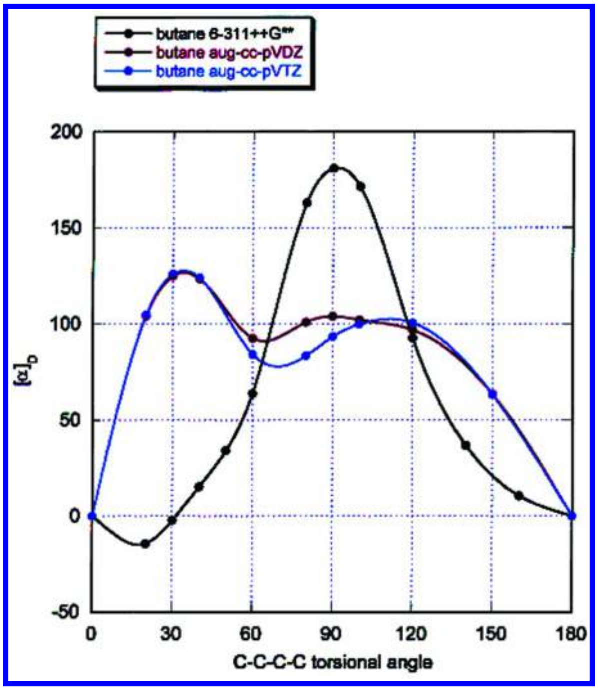

Figure 5. Calculated optical rotations for twisted butane.

The calculated optical rotation as a function of C-C torsion energy for butane has a simple maximum at 90° with the 6-311++G** basis set, but it become much different using the aug-cc basis sets. This is seen more dramatically in a study of 30° rotated ethane (i.e. halfway between staggered and eclipsed). Some calculated rotations are given in Table 2.

Table 2. Effect of basis set on B3LYP calculated specific rotations at 589 nm for 30° rotated ethane.

Basis set	*bf*	*[α]D*
6-311++Gd	86	-495.1
6-311(2+,2+)Gdf	100	-505.1
6-311++(2d,2f)	114	-226.3
6-311++G(3df,3pd)	186	-19.5
cc-pVDZ	58	-208.4
cc-pVTZ	144	-215.3
aug-cc-pVDZ	100	+41.2
aug-cc-pVTZ	230	+53.6
aug-cc-pVQZ	436	+57.8
UGBSIP	766	+59.1

Most of the details concerning the basis functions used in the calculations are not of importance in the present context. The column bf gives the number of functions (s,p,d..) that were used in the calculation, and generally the larger the number the better the result. The first 4 basis functions are of the "Pople" type and they are very satisfactory for most purposes such as geometry optimizations and vibrational frequency calculations, whereas the latter basis functions are of the "Dunning" type that also are normally very satisfactory. But, as seen from the calculated results, especially the change in sign, in the present case there is a large difference with the Dunning functions giving the correct sign as shown by the largest basis set calculations

These basis sets include extra functions beyond the basic group. It is possible to improve on the simple *s*, *p*, *d* .. set by allowing these nucleus centered functions to move in response to the electric fields in the molecule. This happens when a small amount of a *p*-function is added to *s*, and when some *d* is added to *p*, etc. In addition, it sometimes is useful to include "diffuse" functions that are much larger than those in the basic group. They are indicated by + in the Pople sets and by aug in the Dunning sets and are frequently needed in calculations for anions (*61*). Hydrogens diffuse functions are rarely important for geometry optimizations and so only diffuse *s* functions are included in the "Pople" sets but *p*

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diffuse functions also are included to the "Dunning" sets. It is these latter functions on hydrogens that lead to the large differences noted in Table 2. The addition of *p*-diffuse functions to the former set corrects the problem.

Why should these seldom needed functions be so important for optical activity calculations? A clue is given by the density difference plot in Figure 6 that shows the difference resulting from the addition of these functions (*60*). At a relatively far distance from the nucleus, there are some helical differences that result from the directional nature of the diffuse *p* functions. Optical activity results from the helical character of the wave function, and switching stereoisomers results in switching the sense of helicity and the sign of rotation. This effect of helicity is strikingly seen in the optical rotations of helicenes (6) (*62*) and triangulenes (7) (spiro-linked cyclopropanes) (*63*) that give very large rotations.

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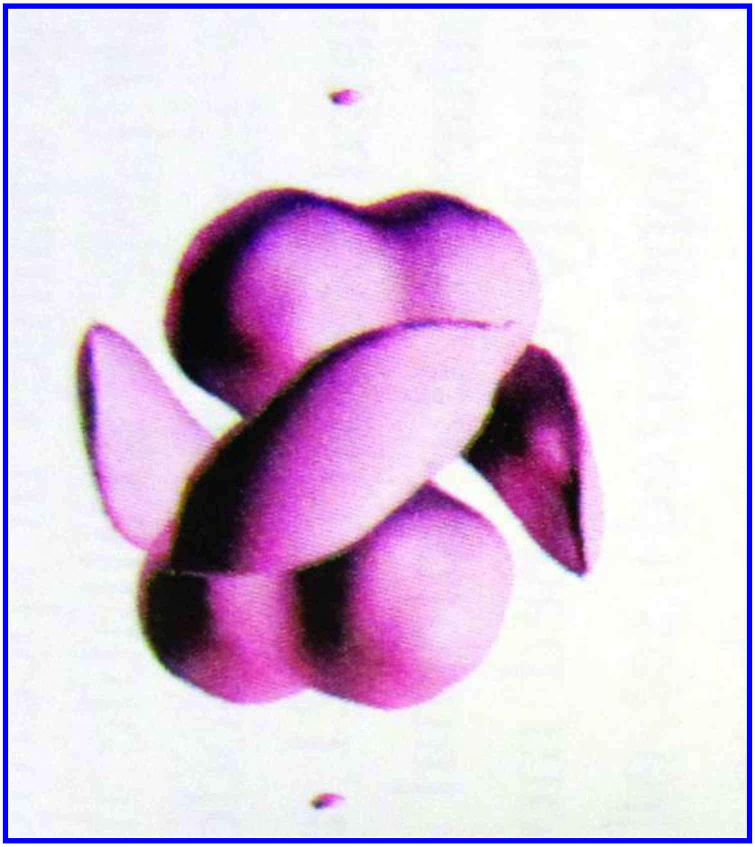

Figure 6. Difference density plot between calculations with and without diffuse p functions on hydrogens of twisted ethane.

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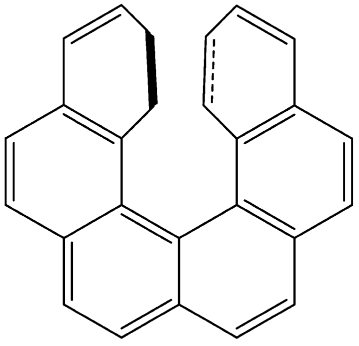

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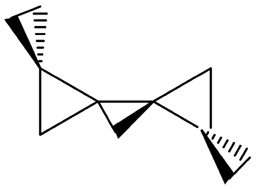

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Use of Minimal Basis Sets

Calculations of optical rotation have come to using increasingly large basis sets with many polarization functions and diffuse functions. The observations given above made us think that much of this complexity might not be essential for the calculations. Would it be possible to reproduce their results using a minimal basis set (STO-3G or 3-21G) to represent the core and valence electrons and then add a full set of diffuse functions (*64*)? Could a minimal basis set "steer" the diffuse functions that are relatively far from the nuclei so that they adopt the essential helical character of the molecule? In a non-resonant situation, the polarized light used to interrogate the molecule might interact mainly with the outer diffuse electron density leading to rotation of the plane of polarization. This seemed something of a wild idea, but we decided to explore it. The study was concerned with how well the large basis set B3LYP calculations could be reproduced.

We used both STO-3G and 3-21G as the minimal basis sets and added diffuse functions from the aug-cc-pVDZ and aug-cc-pVTZ basis set. The object was to see if the results from B3LYP calculations using large basis sets could be reproduced, A number of compounds were examined including α-pinene, 3-carene, norbornenone and 2,3-pentadiene (*64*). The results were quite good, and an example from the carenes is shown in Figure 7.

Here the rotation increases as the number of basis functions is increased. They reach an asymptote as shown by the horizontal lines and the points are numbered. The first two points are for STO-3G and 3-21G that are very small basis sets, and it is clear that they do not give satisfactory computational results. Point 5 is for cc-pVDZ (no diffuse functions). Point 3 involves just the addition of diffuse *s, p, d* functions to STO-3G and gives a calculated rotation that is essentially the same as that derived from the use of a very large basis set . Even with large basis sets such as for points 14(cc-pVTZ) and 20 (cc-pVQZ), diffuse functions are needed giving points 19 and 21. The remaining points are identified in ref. (*64*).

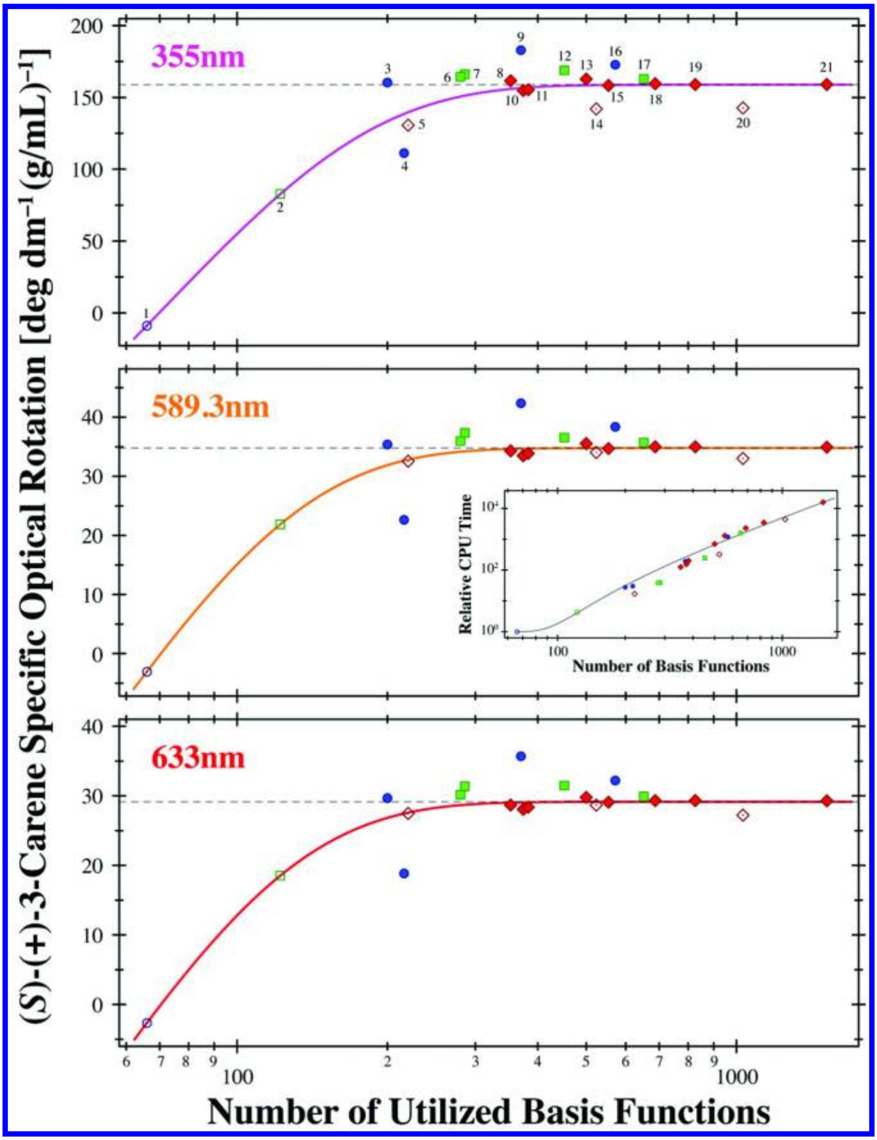

Figure 7. Effect of basis set on the calculated optical rotation of 3-carene at 355 nm (upper), 589 nm (center) and 633 nm (lower). The x axis gives the number of basis functions on a logarithmic scale. The open symbols represent unaugmented basis sets and the solid symbols are for the augmented sets.

Gas Phase Measurements

Until recently studies of optical rotation could not properly compare the calculated values with the experimental results because they were obtained in the condensed phase, either neat or in solution whereas the theoretical calculations refer to the gas phase. Although a heroic effort by Biot (*65*) in 1817 to study the optical rotation of turpentine in the gas phase showed that the vapor had a rotation, the experiment ended rather disastrously when the vessel containing the boiling turpentine broke open and was set on fire. There were some other attempts to carry out gas phase studies but they were hampered by the low density of molecules in the gas phase and the small rotations for most molecules.

This problem was solved by my colleague Prof. Patrick Vaccaro who made use of a cavity ring-down cell that allow multiple passes through the cell (Figure 8) (*66*).

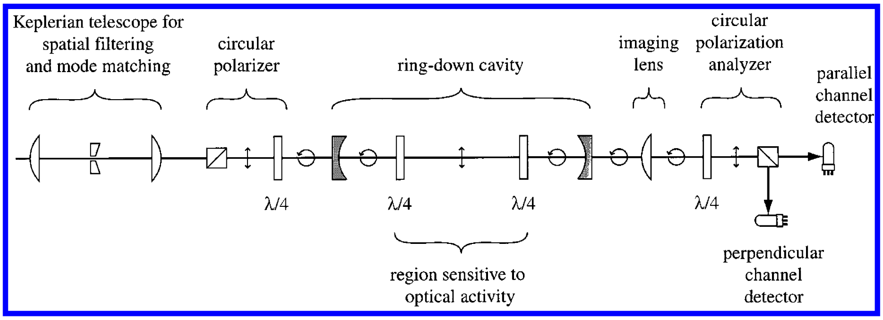

Figure 8. Cavity ring-down polarimeter

Here, the sample is placed in an evacuated cell having high reflexance mirrors at each end. A laser pulse is prepared and sent into the cell though one mirror. The light that gets into the cell will be reflected by the other mirror, and at each pass, some light will leak through the second mirror and will be analyzed. This provides the opportunity to have the effect of a very long path length. But, this alone would not lead to the observation of optical rotation since the effect of light moving in the forward direct would be reversed in the back direction. This can be avoided by inserting two quarter-wave plates, and the region between them will respond to the optical rotation of the sample.

Chloropropionitrile is one of the simplest chiral compounds, and we have examined the (*S*)-(-) form derived from (*S*)-(+)-alanine in some detail (*67*). It has a rotation of $[\alpha]_D = -14.5$ as a neat liquid. A determination of the gas-phase rotation gave $[\alpha]_D = -8.3$. It can be seen that there is a significant effect of phase. The OR in solution was obtained in a number of solvents, giving a range of [α] from -11.6 in acetonitrile, to -17.4 in cyclohexane and -34.6 in benzene.

We have studied solvent effects on equilibria and reaction rates and found that free energies in cyclohexane, di-n-butyl ether, acetone and acetonitrile usually are linearly related to the Onsager dielectric constant function, $(\varepsilon+1)/(\varepsilon+2)$ (*29*). The function takes a zero value for the gas phase and goes to 0.5 for the highest dielectric constant solvents. The correlation would be expected based on the reaction field model of solvent effects (*29*). Extrapolation usually yields a value close to that observed in the gas phase when this is available (*31*).

Application of this model to chloropropionitrile OR gave the result shown in Fig 9. There is a linear correlation, but extrapolation to the gas phase led to a value of -22, quite far from the observed value of -8.3. We have found that this is the usual case for optical rotation. Chemists generally think of cyclohexane solutions to be similar to the gas phase, but for optical rotation, acetone and acetonitrile solutions usually give the closest OR to the gas phase.

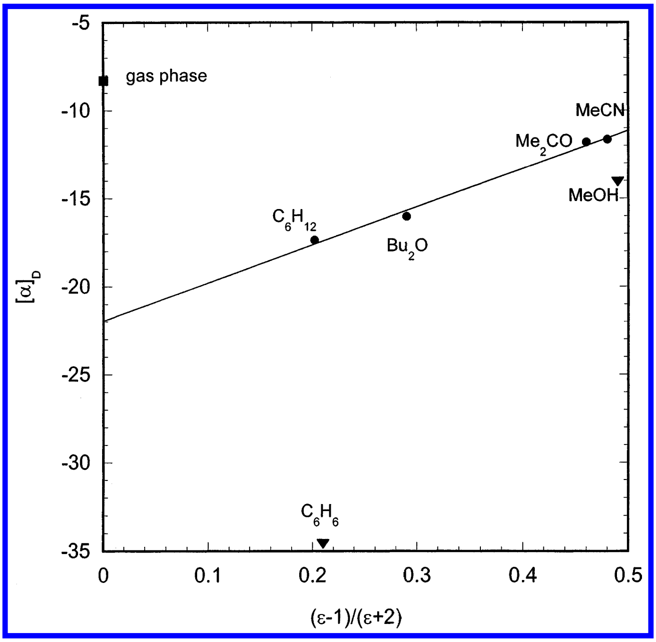

Figure 9. Relationship between optical rotation and solvent dielectric constant

The effect of solvent on optical rotations has been studied computationally at the DFT level by using a polarizable continuum model (PCM) (*68*). It was unfortunately not able to give a very satisfactory result, but better results have been obtained by using discrete solvent molecules in the calculations (*69*). However, this involves averaging over solvent conformations, and the added molecules greatly lengthen the execution times.

Sum-over States Calculations

It is clear that excited states are intimately connected with optical rotation. It would be of interest to know which states are the most important. For example, it is commonly thought that the carbonyl group is very important in the OR of ketones (*2*). It is possible to obtain information on this subject from a sum-over-states calculation of OR making direct use of the Rosenfeld equation. Electronically excited states can be obtained by calculations using time dependent

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density functional theory (TDDFT) and this code in Gaussian also gives the Rotatory strength for each transition. Thus, it is now relatively easy to carry out the calculation. We have examined this for a number of molecules (*70*).

Chloropropionitrile gives a typical result. As with most molecules, the first excited states are not the main source of the observed OR as may be seen in Fig 10. The rotation continues to depend on the number of excited states beyond 100. It is necessary to examine a very large number of states (Figure 11) in order to come to a constant value for this quantity. It is fortunate that linear response methods have been developed that do not need to deal with excited states directly.

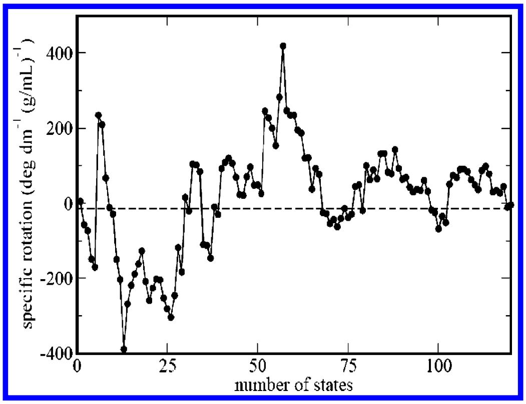

Figure 10. Sum-over-States Study for Chloropropionitrile including the first 125 excited states.

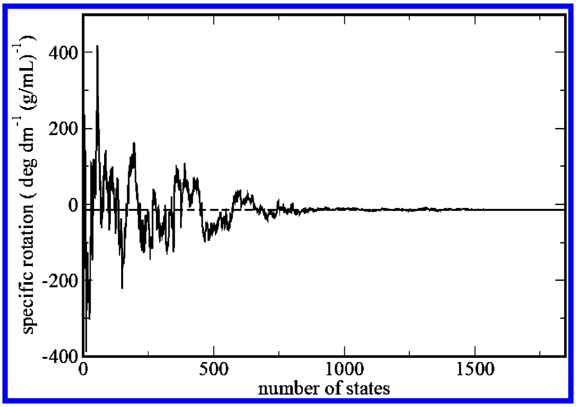

Figure 11. Sum-over-States for Chloropropionitrile including >1500 excited states.

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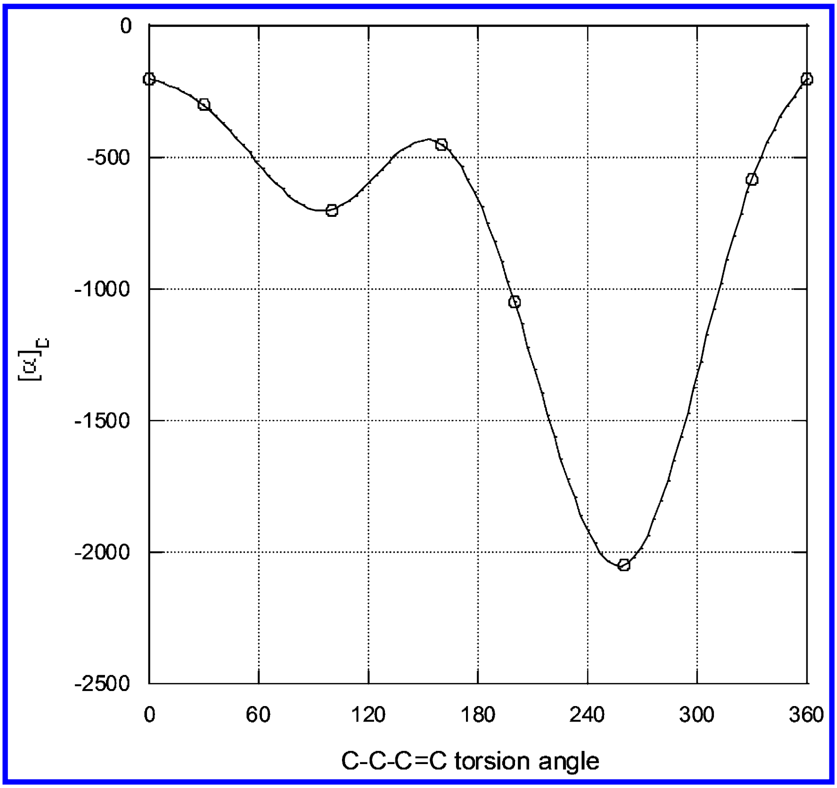
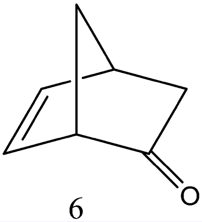


Figure 12. Relationship between specific rotations for a norbornenone model and its C=C-C-C torsion angle

Norbornenone

Of the compounds that we have examined, there is one, (S)-(-)-norbornenone (**6**), that behaves differently. This compound was first prepared in chiral form by Mislow and Berger (*71*). They found a specific rotation in isooctane solution of $[\alpha]_D$ = -1160 that is very large for such a small and relatively simple molecule. The saturated derivative, norbonanone (**7**) has a rotation of ~20. A B3LYP/6-311+G* calculation for **6** gave a rotation of -1260 (*52*) that was in remarkably good agreement with the experiment. A sum-over-states study found that the first electronic transition was largely responsible for the rotation (*70*). This is one of the few molecules for which this is the case.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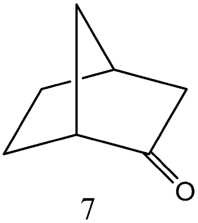
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The large rotation clearly involved an interaction between the n→π* transition for the carbonyl group that leads to a large magnetic transition dipole and the π→π* transition of the carbon-carbon double bond that lead to an electric transition dipole. One way to examine the interaction of these groups is to delete the remote bridgehead carbon and then examine the effect of rotating the $C=CH_2$ with respect to the C=O (*54*). The results of this study are shown in Fig 12. The largest negative rotation is found at (O=)C-C-C=C angle similar to that found in norbornenone itself. This orientation is the one that allows the maximum interaction between the C=C and C=O. This model has been examined in more detail by Caricato, et. al. (*72*) who examined how the relative orientations of the electric and magnetic transition dipoles change with torsion angle. The magnitude of the optical rotation in norbornenone has also been examined by Moore, Srebro and Autschbach (*73*).

It was noted above that the DFT calculated rotation of (*S*)-(-)-norbornenone is in very good agreement with that reported for an isooctane solution However, a later calculation by Mach and Crawford at the CCSD level gave a much smaller predicted rotation (-561) (*74*) whereas for a DFT calculation at the same level, $[\alpha]_D$ = -1260. If that were correct, there must be a large solvent effect or a problem with the CCSD calculations. In order to determine which was correct, I prepared a sample of (*R*)-(+)-norbornenone, and Priyanka Lahiri measured its rotation in the gas phase (*75*). giving $[\alpha]_D$ = 755, about half-way between the two calculated values. Further theoretical developments are needed in order to reproduce the experimental optical rotations.

Norbornenone also shows a large solvent effect on its optical rotation. As compared to the gas phase $[\alpha]_D$ = 755, in acetonitrile it was 950, and in cyclohexane it was 981 (*72*). This shows the importance of referring the solution phase optical rotations to the gas phase rotations.

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I would also like to extend my appreciation to the 100+ graduate student and many postdoctoral workers without whom little could be done. I wish I could have noted all of their work but that would require much more space and time than was available.

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Chapter 3

Some Thermochemical Studies of Solvation from the 1960s and 1970s

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Initial commentary refers to the stressful emergence of physical organic chemistry as a post-WWII interdisciplinary field benefitting greatly from instrument development. Design of a simple solution calorimeter in the author's laboratory allowed the measurement of solvent-solute interactions over the entire range from weak hydrogen bonding to heats of formation of simple carbocations in superacids or of simple, reactive carbanions in superbases.

The Beginnings of Physical Organic Chemistry as a Discipline in the 1940s

Without doubt Louis Hammett's classic monograph, Physical Organic Chemistry (*1*), named the field. So authoritatively and elegantly was it written that seventy four years after its publication in 1940 Hammett's book maintains its rigor and clarity. It contains essentially no errors although, of course, most of the areas in Hammett's original discussion have been enormously expanded and any significant errors of interpretation or prediction on Hammett's part would have long since been revealed.

During the early 1940s most of the world's chemical activity was dedicated to the second World War in which chemistry played a major role. Some of the war effort was applied to mechanistic studies of the reactions, such as nitration, most vital to the conflict. When peace returned there was a cohort of organic chemists eager to apply the principles in Hammett's book to the study of electronic reaction mechanisms as they had been developing since the 1920s, especially by Ingold's "English School" , and which they had been using to solve problems during the war years.

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Of particular significance in gaining recognition for physical organic chemistry as a clearly identifiable discipline was the organization of the first Conference on Reaction Mechanisms by Charles C. Price of Notre Dame and Paul D. Bartlett of Harvard, held in September of 1946 at Notre Dame University. As a vital means of communication in the Physical Organic-Reaction Mechanism Community, this conference has continued steadily through the past seven decades, meeting every two years without pause. During most of this period there have also been regular meetings of the Physical Organic Gordon Conferences as well as major participation in the Organic Symposia at ACS National Meetings and numerous international symposia.

A major contributor to the early growth of the field was the establishmentof the James Flack Norris Award in Physical Organic Chemistry in 1963 by the Northeastern Section of ACS which celebrated the work of the leading physical organic chemists of the time: Christopher Ingold (1965), Louis Hammett (1966),Saul Winstein (1967), George Hammond (1968), Paul Bartlett (1969), Frank Westheimer (1970).

It is significant that although Louis Hammett was a physical chemist, and taught physical chemistry, the great majority of those who have identified themselves as physical organic chemists have been organic chemists, that is, they were trained in and teach organic chemistry. With a few notable exceptions, relatively few academics whose backgrounds lie in physical chemistry, and teach it, have identified themselves as physical organic chemists.

Perhaps the most important contributor to providing a balanced organic and physical approach to the field was Paul Bartlett, who emphasized the role of synthetic chemistry as a means to testing physical organic theories. (For an example of this combined approach see Project 4 below involving the synthesis of a strained molecule, o-di-t-butyl benzene, and measurement of its strain energy). Bartlett was a student of James Bryant Conant (later president of Harvard University) whose approach to organic chemical problems was that of physical organic chemistry decades before publication of Louis Hammett’s book. No other teacher of physical organic chemistry was as influential as Bartlett in terms of the number of successful teachers who were produced in his laboratory at Harvard.

In the 1930s and 40s, it was by no means obvious to the average academic organic chemist that the occasional sallies of their colleagues into chemical kinetics or other traditionally physical disciplines would eventually lead to the fundamental theoretical principles on which the teaching and practice of organic chemistry would depend, even in introductory textbooks. In those times the leading organic chemistry textbooks were devoted to describing synthetically important reactions through the inter-conversion of important functional groups . Little if any consideration was given to the electronic redistributions through which reactants must pass on their way to products. There was little recognition that such a detailed understanding of electron bonding could help to integrate and rationalize organic chemistry and predict new and unexpected reactions.

The increasing attraction of organic chemists towards the elucidation of organic reactions in terms of modern physics followed the well-precedented strategy of *reductionism*, that is, the clarifying of complex systems in terms of “simpler” ones . Elucidating biological systems by breaking them down into chemical reactions is a classic example of reductionism as is the reduction of molecular structures in terms of electrons: that is by explaining chemistry in terms of physics. Note however reference (*2*).

Despite the value of understanding the wonderland of organic chemistry through electronic mechanisms, the establishment of physical organic chemistry was accompanied by the stresses which are almost inevitable as an **interdisciplinary** field is introduced in academe. **Intra**disciplinary stresses arose within the Organic Divisions of many Chemistry Departments. Often the full professors held the power to discourage younger colleagues from their flirtations with physical chemistry instead of by making a name for themselves (and their department) by doing "real" organic chemistry. For example the Organic Chemistry Division of the University of Illinois , was presided over by several of the leading figures in American chemistry who were staunchly opposed to electronic mechanism study as an intruder into the field. It was not until 1955 that Illinois hired a physical organic chemist as an Assistant Professor. Also **inter**disciplinary stresses between the Organic and Physical Divisions of many departments were deeply ingrained in the all too common parochialism of the day.

In the early 1940s while I was an undergraduate chemistry major at the University of Pennsylvania, my research director was Allen Day who was so impressed by the mechanistic insights of the British School that he wrote a textbook for teaching the sophomore pre-med course based on the new principles. Although his work was roundly dismissed by some of the elder Professoriat as "a fad" I believe it was the first undergraduate text to use electronic mechanisms, with curved arrows, as a rational basis for elucidating organic chemical reactions. Also, John Miller, a physical chemist, began teaching a course based on Louis Hammett's book soon after it was published. It was my good fortune to do my doctoral research under the joint direction of Day and Miller.

After several years in a small Philadelphia industrial firm and two years teaching in a small liberal arts college I joined Paul Bartlett's research group at Harvard as a postdoctoral Research Fellow. After two years of total immersion in the superb scientific environment of Bartlett's laboratory, I obtained an Assistant Professorship at the University of Pittsburgh and began years of study on the most general and most important reaction in chemistry, proton transfer.

In the 1950s there was a dearth of data by which the relative strengths of organic compounds as proton acceptors or donors was known. I set about developing this data base building on work that I had begun at Harvard. A natural extension of the study of organic compounds as acids and bases is the study of their behavior as solvents. Considerable work had been done on various aspects of the acid-base behavior of organic compounds, and corresponding solvent effects, by physical chemists but relatively little from the viewpoint of organic chemists looking for quantitative comparisons of the systems most useful to their own work.

Against this background, I was especially gratified to receive the 1977 James Flack Norris award: "for outstanding contributions to our understanding of the profound role of solvation in organic chemistry".

The period following World War II in the 1950s and '60s was a good one for American science and physical organic chemistry benefitted enormously from

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the new generation of organic chemists who were eager to unravel the details of the classical organic reactions in terms of electronic reaction mechanisms. At the same time rapid development of chemical instrumentation was taking place and, of particular importance, the federal government began a program of investment in academic scientific research through a system of financial support especially through the National Science Foundation and the National Institute of Health. Public support was strong through appreciation of the role that science had played in winning WWII . The Cold War with Russia was beginning and American science got a powerful boost when sputnik , the first man made orbital satellite, appeared in the evening skies. The American public recognized at once that a competition of great importance was taking place between American scientists and their Soviet counterparts.

The discovery on December 23, 1947 of semi-conductors in the Bell Laboratories had an immediate impact on two areas from which my research was to grow. Most immediately, the thermistor provided a remarkably delicate sensor for detecting small temperature changes and became the essential element in the simple solution calorimeters that my research group learned to make. Of more general application was the use of transistors to replace vacuum tubes in computers. Without semiconductors the development of computers to their present ubiquitous applications would have been impossible. Significantly, the IBM 360 which filled a large room and was one of the first workhorse institutional computers had 25KB of memory while the tiny iPhone 4 in your pocket boasts 524,300 KB . The difference in capabilities is staggering

As my research group learned how to make simple solution calorimeters (*3*) capable of measuring accurate, precise heats of reaction to the nearest hundredth of a kilocalorie it was clear that we had a tool which would allow us to measure the many interactions of strong acids with weak bases and of weak acids with strong bases which had been our long-term interest, see for example Figure 1. The same tool obviously could be applied to measuring solvent-solute interactions.

On Figure 1 note the tiny thermistor for detecting heat changes in the calorimeter and the heaters used for injecting a measured amount of electrical heat to calibrate each measurement of a heat of reaction. Both of these heat changes were displayed for measurement on a strip chart recorder.

Our calorimeter gave us entrée to a virtually unoccupied niche in physical organic chemistry. Most of the energy changes being studied at the time were free energies in terms of rates or equilibrium constants. Our calorimeter provided immediate access to the corresponding heat (enthalpy) and heat capacity changes which are only obtainable from equilibrium constants by application of the van't Hoff equation to their temperature coefficients. This is a much more difficult operation than the simple measurement of the heat change in a calorimeter. Entropies of reaction were available immediately from the heat of reaction and the Gibbs free energy i.e. the equilibrium constant. It was soon clear from our work and that of many others that there was often an excellent correlation between the heats of reaction for a series of compounds and their corresponding free energies of reaction. Thus, if one measured the heats of reaction for a series of bases in a strong acid, or a series of acids in a strong base , the scale of relative basicities (or acidities) obtained was a very close approximation to the scale that would be obtained from the equilibrium constants for protolysis.

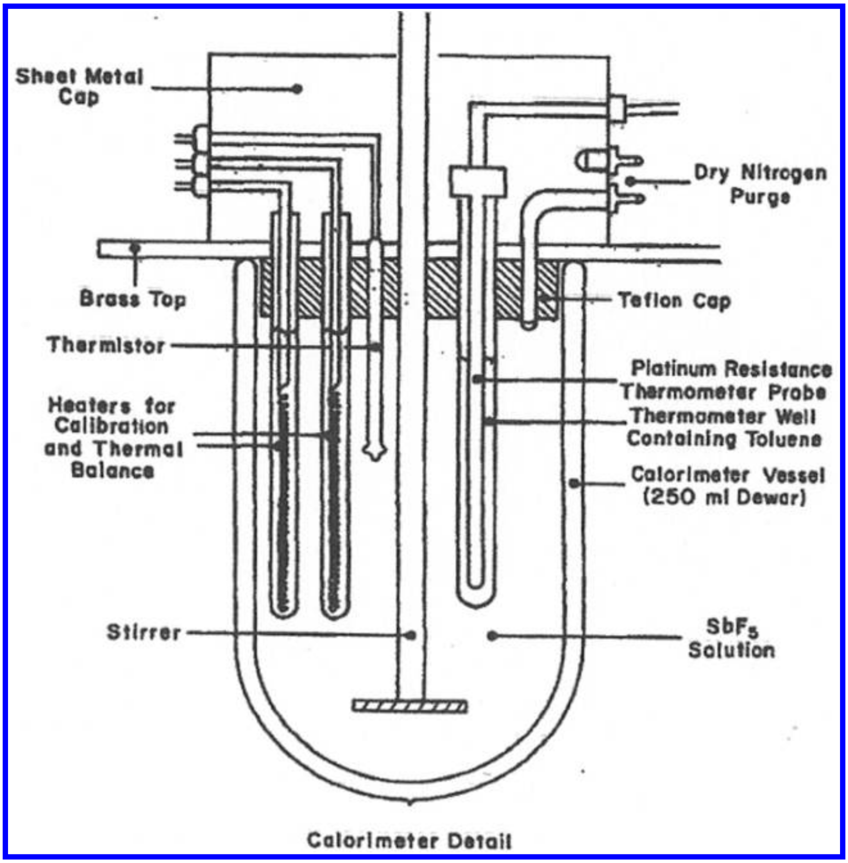

Figure 1. A Typical Solution Calorimeter developed by the Arnett group

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Application of Solution Calorimetry to Four Physical Organic Chemical Problems

Problem 1 - Complete Thermodynamic Analysis of the “Anomalous Basicity Order” of Aliphatic Amines in Aqueous Solution (*4*, *5*)

During the 1960s and ’70s an invaluable breakthrough for the study of proton transfer and solvation studies arrived in the gas phase . Ion cyclotron resonance , high pressure mass spectroscopy and the “flowing afterglow” techniques provided reliable values for the protolysis reaction in the gas phase from which the role of solvent for the corresponding reactions has been removed. A complete description of the new opportunities afforded by this combination of techniques is described in (*4*). The quantitative relations between protolysis in the gas phase and in aqueous

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solution allows calculation of the solvation terms through a cycle and the following equation:

$$\Delta Pi(g)\ (B) = \Delta Pi\ (1\ )(B) - \Delta Ps(B) - \Delta Ps(H+) + \Delta Ps(BH+)$$

where P refers to the property: ΔG, ΔH, ΔS, g refers to the property in the gas phase, i refers to the ionization process and l is the relevant property in solution and s refers to solvation , the transfer from the gas phase to solution. Thus ΔHs(BH+) means “the heat of solvation of the ‘onium ion from the gas phase to solution in the liquid under discussion” and ΔHi(g)(B) refers to the heat of ionization of the base B in the gas phase.

The first solvation problem that we attacked using the newfound ability to study proton transfer in the gas phase was the curious basicity order for amines in aqueous solution: ammonia < primary < secondary > tertiary (*5*) .

In the gas phase the order was quickly found to be: ammonia < primary < secondary < tertiary as would be expected on the basis of simple inductive effects. Obviously, the inverted order for ionization of the tertiary amines in solution is a solvation phenomenon. Accordingly, a complete tabulation of all twelve properties for ΔG, ΔH, ΔS implied by equation 1 was developed for several sets of primary, secondary and tertiary amines and scrutinized for trends that might localize the anomaly to free energies, enthalpies or entropies of solvation of the amines or their ‘onium ions. It was concluded that “complete analysis does not lead to a simple interpretation. The inverted order arises from slight difference in the rates of changes of several thermodynamic properties in response to progressive alkyl substitution”.

It had been exciting to think that some simple solvent-solute interaction was clearly identifiable as responsible for the amine anomaly, but such was not the case.

Problem 2 - Concerning the Ionic Nature of Alkyl Halide Solvolysis Transition States

By the 1960s extensive kinetic studies of the substitution reactions of many tertiary alkyl halides had provided overwhelming evidence for a carbocation intermediate. Similar results for a number of bicyclic halides prompted deeply nuanced investigations of their structure-reactivity relations. Several major conferences featured vigorous debates between leaders in the physical organic community about a special kind of “nonclassical” bonding which might lie at the bottom of the observed behavior. During this period research in the laboratories of Professor George Olah at the University of Southern California showed how to generate stable solutions of the proposed ionic intermediates in various superacidic media (magic acids) employing mixtures of SbFs with SO_2 ClF and SO_2 F_2 of great acidity thanks to anions of very low nucleophilicity. In such solutions at low temperatures t-butyl cation and many others could be examined at leisure by NMR and other means.

In our laboratory, Craig Petro adapted the calorimeter shown in Figure 1 to measure heats of reaction of alkyl halides in magic acid at -80 to -100 deg.C for nearly twenty primary and secondary alkyl and cycloalkyl halides in several superacidic media at temperatures down to -100 deg.C (*6*). Agreement between the results for different solvents and many control experiments implied that indeed the halides had been dissociated to carbocations. These heats of ionization in magic acid were compared with a half dozen gas phase heats of ionization and reference (*7*) describes the correlation between the heats of ionization and the free energies of activation for ethanolyisis of eleven tertiary and secondary chlorides. The slope of the linear relationship was 0.88 with a coefficient of correlation of 0.987 if the free energies of ethanolysis for the secondary halides were corrected suitably for nucleophilic assistance from the solvent.

Finally, a group of carbinols (mostly diaryl and triaryl) whose $pK_{R}+$'s had been measured by Hammett's indicator method were subjected to ionization in the calorimeter at -40deg.C. Plots of heat of reaction in magic acid versus $pK_{R}+$ were linear with coefficients of correlation of 0.95 or better. Such plots allowed interpolation to estimate the $pK_{R}+$ for t-butyl, norbornyl and adamantyl carbinols which could not have been determined by any other method. These correlations of the heats of ionization in superacids with gas phase ionization, free energies of activation for ethanolysis and $pK_{R}+$ show that the same process is being measured in all cases, i.e. conversion of the neutral precursor to an ionic type of product (or intermediate).

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Problem 3 - Dissection of the Bizarre Behavior of the Activation Parameters for t-Butyl Chloride Solvolysis in Highly Aqueous Ethanol-Water Solutions

During the mid-1950s Winstein and Fainberg published their monumental investigation of solvent effects on the solvolysis of various alkyl halides in pure and mixed solvents at several temperatures to discover the effects of solvent variation on the activation parameters (*8*).

One can imagine the Winstein laboratories set up to measure rate constants on a factory production basis with row after row of temperature control baths! The results did not follow any simple physical treatment and were often bizarre. See for example the following plot of the three activation parameters for solvolysis of t-butyl chloride in a series of aqueous ethanol

Note in articular in Figure 2 the painstaking effort that was made to study a large series of solutions in the neighborhood of 0.8 mole fraction water where the fantastic effects on the heats and entropies of activation take place but their combined effect compensates each other so well that it scarcely affects the free energy of activation. Winstein realized that any consideration of the effect of solvent change on the solvolysis transition state could only be isolated if the corresponding solvent effect on the initial state, that is on the free energy, heat, and entropy of solution for t-butyl chloride itself were subtracted out. In fact it might be possible that all of the weird behavior of the activation parameters was due to solvent effects on the t-butyl chloride ground state.

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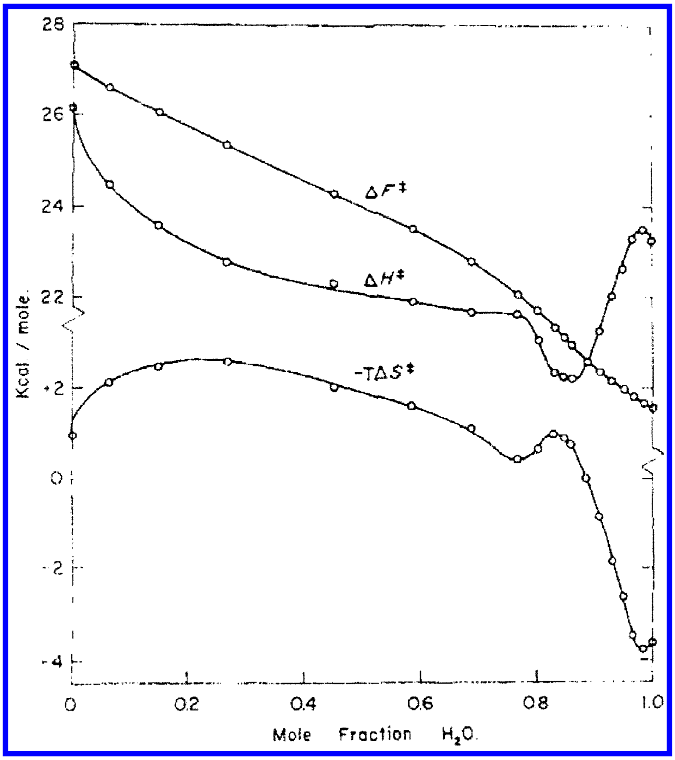

Figure 2. Plot of $\Delta H^{\neq}$, $\Delta F^{\neq}$ and - $T\Delta S^{\neq}$ vs. mole fraction water in aqueous-ethanol solvents

Winstein obtained such data for the free energies of solution for t-butyl chloride in some aqueous alcohol solutions, but Figure 2 shows that the more interesting results are in the solvent effects on the heats and entropies of activation. The corresponding heats and entropies of solution for the ground state of t-butyl chloride were not accessible to Winstein but we could measure them easily using our calorimeter. In fact some of the strangest behavior of the Winstein-Fainberg data was seen in the isokinetic plot of $\Delta H^{\neq}$ vs $\Delta S^{\neq}$. Was this primarily due to the changing solvation of the presumably salt-like character of the transition state, or rather to a reflection of the changing heat and entropy of solvation of ground state t-butyl chloride itself?

We obtained (*9*) appropriate heats and entropies of solution for t-butyl chloride in the same series of aqueous ethanol solutions which Winstein and Fainberg had studied and combined them with the free energies of solution that they had obtained from published articles on solvent effects on the Henry's Law constants. Our combined data for the free energy, heat and entropy of activation, and of solution for t-butyl chloride in seven of the aqueous ethanol system were tabulated. Finally, the three thermodynamic properties for solvation of the transition state itself were determined by subtraction of the ground state contribution from the three activation parameters in each aqueous ethanol solution.

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It turned out that virtually all of the strange behavior of the solvent effects on activation parameters was attributable to varying solvation of the ground state and a simple linear isokinetic plot for the behavior of the transition state was strikingly similar to that for a variety of simple salts in aqueous methanol solutions. Once again the overwhelming evidence indicated that the t-butyl chloride solvolysis transition state is strikingly ion-like.

Project 4 - The Synthesis and Strain Energy in o-Di-t-butyl Benzene

As part of an extensive study of steric effects, Professor H.C. Brown and his students investigated strain energies in ortho di-substituted aromatic compounds The strain present in homomorphs of o-di-t-butylbenzene implied an estimated strain (in o-di-t-butylbenzene) to be a minimum of 25 kcal/mole. and finally Brown (*10*) submitted the challenging statement: "Strains of this magnitude suggest that the preparation of such homomorphs should be a difficult matter." Interest in Brown's studies were so great that at once o-di-t-butyl benzene became one of the "molecules of the year" whose synthesis would assure a path to recognition for aspiring young organic chemists . If o-di-t-butyl benzene could be made it would provide a classical example of a theoretical problem which could be tested by the synthesis of a compound presenting a structural feature which theory predicted would be limiting. Fortunately for the writer, who was at the time an Assistant Professor at the University of Pittsburgh, the reactions of acetylenes with metal carbonyls was being heavily investigated nearby at the U.S.Bureau of Mines. Disubstituted acetylenes were shown to give stable adducts with dicobalt octacarbonyl (*11*)

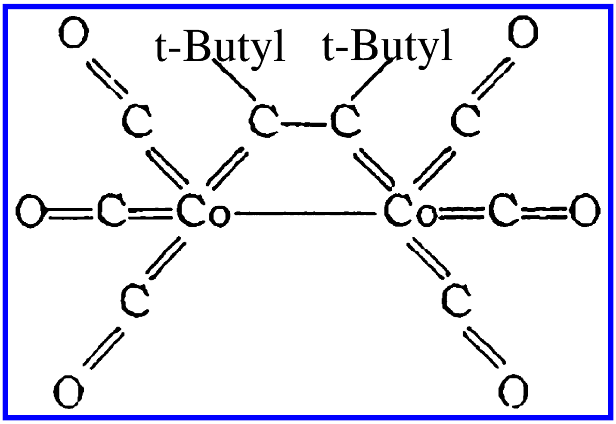

Figure 3. The presumed structure of the adduct formed from di-t-butyl acetylene and dicobalt octacarbonyl based on reference (11)

We were encouraged to believe that if such an adduct could be made between $Co_2(CO)_8$ and di-t-butyl acetylene (Figure 3) that treatment of the adduct with gaseous acetylene under pressure might yield o-di-t-butyl benzene. Indeed, in the hands of Mike Strem the target product was obtained (*12*, *13*) and the first question raised by H.C. Brown was answered; the existence theorem was proved, the strain was not too great to preclude the molecule's existence

Thanks to our reaction calorimeter we were well positioned to answer Professor Brown's second prediction: if o-di-t-butyl benzene could be made, the strain energy from forcing the two bulky groups closely together should be about about 25 kcal/mole. This problem was attacked at once using a strongly acidic $AIBr_3$ solution in CS_2 at 30deg.C to convert o-di-t-butyl benzene into its meta and para isomers (*14*). Many control experiments were done to demonstrate that conversion of the strained ortho isomer to its presumably unstrained isomers was entirely responsible for the large sudden release of heat when reaction was initiated (Figure 4). Many replications anchored the heat of isomerization, and by this reasoning the strain energy to be 22.3±0.5 kcal/mole.

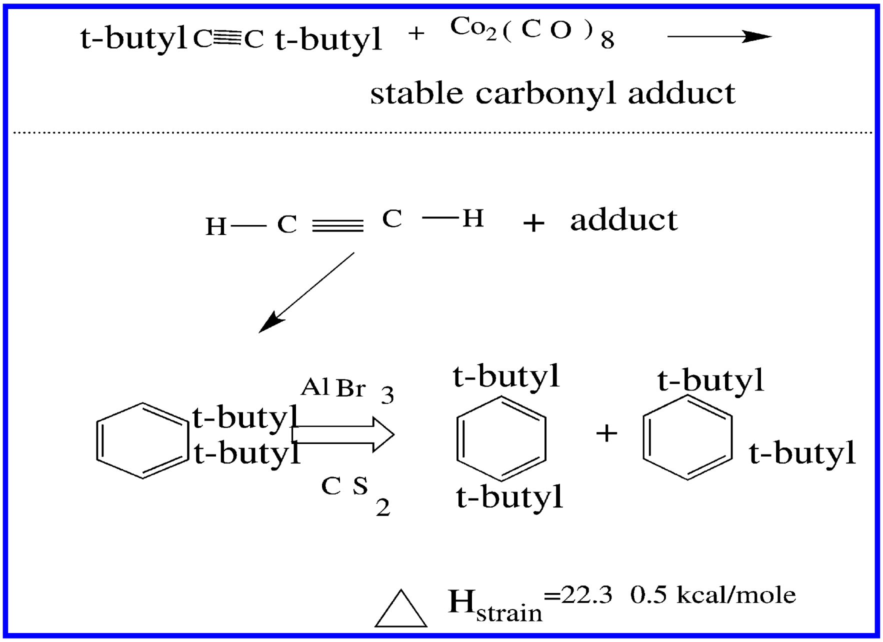

Figure 4. Schematic for preparation of o-di-t-butyl benzene and measurement of its strain energy.

Mike Strem was also able to make 1,2,4-tri-t-butyl benzene, but all attempts to make 1,2,3,4-tetra-t-butylbenzene or the ultimately crowded 1,2,3,4,5,6-hexa t-butylbenzene failed. The ortho disubstituted benzenes were examined by a variety of spectral and other methods for any evidence that the benzene ring was being seriously warped into a "nonaromatic" benzene. Nothing more of particular interest was found. High reactivity to relieve the strain from crowding two bullky groups together was the only unusual property worth noting.

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Chapter 4

A Life in Physical Organic Chemistry

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My life in science has pretty much focused on physical organic chemistry. The topics have included novel aromatic molecules--the cyclopropenyl cations and cyclopropenone--and also antiaromaticity in the 4 pi-electron species including cyclopropenyl anions, cyclobutadiene, and cyclopentadienyl cation. Electrochemistry was an important tool, and esr spectroscopy to detect triplet ground states in symmetrical antiaromatics. We showed that aromaticity added resistance to molecular wires, so non-aromatic wires have higher conductivities. We showed the mechanism by which thiamine pyrophosphate catalyzes important biochemical processes with an intermediate nucleophilic carbene. We devised artificial enzymes and explored hydrophobicity; this furnished a tool to discover the geometries of transition states. We determined some enzyme mechanisms, and experimentally showed a scheme for the way that prebiotic chemistry could have formed L-amino acids and D-sugars. We devised a group of novel catalytic polymers, and also a new anticancer compound with a novel mechanism.

The Importance of Physical Organic Chemistry

Physical organic chemistry combines the most important aspects of both physical chemistry and organic chemistry. It asks about the properties of organic compounds, and it also asks how the transformations of organic compounds occur in chemical reactions, in detail. Organic chemistry itself is concerned with the likely properties of new molecules and how to make them, and of course also with the properties of naturally occuring compounds and their chemical structures. The tools of physical organic chemistry tell us which compounds to make for desired

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properties, including biological and electronic properties. The tools created by physical organic chemists also help synthetic chemists create new reactions and strategies to solve the synthesis problems, and the tools and procedures needed to deduce the structures of both the new compounds and also those found in nature. Physical organic tools also help us understand the ways in which natural enzymes perform their syntheses.

My Studies in Physical Organic Chemistry

As I will describe, my research programs have ranged from experiments to help understand how some important enzymes work, to experiments to see how their reaction mechanisms can be imitated in synthetic enzyme mimics, to the creation of new molecules that modulate biogical differentiation and showing how they work, to showing how the phenomenon of hydrophobicity can be used in artificial enzymes but also how it can be used to deduce the geometries of transition state, to experiments to create and understand the properties of new aromatic systems, to understand and demonstrate the new phenomenon of antiaromaticity, to using electrochemistry to create and measure the properties of antiaromatic systems, and to understand how the electrical conductivities of molecular wires is related to the aromaticity of their components.

The results of this work are described in over 400 publications, too many for a sensible bibliography for this chapter. Thus I will generally cite the first publications in a given area and then either a published review or a recent publication with its own bibliography that has generous citations of the other publications. This plan shortchanges my coworkers who did all the intervening work, but their names can be found in the citations that are in the most recent publications.

Aromaticity

I have been interested in aromaticity since I was 12 years old. I had the good fortune that a close family friend was Max Tishler, director of chemistry at Merck. He gave me a copy of Conant and Blatt, *Organic Chemistry*, when I was seven, and in it I learned about the aromaticity of benzene. I decided that an analog with silicon should also have the special stability of aromatic compounds. I set out to synthesize it--still a challenge for chemistry today--but my efforts helped me become a finalist in the Westinghouse contest for high school students, where I explained why hexasilylbenzene would be an interesting compound. This has to some extent been my style: create an unknown compound predicted to have interesting properties, then study their properties including their chemical reactivities and even their biological properties

I joined the department of chemistry of Columbia University in 1956, as a lowly instructor. The department was very strong, with Louis Hammett (not retired) and Cheves Walling in physical organic chemistry, William Reinmuth in electrochemistry, and Gilbert Stork in synthesis. When I started my independent career, aromaticity in single rings was known to involve 6 delocalized pi electrons,

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as in benzene, or cyclopentadienyl anion, or cycloheptatrienyl cation. However, the theory of aromaticity indicated that there would be other magic numbers, with 4n + 2 pi electrons and n an integer. The simplest aromatic system would be the cyclopropenyl cation, with n = 0, so we set out to synthesize it and see its properties. This is the part of physical organic chemistry relating properties to structures, including those of non-natural synthetic species. We were able to synthesize the 1,2,3-triphenylcyclopropenyl cation in 1957 (*1*), and saw that it was reasonably stable in spite of its tremendous ring strain that would favor addition to the cation. In 1967 we were able to synthesize the unsubstituted cyclopropenyl cation **1** (Figure 1), again surprisingly stable considering its ring strain (*2*).

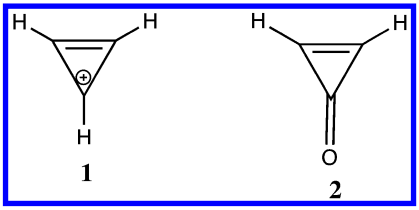

Figure 1. Cyclopropenyl cation and cyclopropenone.

In general carbonyl groups can replace the cationic carbons in such species, and still share the aromaticity. For example, cycloheptatrienyl ketone, tropone, is also an aromatic 6-pi-electron nucleus. Thus we synthesized substituted cyclopropenones (*3*) and the unsubstituted ketone itself **2** (Figure 1) (*4*), and saw that it was strongly stabilized by its 2 pi-electrons and a carbonyl dipole. In fact, in water it existed as the ketone while cyclopropanone, without the double bond, was completely hydrated as a geminal diol to relieve strain. Subsequently others (*5*) have shown that with amino group substituents and an imine in place of the carbonyl group the cyclopropene system is very stable and interesting as a basic unit in novel synthetic procedures. A review of this work on aromaticity is part of a recent publication on the role of aromaticity in molecular electrical conductivity (*6*).

Antiaromaticity

While it was clear that aromaticity in a single ring required 4n + 2 delocalized pi electrons, it was not clear when I started my independent career what the properties would be of monocycles with 4n pi electrons. It was clear that they would not be aromatic, but would they simply be non-aromatic or could they be worse than that? Cyclobutadiene was clearly very reactive, and defied isolation, but could that simply reflect its strain and not a specific destabilization by the delocalization of 4 pi electrons? We set out to examine this question. As our several review articles describe (*7–11*) we concentrated on three species with 4 pi electrons: the cyclopropenyl anion **3**, the cyclobutadiene ring **4**, and the cyclopentadienyl cation ring **5** (Figure 2). We used kinetic studies, and also electrochemistry, to explore these systems. Rate studies showed that cyclopropenyl anion derivatives were very slow to form compared with analogs without the double bond, even though the double bond added additional places to delocalize charge into stabilizing substituents (*6*).

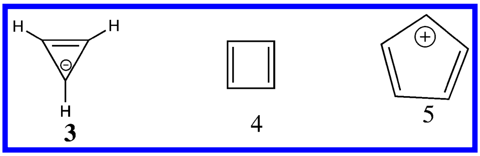

Figure 2. Parent antiaromatic compounds.

Electrochemistry gave us an important way to generate cyclopropenyl anion derivatives, and the parent anion, by adding two electrons to the corresponding stable cations. With modern techniques we could get reversible reduction potentials for the process, giving us solid information about the thermodynamic energy of the anions and thus of the formal pKa's of the cyclopropenes (*12*). We also used these electrochemical methods to determine the pKa's of simple hydrocarbons, getting a good estimate of the pKa of saturated hydrocarbons such as methane for the first time (*13*). Needless to say, with pKa's in the 60's for the cyclopropenes of saturated hydrocarbons there was no way to generate the anions by proton removal with base. We also extended our electrochemical methods to generate and measure the energy content of anions to one-electron reduction processes of cations, or one electron oxidations of anions, that could determine the bond dissociation energies of hydrocarbons to form carbon radicals (*11*, *14*). This technique was then adopted by others, not always with full attribution.

The bottom line of our cyclopropenyl anion studies was clear evidence that it was antiaromatic, especially destabilized by the delocalization of its 4 pi electrons. I coined this word, and Michael Dewar may also have had it in mind as a possible property.

We also used electrochemistry to convert a molecule with only partial cyclobutadiene character (**6**) to one (**7**) where the cyclobutadiene component was greatly increased (Figure 3), and saw that this required a higher (more positive) oxidation potential than did a suitable reference compound (*15*). Since there was no increase in angle strain in this case, it indicated that cyclobutadiene was also antiaromatic, although the extra energy this added to the molecule was not clearly defined. Again this is discussed in our reviews (*10*).

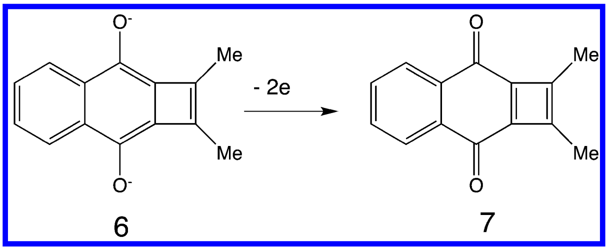

Figure 3. Increasing the antiaromatic cyclobutadiene character.

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The evidence of antiaromaticity was particularly clear in the cyclopentadienyl cation. For one thing, silver cation could not generate it from cyclopentadienyl chloride while cyclopentenyl chloride readily generated the cyclopentenyl cation under the same conditions (*10*). As we will descibe momentarily, cyclopentadienyl cation could be generated from the bromide with powerful Lewis acids, and its structure was very special.

Theory predicted that 4-pi-electron molecules could exist as triplet states, with two unpaired electrons, if they had regular symmetric structures (three-fold, four-fold, five-fold, or later six-fold symmetries). Cyclopropenyl anion was not completely flat but had one proton out of the plane to diminish its antiaromaticity, so it did not meet the requirement of full symmetry and should not be a triplet. Cyclobutadiene is not a square but an elongated rectangle, again to diminish its antiaromaticity, so it should not be a triplet species. However, we thought that symmetrical derivatives of cyclopentadienyl cation could have five-fold symmetric structures, and we knew how to generate them.

We synthesized pentaphenylcyclopentadienyl cation, a reasonably stable symmetric species, and saw an ESR spectrum indicating the presence of a triplet (Figure 4) (*16*). However, when we lowered the temperature the signal weakened, indicating that the triplet was a low-lying excited state of the molecule. Some distortion might explain why it was not the ground state. We then prepared pentachlorocyclopentadienyl cation from hexachlorocyclopentadiene with SnF_5, and saw by temperature studies that it was a ground-state triplet (*17*). Then with Martin Saunders and Mike McBride of Yale we treated 5-bromocyclopentadiene with SbF_5 to create the unsubstituted cyclopentadienyl cation, and it was also a ground-state triplet (*18*). We wrote several reviews of this triplet area (*19–21*), including its possible use in organic ferromagnets. In later work we also created the dication of a fused ring hexaaminobenzene and saw that it was also a potential ground-state triplet (*22*) with possible use in organic ferromagnets. The six-fold symmetry with 4-pi-electrons was what did it.

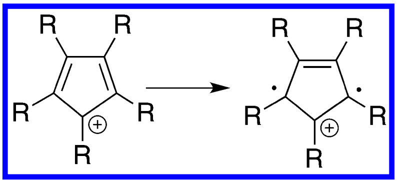

Figure 4. Triplet ground states of the symmetric cations.

It is important to note that the formation of triplets does not explain why the molecules are antiaromatic, of higher than normal energy. Unpairing the two electrons in triplets lowers the energies of the species, by the explanation behind Hundt’s Rule.

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The Electrical Conductivity of Aromatic and Antiaromatic Molecules

I became the scientific co-director of the Columbia University Nanoscience initiative, and set out to create the two important components of nanoscale molecular electronics--devices such as molecular transistors, and molecular-scale wires to conduct electricity and connect the devices. The conductivities of various molecules and corresponding wires were measured in collaboration with Professor Latha Venkataraman with a gold break-junction device. Briefly, a gold wire was stretched to breaking in a solution of the molecule or wire with contacts such as amino groups or thioethers, and the conducting species spontaneously attached across the break in the wire to permit the conductance determination. We made two significant discoveries in this area. In one, we discovered that with trimethyltin groups attached to the molecular wires the gold broken wires inserted between the tin groups and the molecules, eliminating the resistances of the amino groups or thioether groups and yielding high conductivities (*23*, *24*). The other finding was that the aromaticity of such common molecular wires as polythiophenes introduced extra resistance, and that non-aromatic molecules were the best conductors (*25*). In work underway, we are making antiaromatic molecular wires that we predict to be even better conductors.

The Mechanism of Catalysis by Thiamine Pyrophosphate in Biochemistry

At the same time that the early aromaticity work was underway I also published two papers in 1957 on the mechanism of catalysis by thiamine pyrophosphate and related thiazolium cations (*26*, *27*). In this work I showed that the proton on a thiazolium cation ring rapidly exchanges with D_2O using base catalysis. I described the reason for this in a general full paper in 1958 that pointed out that the thiazolium zwitterion from loss of the proton on C-2 has a carbene resonance form, as shown in Figure 5 (*28*). I pointed out that such ion/carbene resonance is quite common. The carbene has the interesting feature that the resonance makes it a nucleophile while electron-deficient carbenes without such resonance are electrophiles. Thus the field of "nucleophilic carbenes" was born, and many examples are now in use as metal ligands and catalysts by others.

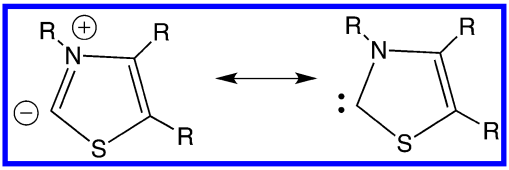

Figure 5. Thiazolium zwitterions and their carbene resonance forms

This mechanism for thiamine catalysis is widely accepted for both the chemical catalyses and the biochemical ones, but more recently a paper in Tetrahedron Letters asserted that it did not fit the observed and plotted data for the chemical catalytic system (*29*). We showed that the data had been incorrectly plotted, and that with a correct plot the thiamine mechanism described above is fully supported (*30*).

Biomimetic Chemistry and Enzyme Mimics

The work to understand the mechanism by which Nature uses thiamine pyrophosphate was only an early example of an overwhelming interest of mine: can we use our insights into how enzymes work to create new chemistry with the same general high selectivity and catalytic effectiveness typical of enzyme reactions? If there is one general principle that differs between synthetic chemistry and enzyme-catalyzed chemistry, it is that synthetic chemistry is dominated by selective reactivity, while enzymes use selective geometry. Of course enzymes still have to carry out favorable reactions, but in biochemical oxidations of steroids, for example, the oxidation chemistry is not special, but where it occurs does not reflect the intrinsic reactivity of various positions on the steroids, it reflects the geometries of the enzyme/substrate complexes. I set out to use such geometric control as a general principle.

Of course other chemists were aware of this idea, but they had generally used the geometry of intramolecular reactions to carry out selective functionalizations. A hydroxyl group of the steroid would be functionalized so it could oxidize a nearby saturated carbon. for instance. I wanted the catalysts or reagents to impose the geometry, so positions could be oxidized in steroids that were remote from any functional groups. I called the results "remote oxidation." We were inventing new reactions guided by the mechanistic ideas of physical organic chemistry, and some of the detailed mechanisms of photochemical reactions and free radical processes.

Reaction of Steroids with Enzyme Mimics

The best place to start was with steroids. They are rigid with well-defined geometries, and there are some syntheses that Nature performs, such as inserting an oxygen into a saturated carbon in the middle of the molecule to make corticosteroids, far from other functional groups, that would be of practical interest since this was not possible with existing chemistry. We started with photochemistry. We attached benzophenone units to steroids with an ester chain and then photolyzed them. The geometry directed the excited state carbonyl group to particular steroid hydrogens, and with this result we could introduce oxygen atoms and double bonds into the steroid, several rings away from the attachment point because of the length and rigidity of the benzophenone system and of the steroid skeleton (*31*, *32*).

We then turned to directed steroid chlorination, since chlorine atoms can easily remove hydrogens from saturated carbons, and unselectively--the trick was to steer them to a desired spot. We found that a general approach works. We attached a long template to the steroid on carbon 3 on the alpha face at one end and performed a free radical chlorination in which a chlorine atom bound to the template, often by a three-electron weak bond, removed the hydrogen that it could reach. The binding

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of the chlorine made it less reactive, so more selective for tertiary hydrogens rather than secondary ones, and in steroids tertiary hydrogens on the alpha face have well-defined distances from C-3. Varying the length of the template let us select any one of those tertiary hydrogens and insert a chlorine in its place (*33–36*).

Of course an enzyme would not attach something to a substrate to steer a reaction, it would simply bind to the substrate and hold its functionalizing component where it could reach within the complex. In more recent work we have figured out how to do that. We used cyclodextrins, doughnut shaped molecules made up of glucose units in a ring, to bind hydrocarbon species into the hole in the doughnut in water solution, using hydrophobicity as the driving force. With two cyclodextrins linked to a metalloporphyrin and steroids with some phenyl rings at the two ends of the molecule we saw spontaneous binding of the steroid into the cyclodextrin dimer in water. Then the metal ion, iron or manganese, picked up an oxygen atom from hydrogen peroxide and the oxygen atom then inserted into a nearby C-H bond, leaving a hydroxyl group selectively on a single position in the steroid (*37–39*). This has a lot of analogy to the biological mechanism by which steroids are hydroxylated.

Cyclodextrins in Enzyme Mimics

Binding substrates into the cavities of cyclodextrins can steer and promote many other reactions in water solution. As our earliest example, we showed that the chlorination of anisole (methoxybenzene) by HOCl is selectively directed to the para position with a cyclodextrin present, while without it both the ortho and para positions are chlorinated (*40–42*). The simplest idea is that the ortho positions are blocked by anisole binding into the cyclodextrin cavity, but our mechanistic studies showed that there was an additional factor: the chlorine atom was catalytically delivered to the bound anisole by a hydroxyl group of the cyclodextrin. This was an extremely simple analog of an enzyme, with binding and selective catalysis by the cyclodextrin.

We have used cyclodextrin for binding substrates where there is a catalyst attached to the cyclodextrin. For instance, we have attached a pyridoxamine species to a cyclodextrin and found that it would bind an α-keto acid in water and then synthesize an α-amino acid (*43*). Perhaps most interesting was the case where we attached imidazole groups to a cyclodextrin and then used them as catalysts for the hydrolysis of phosphate esters that bound into the cyclodextrin cavity. With two attached imidazoles we were imitating the enzyme ribonuclease in which two imidazoles of histidine units cooperate in cleaving RNA (*44*). We could attach two imidazoles on neighboring glucose units of the cyclodextrin or on units further apart. The classical accepted mechanism for the hydrolysis of RNA by the enzyme needs the imidazoles far apart, but we saw that the isomers with imidazoles on neighboring glucose units were the best (*45*). This indicated a new mechanism for the hydrolysis, with a phosphorane intermediate, that we proposed would also be used by the enzyme itself with RNA. Our subsequent work showed that the enzyme in fact used the new mechanism (*46*).

This is a new tool for determining reaction mechanisms in special cases. When there is bifunctional catalysis, with the cooperation of two catalytic species, fixing their relative geometries can help decide between different mechanisms.

Catalysis by Polymers

While many of our studies used single molecules as enzyme mimics, in Nature the catalysts are polymers, polypeptides. Thus we have explored the use of various polymers as artificial enzymes. In one series of studies we have used polyoxazolines, which can produce polyaziridine derivatives with high stereoselectivity (*47*, *48*). More recently we have created and studied a new class of polymers derived by reducing the carbonyl groups of polypeptides to methylene groups (*47*, *49*) . These are again polyaziridines, but with the sidechains and stereochemistry of their parent polypeptides, and chemical and biological stability in contrast with the polypeptides themselves. They are also of completely designed and homogenous length. We introduced this novel class of polymers (we call them DOPPs, deoxygenated polypeptides) in two papers (*47*, *48*) and recently described using them in mimics of ribonuclease (*49*). They have a brilliant unexplored future.

Determining Transition State Geometries Using Hydrophobic Effects

As described above, we have used the hydrophobic effect in enzyme mimics to let substrates bind to catalysts in water. We also saw the hydrophobic effect in simple reactions in water. For example, when we carried out Diels-Alder additions, such as the Diels-Alder dimerization of cyclopentadiene, we saw very high reaction rates with saturated solutions in water, compared with the results in methanol or ethanol (*50*). One way to describe this is to say that water somehow pushes the two molecules together, but another point is that the very low concentration of cyclopentadiene in water has the same free energy as pure cyclopentadiene, since they would be in equilibrium. The free energy of cyclopentadiene in water at saturation is much higher than its free energy would be with the same low concentration of cyclopentadiene in ethanol, for instance.

Hydrophobic effects can be modified with additions to the water. For instance, with added ethanol the water can dissolve more cyclopentadiene before saturation. Previous studies have shown that water solubilities of non-polar molecules can be decreased with added lithium chloride, which increases the hydrophobic effect, but solubilities are increased with guanidinium chloride which decreases the hydrophobic effect. Thus in the Diels-Alder reaction of cyclopentadiene with butenone in water we saw that the rate was increased with the addition of lithium chloride but slowed with the addition of guanidinium chloride (*51*). We examined many different related cases. Then we reasoned that the rate effects could reflect the difference in exposed hydrophobic regions of the transition state relative to that of the substrates. We showed this was true by seeing that it accounted for the observed rate effects in terms of how much of

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the reactant non-polar surface was "hidden" in the transition state TS (*52*). For example, in the Diels-Alder dimerization of cyclopentadiene almost one face of each reactant is hidden from solvent in the TS, but in the final product they have partially opened up. With extensive studies we showed that indeed this was a powerful new tool to determine something important about TS's: not just their energies, as rates reveal, but also their geometries.

Insights into the Mechanisms of Some Enzyme Reactions

Although we concentrated on artificial enzymes and their mechanisms, we did investigate the mechanisms of two natural enzymes. The enzyme carboxypeptidase catalyzes the cleavage of peptides, and the X-ray structure left an ambiguity. It was clear that a zinc cation bound to the carbonyl oxygens of the peptides while a carboxylate of the enzyme then promoted the cleavage, but it was not clear whether it attacked the peptide carbonyl directly, forming an anhydride intermediate that then hydrolyzed, or whether it delivered a water molecule to the peptide carbonyl group without forming an intermediate anhydride. Analogs for both mechanisms were known, but we were concerned that Ginodman claimed that an anhydride was clearly formed by evidence that seemed to us ambiguous (*53*). Thus we performed a series of experiments on the enzyme that clearly showed that the Ginodman finding had a different cause, and that the reaction was a straight hydrolysis with the enzyme carboxylate acting as a simple base, not a nucleophile (*54*, *55*). Since many other peptide cleavage reactions go via covalent intermediates, but not this one, this was an important finding.

The other enzyme whose mechanism was of interest was ribonuclease, which hydrolyzes RNA. We had done extensive work on mimics of this enzyme, including a very recent study of a novel class of catalysts, and had concluded that the enzyme mimics formed a phosphorane interrmediate, a 5-coordinate phosphorus, in the course of the process. In other words, hydrolyzing the phosphate ester in that case went through an intermediate, the opposite of our conclusion in the carboxypeptidase case. However, the mechanism commonly invoked for ribonuclease, in all the biochemistry textbooks, went with direct cleavage of the phosphate, without a 5-coordinate phosphorus intermediate. Thus we investigated it further. Our experiments with ribonuclease and various substrates made it clear that it proceeds via the phosphorane intermediate (*56*), and most modern biochemistry books now have this as the mechanism.

The Formose Reaction and Prebiotic Chemistry

In the course of reading I came across the formose reaction, in which formaldehyde reacts in calcium hydroxide solution to form various sugars, although not with any defined stereochemistry. There was no proposed reasonable mechanism for it--formaldehyde can't lose its proton to make a reactive anion--so we examined the reaction. It had two phases. In the first the system just sat there, with nothing happening, and then it started to make sugars with increasing velocity. Thus it was autocatalytic.

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I proposed a mechanism in which two formaldehydes first condensed to glycolaldehyde, in a slow reaction that may well have involved free radicals and maybe even cosmic rays to initiate the reaction. However, once a single molecule of glycolaldehyde was formed it could enolize and react with formaldehyde to form racemic glyceraldehyde. This then could isomerize to dihydroxyacetone, in analogy to a well-known biochemical triose isomerase process, and this could enolize and add a formaldehyde to form a four-carbon keto sugar mixture. This could isomerize to the aldehyde sugar, which could undergo a reverse aldol reaction to form two glycolaldehydes. Then four, then eight, etc. My proposed mechanism (*57*), consistent with our experiments, was widely accepted--until Steve Benner reinvestigated it.

Steve performed the reaction in D_2O, and saw the various intermediates we had proposed, and that many others had seen subsequently, but they had no deuterium on the carbons (*58*)!! Thus we have recently reinvestigated it, and found the explanation that generally validates the process we had originally proposed, with some important differences (*59*). We had suggested that glyceraldehyde isomerizes to dihydroxyacetone through the initial enol of glyceraldehyde, and this should incorporate deuterium in the dihydroxyacetone from D_2O. However, we have now shown that the isomerization occurs not by enolization but by a hydride shift, by showing that 2-deuteroglyceraldehyde goes to dihydroxyacetone under formose conditions with migration of the deuterium, not its loss as would happen with enolization (*59*). We have recently studied this reaction in detail, and have evidence that it proceeds with quantum mechnical tunneling from a thermally excited state (*60*). Then of course the dihydroxyacetone must enolize, but it is irreversible since the formaldehyde immediately traps the enol. The isomerization from ketosugar to aldosugar at the end also involves hydride shifts and the reverse aldol reaction liberates an enediol that is immediately trapped by formaldehyde. The details are in our paper.

The Creation of Selective Stereochemistry in Amino Acids and Sugars on Prebiotic Earth

Of course the formose reaction could have occurred on prebiotic earth, but it does not select for the stereochemistry we now know is present and necessary in sugars. We came upon the findings that some meteorites that have landed on Earth in recent years carry with them several amino acids with methyl groups instead of alpha protons, so they cannot racemize (normal amino acids are also seen on the meteorites, but racemic unless they have a second chiral center.) The α-methyl amino acids were not racemic, but had small excesses of the L isomer (counting the methyl group as if it were a hydrogen atom) (*61*). So we showed that they could induce the formation of normal L-amino acids under sensible prebiotic conditions (*62*), and we (*63*), and others (*64*, *65*), saw how small enantioexcesses could be amplified to high e.e's under sensible prebiotic conditions.

We then examined the formation of sugars, in particular of D-glyceraldehyde, since it is the simplest sugar with chirality. All other sugars in the D series can form by building on the glyceraldehyde aldehyde group. We saw that under mild acidic conditions the L-amino acids catalyzed the formation of small excesses of D-glyceraldehyde (*66*, *67*), and that this could also be amplified to high enantioexcesses under sensible prebiotic conditions. In current work we are investigating the formation of other important sugars including the D-ribose of RNA and the D-deoxyribose of DNA.

In one earlier study, we examined why the current structure of DNA, 2-deoxy with a 3-5 phosphate linkage, is better than the other possibility: 3-deoxy with a 2-5 linkage (*68*). This was in the spirit of earlier work exploring why thiamine pyrophosphate was particularly suited for its catalytic role in modern biochemistry, all part of what we call Nature's Chemistry Preferences. Our work with the isomer made it clear that the current structure has significant advantages.

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A Novel Mechanism To Combat Cancer

About 30 years ago I was contacted by a friend who had become the head of the Sloan-Kettering Insitute fror Cancer Research, Dr. Paul Marks. He had learned that dimethylsulfoxide (DMSO) was able to induce certain cancer cells to differentiate into adult erythrocytes (red blood cells), and he suggested a collaboration to understand the process and perhaps to then create a more potent compound than DMSO. This was the normal physical organic attempt to understand the relationship between structures and properties, the properties being biological. I set out to see whether our abilities in physical organic chemistry could guide us to better compounds that might, with luck, prove to be useful in the war against cancer (reviewed in (*69*)).

At first we established that DMSO could be replaced by simple amides, and then we decided to use the chemists' version of how to increase potency: double the compound up so the chelate effect comes into play. Starting with acetamide as the DMSO surrogate, we linked two acetamides with various polymethylene chains and found that the magic number for best improvement was six, in hexamethylene-bis-acetamide. Actually, that was my first guess. The compound was safe and effective in animal studies, and even was used in some cancer patients, but it was not potent enough.

I then used chemical reasoning. If an acetamide group was binding to a biological receptor it was either binding to a metal ion or making hydrogen bonds, and in any case an N-hydroxyamide could be better. It is a better metal ion ligand (my guess of what was involved) and could make more hydrogen bonds. Thus we made suberoyl bis-hydroxamic acid (SBHA), and it was a better inducer of differentiation in the cancer cells. However, it was still not quite potent enough. I then decided that it was probably binding to a metal ion, and perhaps one end needed to be a hydroxamic acid for that role but the other end probably contributed something else rather than curl back to the metal ion. We tried hydrophobic binding with a phenyl group, and it was better than SBHA. We called the new compound SAHA (Figure 6), suberoylanilide hydroxamic acid, and it was very effective. By then we knew that it was indeed binding to Zn^{2+}, and that the target was a histone deacetylase with the Zn^{2+} binding to the carbonyl oxygen of the acetyl group. Our drug SAHA bound to this catalytic site and blocked the hydrolysis of acetylated histone, and indeed its structure was exactly what one would design as an active-site directed inhibitor. But it was not derived that way.

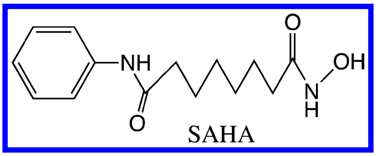

Figure 6. Suberoylanilide hydroxamic acid

Since then the compound has had extensive testing, and was approved for human use against cancer in the U.S. Then approval followed in Canada, and Japan, and the compound SAHA has been in human use for many years. Others have created related compounds, but SAHA was the pioneer. It led to the wide appreciation of HDAC inhibition as a mode of cancer treatment, and of the mechanism involving modulation of post-translational regulation of gene transcription. The field has even received a name, epigenetics, referring to the role that regulation of acetylation levels, and other protein modifications after translation, can have in gene expression.

Predicting the Future of Physical Organic Chemistry

Some time ago I was asked to write a brief prediction of the future of physical organic chemistry (*70*). After describing the wonderful strengths of our field--it combines the strength of synthetic organic chemistry with its unique ability to design and create novel molecules, with the serious scientific aim to fully understand molecular properties in chemical reactions in full detail--I described "Some Goals for the Future." Here I discussed what abilities our field still needs, and what important questions remain to be answered. The list is extensive, but ends with the following statement: "These are some of the challenges, and likely advances, that I can predict, but there is one more prediction I can make with certainty. Smart physical organic chemists will come up with advances and inventions that are anticipated by none of the chapters in this volume, including this one, and we will all say: why didn’t we think of that?"

Physical Organic Chemistry has a wonderful history, putting understanding into otherwise baffling organic processes and properties. It also has a great future, giving us insights into the relationship of structure and properties of species as diverse as molecular electronic materials and natural enzymes. It will also guide us in designing new molecules and new chemical processes. It will increasingly use modern computational methods to help in these adventures. I look forward eagerly to participate in these efforts, and to see with admiration the progress being made by the many other students of that most scientific and creative aspect of organic and physical chemistry--Physical Organic Chemistry.

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Chapter 5

Hydrogen Isotopes in Physical Organic Chemistry

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I was the fortunate recipient of the Norris Award in 1982 but I also played a role in the very first Norris symposium in honor of the first Norris awardee, Prof. Christopher K. Ingold. This first Norris award symposium was a full day affair on Sept 14, 1965, at the 150th American Chemical Society meetjng in Atlantic City, NJ. There were three talks in the morning session, by R. B. Woodward, me and Ingold in that order. Joe Bunnett was the chair (he also gave the final talk in the afternoon). While we were getting set up for the morning session, Joe approached me rather diffidently and hemmed and hawed a bit but I knew exactly what his concern was. Woodward was well known for giving beautiful and elegant talks. In a chalk talk he would start at the top left corner of the board, fill the board with clean graceful structures, and finish at the bottom right corner. But his talks were usually long – sometimes very long. I realized that no matter how long Woodward took for his talk I could not infringe on the awardee's time. I assured Joe that I was aware of this problem and that I was prepared to give an accordian talk. No matter how little time Woodward left for me I would finish on time so that Ingold would have his full allotted time. As it turned out, our fears were groundless. Woodward finished in his allotted time, I gave my normal talk and Ingold gave his award talk as planned.

Seventeen years later I was the Norris awardee "for his pioneering role in the development and application of new experimental and theoretical tools for the study of physical organic chemistry." In this chapter I will emphasize the experimental tools, most of which involve isotopes of one

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> form or another, and particularly deuterium. Deuterium has a number of uses as a tool in physical organic chemistry, many of which are not original with me. Its use as a tracer is one. With hydrogen – deuterium asymmetry there is the possibility of optical activity. In addition there are both equilibrium and kinetic isotope effects. These isotope effects are normally divided into primary and secondary isotope effects; primary when the bond to the hydrogen is broken, secondary when the bond is not broken but can be altered.

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Discovery of Deuterium

The existence of isotopes was realized in the early 1900’s during a period of confusing results from radiochemistry experiments (*1*) . By 1920, isotopes were reasonably well understood, although deuterium, the stable isotope of hydrogen, was not discovered until 1931 by Harold Urey. Ferdinand G. Brickwedde, a physicist friend of Urey’s at the National Bureau of Standards, allowed four liters of liquid hydrogen to evaporate slowly near the triple point. Spectroscopic study of the last milliliter in the Fall of 1931 allowed Urey and his assistant, Dr. G. M. Murphy, to identify the so-called Balmer lines of deuterium. These lines occurred in natural hydrogen but were so faint that they could have been “ghost” images on the photographic plate. In the enriched material, the signal was now much larger and was clearly real. With that Urey announced the discovery of deuterium (*2*, *3*). Two years later, Urey received the Nobel prize in chemistry *for the discovery of heavy water* (*4–6*). This was achieved by electrolysis of water, a method conceived and developed by Edward W.Washburn of the Bureau of Standards and continued by Urey after Washburn’s death early in 1934 (*7*). It seems quite likely that Washburn would have shared this Nobel prize except for his untimely death. Pure heavy water was first accomplished by G. N. Lewis at Berkeley in 1933 (*5*, *6*), but followed closely behind by Bonhoeffer in Frankfurt (*8*). Lewis also suggested the “deut” stem that Urey adopted in coining the name “deuterium” (*9*).

What is amazing is how quickly deuterium went from being an oddity to a tool in chemistry. By 1935, there were already several exchange reactions that had been studied with heavy water with various organic and inorganic compounds and even with living materials like fungi. So much so that even as early as 1935, Wynne-Jones was able to write a *Chemical Reviews* article summarizing the results of the exchange reactions that had been run up to that time (*10*).

Fifteen years later I was a graduate student at Columbia in the laboratory of William von Eggers Doering. In his group were several projects making use of deuterium, usually as a tracer, following the course of hydrogen in various reactions. An example was that of Alfred Wolf, whose lab bench was close to mine. Al used deuterium to trace hydrogen migrations during the acid-catalyzed rearrangements of fenchene to other terpenes (*11*).

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Hydrogen-Deuterium Asymmetry

As shown above, the idea of deuterium as a tracer was not strange to me. When it came time for me to think about post-doctoral work I applied to the Atomic Energy Commission for a post-doctoral fellowship. For the original project required for the application I proposed a base-catalyzed exchange study of esters using deuterium. This proposal was good enough to get my fellowship, but by the time I got ready to go to MIT to work with Jack Roberts, I thought of a better project. I proposed to synthesize an optically-active primary alcohol of the type RCHDOH in which the chirality comes from hydrogen – deuterium asymmetry. With it I could study the stereochemistry of various reactions at a primary alcohol center. The genesis of this idea is clear. In my PhD work with Doering my project was working with an optically-active tertiary alcohol. The first tertiary alcohol had been resolved by Harold Zeiss (*12*) before I got to Columbia, and my project was to follow-up that work and study that chemistry. Subsequent thinking about the stereochemistry of reactions of a primary alcohol is an obvious association. I had expected hydrogen-deuterium asymmetry to provide sufficient optical activity to be experimentally useful in studying its transformations based on recent results by others.

The search for measureable optical activity in compounds of the type RCHDR’ had been tried for several years, but the first apparent success was that of Elliott R. Alexander, who took camphene and on reducing it with deuterium got the di-deuterio system having a small rotation (Figure 1) (*13*). That small rotation was a problem, because in those days, before chromatography, the purification of small amounts of liquids was difficult. Alexander did the control reaction with hydrogen to give product that was racemic but there was always the possibility that in the deuterium case a trace of some impurity which was highly optically active – we note that camphene itself has a very high optical activity – was present. It wouldn’t take much to give this tiny rotation. Ernest Eliel, shortly thereafter, looked at the same problem, but in a more straightforward way. He took optically active phenylethyl chloride and treated it with lithium aluminum deuteride to yield a deuterio-ethylbenzene that was optically active (Figure 1) (*14*). He had the same problem; the product is a liquid having a small rotation, but he was able to convert it to a solid derivative and then on numerous recrystallizations show that the optical activity did not change upon subsequent crystallizations. Thus, there is no question that his ethylbenzene really was optically active because of the hydrogen-deuterium asymmetry.

I expected to prepare the optically active alcohol by use of a partially asymmetric reduction such as that being done in Doering’s laboratory at that time. A labmate, Dick Young, was studying the Meerwein-Ponndorf-Verley reduction using an optically active secondary alcohol as a hydride source to make other optically active alcohols (*15*). I first made 2-octanol-2-*d* by reduction of the ketone with $LiAlD_4$ and resolved it in a standard manner. The alcohol was converted to its oxymagnesium salt by treatment with a Grignard reagent and was then allowed to react with butyraldehyde (Figure 2). This use of the magnesium derivative instead of the aluminum salt that is commonly used in the

Meerwein-Ponndoff-Verley reduction was suggested by Bill Saunders, who was also a post-doc with Jack Roberts at that time. His suggestion worked out quite well. Because my reaction involved the exchange of an aldehyde carbonyl group to a ketone carbonyl, the reaction has a much better driving force than the normal Meerwein-Ponndoff-Verley reactions using secondary alcohols to ketones. The presumed transition state is shown in Figure 3, a cyclic transition structure with the magnesium coordinating to the two oxygens. Of the two diasteriomeric transition structures the favored one is shown in which the smaller group is opposite the larger group on both sides of the coordination ring.

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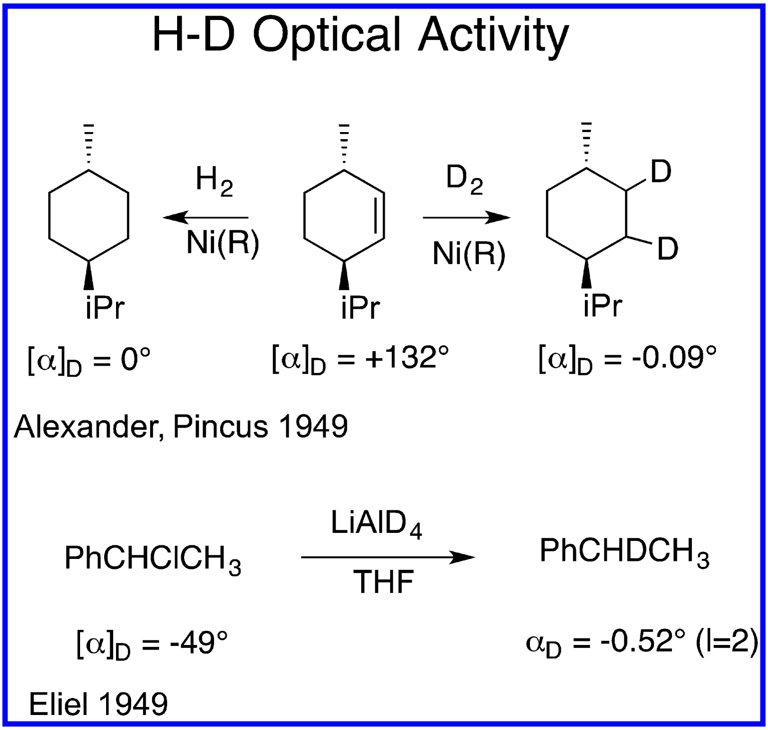

Figure 1. Early optically active deuterium compounds

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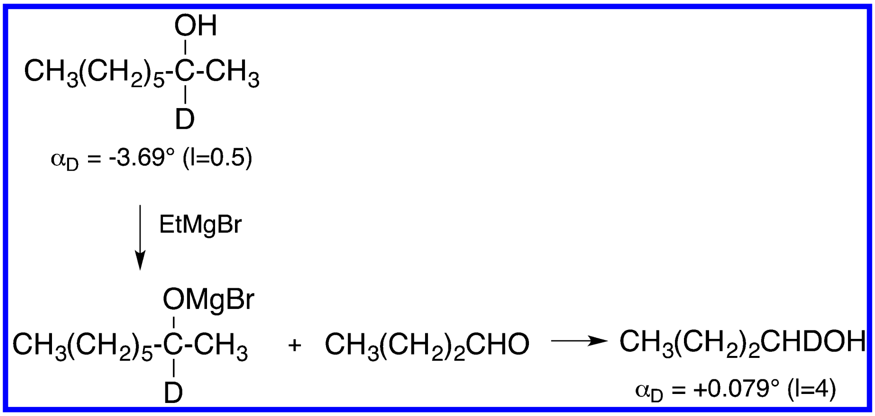

Figure 2. First preparation of optically active 1-butanol-1-d.

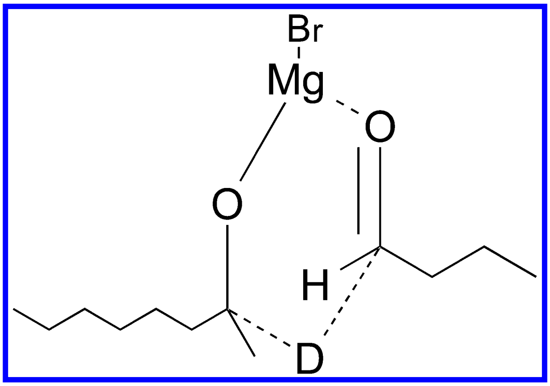

Figure 3. In the favored transition structure the smaller methyl is opposed by the larger propyl group and hexyl is opposed to hydrogen. In the alternative diasteriomer, the large propyl is opposed to the large hexyl.

I still had the same problem as my predecessors – proving that the small observed rotation was that of the butanol-*d* and not from some impurity. I made use of the famous experiment (Figure 4) of Hughes, Juliusburger, Masterman, Topley and Weiss in the mid 30's in which they showed that in the radioactive iodine exchange of an S_N2 reaction, the rate of racemization of the optically active iodide was exactly twice that of the rate of isotope exchange (*16*). This experiment was one of the important demonstrations that each S_N2 reaction occurs with complete inversion of configuration. In my case, La Roux and Sugden had already published the rate of reaction of butyl bromide with bromide ion using radioactive bromine (*17*).

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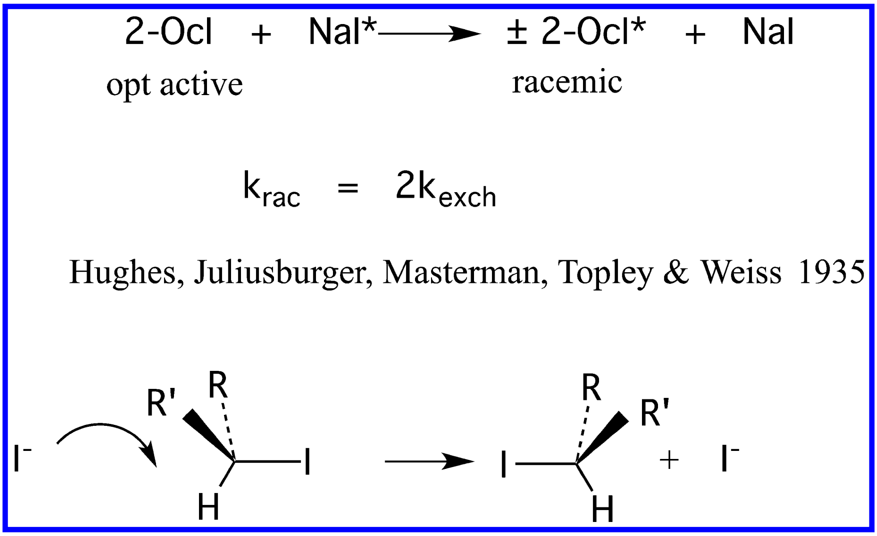

Figure 4. Each S_N2 exchange of iodine isotopes occurs with inversion of configuration.

Treatment of the butanol-*d* with phosphorus tribromide gave optically active 1-bromobutane-1-*d* which was allowed to react with lithium bromide in 90% aqueous acetone under the same conditions as Le Roux and Sugden (*17*). After varying lengths of time the butyl bromide was isolated and its optical rotation was measured and compared with the radiochemical exchange rate as shown in Figure 5 (*18*). The good agreement shows that that the optical activity is truly that of the 1-deuterio species.

My first graduate student who got his PhD with me, Bill Schaeffer, took over this problem. He made a large amount of the optically active alcohol and used it in several studies that resulted in a number of papers in the late 1950's, under the general title of *The Stereochemistry of the Primary Carbon*. An example is his study of the reaction of the alcohol with thionyl chloride, an important procedure for the preparation of alkyl chlorides. The reaction first forms a chlorosulfite that decomposes to give the alkyl chloride and sulfur dioxide. When applied to our optically active butanol-1-*d* the product 1-chlorobutane-1-*d* was found to have about 90% inversion of configuration (*19*). This result suggested that almost all of the reaction involves an S_N2 displacement of the type shown in Figure 6.

At about the same time and independently of my work, Westheimer, Venneslan and Loewus showed that deutero acetaldehyde could be reduced in an enzymatic reduction to optically active ethyl alcohol. In their first experiment in 1953 the amount of ethyl alcohol that they made was too small to measure the optical activity directly (*20*). So they showed by a clever technique that their ethanol-*d* was enantiomerically pure and that the S_N2 reaction used went with complete inversion of configuration. Later, enough of the alcohol was made so that the optical rotation could be measured (*21*). Enzyme routes have been used to prepare a number of optically active primary alcohols (*22–26*). This approach has the important advantage that it gives product with high enantiomeric purity but the method fails for some alcohols (*27*). We showed (*28*) that the use of isoborneol is advantageous compared to 2-octanol but other partially asymmetric chemical reducing agents have been developed that are improvements over my original synthesis (*29*, *30*).

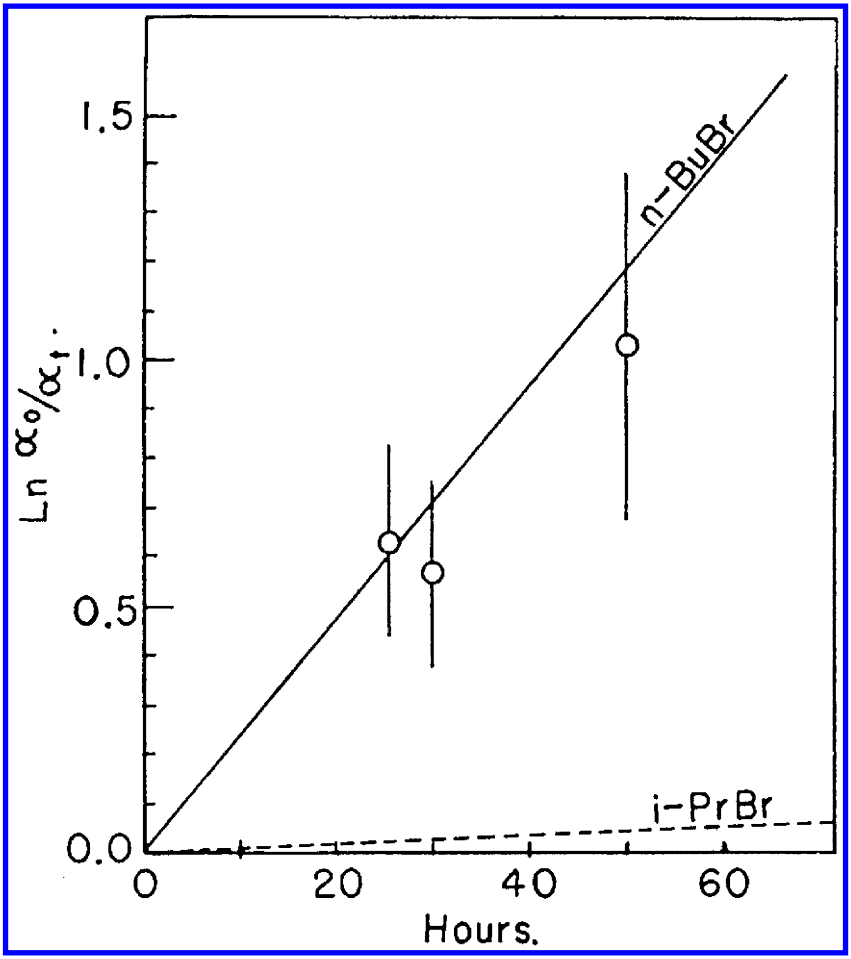

Figure 5. Racemization of 1-bromobutane-1-d with LiBr in 90% aqueous acetone. The line shown is that calculated friom the rate constants of Le Roux and Sugden (ref. (17) . The experimental points are shown with estimates of uncertainty. The dotted line is that calculated for isopropyl bromide showing that the observed racemization cannot be that of a secondary bromide derived from some rearrangement. This figure is taken from ref. (18)

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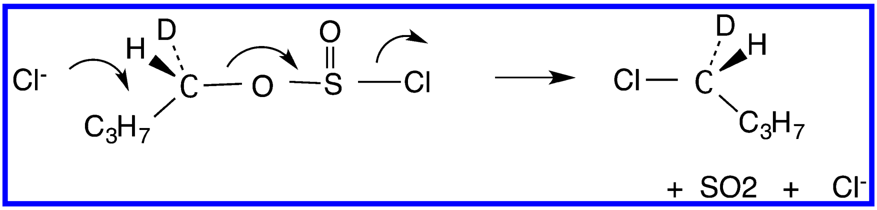

Figure 6. S_N2 reaction on chlorosulfite gives inverted product

Within the next few years a number of optically active 1-deuterio primary alcohols had been prepared and their absolute configurations were determined. These compounds rapidly became quite valuable in the study of the mechanisms of various chemical and biochemical reactions (*29*). Many of the early studies have been reviewed (*31*, *32*). Two examples will illustrate the range of applications. H. C. Brown's partially asymmetric hydro-boration (*33*) method applied to cis-butene-1-*d* gave optically active butanol-1-*d* of relatively high optical purity but of opposite configuration from that expected on the basis of the accepted reaction mechanism. A small but significant change in this mechanism accounted for the observed configuration of the product; the new mechanism was also consistent with the other chemistry known for the reaction (*34*).

Mosher (*35*) prepared optically active neopentyl alcohol, $(CH_3)_3CCHDOH$, and ran a number of reactions with the tosylate. The neopentyl system is known to rearrange readily under carbocation conditions and its t-butyl group is so close to the reaction center that S_N2 reactions are relatively slow. Nevertheless, reaction with a number of nucleophiles was shown to proceed with complete inversion of configuration, just as normal S_N2 reactions on less hindered systems.

Secondary α-Deuterium Isotope Effects

Even early in the development of deuterium chemistry, in the middle 30's, when many exchange reactions were being studied, it had been noted that reactions with deuterium were frequently slower than the corresponding reactions with hydrogen. Even then it was realized that this was probably an effect of zero-point energies. But it wasn't until after the war that Jake Bigeleisen was able to publish his work with Maria Goeppert-Mayer on the theory of equilibrium isotope effects (*36*). Shortly thereafter, Bigeleisen also applied the theory to reaction rates as well. One expression of the theory for hydrogen-deuterium isotope effects is given as 1:

$$\frac{k_H}{k_D} = \frac{\kappa_H}{\kappa_D}\left(\frac{m_D^{\ddagger}}{m_H^{\ddagger}}\right)^{1/2} \mathrm{X} \; \frac{\;\frac{\sigma_H}{\sigma_H^{\ddagger}}\;}{\;\frac{\sigma_D}{\sigma_D^{\ddagger}}\;} \; \mathrm{X} \; \frac{\prod_i \frac{u_{Hi}^{\ddagger}}{u_{Hi}} e^{(u_{Hi} - u_{Hi}^{\ddagger})/2}(1 - e^{-u_{Hi}})(1 - e^{-u_{Hi}^{\ddagger}})^{-1}}{\prod_i \frac{u_{Hi}^{\ddagger}}{u_{Hi}} e^{(u_{Di} - u_{Di}^{\ddagger})/2}(1 - e^{-u_{Di}})(1 - e^{-u_{Hi}^{\ddagger}})^{-1}}$$

$$u_i = h\nu_i/kT \qquad \text{Eq. 1}$$

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This equation embodies a number of approximations such as the Born-Oppenhimer approximation and Absolute Rate Theory (*37–39*). In essence, the isotope effect arises from differences in vibration frequencies between the reactant state and the transition state. Wolfsberg prefers to think in terms of the corresponding differences in force constants (*40*, *41*), but these are essentially equivalent.

One of the first projects I worked on when I got to Berkeley was an isotope effect of deuterium in the solvolysis reaction. The secondary deuterium effect in the β position had already been done and turned out to be useful as a measure of hyperconjugation (*42*, *43*). Instead, I suggested to an undergraduate student, Bob Fahey (now a chemistry professor at UCSD), that we measure the effect of an α-deuterium. Bob compared the rate of solvolysis of cyclopentyl-1-*d* tosylate in acetic acid with that of the undeuterated compound (*44*, *45*). Considering only the C-H stretching frequency, which is greater for the Csp^2 –H bond of a carbocation than the Csp^3 –H bond in the reacant I had anticipated an inverse isotope effect. I was quite surprised when Bob found that the reaction rate was actually slower for the deuterio system. I then quickly realized the importance of considering the bending vibrations. One in particular stood out, the out-of-plane bending of the α-CH bond in the carbocation. As shown in Figure 7 in which an aldehyde C-H is used as a model for a carbocation, the inplane bending vibration is similar to that in a tetrahedral C-H but the out-of-plane bending vibration has much lower frequency.

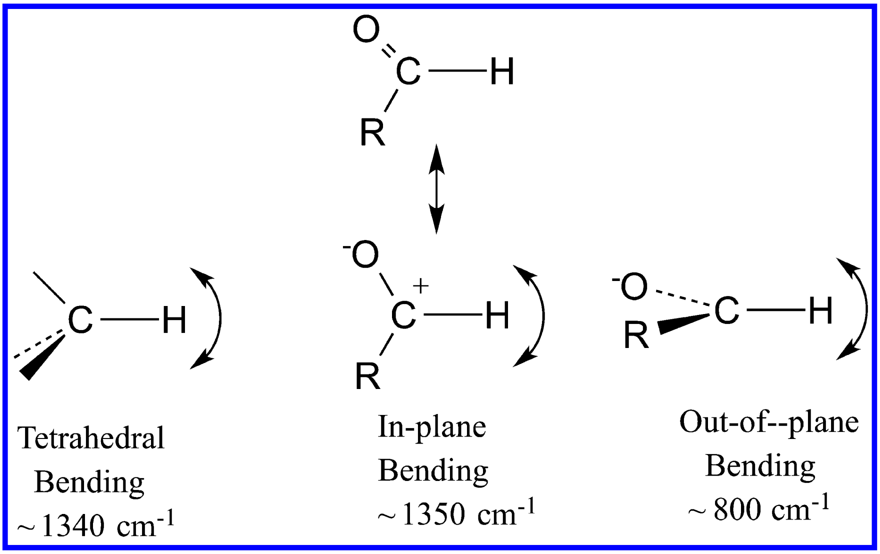

Figure 7. Some bending vibrations

With some additional approximations, including putting in the reduced masses of C-H and C-D and considering the isotope effect to come primarily from zero point energy differences (*46*), I simplified 1 to 2, in which the isotope effect is

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related directly to frequency differences between reactant state and transition state (*45*).

$$\frac{k_H}{k_D} \cong e^{\frac{0.187}{T}\Sigma_i(\nu_{Hi} - \nu_{Hi}^{\ddagger})} \qquad \text{Eq. 2}$$

The largest frequency difference is that from a tetrahedral C-H bend to the out-of-plane Csp^2 –H of the carbocation, about 550 cm^{-1} but this leads to an isotope effect of about $k_H/k_D = 1.4$, much higher than the observed $k_H/k_D = 1.15$. It was clear that the free carbocation is not a suitable model for the transition state – the leaving tosylate group is still close and would impede the vibration of the hydrogen. This interpretation was consistent with the result that Shiner had reported (*47*) of $k_H/k_D = 1.0$ for the S_N2 reaction of isopropyl bromide with sodium ethoxide. In this case, the entering and leaving groups would doubly impede the H vibration leading to a higher frequency and a smaller isotope effect. This effect is summarized in Figure 8. In this figure A is a model for an isolated carbocation, B is a model for an S_N1 transition state, C is that of an S_N2 reaction and D shows the bending vibration of a tetrahedral hydrogen. The effect of the X and Y groups in increasing the zero point energy is apparent from the simplest particle-in-a-box model.

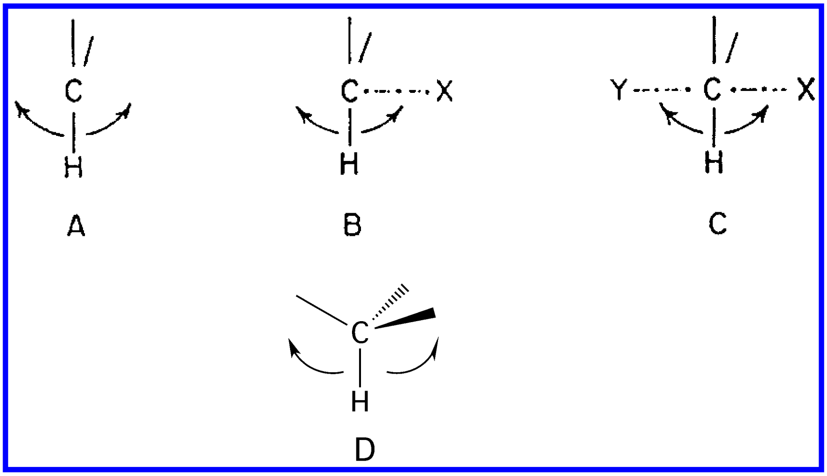

Figure 8. Out-of-plane bending motions in various structures

Alternatively, we can now make quite good calculations of vibration frequencies for different models although such computations usually apply to the gas phase. Moreover, in real molecules the various atomic motions frequently couple to give complex vibrations in which it can be difficult to perceive simple components such as the motions of only one hydrogen as in Figure 8. For demonstration purposes the computed frequencies in Figure 9 were made on chlorine compounds in which the heavy chlorines effectively do not couple with the motions of the light hydrogen and one can clearly see the effect of additional groups near the vibrating hydrogen. Structure A is that of an isolated carbocation with no group at either end of the bending motion of the hydrogen. B is a model of an ion pair with a group at one ond of the vibrating proton. C is a model of an S_N2 reaction with groups at both ends hemming in the hydrogen. The lines attached to the hydrogen are the displacement vectors for the vibrations. The absence of such vectors on the other atoms indicates that they all are essentially motionless in these vibrations.

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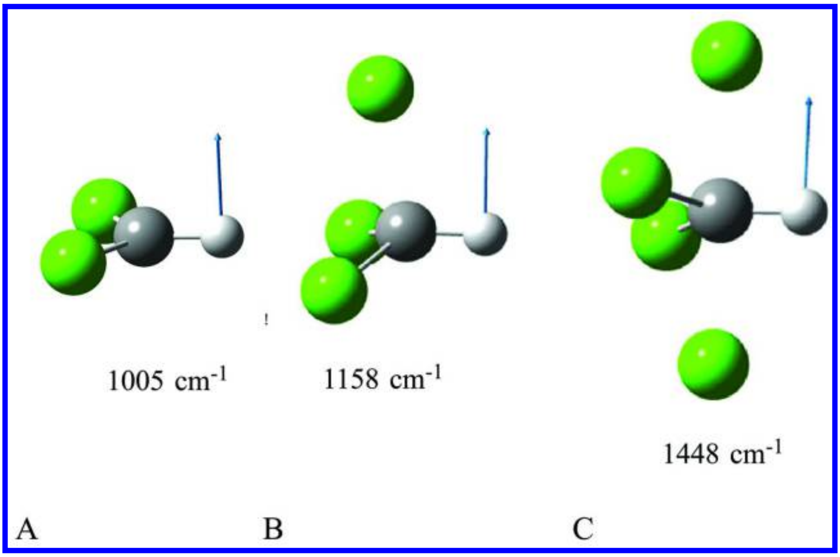

Figure 9. Effect on the vibration frequency of groups near the bending hydrogen

The net result of this analysis is that the α-deuterium provides a sensitive measure of the region near the α-hydrogen in the transition state. This interpretation was quickly accepted (*48*) by others and has become an important tool for the physical organic chemist. Our experimental results were soon confirmed by others (*48*, *49*) and were extended to related solvolyses. Shiner (*50*) has given a thorough review on applications of the α-isotope on solvolytic displacement reactions. Lee and Wong (*51*) provided an important application in their studies of the neighboring group effect in solvolyses. As summarized in Figure 10, the solvolysis of *endo*-norbornyl brosylate gives an essentially normal α-*d* effect as expected for a solvolyis of the limiting type. The *exo*-isomer, however, shows a much lower isotope effect, indicative of neighboring group participation to give the bridged norbornyl cation intermediate. This and other examples have been reviewed by Sunko and Borcic (*52*) and by Scheppele (*53*).

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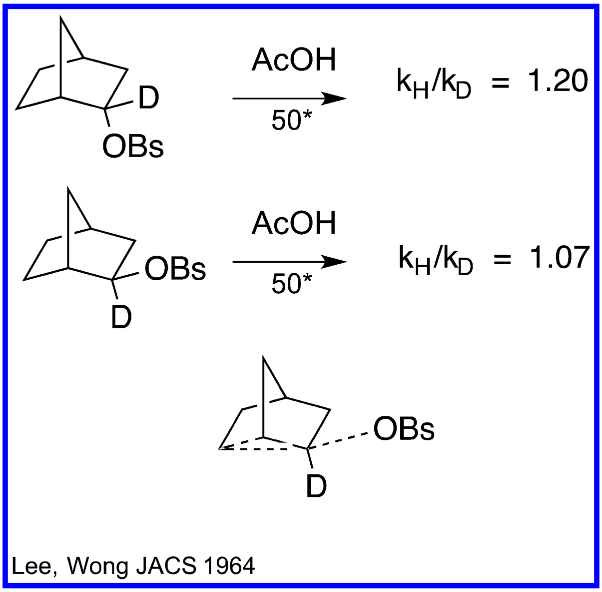

Figure 10. α-d Isotope effects in solvolysis of norbornyl brosylates.

Another useful application has been to cycloaddition reactions. The question indicated in Figure 11 is whether one bond forms first to give an intermediate diradical or whether the two bonds form concurrently and, if so, whether they are of equal strength at the transition state or different.

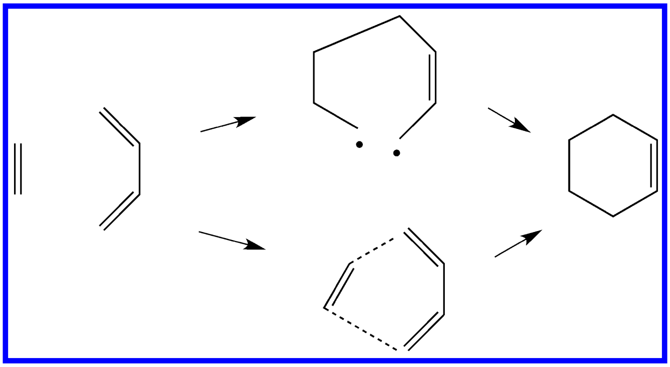

Figure 11. Synchronicity question of cycloaddition reactions.

α-Deuterium isotope effects have been used for this problem as shown in the recent example in Figure 12 (*54*). For a two-step reaction there would be no isotope effect at one end. The isotope effects found are on the low side and slightly different indicating that the reaction is concerted but not equal and with an early transition state. Note that the isotope effects are inverse because the CH bonds involved are changing from sp^2 to sp^3.

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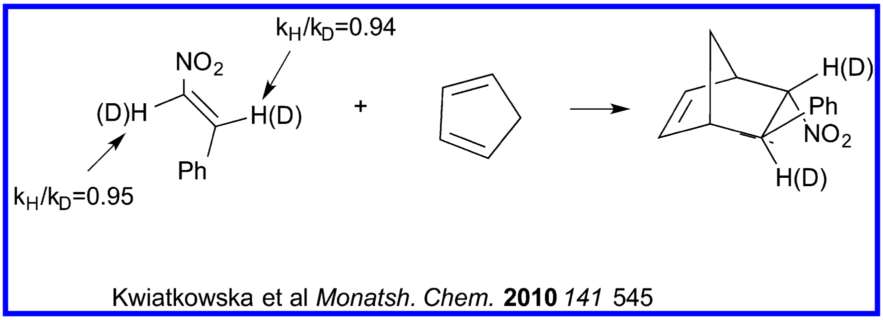

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Figure 12. Isotope effects in cycloaddition of nitrostyrene to cyclopentadiene (54).

Tritium

Tritium is highly radioactive with a half-life of 12.3 years but as a weak beta-emitter it is safe in external use and needs only reasonable precautions in use. It is useful as a tracer just as deuterium but with some distinctive differences. In particular, it can be used to measure small amounts of reaction. For example, in early experiments in my laboratory we used tritium exchange to measure the kinetic acidities of hydrocarbons using a strongly basic system, cesium cyclohexylamide (CsCHA) in cyclohexylamine (CHA).

Some measurements were relative to benzene; others referred to cyclohexane. To put all on the same scale we required the relative rates of benzene and cyclohexane. Under typical conditions benzene has a reaction half-life of about half a minute, whereas that of cyclohexane is several years. Nevertheless, we were able to run a mixture of both hydrocarbons in CHA containing tritium, taking several aliquots within a few minutes and spacing others over days. This type of procedure requires careful technique and pure materials. The results of three runs gave k(cyclohexane)/k(benzene) = 1.11 x 10^{-8}, 1.05 x 10^{-8}, 0.97 x 10^{-8} (*55*). The good reproducibility suggests that the results are reliable.

We were also able to measure the primary isotope effect for the exchange with cyclohexane. Deuterium exchange with cyclohexane is too slow to be practical but could be done using tritium exchange. We used a mxture of cyclopentane and cycloheptane in CHA containing tritium with cyclohexane-d_{12} in one run and cyclohexane in another. The relative rate cyclopentane/cycloheptane should be the same in both runs and serves as a check. One can show that for small extents of reaction, the rate of incorporation of tritium into cyclohexane-d_{12} is actually k_D. The experimental results gave k(cyclopentane)/k(cycloheptane) = 7.5 and 7.8 for the two runs (*56*). These results were part of a larger study on the kinetic acidities of cycloalkanes (*57*, *58*). The isotope effect found in this study was k_H/k_D = 6.5 after correction for the small amount of H in the C_6D_{12} (*55*).

These results with tritium point out that as a highly radioactive element, it can be uniquely useful for measuring slow hydrogen exchange rates. One limitation, however, needs to be added. The experimental kinetic acidity measured by the rate of incorporation of tritium into a molecule does not tell us which hydrogen positions are involved. This is not a problem for symmetrical molecules like benzene in which all of the hydrogens are equivalent. It is a limitation for cyclohexane; the reactivity discussed above does not distinguish between the *exo* and *endo*-hydrogens. The measured kinetic acidity is the average of the two positions.

Acknowledgments

At the time of my Norris award in 1982 I was just finishing my third decade at Berkeley. During that time some 168 undergraduate, graduate and postdoctoral coworkers had worked in my laboratory and I thank them for enjoying chemistry with me. I also thank the several funding agencies (PRF, AFOSR, NIH, NSF) for making it all possible.

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Chapter 6

Exploring Free Radicals: The Life and Chemistry of Glen A. Russell

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The career of Glen A. Russell essentially covered the second half of the 20th century. Russell carried out free radical research using traditional methods and the then new technique of electron spin resonance spectroscopy. The results were ground-breaking research on free radical conformations, halogenations, oxidations, directive effects, substituent effects, and electron transfer. This chapter deals with the early research themes of the Russell group and describes Russell's career, accomplishments, and personality.

Introduction

Even today, some 115 years after the first convincing proof of their existence, organic free radicals tend to be the Rodney Dangerfields of chemistry, *i.e.*, "They don't get no respect!" Consider the normal organic chemistry textbook and measure the page counts devoted to heterolysis versus homolysis or heterolytic reactions versus homolytic reactions. The page count for the former is normally an order of magnitude greater than that for the latter. This ratio faithfully reflects the emphasis given ionic reactions versus free radical reactions during the first half of the 20th century. The second half of the 20th century featured large advances in the knowledge of free radicals and their reactive chemistry, and Glen Alan Russell (Figure 1) was one of the prime movers in this effort.

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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Figure 1. Glen Russell as an Iowa State faculty member in the '60's. Photo courtesy of Iowa State.

Most of the chemical career of Glen A. Russell was spent searching for free radicals and exploring their chemistry. This chapter proposes to tell something of the life of Glen Russell and to give a broad overview of his chemistry research. This is an apt time to do so, as many of the people who knew Russell and helped in his work are passing from the scene. We two were part of the early group of Russell graduate students, and we can testify first hand about the brilliance of the man. Russell's many avenues of free radical research helped move this area into the mainstream of physical organic chemistry, and consequently he was honored with the 1983 Norris Award.

For another view on research in the Russell group, we also recommend a memoir by our fellow graduate student Edward G. Janzen (*1*) that covers Janzen's early days in the group. The Janzen book covers some of Russell's career during the 1960-64 time period, gives a sense of the excitement of being in a burgeoning research group about to "take off" in creativity, and shows the transitions a graduate student goes through in the path to becoming an independent researcher.

The proof that such an entity as a free radical existed is quite reasonably attributed to the synthesis of triphenyl methyl radical (Figure 2) by Moses Gomberg in 1900 (*2*). However, the radical was not stable enough to be characterized by the traditional methods, such as taking a melting point. Syntheses of free radicals were viewed with some suspicion by other chemists.

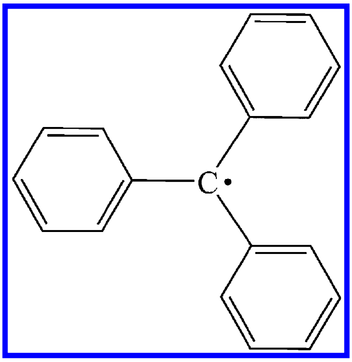

Figure 2. One of the resonance structures of triphenyl methyl radical.

Indeed, as you can read elsewhere in this volume in Arthur Greenberg's chapter on James Flack Norris, Norris himself was dubious of Gomberg's claim. Examples of stable radicals were found in the realm of organic nitrogen compounds, with Goldschmidt's 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Figure 3) the prime example (*3*). Nevertheless, the agnostic view of many chemists toward free radicals is shown by the treatment of Koelsch's radical, 1,3-bisbiphenylene-2-phenylallyl, by some unknown referee (Figure 4).

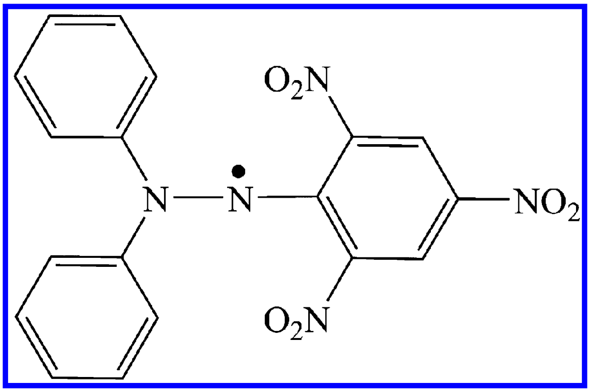

Figure 3. One of the resonance structures of DPPH.

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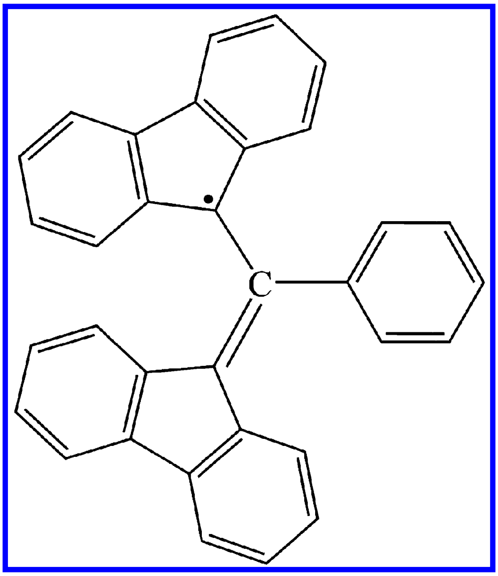

Figure 4. One of the resonance structures of Koelsch's radical.

In a series of elegant synthetic papers, C. Frederick Koelsch painstakingly worked his way toward his landmark synthesis of the radical. The last paragraph of a paper published in 1932 claimed the synthesis of the radical and promised a further paper on the radical (*4*). That paper on the radical's synthesis was submitted on June 9, 1932, but the paper on Koelsch's radical had to wait 25 years for publication (*5*). A referee held that "*the properties of the chief compound could not be those of a radical.*" Koelsch's radical was incredibly stable to oxygen. The convincing factor behind the final, long-delayed acceptance of Koelsch's paper on the radical was that of electron spin resonance (ESR). An ESR experiment proved that this stable material was in fact a free radical.

The paramagnetism associated with unpaired electrons obviously provided a clear route to proving the existence of a free radical, provided the radical stayed around long enough for a measurement. Magnetic susceptibility measurements were one way of accomplishing this. However, it was the invention of electron spin resonance spectroscopy in 1944 by the Russian scientist E. K. Zavoisky at the University of Kazan that opened a new era in the exploration of free radical chemistry (*6*). (It should be noted that the current fashionable term for this type of spectroscopy is electron paramagnetic resonance (EPR). The reasons for this switch are neither clear nor convincing to us.)

If not for the dislocations caused by World War II, Zavoisky might have been known as the inventor of nuclear magnetic resonance spectroscopy (NMR) and a Nobel Laureate to boot. In 1940 Zavoisky and two colleagues set out to search for proton magnetic resonance (*7*). They decided to use pure water containing copper and manganese salts. Zavoisky detected the proton magnetic resonance of water in May/June, 1941. Hitler invaded the USSR in June, 1941. Many important Russian scientists were sent east to Kazan, causing disruption of research by home scientists. Zavoisky's laboratory was closed down. When he started up work again, he moved his efforts into paramagnetism, with ESR spectroscopy the result.

Glen Russell's entry into independent free radical chemistry took place as ESR spectroscopy began to flower. When Varian Corp. began to manufacture commercial ESR spectrometers, the field of free radical chemistry was forever changed. Instead of having to prove the existence of free radicals by indirect methods, one could actually see them form, react, and decay. For coverage of the foundations and history of this spectroscopy, we recommend the volume edited by Eaton, Eaton, and Salikhov (*8*). ESR studies became a major element in Russell's research, although he accomplished much also with traditional methods. After this introduction, we continue on to cover some of the details of Russell's life, followed by an examination of much of his important chemistry.

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Russell's Life and Career

Unless otherwise referenced, the material in this section was obtained from Russell's daughters June and Susan, his widow the late Dr. Martha Russell, the Russell archive at Iowa State University, and our own personal knowledge. Since there are two of us writing this material, the authors will normally use the term "we" when referring to material known to the two of us. Occasionally stories and incidents will come up involving only one of us. We will introduce that material by giving the name of the person involved, either Kathy or Tom, in the first sentence, and then using the first person pronoun for most of the material. The early biographical material cited immediately below was obtained from Susan Russell.

Glen Allan Russell was born on Aug. 23, 1925, in Pittstown in Rensselaer County, NY, near the border with Vermont. He was the only child of John Allan and Marion Russell. Russell had Indian ancestry on his father's side and was 1/16 Cherokee. He grew up in the country on a farm that had dairy cows (Figure 5).

With the onset of the great depression, times were hard, and Russell's father supplemented the farm income by doing work with explosives. This resulted in his losing sight in one eye. The house was an old foursquare farm house with four large upstairs bedrooms. Russell's parents had one bedroom, each set of grandparents had another bedroom, and Russell had the final room.

Russell was interested in science and math early on. His mother bought him a chemistry set when he was young. He was fascinated with the set and regularly conducted experiments in his room. At least one of these experiments had a bad outcome, resulting in an explosion that left burn marks on the ceiling. When he wasn't doing science experiments in his room, young Glen was busy hunting squirrels which he shot and the family ate.

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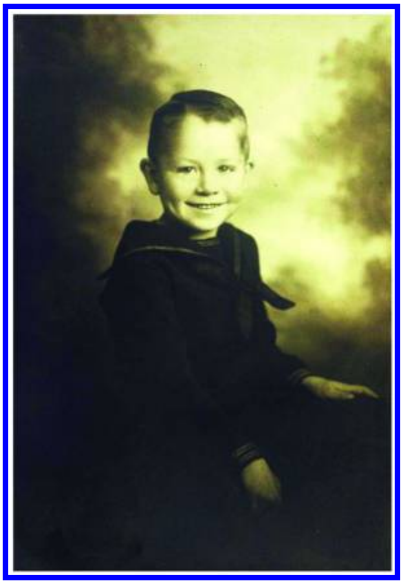

Figure 5. Glen Russell around age 6. Photo by Marion Russell.

He attended public schools in Hoosick Falls, NY. His elementary school was very small—a one-room rural school house. He finished his studies there quickly, because he was soon convinced that he knew more than the teacher. He did study chemistry in high school. At the age of 16 he entered nearby Rensselaer Polytechnic Institute (RPI). He had a full scholarship, and that way he could still help out on the farm. He majored in chemical engineering, because his mother thought this was a more practical and profitable choice with respect to jobs. *(Sadly, that's still true!)* He didn't care for the engineering classes, though, and told his daughter the story of the only poor grade he got. This was in a drafting class. The student behind him kept pestering him during the exam, asking how to complete the question. Russell finally stood up, went to the student's desk, and completed the question for him. As a result, Russell got an F for the exam. At RPI he was awarded the Ricketts Prize in Chemical Engineering, given to the top student, and the Research Prize awarded for the best senior thesis. That topic was "The Hydrolysis of Diphenylketimine Hydrochloride." He was also elected to Phi Lambda Upsilon, Tau Beta Phi, and Sigma Xi.

After receiving his BChE degree from RPI in 1947, he stayed on to receive an MS in chemistry in 1948. He was accepted to graduate school at both Purdue and Harvard, but he chose Purdue, because, unlike Harvard, he could enter Purdue mid-year. He didn't start graduate school with the idea of working for H. C. Brown, but Russell realized that his first choice as a mentor was not scientifically sound. He switched to Brown rather soon, and his Ph.D. was completed in 1951 (Figure 6). Brown felt that free radicals were not a "hot" area for research. Russell felt otherwise, and he went ahead single mindedly on free radical projects to prove Brown wrong. His dissertation topic was "The Effect of Structure on the Relative Reactivities of Hydrogen Atoms as Determined in Photochemical Halogenations."

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Figure 6. Russell in academic gowns at the awarding of his Ph.D. Photo by Marion Russell.

Russell's thesis is an intimidating 150 pages, but there was more. The table of contents also promised four abstracts. In fact, those four abstracts were instead four full papers that totaled 60 additional pages; papers that were clearly destined for *J. Am. Chem. Soc.* They were written up as authored by Russell and Brown, with Brown's name first. These four papers were eventually published over the next four years with some of the titles slightly changed (*9–12*).

There was a perception among his graduate students that Russell had little or no help from Brown, and that Brown did no free radical work before or after Russell's time. As noted above, Russell worked essentially independently, but any belief that Brown was a novice at free radical studies is incorrect. After obtaining his Ph.D. at Chicago, Brown did a post doc with Kharasch on free radicals. One important paper dealt with peroxide catalyzed chlorination of hydrocarbons (*13*). Brown continued to publish occasional free radical papers in the '40s. A 1948 paper written with Ash covered directive effects in aliphatic chlorination (*14*). It is true, however, that after Russell's time Brown focused more on the research which eventually resulted in a Nobel Prize. Certainly there was mutual respect between the two. An incident related by Russell graduate student Kirk Schmitt (*15*) illustrates the bond. In a group meeting a debate was going on between a graduate student and a post doc about the nature of the bonding in a cyclopropyl-substituted radical. This was still at the time of the dispute between Winstein and Brown about whether norbornyl cations were non-classical or two rapidly equilibrating classical cations, a topic covered elsewhere in this volume by Paul Schleyer. In the course of arguing about the sign of the coupling constants, all sorts of structures were drawn, one of which the graduate student referred to as "classical." The post-doc said, "Aha, I think I smell a Brown man." From the back of the room in a clear, low voice Russell said, "We're all Brown men here." End of discussion!

Russell was definitely interested in an academic position, and he had won a Fulbright scholarship for post-doctoral work in England. However, the Korean War was still going on at that time. Russell was under 26, and his draft board informed him that he would be drafted from any post-doctoral position. Consequently, he took a position with GE in Schenectady, NY, close enough to the family farm that he could work there weekends. Russell was promised he could have substantial amounts of time to do basic research at the GE facility. Both Kirk Schmidt (*15*) and Keith Ingold (*16*) report that what that meant in real life was that he could spend all the time at night he wanted to do basic research, but during the day he had better work on silicones.

Nevertheless, noted free radical chemist Frank Mayo was also at the GE lab, and the situation regarding pure research was much better than at the usual industrial laboratory.

At Purdue Russell met fellow Brown graduate student Martha Havill. Martha had graduated with a mathematics degree from the University of Rochester in 1945 at the age of 19, and then she obtained an M.S. in chemistry from the University of Buffalo in 1947. She went to work at National Aniline. She described her job as "Diazotize in the morning and couple in the afternoon, day after day." To find a more fulfilling career, she entered graduate school at Purdue, where she joined Brown's group (Figure 7). When Martha took Brown's course in organometallic lab techniques, Glen Russell was the "obnoxious" TA. On a long train trip home to upstate New York for Christmas, they became better acquainted and "formed a more comfortable relationship" from then on. They became engaged after Russell graduated and took the position at GE. It was another two years before Martha graduated. She frequently said that Brown was fond of telling people that women in his group got TWO Ph.Ds, their husband's and their own. Brown no doubt thought that was clever, but nowadays we would view his comment as sexist. And it was.

Russell and Martha were married on June 6, 1953. Figure 8 shows the happy couple in the MG that Glen had purchased in 1953 and which became one of his great passions in life. Russell drove the car to the university nearly every day for 40 years, including through brutal Iowa winters. After his death his daughter Susan had it shipped to Portland, where she still drives it regularly. To us graduate students, it seemed that Glen and Martha complemented each other very well. Where Russell was very reserved and reflective, Martha was warm, outgoing, and bubbly. She kept up contact with all of his graduate students, and she had a long, successful teaching career at Iowa State. When she retired in 2005 at the age of 79, the Iowa State Chemistry Department changed the name of the chemistry help room to the Martha E. Russell Chemistry Help Center in recognition of her career as an outstanding educator. She died on July 6, 2014 and is buried with her husband

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at the Iowa State University Cemetery. To hear Martha Russell in her own words, we recommend reading her letter in Janzen's memoir (*17*).

After she received her Ph.D., Martha Russell eventually went to work at GE. Their daughters testify that neither Glen nor Martha were motivated by financial gain. Since most people spend the majority of their lives working, their view was that it was absolutely critical to work at something you love, which for them would have been academic jobs. At GE they lived on one salary, with the other salary being put aside for the purchase of a house one day for cash, which they did after their move to Iowa State. When GE suffered some financial reverses, it was Martha who was laid off. Martha said she was told this was because she was a married woman and had a husband to support her.

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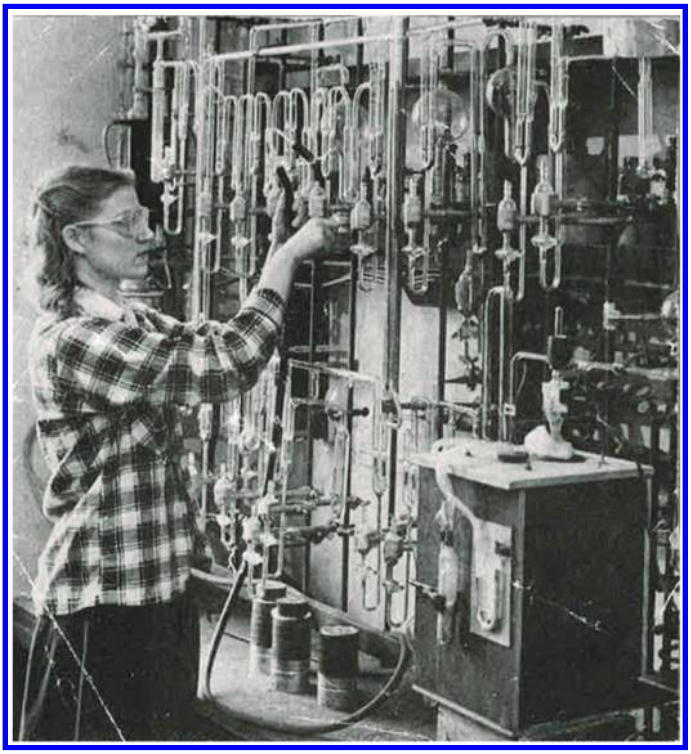

Figure 7. Graduate student Martha Havill at Purdue. Photo by Glen Russell.

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Figure 8. Glen and Martha Russell in the MG on their wedding day. Photo by Marion Russell.

Whatever limitations on basic research that GE put in Russell's way proved ineffective, because he published 13 papers from there, all but two with himself as sole author and all but two appearing in the prestigious *Journal of the American Chemical Society (JACS)*. In 1956 he published four significant papers back to back in *JACS* (*18–21*) as sole author, and in 1957 he published a *JACS* communication on his ground-breaking work on solvent effects on the reactions of chlorine atoms (*22*). The story in our group was that Cheves Walling from Columbia had sent Russell a congratulatory telegram on the publication of this work. With his credentials as a basic researcher demonstrated, Russell was ready to seek an academic job, and one was about to open up.

Iowa State's George Hammond of "Hammond postulate" fame had just started working in the area of photochemistry. Iowa State not only had chemistry courses for chemistry and chemical engineering students, but agriculture and home economics students also had to take elementary chemistry courses. Hammond did not like teaching agriculture students and expressed his distaste for this task quite colorfully—so colorfully that we won't repeat it. In any event, Cal Tech lured Hammond away, so there was an opening for a physical organic chemist on the Iowa State faculty. Glen Russell submitted his application to the head of the search committee, the renowned organometallic chemist, Henry Gilman. H. C. Brown (*23*) wrote an extremely strong supporting letter, mentioning that Russell was his leading student and that he had published a huge number of significant publications. Brown finished his letter by saying

> *"In my opinion Dr. Glen Russell is the most capable of our younger men in the physical organic field. Considering what he has been able to accomplish primarily through his own efforts, there is little doubt that with only a few students to assist his research progress he would soon develop into one of the top leaders in the field."*

Consequently, in May, 1958, Charles Goetz, Chair of the department, offered Russell a position of Associate Professor for the sum of $10,000 a year (*24*). At that time GE was paying Russell $12,000 a year. His teaching load was to be six lecture hours a week.

Readers who are non-academics would not find anything remarkable in this offer. Academic readers, however, would be surprised. All chemists know that "Like dissolves like." Academicians also know that "Like hires like." For a chemist to come in from industry at the tenured level of associate professor is almost unheard of. The Iowa State offer testifies to the high quality of Russell's previous publications and the respect that everyone had for H. C. Brown's judgment.

Despite the loss of Hammond, the organic faculty at Iowa State was still of high quality. Henry Gilman had an active research group, although Gilman's failing eyesight made it difficult for him to keep up with the literature. Ernest Wenkert was a fine natural products chemist, and Charles DePuy was well underway in his career, which resulted in his being chosen as a Norris Award winner in 2002. In 1957 Iowa State had hired as instructor a bright young chemist named Orville Chapman. We graduate students were intimidated by Chapman, who was just a few years older than we were and incredibly sharp. Chapman worked in organic photochemistry and won the ACS Pure Chemistry Award in 1968. He was elected to the National Academy of Sciences in 1974, joining Iowa State chemists Henry Gilman and Frank Spedding in that august body.

Then UCLA snatched him away. Russell and Chapman were close friends and had coffee together every day, joined later by Walter Trahanovsky when he joined the faculty.

Russell was offered $500-600 in "start up" funds, which seems puny now, but this research support was adequate for a new faculty member. Large numbers of teaching assistants were needed, since Iowa State required so many of their students to take chemistry. Physical, inorganic, and analytical chemists were well supported as research assistants at the Iowa State Ames Lab of the AEC. Consequently, most of the department's general fund was available for the organic chemists to use. Russell took up the appointment on Aug. 15, 1958. Glen and Martha bought the ranch-style house on Murray Drive, which they lived in throughout their time in Ames. It was to be the site of many memorable parties for the grad students and post-docs.

Within a couple of months Russell developed three research proposals: Directive Effects in Aliphatic Substitution (sent to the Office of Naval Research);

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Electrophilic Substitution on Saturated Carbon Atoms (directed to the NSF); and Solvent Effects in the Reactions of Free Radicals and Ions (sent to the PRF). Also, Goetz recommended Russell for an Alfred P. Sloan Fellowship, and Russell was a Sloan Fellow from 1959-1962. Russell's salary for 59-60 had a significant jump to $11,500, and in 60-61 it was $12,250. Goetz then negotiated a $500 mid-year raise when he heard that Penn was interested in hiring Russell. In 1961 Russell was promoted to full professor. We are not sure whether all of Russell's original proposals were funded, but our experience was that there was always plenty of money. After one year as a teaching assistant, a Russell student normally became a research assistant; and highly qualified graduate students, Ed Janzen for example, could start out as a research assistant.

Much of the basic equipment from Hammond's group was turned over to Russell. One large lab had a wall of distillation columns and a smaller lab had a large vacuum rack in the center. Russell was an expert glassblower, and he also continued to use the carpentry and mechanical skills that he had learned on the farm, building three gas chromatographs that were used by the group through the early '60's.

Russell started out with two graduate students, Anthony Moye and Dale Hendry. In 1959 the group expanded with new graduate students Robert Bridger, Roger Williamson, Richard Kriens, and Akihiko Ito plus post doc Krishna Nagpal. Russell's graduate students seemed to be older than the norm and interested in eventually working in industry. Several were veterans, and several were married. The group generally chose physical chemistry as their inside minor (after all, we were going to be physical organic chemists) and many emulated their mentor by choosing chemical engineering as their outside minor. Along with the expansion of Russell's group came expansion of his family. Martha had lost a still-born girl just before the move to Ames, but Martha gave birth to daughters Susan in 1960 and June in 1961.

We two entered graduate school in Sept., 1960. Our fellow student Ed Janzen had come at the beginning of the summer. Kathleen Desmond (later Kathy Trahanovsky) came from Emmanuel College in Boston with the intention of getting a master's degree and returning home to New England. When I did well on the physical chemistry qualifying exam, Russell suggested that I major in that area; but I liked organic more and became the first female member of the group. There was only one other woman organic graduate student in the department, and she was finishing up an MS with DePuy. Russell suggested I study the reactivity of the succinimidyl radical, as it would make a tidy master's project. That project turned out to be very significant, and we will return to it in part 3 of this chapter. After completing my MS degree, I returned to New England to a temporary teaching position at Emmanuel for three years. I enjoyed teaching and realized that I would need a Ph.D. to make a career of it. I considered Princeton, but, when I requested an application, I was told that they did not accept women graduate students. I had left Iowa State in good standing, so I returned to the Russell group, doing a thesis on ESR of some semiquinones and graduating in 1969. Walter Trahanovsky joined the Iowa State organic faculty in 1964 while I was gone. We were married in 1967. I eventually became a teaching member of the Iowa State chemistry faculty. Martha Russell and I progressed together from

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part-time Temporary Instructors to Continuous Adjunct Associate Professors and Associate Coordinators of General Chemistry over the next thirty years.

In the early ‘60’s, students routinely worked in the lab nights and weekends. Russell was in his office every Saturday morning for 40 years, if he was in Ames. When he was hired, the college work week was 44 hours, and there were Saturday morning classes. There was an easy camaraderie among students and lots of interactions among groups. In a time before so many OSHA/EHS rules, lab doors were usually left open and cross fertilization of research ideas and equipment sharing flourished, along with coffee breaks and football pools. I was accepted as a peer, even garnering an invitation for beer at Dave’s Lounge in downtown Ames shortly after joining the group. However, I was presented with a large bell to ring when approaching the large lab, because there Bob Bridger and Roger Williamson often regaled their lab mates with war stories and bawdy songs.

E. Thomas (Tom) Strom entered graduate school with an MS in nuclear chemistry from UC-Berkeley. My mother had developed leukemia, so I wanted to finish my graduate work near to our home in Des Moines, IA. Ames was just 30 miles away. Although my BS Chem degree was from the University of Iowa, I was well aware of Iowa State’s strength in engineering and the sciences. My experience in nuclear chemistry convinced me I would do better in organic chemistry, but my time at UC-Berkeley did give me a strong P-Chem background.

Russell first thought I might do some P-Chem on the solvent-chlorine complexes he had proposed earlier (*22*), but then he suggested that Ed Janzen and I look into using the electron spin resonance (ESR) spectrometer he had recently acquired. Dr. Roy King from England was a former DePuy post-doc, who was very skilled in electronics. His position had morphed into that of instrument specialist. Russell knew nothing about the instrument, so Roy taught us both. Roy believes that the ESR and NMR spectrometers recently purchased came from a $50,000 Army grant that Russell had obtained, but we cannot confirm that (*25*). There was one huge problem with the instrument set up. There was only one 12-inch magnet for the two spectrometers! Consequently, every time we wanted to do ESR work, the NMR spectrometer had to be shut down. Then as now, NMR was the work horse instrument for proving the structure of an organic compound. When we did ESR work, Ed and I got dirty looks; and we felt that we had to be on the instrument 24 hours a day to justify shutting down the NMR. Roy worked out a procedure wherein the ESR would be operating one week out of four. As our ESR work progressed, we needed more and more time. Russell finally got the funds to buy a new six-inch magnet solely for the ESR, which ended the problem. However, he did not buy the Varian water-cooling system that went with it. Instead he bought a huge milk can, a pump, and lots of copper tubing and had the shop put it all together to form a water cooling system for the magnet. Perhaps this was a throwback to his old dairy farming days. Roy felt this makeshift setup looked unprofessional, but it did the job for a long time.

More top notch students such as Ed Geels, Jerry Hunt, Al Bemis, Joe Schoeb, Leo Chang, Steve Weiner, Gary Mikol, Maria Young, and Wayne Danen joined the group, as did post-docs Hans Dieter-Becker (a wizard in the lab!), Frank Smentowski, Ryusei Konaka, and John Gerlock; and the research really started to roll. A tangible demonstration of this was Russell’s winning the 1965 ACS

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Award in Petroleum Chemistry, now known as the George A. Olah Award in Hydrocarbon or Petroleum Chemistry. Kathy and Tom were in Detroit for the ACS meeting at which Russell received this award. Russell had the custom of inviting all of his students, both present and past, to dinner at his expense at national ACS meetings. We both remember having the Detroit dinner at the Playboy Club, a first visit for both of us. It was tamer than Kathy expected, but the matchbook was a super souvenir for her, then a teacher at a Catholic women's college.

There seemed to be some mystique about this award, but its origins and character are not clear to us. Russell received congratulatory messages from previous winners Vladimir Haensel (*26*), Robert Taft (*27*), George Hammond (*28*), Harold Hart (*29*), and George Olah (*30*). A letter in the Russell archives from George Pimentel to George Olah (*31*) refers to a "club" or society of petroleum chemistry award winners, a term also used by Harold Hart (*29*) in his letter. At this late date neither 1964 winner George Olah (*32*) nor 1967 winner Andrew Streitwieser (*33*) remembers what this club or society of recipients was. 1968 winner Keith Ingold believes this might have been something set up by the award sponsor (*34*). He thinks that the sponsor, then Precision Scientific, displayed full face, color photos of the winners at their head office, since he had to supply such a photo. Perhaps the "club" may only have referred to a dinner given by the sponsor for the current winner to which previous winners were invited.

As the years passed, the honors and recognition for Russell increased. He was chosen as a Fulbright Hayes Lecturer at the University of Wurzburg. In 1966 he was the Reilly Lecturer at Notre Dame. In 1967 he was Chair of the Gordon Conference on Radical Ions. In 1972 he was a Guggenheim Fellow at the Centre d'Etude Nucleaires de Grenoble. That year he also won the Iowa Medal given by the Iowa City ACS Section, while being promoted to the rank of Distinguished Professor at Iowa State. He was the recipient of the ACS Midwest Award in 1974. In 1975 he participated in the USA-USSR NAS Exchange Program. His entire family was with him for summer conferences in Europe or Japan, for his sabbatical in Grenoble, and for an extended stay in the then Soviet Union. He also was fond of finding an excuse to go to Germany for Oktoberfest. In 1983 he won the award that has justified this chapter, the Norris Award in Physical Organic Chemistry. He won the Iowa Governor's Medal for Science Achievement in 1988.

Russell thought every family should have a sport they could do together, and he chose skiing (more about that later). Figure 9 shows the Russell family at Sun Valley during the week of Christmas of 1970. On his trips to Germany, Glen picked up various beer drinking dances, which he was fond of demonstrating during parties for his group (Figure 10). Through the years his research output slowed down a little, but it was still significant. He participated in the various meetings and conferences concerning free radicals. Figure 11 shows Russell with his former graduate student James Tanko, now of Virginia Tech, at the 1993 Gordon Conference on Free Radicals.

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Figure 9. From left to right, Glen, Susan, Martha, and June Russell at Sun Valley. Photo by Glen Russell using a photo timer.

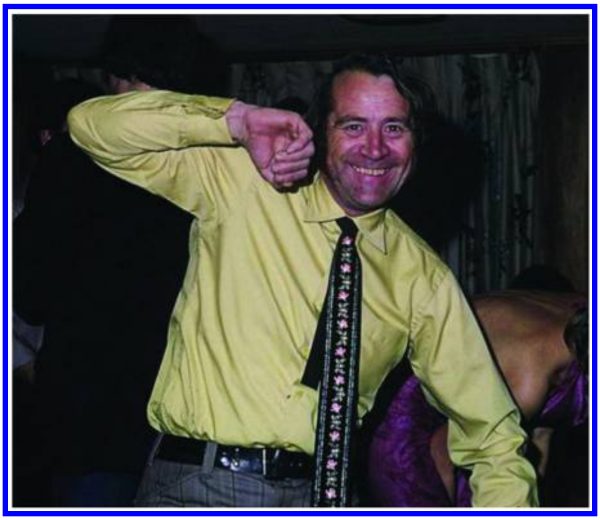

Figure 10. Russell showing off his dance skills. Photo by Susan Russell.

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Figure 11. James Tanko and Glen Russell at the 1993 Gordon Conference. Photo by Naushadalli Suleman.

In either late 1993 or early 1994, Tom realized that Russell was nearing his 70th birthday. I remembered that the *Journal of Organic Chemistry (JOC)* had published a special issue for the 70th birthday of Henry Gilman, so I thought that surely they would do the same for Glen Russell. I contacted *JOC* Editor-in-Chief Clayton Heathcock about my suggestion. Heathcock gently but firmly told me that Henry Gilman was a special case in view of his effort towards establishing that journal and also, if he published a special issue every time a significant organic chemist reached his or her (back then it would have been his) 70th birthday, he'd have nothing but special issues. ***However*,** there would be nothing wrong with having a number of Russell ex-students, friends, and colleagues submit papers and asking them to be published in the same issue, each paper with a dedication to Russell. Therefore, that was the route we took. Tom asked all the Russell students, friends, and colleagues he knew to submit papers, and at Iowa State Walter and Kathy Trahanovsky did the same. For a long time we kept Russell in the dark about the effort, but eventually we had to let him know what was happening. For one thing, what would a special Russell issue of *JOC* be without a Russell paper. Issue No. 17, Volume 60 of *JOC* appeared on August 25, 1995, just two days removed from Russell's 70 birthday. The articles in the issue led off with a paper by Russell, Wang, and Yao on "tert-Butylation of Quinolinium Cations and Quinoline N-Oxides by tert-Butyl Mercury Halides" that was paper number 60 in Russell's long-running series on Electron Transfer Processes (*35*). There followed 19 consecutive articles, all dedicated to Russell for his 70th birthday. The first three notes in the issue were dedicated to Russell as well. The writers were ex-students or post-docs, friends, or academic colleagues, and the countries of origin besides the US were Japan, Korea, Germany, Italy, Australia, Poland, Spain, and Canada, testifying to Russell's wide network of influence.

We also planned a Russell 70th birthday symposium at Iowa State, with the Trahanovskys handling the details. The celebration at Iowa State, which took place on Aug. 26, just three days after Russell's birthday, featured talks by former student Ed Janzen, former post-doc John Gerlock, friends Keith Ingold, Henry Shine, and Cheves Walling plus Russell himself (Figure 12). At least 50 students and friends with their spouses were at the function. The symposium was supported by Ford, Chevron, Rohm and Haas, Amoco, and Bridgestone-Firestone plus Dr. Christoph Osuch, Dr. David Lawson, Dr. and Mrs. George Holland, and Dr. and Mrs. Kenneth Mattes. In retrospect, it was providential that Russell's 70th birthday was chosen for the celebration, for he would not see his 75th birthday.

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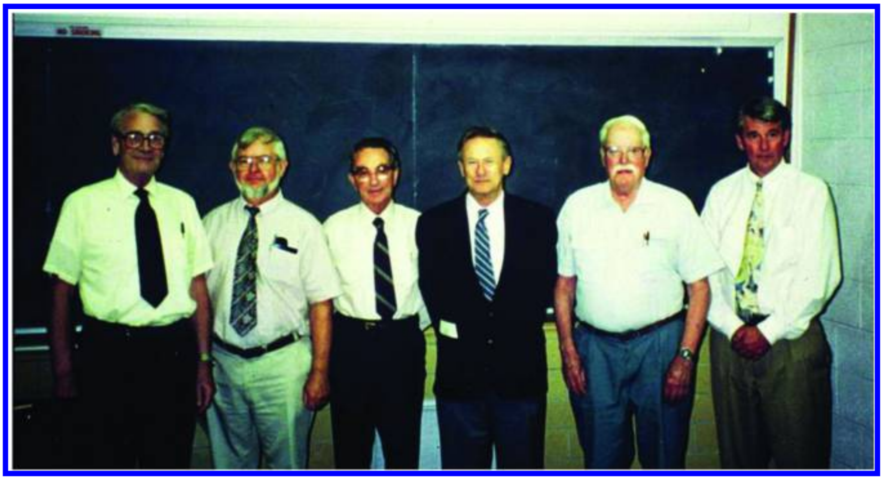

Figure 12. Glen Russell, Edward Janzen, Henry Shine, Keith Ingold, Cheves Walling, and John Gerlock at Russell Symposium, Aug. 26, 1995. Photo by Iowa State.

The year 1997 started out like any other. Russell still drove to work six days a week in the old MG (Figure 13). Russell rebuilt the MG engine himself and had the MG repainted in the exact shade of British racing green originally used on the car. This was thanks to daughter Susan who had spent four years at the London School of Economics and who brought MG parts and the green paint in her carry-on luggage when she came home for visits. In June, Russell traveled to Portland, OR, to help Susan put a deck on her house. That summer also marked the birth of the first Russell grandchild on June 30, granddaughter Kylie (Figure 14), born to Russell's chemist daughter June Russell and her chemist husband Jeff Bjorklund. (Grandson Tristan Russell was born on July 17, 2000.)

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Figure 13. Russell in the Chemistry Department Parking Lot with the 1952 MG. Photo by Martha Russell

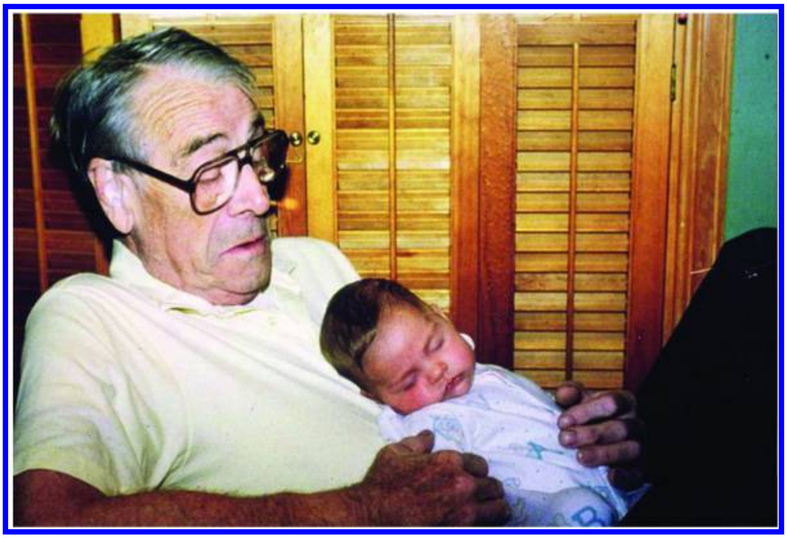

Figure 14. Russell with new granddaughter Kylie. Picture by June Russell.

Russell returned from a summer Gordon conference not feeling well. There was fluid build up in his chest. A large amount of fluid was drained from his pleural cavity, and it was found to contain cancer cells. We can testify that Russell for most of his life was a chain smoker. He gave it up for a time, but he took up the habit again when he was in Russia in 1975 as part of the USA-USSR Exchange Program. Whatever the cause, he was diagnosed with stage 4 lung cancer. There was little hope for successful treatment. He was cared for at home by his family with the help of hospice, and he died on Jan. 1, 1998, age 72. The memorial service took place on Jan. 16 at the Memorial Union at Iowa State with burial in the Iowa StateUniversity Cemetery. Interestingly, his mother Marion Russell survived him and lived to be 100.

Nobel Laureates H. C. Brown and Jean-Marie Lehn sent memorial tributes to Russell's friend Walter Trahanovsky, as did great chemists such as Cheves Walling, George Hammond, Frederick Greene, Emanuel Vogel, Keith Ingold, Joseph Bunnett, and Robert Norris. However, the tribute with the most resonance for us is from his former colleague Orville Chapman (*36*).

> *"When I think of Glen, the word that most frequently comes to mind is silence. That's odd, isn't it? Some of you know that for sixteen years Glen and I went out for coffee twice a day, six days a week. Sometimes others joined us, but more frequently it was just the two of us. On frequent occasions, we never said a word. We were content with each other's company, and we could share silence. How rare and wonderful is a friendship so complete that it can share silence—share silence and yet value companionship dearly. Of all the things I missed after leaving Iowa State University, having coffee with Glen was the thing I missed most. I enjoyed sharing the latest research results and even more the as yet unexplained observation. Every conversation lightened with Glen's wry observations, his piercing wit, and his unforgettable epigrams of pompous people. But as the ancient proverb says: "Words fitly spoken are like apples of gold in pictures of silver, but silence is golden." And so it is; silence is golden. In the end, I value the silence—and the companionship. Death has ended the conversations, but it can never end the silence or the companionship."*

In view of his 50 years of research on free radicals, we thought appropriate to have a Russell memorial symposium at a national ACS meeting. The officers of the organic division were agreeable, and we also got a PRF grant to support travel. The symposium "Free Radical and Electron Transfer Chemistry: A Legacy of Glen A. Russell" was held on Mar. 28, 2000 at the ACS National Meeting in San Francisco. The invited speakers were Kathleen and Walter Trahanovsky, E. Thomas Strom, Hans Dieter-Becker, Martin Newcomb (Norris Award 2000), Keith Ingold (Norris Award 1993), Charles Perrin (Norris Award 2015), Henry Shine, Dennis Tanner, and Bernd Giese (Norris Award 2009). Russell's family were present at the symposium.

Thus far we have given you an overview of Glen Russell's career, and it is quite clear Russell was a brilliant physical organic chemist. But, how brilliant or why brilliant? Edward G. Janzen is one of Russell's best known students. Janzen had a long academic career, first at Georgia and then at Guelph, and was a pioneer of the spin trapping method of detecting free radicals. Here is Janzen's view on the matter (*37*).

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> *"He was creative, yes, but there are a lot of creative people and some are scientists. So that's not it. He wasn't particularly good at designing experiments. You as a graduate student had to think these up yourself. But—here is his brilliance. He had the uncanny skill at figuring out what the results meant and where they would go if continued. And, most importantly, he had the courage to stick his neck out and predict what future results would be. I often thought more experiments were needed to make the statements he made. But Glen said NO! We don't need more. He could sense what was really happening even though not all the results were in. Some people have the "hunch." Russell did."*

What was Russell really like? Orville Chapman's tribute clearly showed that he was a quiet man. What adjectives would you use to describe that—shy, reserved, distant, taciturn, cold? We both thought he was a kindly man, so we wouldn't use the adjective "cold," but we might come down on the side of "shy" or "reserved." We'll give you input from his friends, former students, and his daughters in the pages to follow, and then you can make your own assessment.

One thing we students had to get used to was that he would seemingly ignore us when we passed him in the hall. Al Bemis remembers that he would say "Hi, Dr. Russell" and get no response, although he was always friendly and interactive to Al when Al saw Russell in class or in his office (*38*). Russell had the habit of always walking down the right side of the hall, while dragging the knuckles of his right hand against the wall. Some of the older graduate students, seeking to play with his mind, would deliberately get between him and the wall. He would look vaguely troubled, but he would say nothing about their interference. Ultimately we concluded that he was deep in thought on those occasions. Shy people are rarely dynamic lecturers, but Russell was a skilled and interesting teacher. Ed Geels testifies that his lecture style was casual, but he kept the students up with him at all times (*39*). His presentations at meetings were also clever and forceful. Jim Tanko remembers that he would seem almost dozing during departmental seminars, but, when the time for questions arose, he roared awake like a lion (*40*).

Russell was a chain smoker most of his life. Tanko states that when he was particularly agitated and engaged during a conversation on chemistry, he would sometime light up a second or even a third cigarette. He thought that perhaps the number of cigarettes lit was a measure of his interest.

Tanko relates the following incident.

> *"And of course, there was the time he tossed the lit cigarette into the trash behind him. It started smoking, and the grad student to whom he was talking had so much admiration and respect for Glen that it took him several minutes (and a rapidly decaying situation) to interrupt to say, "Professor, I think we have a problem." Glen put another trash can on top to snuff out the fire and returned to the conversation as if nothing had happened."*

Geels (*39*) describes a lecture incident where Russell after finishing his cigarette took the next one from the pack and placed the non-filtered end in his mouth.

> *"Immediately the entire class noticed this as he sort of lost us as we waited for him to light up the filter end. He kept us in suspense quite a while as he kept on lecturing while even removing the cigarette from his mouth while making a point about his subject. Finally he placed it back in his mouth, removed his lighter from his pocket and proceeded to light the filter end. The filter got very hot and mostly just melted. This stopped his lecture, and he also noticed both his mistake and the amusement of the entire class at this point. This produced a small smile on his lips. He broke the filter from the end and relighted the remainder of the cigarette, continuing his lecture."*

These two incidents aren't so amusing when we remember that Russell died of stage 4 lung cancer.

Russell's students tended to get jobs in industry rather than in academia. This may have been because he had developed many contacts through his years at GE and from his consultancies with a variety of industrial labs, both oil and traditional chemical companies. His previous industry experience resulted in a practice that his students appreciated. He felt that, if you could buy a chemical needed for your research, you should buy it. When you factored in the time it took to make it, it was cheaper to buy it, no matter how expensive it might seem. Other faculty members thought graduate student time was cheap. It wasn't to the graduate student. Also, Russell tried to get his students finished when he felt they had completed a significant chunk of research. It was certainly possible to get a Ph.D. in three years, and the usual time period was between three and four years.

Simply said, Russell respected the time and effort of the graduate students. Jim Tanko (*40*) had come to Iowa State with the idea of working for another organic faculty member. He had corresponded with that individual several times, so when the time came to choose a research director, he went in to see the faculty member, expecting to sign up. During the interview the faculty member took a personal call and stayed on the line for some 30 minutes. This made a very bad impression. Tanko had been taking a course from Russell and considered him an incredible lecturer, so he decided to check out what Russell would have to offer. Russell described about a dozen projects, when the phone rang. It was personal. Russell said immediately that he was in conference and would return the call later, hung up, and returned to discussing research projects. The point of Tanko's story is that Russell was respectful of people and particularly his students. As an example, Russell's office was covered with color photos that he had taken of his graduate students and post-docs.

Fellow faculty member Walter Trahanovsky noted that Russell enjoyed interacting with visiting chemists (*41*). He was very good at summarizing seminars, and Trahanovsky recalls that he felt he got more out of Russell's summaries than the presentation itself. Russell played a major role in establishing the Gilman Lectures, an endowed lectureship in honor of Henry Gilman. He worked very hard to insure that early lectures were presented by the very cream of organic chemists. Trahanovsky remembers the time an invited chemist turned down the invitation to be a Gilman Lecturer. Russell wrote this chemist and asked him to accept the invitation for next year. He pointed out that the only other person who had turned down the invitation had passed away within a year. The invitee replied, accepting the invitation for the next year.

Ron Blankespoor recalls with pleasure that Russell was not a micromanager (*42*). He was always available to talk about research results and future experiments, but he wasn't looking over your shoulder in the lab. Tom recalls that he was open to your research going in different directions from what had been envisioned. Above, Janzen had said that you had to design your own experiments (*37*). Tom would take the view that Russell was always available to brainstorm with and would help you get started, but then you had to find your own way. Isn't that what is supposed to happen, as a graduate student makes the transition to becoming an independent researcher?

If Russell felt that you were deserving of a Ph.D., he would protect you on your way through the process. Some background is necessary here. Nowadays the two main ways of determining whether a student should progress toward a Ph.D. are (1) defending a research proposal, either your own or an independent proposal, or (2) passing a set number of cumulative exams over a certain time period. In those days at Iowa State, the process resembled an obstacle course. First of all, on entrance to graduate school, you took qualifying exams in the four areas of chemistry. Back then, biochemistry wasn't one of the group. If you failed a qualifying exam, you had the option of taking a refresher course, and then taking the exam again. Obviously there was course work, and at that time a B was still considered a pretty good grade. Course work was not only in your major, but in your inside minor and in your outside minor. Then came written prelims in your major, your inside minor, and your outside minor. These were followed by an oral prelim in which the oral committee consisted of your major professor, a second professor from your major, a professor from your inside minor, a professor from your outside minor, and one other faculty member.

In contrast to the oral defense of the Ph.D. thesis, which was a love fest, it was entirely possible to blow your degree in the oral prelim. To show the stakes, consider two graduate students from our time—student P and student D. Student P went into the prelims with fear, because he knew that his major professor felt he had not done enough research to advance. However, student D was taking the prelims at the same time. Student P reasoned that if he outscored student D on the written organic prelim, he would be OK, for student D was a Gilman student. Gilman students who advanced to the prelims always passed, probably in compensation for the fact that they would spend two more years for their Ph.D. than the other organic students. However, the faculty were too smart for student P. Both student P and student D received grades of "condition" on their written exams. This meant that their advancement to the Ph.D. was conditional on their doing well on the oral prelim. Of course, student P failed his oral, and student D passed his oral. However, there was a happy ending. Student P was allowed to take prelims again the next year, after he had done enough research to satisfy his professor. This time he passed and progressed to the Ph.D.

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We graduate students were concerned about how our fellow student J would do on the oral prelim. By chance, the oral was scheduled on the very day the winners of the 1963 Nobel Prizes in chemistry were announced. They were Karl Ziegler, honored for work on low pressure polymerization of ethylene, and Giulio Natta, honored for synthesizing stereoregular polypropylene. (In the interests of historical accuracy, we should interject that polypropylene had been made several years earlier than Natta's synthesis by J. Paul Hogan and Robert Banks of Phillips (*43*), a fact normally ignored in the usual polymer chemistry textbook.) Russell showed up at student J's desk early in the morning, telling student J that Ziegler and Natta had won the Nobel Prize for chemistry, and it might be a good idea to know something about their research. Russell then gave the student several reprints of Ziegler and Natta's work. Student J's oral prelim was in the afternoon. Russell opened the proceedings by noting they must be in mourning at Harvard today. The other organic committee member, Orville Chapman, inquired why. Russell then responded that R. B. Woodward had once more been overlooked for the Nobel Prize. (Woodward would win in 1965). Chapman then asked who had won the prize. Russell responded that it was Ziegler and Natta. Chapman took the bait and opened the oral by asking, "Student J, what do you know of the work of Ziegler and Natta?" And, of course, he knew a lot, so the rest of the oral prelim went smoothly.

By all accounts, Russell was a formidable bridge player. If a visiting speaker was a bridge player, certain skilled graduate students would be invited to the Russell home to make a fourth in bridge. Neither of us had the skills at bridge to qualify for such an invitation.

Russell had the reputation of being able to drink anyone under the table. This was not a contest that either of us wished to enter, but we always wondered whether this perception was true. Information from Russell student Kirk Schmitt gives us some hard data on the matter (*44*). Kirk tells of a memorable Russell group Christmas party.

> *"I was used to beer from a small boy, but no one warned me that Martha's rum punch was, well, rum and that the "punch" ingredients were mainly an after-thought. Nevertheless, on my first such party I was doing well and made it to midnight. I was actually proud that I had done better than a Polish post-doc who had tried to go head-to-head with Glen, drinking "wodka" from water glasses. It was reported that Glen winked when the post-doc said "I am the Polish embassy."*
>
> *However, at midnight, Glen got out what he considered an appropriate nightcap, the Greek liqueur ouzo. He poured us all a shot glass, straight, and I took mine while leaning on the bar. I had never drunk the stuff before but had some experience starting siphons for gas and diesel by mouth and was pretty sure I recognized the vile flavor. As I sat dipping my tongue into the ouzo, trying to figure out how to get rid of it, Glen leaned across the bar, looked me in the eye, and said, "You know, no real man sips his ouzo." Well, bottoms up. I wish I could report more about the party, but I only remember waking up the next morning."*

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On this basis of this information, we conclude that the perception was probably true.

As noted above, the Russell family sport was skiing. His daughters date those trips back to the '60's. Russell regularly took graduate students on weekend winter ski trips to Minnesota. Probably an early exposure to heavy duty skiing came courtesy of Keith Ingold (*45*). Keith was surprised when Glen expressed a desire to ski the Expo downhill run at Mont Tremblent in Quebec. The run had opened recently and had an awesome reputation. Glen came to the National Research Council in Ottawa to give a talk, and Martha accompanied him. The couple stayed at Keith's house, and Keith, his wife Cairine, Glen and Martha went to Tremblent for a three day stay after Glen gave the talk. Here is Keith's description of the skiing trip.

> *"I led Glen to the top of Expo, a 1600 foot hair-raising slope with no easy sections—and no escape routes to easier slopes. Expo is just steep and steeper! Glen looked a bit aghast, gulped, then grabbed his resolution (and his poles) in his hands and pushed off. Seconds later a cloud of snow erupted 80-100 feet down the slope as Glen had a spectacular "egg-beater" fall with arms, legs, poles, and skis flying everywhere. Fearing multiple fractures, and even worse, for Glen was lying unmoving, I skied down to him. There he was lying in the snow with a silly grin on his face. To my anxious questions he said only: "That was fun!" He got up, brushing off my concerns (and a whale of snow) while I gathered up his poles and skis. Then he was off again for another egg-beater fall after another 100 feet or so. His "take off and fall" skiing technique did get him down Expo in one piece to my relief. —When we got to the bottom, I thought he'd be through skiing for the day. Not a bit of it, we had to return immediately to the top of Expo for another descent, then again, and again, and again, until the lift closed. —However, his last two runs on that first day were made without a single fall.*

The favorite companions of the Russell clan on skiing trips were his former post-doc John Gerlock and John's wife Sandra. With Russell's encouragement John and Sandra became pretty good skiers. John tells the tale of the group skiing at Jackson Hole (*46*). After the first day, two to three feet of powder snow fell on the place. Russell advised John to rent "noodles" for skiing that day, and John did so. "Noodles" are long, flexible, difficult-to-control skis. Russell and John went to the top, and John started down on his noodles. With his first time on noodles, John would ski only a few feet, fall, and then reproducibly repeat the process. Russell told John to ski on down as best he could, and he would follow.

> *"After I floundered about halfway down the slope, I looked up slope and saw Russell shooting down the hill at great speed. —It was really an awesome thing to see. —Suffice it to say that when he blew by me spraying powder, he looked better than Jean-Claude Killy ever did right up to the moment that he became airborne, summersaulted and disappeared in a huge cloud of powder. When I reached him, he was bleeding profusely*

> *from the mouth. —It was obvious to me that we needed a helicopter to medevac us to safety, but that was not what happened. Spitting blood while speaking, just like in the movies, Russell told me in no uncertain terms that he was going to ski down and I should follow, which I did."*

John states that Russell got a bunch of stitches in his lip. When they had margaritas afterward, with the usual heavy salt layer on the rim of the glass, Russell drank his ice-cold, salt-laden margarita through the gash on his lip without flinching. He was just that tough.

Tough also characterizes the way he carved out his area in research. He defended his turf strongly. He was very thorough in his reviewing of articles and research proposals. Occasionally we would have the opportunity to see his reviews of papers. He was a tough reviewer, and sometimes he crossed the line from "tough" to "nasty." Yet overall, he was a very generous man, as Tom can testify.

During my last year with Russell, I had an offer in hand from Mobil Research and Development Corp. in Dallas. I also had a two year ROTC commitment with the US Army. Mobil had agreed to keep the position for me while I was in the army. My Army duty was due to start in March, 1964. I knew that my Army salary would be a lot less than what Mobil would pay me, so I tried to finish my thesis early to get as much Mobil money as possible. I had it worked out that I could start with Mobil Dec. 1, 1963. In the early fall Russell came to me and said that it would be a pity if I couldn't spend the Christmas holidays with my Iowa family. He then offered to pay me a post-doc's salary for the month of December. I took him up on his generous offer. I'd like to say that I got a lot of research done during that extra month, but I didn't. However, my wife and I did get to spend Christmas and New Years with our families. Ed Geels (*39*) tells of Russell putting him on a post-doctoral appointment for six months after the Ph.D., while Ed was waiting to start his appointment at Dordt College. When Ron Blankespoor (*42*) received his first academic position, he had no research funds to carry him over the summer. Russell gave him a post-doctoral appointment for that first summer.

The picture that most of us have about a successful academic researcher is that he/she is a driven individual, who works the students hard and himself/herself even harder. His daughters testify that Russell was a devoted family man. He would come home soon after 5 p.m. on weekdays and noon on Saturday. His daughters remember hearing the sound of the MG's motor before he ever turned into Murray Drive. He seemed to almost effortlessly draw a balance between work and non-work. He left his work behind in Gilman Hall and focused on his wife and daughters and the recreational activities that all would enjoy. He bought a trampoline for his daughters before they could barely walk. When they were young he tried to teach them French from an old Berlitz language book. Nearly every summer the Russell family went abroad for a month, one week at a chemical conference and three weeks as a family, traveling and exploring new places. He was an avid photographer, and he took many photographs of their travels. Overall, he had incredibly diverse interests.

Russell never lost sight of his farm boy upbringing, and he always relished working physically with his hands. As soon as he got home in the evening, he

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would change into his work pants and garden, work in the yard or greenhouse, or complete various house projects, often incorporating his daughters into those tasks.

The greenhouse was the site of Russell's orchid collection. When the family was away on travels, Kirk Schmitt (*15*) states that certain trusted graduate students or post-docs were allowed to house sit. Post-docs Gerlock and Balleneger were trusted to house sit during a bad winter when the heater in the greenhouse failed, killing Russell's beloved orchids. Kirk remembers helping restore some of the plumbing and musing whether the research budget could be diverted into getting replacement orchids before Russell returned.

The summing up of Glen and Martha Russell's characters and relationships is best done by their daughters (*47*).

> *"Our parents were a good match. They complemented one another and helped each other shine. They were both very social, each in their own ways, and generous with their time. They loved opening their home to students and visiting faculty through the rousing parties they hosted.*
>
> *Our parents were also politically engaged and very mindful of the opportunities they had and their good fortunes in life. They focused on doing what they could to ensure that others could achieve similar outcomes, not only their students, but the community in general.*
>
> *We were very lucky to have parents that were so positively and actively engaged in our daily lives yet at the same time always served as strong role models on the bigger issues, inspiring us to pursue our goals and visions fairly and to keep a healthy and balanced outlook on life. Our parents were always there for us, in the little and big ways, and a day doesn't go by when they are not in our thoughts."*

Some later chemical historian can measure Russell's impact on science by simply reading through and evaluating his many publications. We will do some of that ourselves in the next section. But, what was Glen Russell really like? Thirty years from now it is doubtful that there will be anyone living who really knew Glen Russell. These preceding pages are meant to show something of what Russell was really like. He was our professor, our mentor, and our lifelong friend. He was brilliant yet considerate, listened to our research ideas, and helped us think for ourselves. His was a life well-lived, and it had a powerful influence on our own lives. We believe that it also had a powerful influence for the better on the course of free radical chemistry.

Russell's Research

Glen Russell's first article was published in 1952 (*9*), and the last publication we can find has a date of 2001 (*48*). His free radical research begins in 1949, when he began working with Brown, so his research career was around 50 years.

Those 50 years pretty much coincide with the last half of the 20th century. Russell had well over 200 publications. We will be selective instead of comprehensive in our coverage of his research. We will focus on the main themes. Those themes originated early on and continued throughout his career. Furthermore, one can readily discern those themes, because the titles of his articles would often include a classification with a number. For example, a 1998 posthumous publication was titled "Electron Transfer Processes. Part 63. Reactions of p-Nitrobenzyl Halides with Dialkyl Phosphite Anions in Dimethyl Sulfoxide." (*49*). His series on semidiones was numbered into the 40's.

We will concentrate mainly on the early research. We will give a little more detail about the projects on which we worked. This is not because we think our research was more significant than that of any other Russell student, but the usual journal article is linear, wherein the workers start a project and carry it through successfully via obvious steps. End of story! Researchers know this is far from the usual case. There are all sorts of starts, stops, and side steps on a project, and the results often come from luck rather than design. Like the late Paul Harvey, we will give you "The rest of the story!"

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Early Research at Purdue and GE on Solvent and Polar Effects on Radical Reactions

Glen Russell's first paper (*9*) made it into a significant textbook quite soon. In the first edition of the classic text by Morrison and Boyd, the work of Brown and Russell on the chlorination of a deuterium-labeled isobutane was cited via an illustrative problem as demonstrating that free radicals had very little tendency to rearrange (*50*). In the second edition of the text, this result was expanded into a three page section about the lack of rearrangement of free radicals and on the utility of isotope labeling to study mechanisms (*51*). This discussion of the work of Brown and Russell continued to appear in later editions of the textbook.

That first paper from Russell's thesis was designated as Part I in the series "Directive Effects in Aliphatic Substitution" and told of his intent to do further investigations in "this little explored field." Three additional papers from his thesis, now with Brown as the second author, were numbers III, IV, and V in that series (*10*–*12*). (We have not been able to find a part II.) They described further studies of chlorination and bromination substitution reactions. They pointed out the need to consider polar effects on the transition states and intermediates in the free radical reactions and not just the strength of the C-H bond being broken. The bromination papers (see below) with DeBoer and Desmond in 1963 were numbers XVIII and XIX in the series.

At the General Electric laboratories, working with Frank Mayo, Russell became involved in the study of liquid phase autoxidation of hydrocarbons. These reactions are of great importance because many industrial processes are based on them. The mechanisms are especially difficult to study. This work shows Russell's ability to choose elegant experiments which simply but critically distinguish among mechanisms. He continued to publish under the Directive Effects heading. Paper VI, submitted from GE in early 1955, was a study of the

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competitive oxidation of cumene and tetralin, with Russell as the sole author (*52*). Here he observed that tetralin can serve as a retarder in the oxidation of cumene. Think about that for a minute. For the same amounts of initiator, tetralin is much more oxidizable than cumene, yet Russell found that small amounts of tetralin could actually act as a retarder. Russell showed that there was widespread generality to such an effect. Furthermore, he was able to unravel the complicated kinetics associated with four competing propagation reactions and three competing termination steps, an analysis that Keith Ingold regarded as an intellectual tour de force. He also concluded from rate constant data that the secondary peroxy radicals from tetralin terminated 500 times faster than the tertiary cumene peroxy radical. Prior to Russell's work it had been assumed that all peroxy radicals interact with one another at the same rate to terminate oxidation chains.

A series of papers in 1956 under the heading "Oxidation of Unsaturated Compounds" began with two papers by A. A. Miller and Mayo on the oxidation of styrene (*53*, *54*). Russell was the sole author on papers III and IV in that series, which examined the oxidation of indene with oxygen (*18*, *19*). These papers were followed by two additional papers on oxidation kinetics by Russell alone (*20*, *21*). The latter of the two looked at the relative reactivities of a series of aralkylhydrocarbons toward peroxy radicals. Data were tabulated for 32 hydrocarbons having a 1000 fold difference in reactivity. The differences were attributed to differing radical stability but also to polar effects on the transition states of the propagation steps. A communication in *Chemistry and Industry* in 1956 (*55*) and Paper IX in the Directive Effects series, published in 1957 (*56*), described results of a study initially presented at an ACS meeting in the fall of 1956. The conclusions from that study were a major contribution to understanding autoxidation chemistry. Russell suggested that the termination reaction of secondary peroxy radicals involved two radicals coming together, most likely in a cyclic transition state or an actual intermediate, which then collapsed to the observed products: ketone, alcohol, and oxygen. This elegant study using deuterium-labeled cumene and ethylbenzene explained why secondary peroxy radicals terminated much more rapidly than tertiary peroxy radicals, where there was no possibility of transfer of an alpha H. The postulated mechanism is now known as the Russell mechanism (Figure 15).

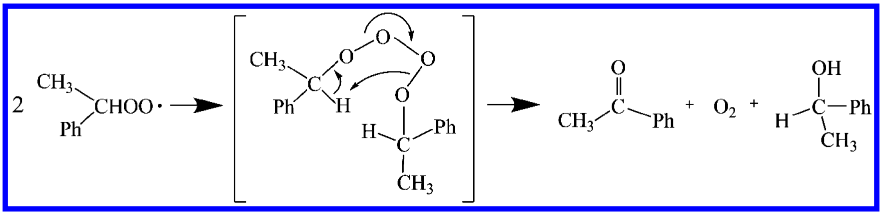

Figure 15. The Russell Mechanism.

Russell also continued to illuminate aspects of free radical halogenation while at GE. He was able to show that confusing data about relative rates of hydrogen abstraction by various radicals could be understood in terms of a theory invoking polar effects in the transition state for hydrogen abstraction. He made the dramatic discovery that different solvents can drastically alter the position of attack of chlorine atoms on a branched chain hydrocarbon. This was first reported in a communication (*22*) and then followed up in a series of papers (*57–62*). Russell observed that electron rich aromatic solvents had the ability to change the orientation of substitution and suggested that this was due to formation of a pi complex with the Cl atom. The complexed atom is then able to be more selective in abstracting hydrogen atoms, favoring tertiary over primary halogenation to a greater extent than was observed for an uncomplexed Cl atom. Solvents like carbon disulfide could form sigma complexes with the Cl atom, which also modified the selectivity of substitution.

Russell's lecture entitled "Solvent Effects in Free Radical Reactions" at the Reaction Mechanisms Conference in 1958 created a great stir. Before that time, many texts and references stated that the absence of solvent effects was strong evidence for a free radical mechanism. Russell was one of a very few industrial chemists to have been invited to speak at the Reaction Mechanisms Conference, and he was invited to lecture again at the 1966 Conference. He was only the third person at that time to have been invited twice. The other two were George Hammond (Norris Award 1968) and Paul Bartlett (Norris Award 1969).

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Early Work at Iowa State on Solvent and Polar Effects on Radical Reactions

Russell would continue to explore solvent and polar effects on radical reactions during his early years at Iowa State. In 1963 Russell and Bob Bridger published a monumental study of the reactivity of a large variety of C-H bonds toward the phenyl radical, a classic that has become a standard in the field of homolytic substitution (*63*). This was Part XXIII in the Directive Effects in Aliphatic Substitution series. Sadly, Bridger died suddenly after a short time at the Mobil Research Laboratories in Princeton, NJ. Dale Hendry, another early member of the group, did extensive studies of the solvent effects in oxidation and chlorination reactions (*64*, *65*). He also passed away at a young age while working at Stanford Research Institute. Additional work in this area was also carried out by Russell student Roger Williamson (*66*, *67*).

Russell reviewed much of the work on free radical substitution reactions in a comprehensive chapter in the book *Free Radicals*, edited by Jay Kochi (*68*), who had worked with Hammond in the same labs that Russell used at Iowa State. The chapter is titled "Reactivity, Selectivity, and Polar Effects in Hydrogen Atom Transfer Reactions" and contains 220 references to research done through 1971.

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The NBS Story

As mentioned earlier, in the fall of 1960 the Russell group was all male. I (then Kathleen Desmond) arrived in Ames that fall with the intention of getting a Masters degree. All the forms had only two categories for MS students, MS Prerequisite for those in academic difficulty, MS Terminal for those who failed courses or prelims, and would not be allowed to go on for the Ph.D. I crossed those out and added MS By Choice whenever I could. The idea of five years in Iowa was not appealing. Fifty-five years later I am still in Ames.

I was assigned to Russell as an advisee and chose to stay in his group. When it was time to start a research project, Russell suggested that a study of the reactivity of the succinimidyl radical (NS), the presumed chain carrier in free radical bromination by NBS (N-bromosuccinimide), would be an appropriate masters project and would fit in with the other radical reactivity studies being done in the group. At the same time a bright undergraduate, Chuck DeBoer, had signed up to do research with Russell. He was placed in a different lab and given another well-defined problem to work on, the relative reactivities of benzylic hydrogens in photobromination, also a free radical substitution reaction. At that time, the mechanism of the NBS reaction was widely assumed to involve abstraction of an allylic or benzylic hydrogen by the succinimidyl radical as the rate determining step, with chain propagation following by the aralkyl radical reacting with NBS to give the brominated product and a new NS radical.

At my small undergraduate school, Emmanuel College in Boston, there had not been an opportunity to do laboratory research, so my experimental skills were not strong. Initially my "big brothers" in the lab would check to see if my clamps were tight enough or my rate of heating things was appropriate, but they soon relaxed and let me work on my own. The NBS reaction was very simple. The reaction is initiated by visible light, so all I needed was an ordinary light bulb. The solvent we used, methylene chloride, boils at 40 C., and refluxing in it provided a constant temperature. The insoluble, solid NBS is more dense than the solvent, and the insoluble, solid succinimide is less dense than the solvent. Consequently, the progress of the reaction is visually apparent as the solid on the bottom dissolves and a new layer of solid appears on the top. The relative rates of disappearance of reactants in competitive reactions were calculated using data obtained from gas chromatography. A planimeter was used to manually measure the areas of the peaks before and after reaction, and these were related to areas from standard solutions to get initial and final concentrations of the competing hydrocarbons. It sounds primitive now, but the results were highly reproducible. The biggest challenge was sharing the one planimeter in the group.

DeBoer and I used the same experimental approach to our respective problems, *i.e.*, the study of the relative reactivities of toluene, ethylbenzene, cumene, and diphenylmethane in competitive reactions, but we worked in separate laboratories and had limited contact with each other. It was customary for students to rotate presentation of research results at weekly group meetings. When the time came for Desmond and DeBoer to present, much to our surprise, we reported relative reactivity numbers that were essentially the same for both NBS and bromine. This meant that the rate determining step in both cases

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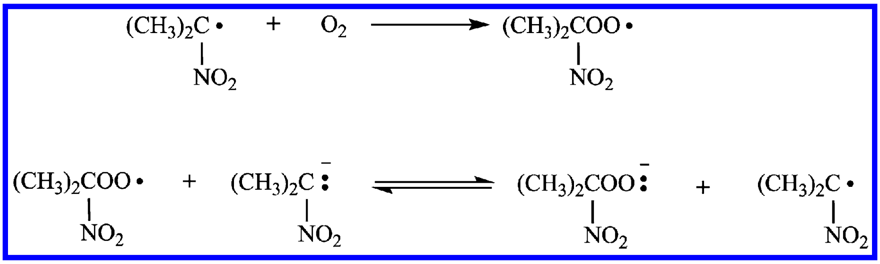
probably involved hydrogen abstraction by the bromine atom. Apparently even traces of moisture or HBr, which is very hard to remove from the NBS, can lead to the formation of very small amounts of molecular bromine, and photobromination is then initiated. The HBr formed in each H abstraction can then lead to more bromine and propagate the chain reaction.

My college background may not have been heavy in experiment, but I was taught the value of a good literature search. So, I looked back at earlier studies of NBS bromination. The succinimidyl radical pathway had been proposed by Bloomfield (*69*) as a reasonable explanation of the reaction. It looked quite sensible on paper, but there was no direct evidence for a succinimidyl radical. A bromine atom mechanism had been suggested by Goldfinger (*70*), but most researchers and textbook writers ignored that possibility and continued to assume that the succinimidyl radical mechanism was correct. Our conclusion made even more sense in light of studies which showed that in reactions of alkenes with bromine in the presence of light, very low concentrations of bromine favored allylic substitution, a probable free radical substitution, while higher concentrations lead to addition (*71*, *72*).

At a meeting, Russell discovered that J. C. Martin, a young assistant professor at Illinois, was doing a study of the relative reactivities of a series of substituted toluenes, with NBS and bromine. His results were also leading to the conclusion that bromine atom was the hydrogen abstracting agent. Russell and Martin agreed to submit articles for simultaneous publication. Communications to *JACS* were published in early 1963 (*73*, *74*). The full *JACS* papers later that year were part of a series where the lead article was by Cheves Walling and co-workers, who were also studying NBS reactions (*75–78*). Walling stated that their results agreed with other recent work in supporting the conclusion that a Br atom chain is the most plausible mechanism for NBS bromination. In a footnote in his paper, Walling said, “We wish to acknowledge that Martin’s and Russell’s results were made available to us prior to publication and led to revision of some of our tentative conclusions.” Since that time, all major organic chemistry textbooks have presented the Br atom mechanism as the way to explain benzylic free radical bromination of aralkyl hydrocarbons by NBS.

Oxidation of Carbanions

Russell’s second and third published papers were submitted from GE and dealt with the oxidation of anions (*79*, *80*). The second of these was a study of the oxidation of 2-nitropropane in basic solution. There had been suggestions that some carbanion oxidations had a free radical nature, but they often occurred too rapidly for mechanistic studies. Russell thought that use of a resonance stabilized anion would moderate the rate and allow for closer study. He concluded that the reaction did involve a free radical mechanism proceeding by an ion-radical chain with a hydroperoxide intermediate. He observed autocatalysis, an induction period, and inhibition by standard free radical inhibitors, all hallmarks of free radical chain reactions. His suggested mechanism proposed a one electron transfer between a peroxy radical and the resonance stabilized anion to start the chain process (Scheme 1).



Scheme 1. Russell's suggested chain reaction.

Tony Moye was Russell's first graduate student at Iowa State, and he took up the study of the oxidation of resonance stabilized carbanions along with post-doc Nagpal (*81*). It was difficult research, because radical anions were rapidly quenched in most solvents; and the evidence for free radicals was indirect. By the time Moye was leaving in 1960, two remarkable advances had become available: one in instrumentation, ESR; one in solvent chemistry. DMSO, otherwise known as dimethyl sulfoxide.

Edward Janzen continued the study of base catalyzed oxidations after Moye's departure and had constructed a device to maintain constant oxygen pressure (*82*). Ed relates that Russell had returned excited from a conference in California, where Donald Cram reported spectacular results with a new solvent called DMSO (dimethyl sulfoxide) (*83*). The compound was not yet commercially available, but Ed remembered seeing an advertisement from Crown Zellerbach offering free samples of the compound. When the compound arrived and was used by Janzen, his oxidations went way too fast to be followed with his equipment. He finally moderated the process by using a mixture of 80%-DMSO/20%-t-butyl alcohol, with potassium t-butoxide as the base. This allowed for kinetic measurements, and this mixture was used by many Russell students for ESR experiments. Some of this oxidation work appeared first as a communication (*84*). This publication also reported initial work with the anion derived from DMSO. The methyl sulfinyl carbanion had been reported by Corey and Chaykovsky (*85*), but the carbanion had been synthesized independently and likely earlier by Janzen. Much of this early carbanion oxidation work plus some electron transfer work appeared in 1965 in a long article in the ACS Advances in Chemistry series (*86*). This topic was revisited in 1966 (*87*), 1967 (*88*), and in another long ACS Advances in Chemistry article in 1968 (*89*).

The Semidione Story

The radical anions for which Russell coined the name "semidione", anion radicals of alpha diketones, were studied as part of Russell's program on electron transfer reactions. Electron transfer deserves a section of its own (see below), but so do semidiones. I (Tom) made my big discovery in August, 1963, just when I was

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finishing up the writing of my thesis. As a consequence, my thesis was expanded by about a third.

The electron transfer reactions studied involved transfer of an electron from an anion or dianion to an electron acceptor. The progress of electron transfer was monitored by ESR by measuring the growth of electron acceptor anion radical . Using present day language, you would want your electron acceptor to have a low energy LUMO and for the ensuing radical to be stable for quite a while. Quinones would certainly be expected to be good electron acceptors in view of the stability of their one electron reduction products, semiquinones (Figure 16). However, I was against using the alpha diketone cousin of the quinone as an electron acceptor, because of a prejudice I had developed during my literature search. I found in a paper that researchers had reduced diacetyl (2,3-butanedione) under basic conditions and found they had formed 2,5-dimethylbenzosemiquinone, clearly from a dimeric condensation. I jumped to the conclusion that any anion radical of a 1,2-diketone that had alpha hydrogens would probably undergo condensation reactions. Nevertheless, I did synthesize a number of acyloins (alpha hydroxyl ketones). It seemed that oxidation of the acyloins in DMSO might give the anion radical of the alpha diketone as an intermediate. I was unsuccessful in most of those attempts; and I still don't know why, because we now know that acyloins are the prime intermediate from which to form semidiones. Following my belief that alpha hydrogens should be avoided, I did synthesize the appropriate acyloin lacking alpha hydrogens, 4-hydroxy-2,2,5,5-tetramethyl-3-hexanone. Oxidation in the 80%-DMSO/20%-t-butyl alcohol solvent gave the anion radical of the di-t-butyl alpha diketone (Figure 17). Later on, I was able to optimize conditions to synthesize purely alkyl semidiones containing alpha hydrogens (*90*).

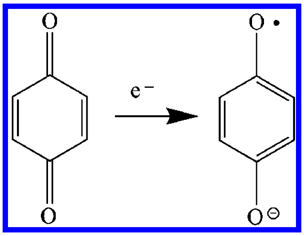

Figure 16. One electron reduction of p-benzoquinone to give the semiquinone.

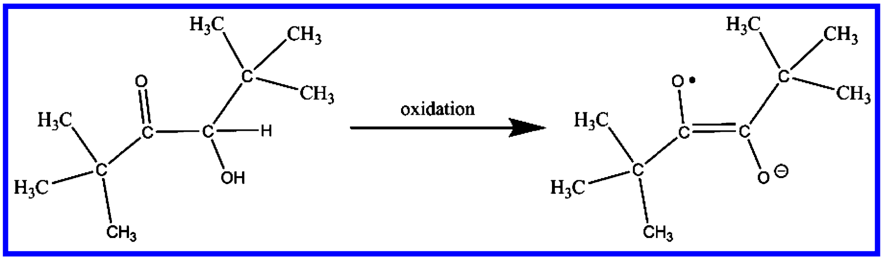

Figure 17. Oxidation of the acyloin to give the di-t-butyl semidione.

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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If one wants to shun alpha diketones with alpha hydrogens, then the obvious thing to do is to substitute them with benzene rings. There were precedents to indicate that such compounds might undergo electron transfer reactions to give anion radicals. Michaelis and Fetcher had clearly shown that the purple colored intermediate in benzoin-benzil mixtures was the benzil anion radical (*91*). Buried in the experimental details from an early Fraenkel group publication was the information that they had synthesized the benzil anion radical (*92*). About the time of our work, the Fraenkel group published an ESR paper on benzil anion radical (*93*), while Luckhurst and Orgel published ESR data on benzil anion radical and the di-t-butyl semidione (*94*). My literature search indicated that the heteroaromatic analogues probably could be oxidized to give free radicals. Fischer found that 2,2′-furoin gave a blue color (*95*), while Cardon and Lankelma observed that 2,2′-thenoin gave a green color (*96*). When I carried out ESR experiments on these systems, the anion radicals from these two systems were observed (Figure 18). This work was published several years later as Part II of the Russell Semidione series (*97*).

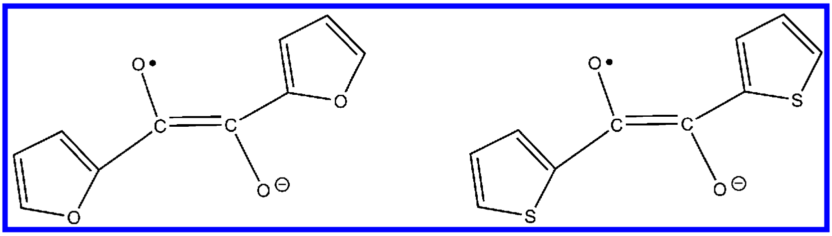

Figure 18. Anion radicals (semidiones) of 2,2′-furil (left) and 2,2′-theril (right).

I finally overcame my prejudice against alpha hydrogens when Aldrich Chemical Co. offered a new compound for sale that was an acyloin, 2-hydroxycyclohexanone. I reasoned that the structure of the likely product, the 1,2-dione, was unlikely to give an alpha condensation, so it was worth a try. I used our normal solvent mixture of 80% DMSO/20% t-butyl alcohol with potassium t-butoxide as the base, and I was rewarded by seeing a 1:4:6:4:1 quintet, with a 9.82 gauss splitting, The five peaks clearly were from the four alpha methylene hydrogens in the anion radical of 1,2-cyclohexanedione. I bought 4-t-butylcyclohexanone to see what would happen if the ring were locked. In this case, since there was no longer an oxygen alpha to the carbonyl, I bubbled oxygen into the system to ensure a surplus of oxygen. The ESR spectrum obtained consisted of seven peaks from two kinds of alpha hydrogens, with splittings of 13.10 gauss from two hydrogens and 6.55 gauss from two hydrogens. Note that their average is equal to the splitting from the unsubstituted compound. These two spectra are shown in Figure 19. Any reasonable picture of hyperconjugation dictates that the larger splitting must come from the pseudo-axial protons and the smaller splitting from the pseudo-equatorial protons. Of course, the t-butyl group removes the symmetry element from the radical, so those two axial-type protons can’t be exactly equal nor can the two equatorial-type protons. However, the resolution of the system wasn't sufficient to pick up these differences. I applied the Heller-McConnell equation (*98*) to calculate the angle of these protons with the free radical site, getting a value of 13 degrees for the axial hydrogens. This was close to the value calculated for the axial bond angle by nmr for cyclohexene (*99*), suggesting that the cyclic semidiones might model the corresponding cyclic alkenes.

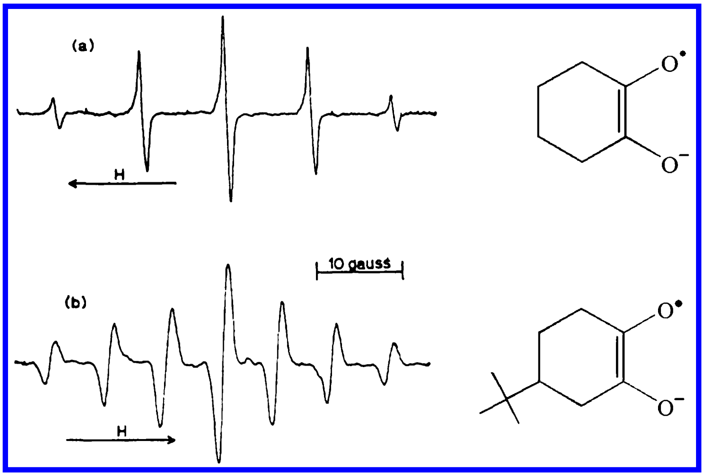

Figure 19. ESR spectra of (a) 1,2-cyclohexanesemidione and (b) 4-t-butyl-1,2-cyclohexanesemidione.

Because of this encouraging result, I ordered every cyclic ketone that Aldrich had on hand. I studied the five, seven, eight, nine, ten, twelve, and fifteen membered rings. All of them appeared to give semidione radicals. They all seemed to have alpha methylene splittings, and some, not all, showed two kinds of alpha protons, consistent with one favored conformer. This work was published as a communication with the radicals called alicyclic semiquinones and with the conformational aspects emphasized (*100*). Russell later called this his first semidione publication, although he had not yet coined the name. I also had found that acyl benzenes could be oxidized to give phenyl alkyl semidiones. The paper from that work received the designation Semidiones I (also Reactions of Resonance Stabilized Anions XXI) (*101*). The series reached its climax with paper No. 44, published in 1985 (*102*). Some of the early ways of forming these radicals are summarized in Figure 20. (The symbol B^P stands for potassium t-butoxide.) Russell reviewed much of this work at a fairly early stage (*103*, *104*).

We will not cover all those 44 publications. Instead we will briefly mention four interesting paths. Any simple HMO calculation for a semidione will give a significant bond order for the carbons in the LUMO. Russell and Stephens found that aliphatic semidiones occurred in both cis and trans forms (*105*). As would be expected, the trans was favored, but the balance could be shifted toward the cis via ion pairing.

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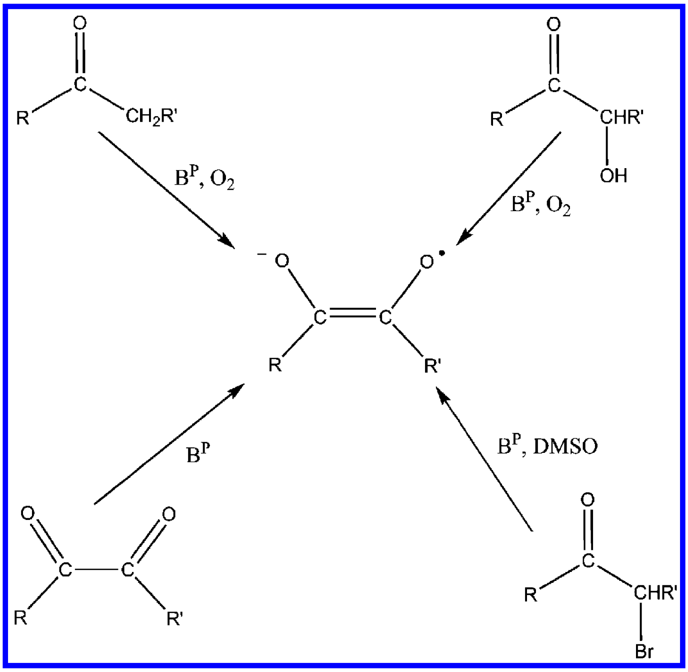

Figure 20. Early synthetic methods for forming semidiones.

With the importance of many steroidal ketones, this was an area ripe for exploration by ESR. A very talented post-doc named Erach Talaty joined the group. His research was part of a new Russell series called "Application of Electron Spin Resonance Spectroscopy to Problems of Structure and Conformation." Russell and Talaty explored simpler fused ring systems such as decalones as well as steroids (*106*, *107*). They were able to obtain useful information on the A/B junction, and they later investigated aspects of the D-ring ketones (*108*).

Bicyclic semidiones proved an additional fruitful area for research. Russell's student K.-Y. (Leo) Chang initiated this work (*109*, *110*). In my original communication, I had reported a 2.66 gauss splitting from the oxidation of camphor, which appeared to come from three protons. I guessed it was from the 7-syn-methyl group, but I was wrong. Leo found that this splitting had come from the single bridgehead proton plus the two exo protons from across the ring, all three protons accidently having the same splitting constant. The surprising result was the large splitting from the exo protons. There are three single bonds between exo protons and the radical site. The exo protons, however, are perfectly aligned for a W or zigzag arrangement, which transmits the spin information across the gap. Figure 21 shows the results from the simpler bicyclo[2.2.1]heptane-2,3-semidione (*109*). Note the large 6.35 gauss splitting constant from the 7-anti-H, also in a W alignment with the radical site. Russell extended this work to many different bicyclic systems.

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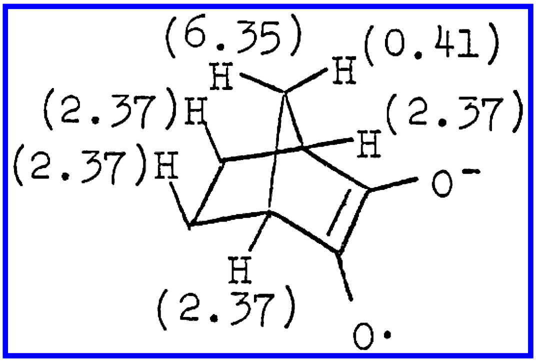

Figure 21. Proton splitting in bicyclo[2.2.1]heptane-2,3-semidione.

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The conditions under which I synthesized that first group of cyclic semidiones left much to be desired. My use of large amounts of oxygen caused line broadening when the paramagnetic oxygen molecule underwent spin exchange with the semidione. My results for the 5- and 6-membered rings hold up fairly well, but things become more complicated from the 7-membered ring on up. Long range interactions can start to show up, and for very large rings both cis and trans semidione isomers can exist. For example, consider the 7-membered ring. I found splittings of 6.70 gauss and 1.97 gauss from two pairs of protons. I interpreted the spectrum as coming from two axial-type alpha hydrogens and two equatorial-type alpha hydrogens in a single preferred conformation. Well, the large splitting came from two axial-type alpha hydrogens all right, but later work showed that the 1.97 gauss splitting came from two equatorial-type **beta** hydrogens! Go figure. Russell soon realized the potential complications present in the conformations of large rings, so he started the systematic reinvestigation of all of these systems. Russell, Keske, and coworkers looked at the 7-membered ring system again (*111*, *112*). When they carried out deuterium exchange reactions on the alpha hydrogens, they found that the 1.97 gauss splitting (now refined to 2.05 gauss) remained. They deduced that this splitting came from the beta equatorial hydrogens, now aligned in a trans arrangement which allowed for a strong W-type coupling. Their conclusion was that the seven-membered ring system had the pseudo-chair conformation.

Russell and coworkers next investigated the 9-membered ring semidione (*113*, *114*). They found that the parent compound existed as the cis isomer with a pseudo-chair conformation. However, for some of the derivatives, the trans compound became an important competitor. Russell, Osuch, and Suleman then examined the macrocylic rings from C-11 to C15 (*115*, *116*). Here at last the trans isomer could be observed as well. With potassium ion present, the cis isomer was favored, but with a cryptand to complex the potassium ion the trans isomer was readily detected.

Elsewhere in this volume, Keith Ingold mentions the various descriptions of free radicals, discussing the terms “stable,” “transient,” and “persistent.” Ingold felt that the word “stable” should be confined to radicals that could be “put in a bottle.” By this criterion, semidiones could be described as persistent if not stable. Although there were exceptions, the semidiones generally stayed around in the

ESR cell for many minutes. In view of the synthesis a few years ago of potassium benzophenone ketyl and potassium naphthalenide (*117*), we would hate to say that semidiones could not be made in a stable form. However, just in their persistent form they provided a source of chemical riches for the Russell group for 20 years.

Electron Transfer

Fortunately, Russell did write down an overview of his early work on electron transfer sometime after 1982 plus more material about his later work in Jan., 1993, but these write-ups are very terse (*118*). Consequently, our discussion of this work will rely mainly upon the recollections of Ed Janzen (*119*) and Tom Strom along with our analysis of the early publications in this area.

Russell himself considered his 1954 paper on the autoxidation of 2-nitropropane to be his first paper concerning electron transfer (*80*). However, this work really got started in 1962. Ed Janzen was working on the oxidation of carbanions, while I (Tom Strom) was working on making various anion radicals. Russell thought that the oxidation process possibly entailed the transfer of an electron to the oxygen molecule. Janzen felt that proof could be obtained by using an organic catalyst to accept the electron. Ed suggested using nitrobenzene, as its radical anion was stable and could be readily detected by ESR. Russell was dubious about this, but Ed went ahead and did the experiments anyway, using the hydrocarbon fluorene as the carbanion source after ionization with potassium t-butoxide. The ESR experiments showed that nitrobenzene anion radical was present, and oxidation rate experiments with fluorene demonstrated that nitrobenzene greatly enhanced the uptake of oxygen. The publication from part of this work has been referred to before (*82*). Probably it should have been referred to as “Electron Transfer. II,” but Russell labeled it as “Reactions of Resonance Stabilized Anions. II.”

Janzen followed up this work with a truly spectacular example of electron transfer. When a solution of p-nitrotoluene was treated with potassium t-butoxide in t-butyl alcohol under a nitrogen atmosphere, first a yellow color was observed, possibly the carbanion, followed by the development of a blood red color in tandem with the growth of the ESR spectrum of p-nitrotoluene anion radical. The conclusion seemed inescapable that the carbanion transferred an electron to unionized p-nitrotoluene. This work was published as a communication in 1962 (*120*) with the full paper following years later (*121*).

That same year I (Tom) had been drafted to work on electron transfer reactions. It looked like an interesting area which would use my growing skills in ESR, so I was glad to participate. It appeared that the electron transfer process as studied thus far would be irreversible, but Russell thought that reacting di-anions from a dihydro derivative of an unsaturated compound **with** the unsaturated compound, for example, benzoin/benzil, hydrazobenzene/azobenzene, would give two of the anion radical intermediates in an equilibrium process, with the equilibrium possibly lying to the right. The two kinds of processes are shown below in Figure 22. Ed and I studied a variety of the dihydro π compound/π compound systems, the type shown in Figure 22b. We found that for a number

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of the systems the ESR experiments showed that the equilibrium was well to the right (*122*). The experimental procedure involved making up solutions of the dihydro compound and its π parent in separate reservoirs, purging the reservoirs of their oxygen, sending the separate solutions through flow tubes to a mixing chamber, and then sending the mixture to the cell in the ESR cavity. Russell was pleased with these results, and he wanted us to delineate the scope of the reaction using mono carbanions, the system described in Figure 22a. He wanted us to use lots of carbanions and lots of π acceptors. Our previous system had used copious amounts of chemicals and even more DMSO. We needed to speed things up and scale them down.

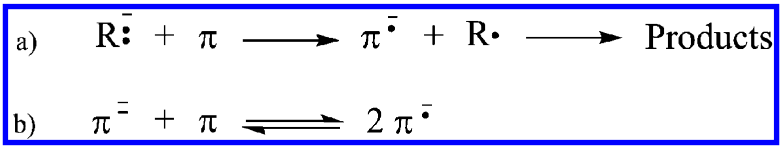

Figure 22. Electron transfer to unsaturated systems (Π) with (a) mono-anions or (b) di-anions.

Working together we designed the H cell (*119*). The cell consisted of two small glass chambers connected at the top with a glass bridge. The top of each chamber had a small 6 mm opening which could be plugged with rubber septa. A small pierced glass joint at the top of the bridge was made to fit the top of the ESR cell. The desired chemicals were weighed and along with solvent were transferred into the two chambers through the small openings, the rubber septa closed the openings, the septa were both pierced with hypodermic needles attached to tubes from a cylinder of pre-purified nitrogen, and nitrogen was slowly bubbled through the two chambers, with the gas being vented through the bottom of the ESR cell attached through the glass joint. When the system had been sufficiently purged of oxygen, the needles were pulled out of the septa, the bottom of the ESR cell was plugged, and the contents of the two chambers were mixed and shaken down into the ESR cell. It was possible to observe ESR spectra within a very few minutes after mixing.

To keep track of the progress of the work, we made a chart similar to a Sunday School attendance chart, with electron donors on one axis and electron acceptors on the other. Those experiments that were successful got a gold star. Tom remembers that Russell took his farewell photo of Tom with that chart.

The results of this work were published in 1964 (*123*), and a few years later the Institute for Scientific Information designated it as a Citation Classic, one of the most cited papers ever in its area. However, the article was almost turned down. We had covered so many systems, about 40 carbanions and about a dozen π acceptors, the latter ranging from ketones to azo compounds to nitro compounds to hydrocarbons, that the paper was almost all data and little interpretation. The referees felt the paper was "too diffuse" and were equally balanced between acceptance and refusal. Fortunately, Russell had given a talk on this work at the University of Rochester during that time, and *JACS* editor Marshall Gates was in the audience. After the talk, Gates came up to Russell, telling him, "Now I

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know what you've been doing." Consequently, the editor came down on the side of acceptance.

A later paper previously mentioned in connection with hydrocarbon oxidation also had a large component involving electron transfer to nitro compounds (*88*). Shortly thereafter, Russell published an additional article in which azo compounds and their dihydro derivatives were the π acceptors and di-anion donors (*124*).

When Janzen and Strom received their degrees and left Iowa State, additional significant electron transfer research was carried out by Ed Geels (*125*, *126*). He found that a deoxygenated mixture of nitrosobenzene and phenylhydroxyamine gave an essentially quantitative yield of nitrosobenzene anion radical in the 80%DMSO-20%-t-butyl alcohol, with potassium t-butoxide as the base. If the experiment was carried out in ethanol, up to 96% of azoxybenzene could be isolated.

This next example of electron transfer research should be prefaced by an incident Tom remembers from a group meeting sometime in 1963. Joseph Schoeb was giving a talk to the group on Nathan Kornblum's work on O- versus C-alkylations. Russell got up during the talk and very animatedly pointed out that the presence of a nitro substituent in any of those reactions might mean that an anion radical was operative in those mechanisms. After the meeting Joe said he had thought "Russell has lost his marbles." No, Russell hadn't! He had had a flash of insight, which he shared with the group, albeit in a loud voice with rapid speech. The timing is significant, because in 1964 and 1965 the Kornblum group at Purdue published work about the involvement of radical anions in the carbon alkylation of nitroparaffin salts (*127*, *128*). Clearly Russell had come up with the idea independently. He put Wayne Danen to work on the problem, and two significant publications followed (*129*, *130*). He later returned to several studies of this type, which he later classified as examples of Joe Bunnett's $S_{RN}1$ mechanism.

Russell looked at other electron transfer processes throughout his career. He examined the reactions of alkyl lithiums with alkyl halides, of titanium tetrachloride with alkyl lithiums, of alkyl mercury chlorides with nitro-substituted carbanions, and more. The study of electron transfer for him was a lifelong quest, but we will stop our analysis of his quest here.

Research on Organic Synthesis

The basic DMSO system also had synthetic utility, and post-doc Hans Dieter-Becker and graduate student Gary Mikol, later joined by others, made many contributions in this area, examining condensations between the DMSO anion and aldehydes, ketones, esters, etc. (*131*). Condensations with aromatic esters gave beta keto sulfoxides. In mild acids these underwent the Pummerer rearrangement to hemimercaptals of alpha keto aldehydes, which behaved like typical glyoxals (*132*). This sequence provided a short, inexpensive route to ninhydrin from ethyl phthalate (*133*). Hans Dieter-Becker characterized his discovery in this way. *"I got a little of the white product on my hands, and I saw ninhydrin!"* Ninhydrin gives a purple color on contact with peptides and proteins.

A variety of conversions were studied where a sulfur functional group was retained (*134*). A series of transformations giving sulfur-free products provided a method for extending the carbon chain by alkylation at the alpha carbon atom (*135*). A number of papers in 1969 and 1970 described additional chemistry of the beta keto sulfoxides (*136–142*).

The Exploration Comes to an End

After the death of Russell, his last graduate student, Chen Wang, completed his degree with the guidance of Walter Trahanovsky. The last publication with Russell as a coauthor appeared in 2001.

We chose for the first part of the chapter title the phrase "Exploring Free Radicals," and what a glorious 50 years of exploration it was. Remembering we were writing a chapter and not a book, we tried to be selective and not comprehensive. We dealt mainly with Russell's early themes of research, and usually we did not follow those themes too far forward in time. Perhaps some future chemical historian will explore these research themes fully. We were grateful for the opportunity to learn how to do research from Glen Russell, and physical organic chemistry is the richer for Russell's body of work.

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Acknowledgments

We were grateful to be able to provide a chapter on Glen Russell as part of this volume on great physical organic chemists, a group to which Glen Russell clearly belongs. First and foremost, we thank Susan and June Russell, his daughters, for sharing their memories, photos, and other memorabilia with us. We acknowledge the utility of the Russell Archive in the Special Collections Department of the Iowa State University Library. The archive was also the source of that fine early photo of Russell that served as our Figure 1. The archive allowed us to read important correspondence written to and by Russell. We thank Vera Mainz for her invaluable assistance in formatting this chapter and in preparing the figures to be included.

We are grateful for Edward Janzen's reading and commenting on all sections of this chapter as it was being prepared. Janzen's memoir of his time in the Russell group was both a source and an inspiration for us. We are pleased to learn that volume 3 of his memoirs has been completed and is now in the publishing process.

We thank Keith Ingold and Henry Shine for carefully reading this chapter and pointing out the errors they found. Any remaining errors are clearly our fault. For answering our questions, sharing recollections, and assisting in other ways, we thank the following people: Al Bemis, Ron Blankespoor, Ed Geels, John Gerlock, Keith Ingold, Ed Janzen, Roy King, George Olah, Kirk Schmitt, Henry Shine, Andy Streitwieser, Naushadalli Suleman, James Tanko, and Walter Trahanovsky. We are grateful to Tim Marney of ACS Books for agreeing to the submission of this chapter and to Bob Hauserman of ACS Books for facilitating the rapid completion of this chapter.

Last but by no means least, we thank our respective spouses, Walter Trahanovsky and Charlotte Strom, for their encouragement and patience during our completion of this chapter.

The task of a historian of chemistry is to somehow help the reader make sense of an area of chemical history and learn about the chemists involved. We hope this chapter will enlighten the reader about the history of free radical chemistry. We also hope that the reader will be convinced that one of the seminal figures of 20th century free radical chemistry was Glen A. Russell.

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Chapter 7

Norbornyl Cation Isomers Still Fascinate

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The proposal by Winstein and Trifan that the 2-*exo*-norbornyl cation has a bridged, non-classical structure initiated a number of investigations into this system. In 1962, H. C. Brown entered into the fray by proposing a pair of rapidly-equilibrating cations and steric effects as alternative explanations. The 2-norbonyl cation was investigated via rate studies, nmr experiments, theoretical calculations, and other methods over a number of years by a number of workers. While the X-ray determination of the 2-*exo*-norbornyl structure by Scholz et al. (*Science*, **2013**, *341*, 62) brought long overdue closure to the vituperative structure controversy, this chapter summarizes other remarkable issues currently engaging research groups worldwide. Unexpectedly, Duncan et al.'s gas phase protonation of norbornene gives the 1,3-dimethylcyclopentyl cation, the C_7H_{11}+ global minimum. Merino et al.'s molecular dynamics simulations reveal many acyclic as well as monocyclic intermediates along the reaction pathway. Finally, the 2-*endo*-norbornyl cation also has a bridged minimum, but "leakage" to the 2-*exo* cation has a very low barrier. This bridging of the 2-*endo* cation explains products found from the reaction of α-pinene with acetic acid. Thus, even at this late date, norbornyl cation isomers still fascinate.

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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Introduction

We truly wish that this Introduction were being written by Paul Schleyer (Figure 1), but, sadly, Paul passed on before completely transforming his talk from March, 2014, at the Dallas Symposium on the Norris Award into a written chapter for this book. We had provided Paul a written transcript of his talk with which to work. In his message to us of July 15, 2014, he noted that his talk "needs extensive stylistic editing to refine oral into written English." In his last message to us on Nov. 19, 2014, he stated that he planned to finish work on it the very next week; but then he passed on two days later. He certainly had begun the process of revision, but there was still more to be done. We have undertaken to finish the effort that Paul started. Elsewhere in this book you can read Paul's unfinished memoir as edited by Andrew Streitwieser and decide for yourself whether we have captured Paul's authentic writing style.

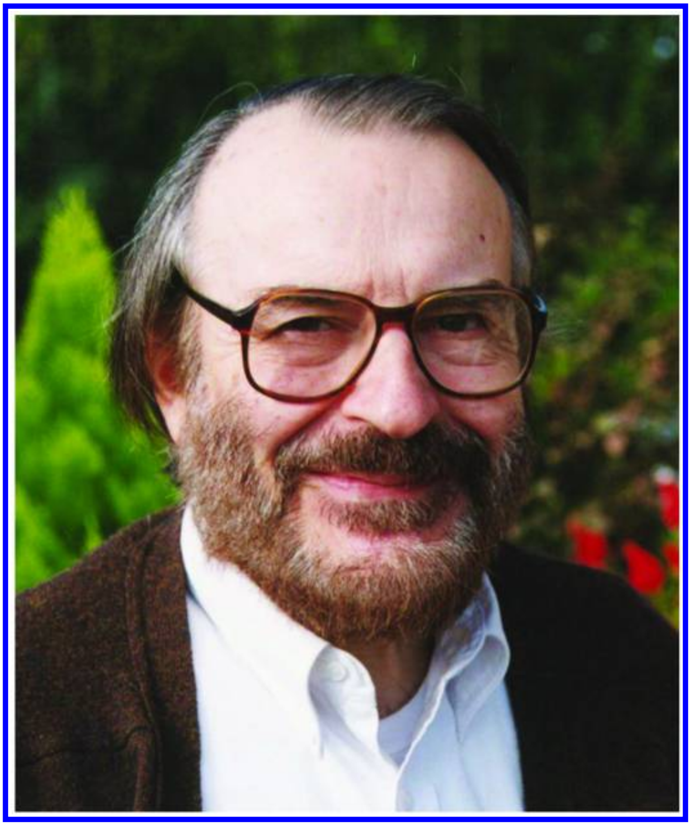

Figure 1. Paul von R. Schleyer. (Photograph courtesy of István Hargittai).

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

Our revisions included constructing an abstract, correcting non-fluencies, inserting a sentence or so to improve clarity, providing figure captions, and finding the references Paul cited incompletely in his text. We have done our best to capture the essence of Paul's analysis of this fascinating norbornyl cation research. In a very early e-mail message to us (April 12, 2014), Paul stated "My talk reported on research primarily by others (my participation was minor)---". We think otherwise. We think Paul was a significant actor in the norbornyl cation problem. This chapter may not be the last word on the topic, but it is Paul's last words on the matter and as such is well worth reading.

Overview

It is appropriate that somebody should talk about the norbornyl cation on the 50th anniversary of the founding of the James Flack Norris Award. A search of Web of Science under "norbornyl" (Figure 2) shows the yearly progression of the citations. Astonishingly, today there are still a thousand citations per year for the word norbornyl. These citations include the cation and a few other things.

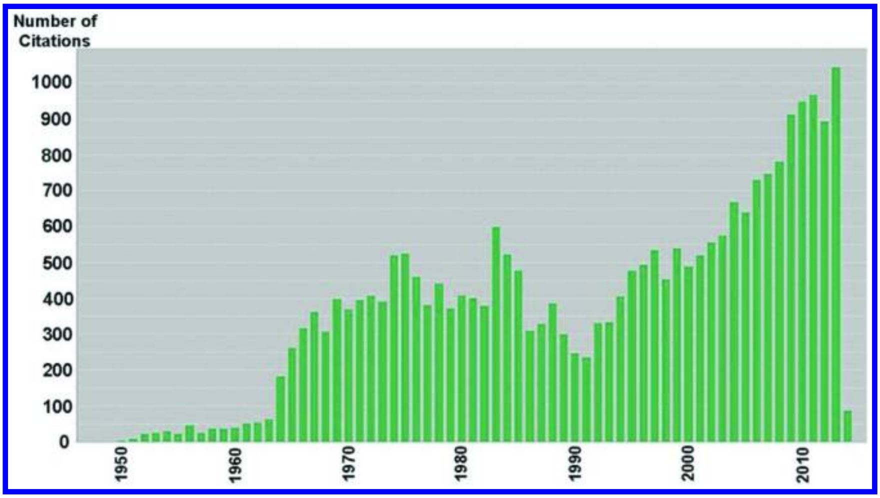

Figure 2. Web of Science: Number of "norbornyl" citations per year.

If you search for "norbornyl cation" you will also find a goodly number of citations (Figure 3). More than half of the hits for norbornyl are due to the norbornyl cation. It is still with us.

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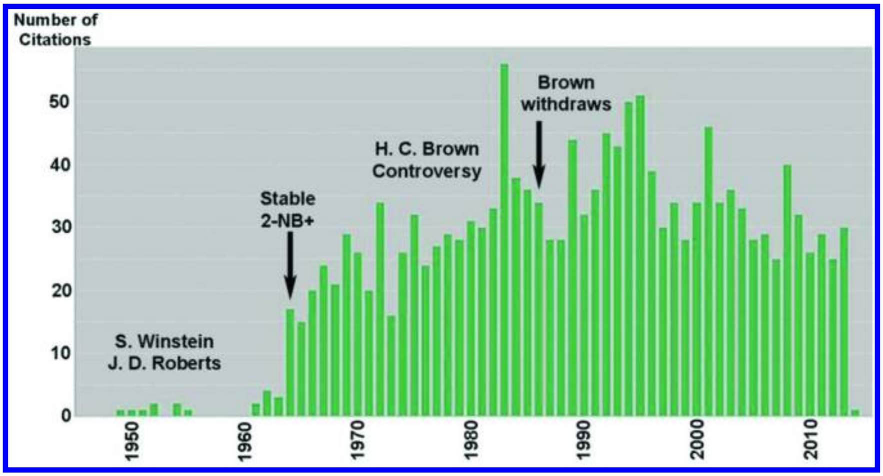

Figure 3. Web of Science: Number of "norbornyl cation" citations per year.

The first papers on the norbornyl cation were written by Saul Winstein (*1*) and Jack Roberts (*2*). Some high points of the investigations are marked in Figure 3.The first production of the stable norbornyl cation was by Olah (*3*) in 1964. In 1962, Brown began to criticize Winstein's interpretation (*4*) of the σ-bridged 2-norbornyl cation (and other σ-bridged carbocations). This controversy continued very heatedly – it was most vituperative (*5*). Brown withdrew from the fray in 1986 (*6*), after over a dozen years of keeping things at a boil, calling for experimental evidence. He was still unconvinced as only theoretical evidence had been presented to date, but in particular, the X-ray structure was not available. An X-ray crystal structure is an obvious way of solving a structural problem and was not available. Many people had tried but failed to solve the X-ray structure due to disorder. I'll come back to this point later. Note that at this point the structure in the gas-phase had not been realized either, but other experimental evidence and definitive theoretical calculations had established the bridged structure reliably.

Historical Background

The story, however, goes back a lot further, to the paper by Wagner in 1899 (*7*), which proposed carbonium ions as intermediates in terpene rearrangements. The mechanism of the rearrangement of camphene hydrochloride into isobornyl chloride was further elucidated by Meerwein and van Emster in 1922 (*8*), see Figure 4. Proving the structures of these products and starting materials was very difficult. And we should remember that these types of rearrangements were hardly known at the time. People expected the least structural change in moving from starting materials to product. The first formulation of a non-classical ion is usually attributed to Christopher Wilson (*9*), although Ingold (*10*, *11*) has some claim for it, too. These terpenes, of course, have three more methyl groups than norbornyl.

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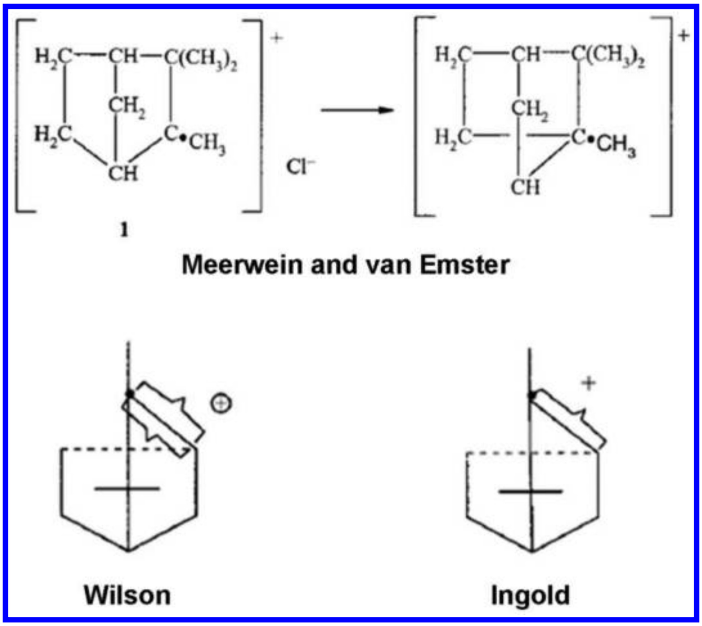

Figure 4. (Top) Representation of the camphenyl cation to isobornyl cation rearrangement (8). Wilson (9) and Ingold (10) representations of the camphenyl cation. [(Reproduced with permission from refn. (8). Copyright (1922) Wiley-VCH Verlag GmbH & Co. KGaA); (Reproduced with permission from refn. (9). Copyright (1939) The Royal Society of Chemistry); (Reproduced with permission from refn. (10). Copyright (2001) American Chemical Society)]

The chronology of the 2-norbornyl cation controversy is summarized in Table 1. We start our history with Winstein and Trifan (*1*). Trifan was a faculty member at Princeton at the time I was there, so I knew him personally. They proposed the bridged, non-classical structure. The first refutation of this by Brown was in 1962 (*4*). In 1977, Brown published *The Nonclassical Ion Problem* (*12*), with my comments included. I talked about the stable ion, the rearrangements, the nonclassical vs. classical carbocation problem. And then a number of important works appeared supporting the nonclassical structure. NMR, in particular Yannoni's ^{13}C 5K NMR data (*13*) failed to find equilibration of localized (classical) ions. Saunders's isotopic perturbation method (*14*) was applied to the ^{1}H NMR spectrum of the norbornyl cation and the model supported the nonclassical structure. In 1983, Fritz Schaefer and I published the first computations that got the right answer for the right reason (*15*). Prior to 1983, many people had published calculations on this system but they were not reliable because you need to have a large enough basis set and explicitly include electron correlation corrections in the calculation. There was considerable debate about the interpretation of the ESCA spectra (*16–21*). And as I said already, Brown withdrew from the fray, unconvinced (*6*). Efforts to get the crystal structure went on in many laboratories (*22*, *23*), probably more than I've listed here, but their efforts failed due to disorder. The X-ray crystal structure was finally solved in 2013 by German groups under Meyer and Krossing (*24*). Mike Duncan, my colleague at Georgia is still seeking the gas-phase IR spectrum and I'll say something about that later.

Table 1. The 2-Norbornyl Cation (2NB+) Controversy: A Chronology

1949, 1952	*Winstein* and *Trifan* propose the bridged, non-classical structure of 2NB+ (*1*)
1962	*H. C. Brown* refutes their evidence; proposes a pair of rapidly-equilibrating classical cations and steric effects as alternative explanations (*4*)
1964	*Schleyer, Olah, Saunders, et al.* report preparation of the stable 2NB+ and interpret its temperature-dependent NMR spectra - rearrangements (*3*)
1977 book	"The Nonclassical Ion Problem," *H. C. Brown* (with *Schleyer* commentary) (*12*)
1982	*Olah, Prakash, Anet* variable temperature NMR and isomerization barriers (*25*)
1982	*Yannoni, Mhyre* 5 K MAS NMR fails to find evidence of equilibration (*13*)
1983	*Saunders*, *Kates* isotopic perturbation method applied - nonclassical (*14*)
1983	*Schaefer, Schleyer, et al.* first adequately high-level computations - nonclassical (*15*)
1982 - 1985	*Olah, Prakash*, further support the nonclassical 2NB+ structure (*26*), but considerable debate continues (e.g., ESCA spectra interpretation) (*16–21*)
1986	*H. C. Brown*, his major objections never answered directly, withdraws unconvinced from the debate, calling for decisive experimental evidence (*6*)
1960s - now	*R. Bau* (unpublished results), *J. C. Huffman* (*22*), *T. Laube* (*23*), *M. Goldstein* (unpublished results), *others*. Many attempts to solve the X-ray structure of 2NB+ failed due to disorder problems
2013	*Scholz, Himmel, Heinemann, Schleyer, Meyer, Krossing* (*24*) finally solve the 2NB+ crystal structure - a *tour de force*!!

The Winstein evidence for bridging in the beginning was rather flimsy (*1*) but was convincing to most people. The high 2-norbornyl *exo*/*endo* solvolysis rate (Figure 5) and product ratios were the basis for Winstein and Trifan's non-classical ion formulation. The bornyl, norbornyl, and isobornyl structures have very high *exo*/*endo* rate ratios which Winstein and Trifan interpreted as indicating participation of the neighboring C-C bond. Brown argued (*4*) that steric effects are responsible since the tertiary analogs also have high *exo*/*endo* rate ratios. His

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rebuttal, *inter alia*, in his 1977 book with me as commentator (*12*), pointed out many imperfections in interpretations based on nonclassical ion theory, which still remain unanswered even to this day. So to some extent the controversy still goes on.

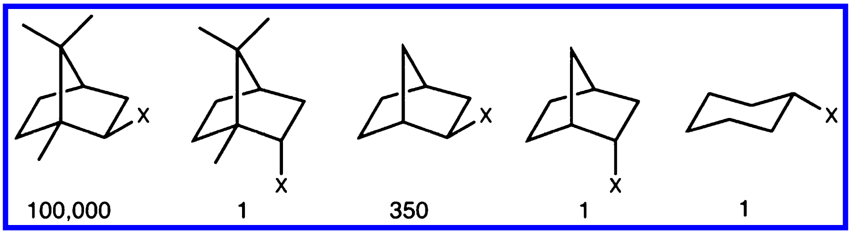

Figure 5. Solvolysis rates for norbornyl compounds vs. cyclohexyl

Two Classical Ions in Rapid Equilibrium or Symmetrical Bridged Structure

The issue was the decision between the double-well minimum, two classical ions in rapid equilibrium, or a symmetrical bridged structure (Figure 6). This is not unlike the benzene problem, whether benzene oscillates back and forth between two Kekule structures or has a single minimum. Winstein and Trifan (*1*) suggested both, but favored bridging. Solutions of such double- vs. single-well potential problems are difficult!

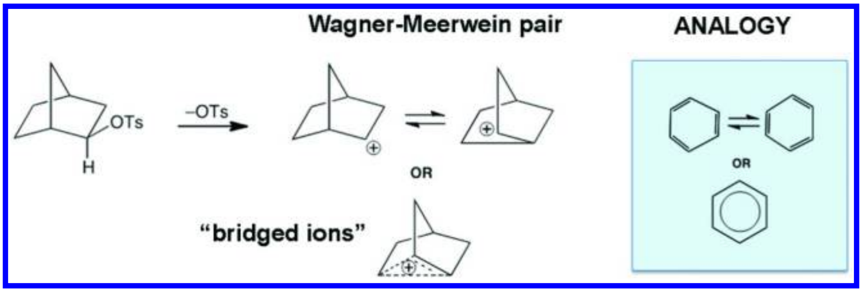

Figure 6. Nonclassical ion vs. rapid equilibrium model.

The Winstein evidence (*27*) was not just based on high *exo*/*endo* rate ratios but also on the product (Figure 7). The products were exclusively *exo* starting from both *endo* and *exo* starting materials. But there was something funny from the *endo* starting material, because if optically active starting materials were used, the products were not completely racemized.

> *"In anchimerically unassisted solvolysis of endo-2-norbornyl-X chemical capture of an unsymmetrical norbornyl cationic species is quite evident, however. While most of the initially formed classical species becomes nonclassical before giving rise to product an appreciable fraction does*

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give optically active inverted product. In the more nucleophilic solvents this amounts to 13%." --- *Winstein* (*27*) (Reproduced with permission from refn. (*27*). Copyright (1965) American Chemical Society)

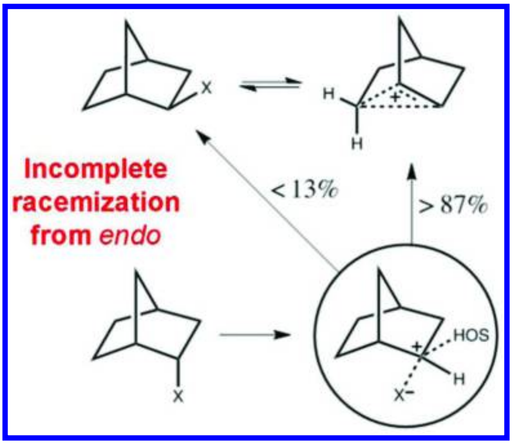

Figure 7. Exo vs. Endo 2-Norbornyl Solvolyses [Endo-Product Complexities]

So it doesn't go completely through the nonclassical ion. It was supposed that some sort of classical ion intervenes in the *endo* case – and I'll come back to that, later on.

Direct Observation of the 2-Norbornyl Cation

In 1962, Olah gave his memorable lecture at the Ninth Organic Reaction Mechanism Conference held at the Brookhaven Natural Laboratories and announced that he was able to get stable norbornyl ions in solution. We agreed then to attack the norbornyl problem. He pointed out that he worked for Dow and they didn't have a preparative laboratory, and asked if I would make starting materials for him. My research group then made these various starting materials and sent them to George and he converted them to the same norbornyl ion. We published these results (*28*) in 1964 (Figure 8).

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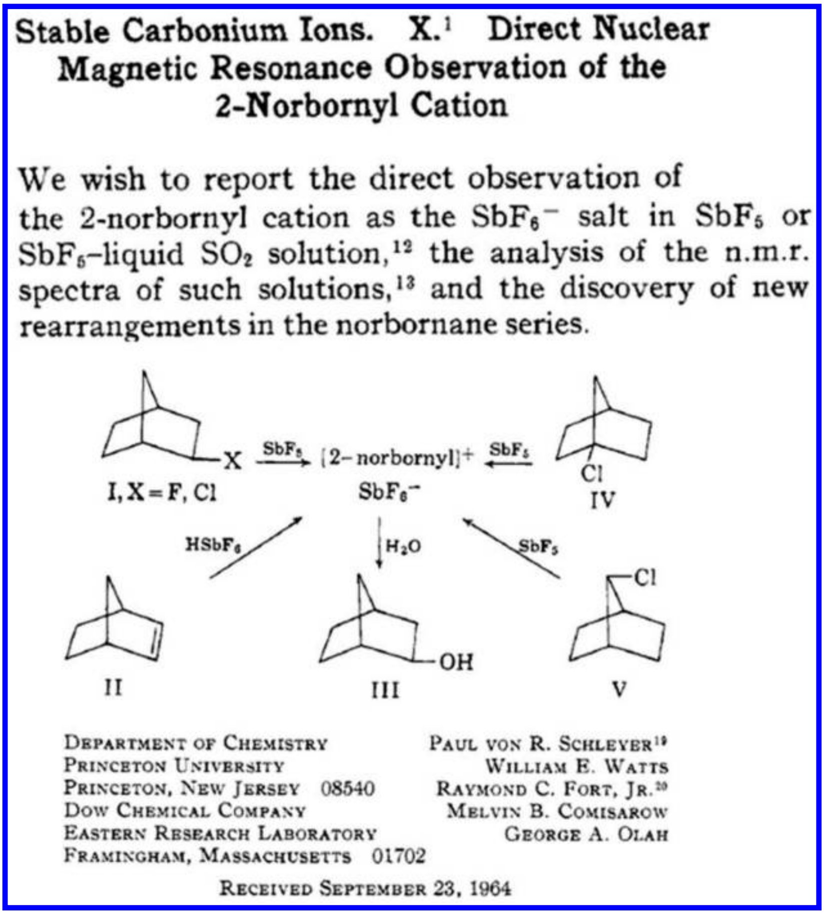

Stable Carbonium Ions. X.[1] Direct Nuclear Magnetic Resonance Observation of the 2-Norbornyl Cation

We wish to report the direct observation of the 2-norbornyl cation as the SbF_6^- salt in SbF_5 or SbF_5–liquid SO_2 solution,[12] the analysis of the n.m.r. spectra of such solutions,[13] and the discovery of new rearrangements in the norbornane series.

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Melvin B. Comisarow
George A. Olah

Received September 23, 1964

Figure 8. Excerpts from Schleyer, Watts, Fort Jr., Comisarow, and Olah, 1964 (28). (Reproduced with permission from refn. (28). Copyright (1964) American Chemical Society)

Olah and I enlisted Marty Saunders's help, as he had better NMR facilities at the time, and he found evidence (Figure 9) for three types of internal rearrangements: the Wagner-Meerwein, (which is at least the nonclassical ion), the 6,2-hydride shift, and the 3,2-hydride shift.

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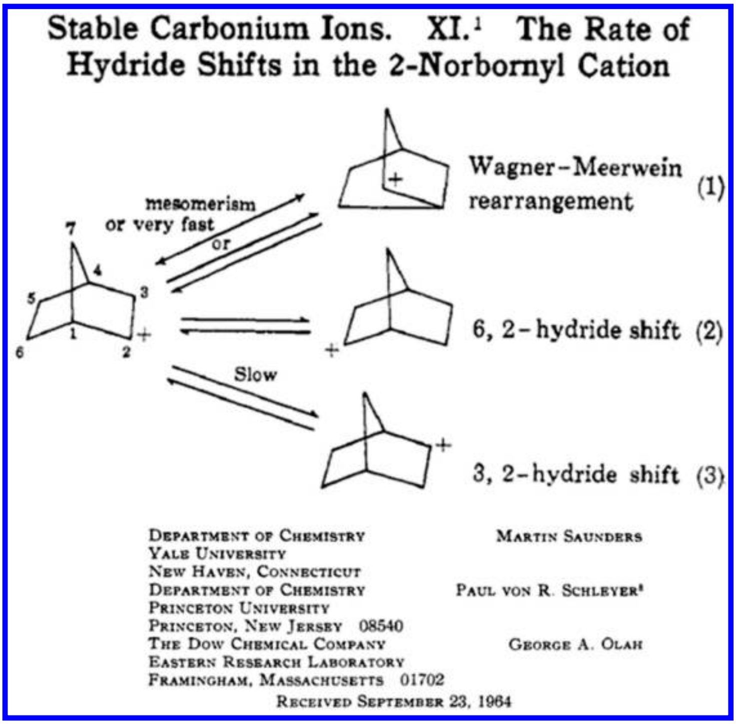

Stable Carbonium Ions. XI.[1] The Rate of Hydride Shifts in the 2-Norbornyl Cation

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RECEIVED SEPTEMBER 23, 1964

Figure 9. Excerpts from Saunders, Schleyer, and Olah, 1964 (3). (Reproduced with permission from refn. (3). Copyright (1964) American Chemical Society)

In Jack Robert's isotope-labeling study of Wagner-Meerwein and 6,2-hydride shifts in the 2NB+ (*29*), Roberts anticipated the 1964 NMR observations of complete scrambling, when the slower 3,2-hydride shifts also took place. Jack pointed out in this paper that if the 3,2-hydride shift also went fast enough it would lead to scrambling of all the ions.

> *"The observed near-equilibrium distribution rules out any 2,3-hydrogen shifts which would be associated with such an intermediate as shown [M. J. S. Dewar, Ann. Reports (Chem. Soc.), 121 (1951)], since cations of this type in combination with III and XIII would lead to 'scrambling' of all of the atoms." --- Roberts* (*29*) (Figure 10). (Reproduced with permission from refn. (*29*). Copyright (1954) American Chemical Society)

And in fact, that scrambling is what the NMR spectra show at higher temperatures (Figure 11), where you see only a single hydrogen peak. At lower temperatures, the rapid rearrangements slow down and you see a more highly resolved spectrum.

So this is the nub of the problem once again: does the 2NB+ structure have C_S symmetry or two C_1 symmetry enantiomers which rapidly equilibrate (Figure 12).

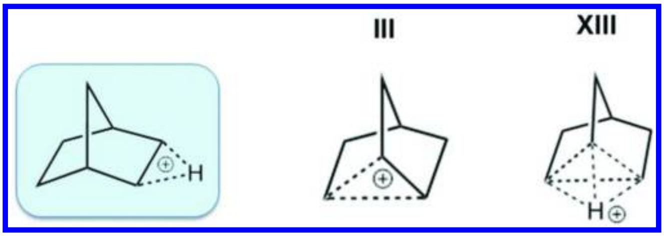

Figure 10. Excerpts from Roberts, Lee, and Saunders, 1954 (29). (Reproduced with permission from refn. (29). Copyright (1954) American Chemical Society)

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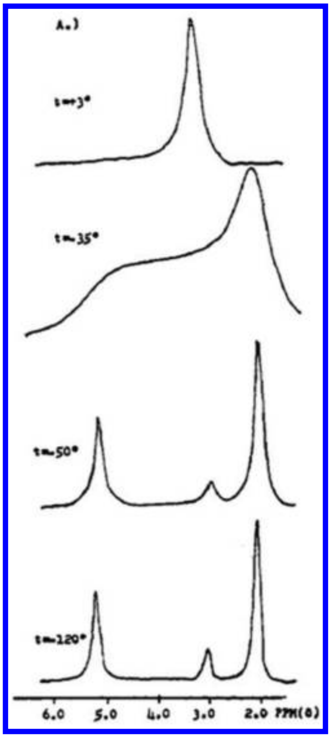

Figure 11. ^{1}H NMR spectra of the 2-norbornyl cation at various temperatures (3). (Reproduced with permission from refn. (3). Copyright (1964) American Chemical Society)

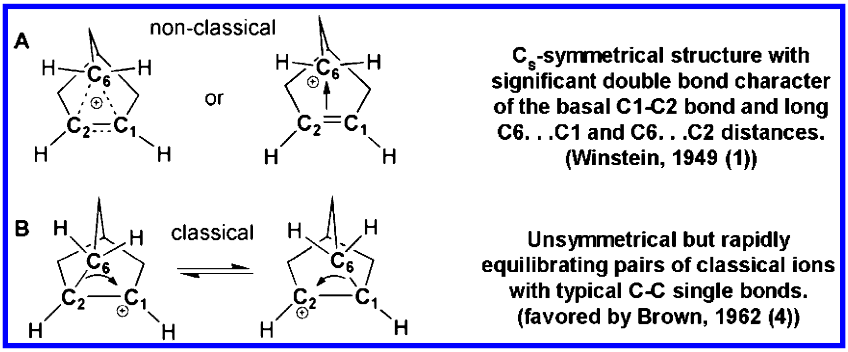

Figure 12. The 2-norbornyl cation: nonclassical (A) (1) vs. classical structure (B) (4). [(Reproduced with permission from refn. (1). Copyright (1949) American Chemical Society); (Reproduced with permission from refn. (4). Copyright (1962) The Royal Society of Chemistry)]

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Adventures in X-Ray Crystallography

Much evidence, computational and experimental, supports the nonclassical structure, but the X-ray structure was strangely missing. The problem is that the norbornyl cation is more or less spherical and rotates rapidly in the crystal, so therefore it causes disorder. You can try to freeze it out but no one had succeeded. The final solution came in 2013 (*24*) by two German associates of mine. Karsten Meyer at Erlangen-Nürnberg and Ingo Krossing at Freiburg recognized that not only was there disorder due to the rotation in the crystal but there was also disorder due to the rapid rearrangements (Figure 12), and you had to freeze both types of disorder out. In order to do that, 20-fold annealing, from about 86 K to about 40 K had to be carried out. The experiment cost about 10,000 euros in liquid helium – so it was a *tour de force* to say the least. I won't go into this, but at 86 K the half-life is still pretty fast. Figure 13 summarizes this data.

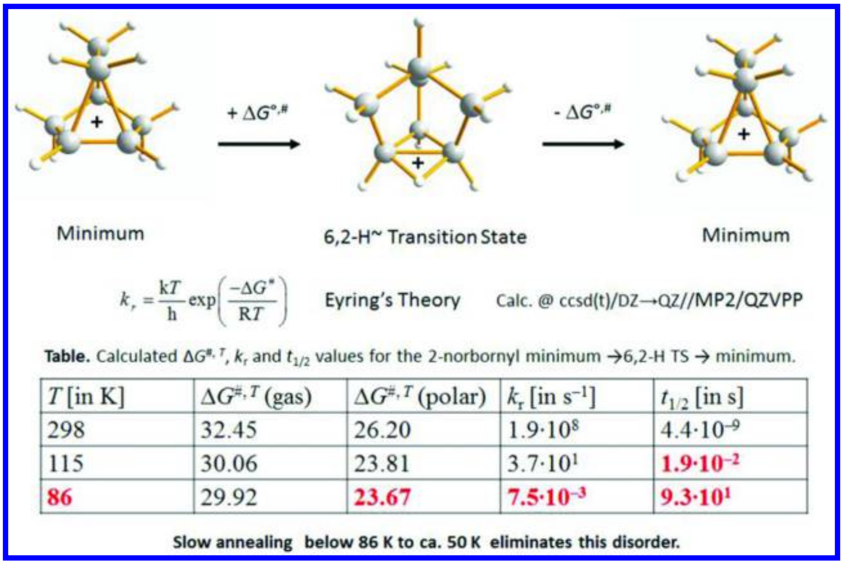
In our publication of the X-ray structure (*24*), we summarized the situation as follows:

> *"After decades of vituperative debate over the classical or nonclassical structure of the 2-norbornyl cation, the long-sought X-ray crystallographic proof of the bridged, nonclassical geometry of this prototype carbonium has finally been realized. Exceptional treatment was required. Crystals of the solvated* $[C_7H_{11}]+[Al_2Br_7]-$ • CH_2Br_2 *salt, obtained by reacting norbornyl bromide with aluminum tribromide in* CH_2Br_2*, undergo a reversible order-disorder phase transition at 86 K*

due to internal 6,1,2-hydride shifts of the 2-norbornyl cation moiety. Cooling with careful annealing, data collection and refinement at 40 K revealed three similar independent 2-norbornyl cations structures in the unit cell. All agree very well with ab initio computations at the MP2(FC)/def2-QZVPP level." -- Scholz, Himmel, Heinemann, Schleyer, Meyer, and Krossing, 2013 (*24*). (From refn. (*24*). Reprinted with permission from AAAS)

The left side of Figure 14 shows what the norbornyl cation looks like to the X-ray diffractometer. When it is disordered you just have a jumble of atoms for the norbornyl cation. But after the annealing process the unit cell has three norbornyl cations in it (right, Figure 14), so you get three for the price of one. And in fact, fortuitously and coincidentally, the cover of Brown's book (*12*) has those three norbornyl cations (see Figure 15). So, somehow, this result was anticipated!

The three cations in the tripled unit cell have roughly the same bond lengths - the average agrees with good ab initio calculations and without a doubt the structure has the bridge form and C_S symmetry. This data is summarized in Figure 16.



$$k_r = \frac{kT}{h}\exp\left(\frac{-\Delta G^{*}}{RT}\right)$$

Eyring's Theory Calc. @ ccsd(t)/DZ→QZ//MP2/QZVPP

Table. Calculated $\Delta G^{\#,T}$, k_r and $t_{1/2}$ values for the 2-norbornyl minimum →6,2-H TS → minimum.

T [in K]	$\Delta G^{\#,T}$ (gas)	$\Delta G^{\#,T}$ (polar)	k_r [in s^{-1}]	$t_{1/2}$ [in s]
298	32.45	26.20	$1.9\cdot10^{8}$	$4.4\cdot10^{-9}$
115	30.06	23.81	$3.7\cdot10^{1}$	**$1.9\cdot10^{-2}$**
86	29.92	**23.67**	**$7.5\cdot10^{-3}$**	**$9.3\cdot10^{1}$**

Slow annealing below 86 K to ca. 50 K eliminates this disorder.

Figure 13. Disorder in 2-norbornyl cation due to rapid 6,2-H shift.

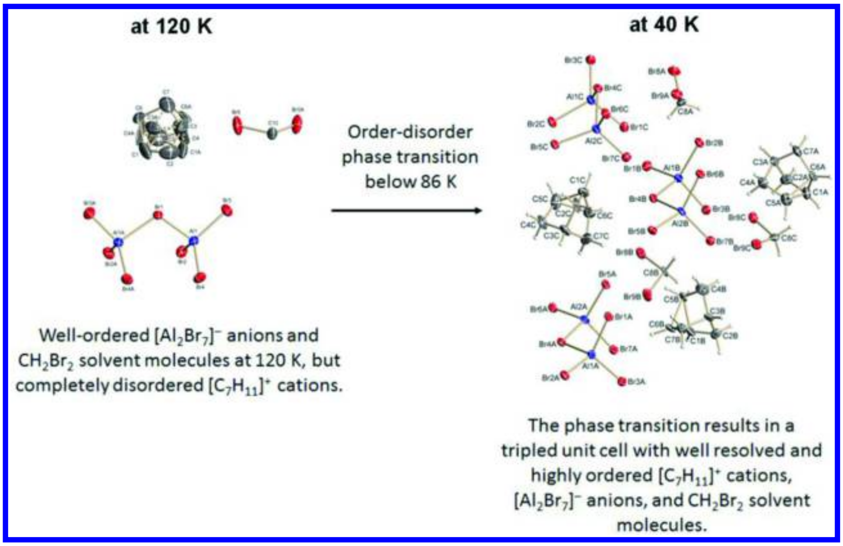
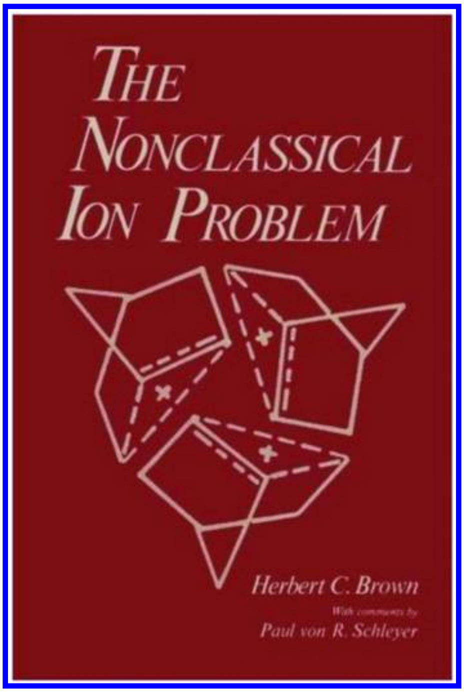


Figure 14. Asymmetric unit of the $[C_7H_{11}]+[Al_2Br_7]- \bullet CH_2Br_2$ *crystal structure.*



THE
NONCLASSICAL
ION PROBLEM

Herbert C. Brown
With comments by
Paul von R. Schleyer

Figure 15. The cover from The Nonclassical Ion Problem by Herbert C. Brown (12). (Reproduced with permission from refn. (12). Copyright (1977) Plenum Press. With permission of Springer Science+Business Media)

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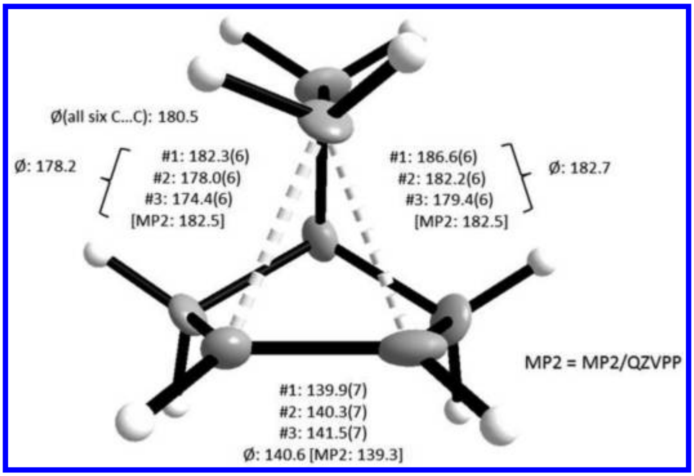

Figure 16. Unsubstituted 2-norbornyl cation XRD Structure (24) showing the data for the three independent cations in the unit cell. (From refn. (24). Reprinted with permission from AAAS)

Classical vs. Nonclassical Structure via Infrared Spectroscopy

Another way this problem might be solved would be to compare the experimental infrared spectrum with those that have been computed for the classical and nonclassical alternatives (Figure 17). So which one does it fit? The solution spectra that George Olah and others have reported are not very sharp; the lines are broad in solution. Getting a spectrum in the gas phase would be better and my colleague Mike Duncan at Georgia has an apparatus that does exactly that. So one has to decide if the experimental spectrum fits the nonclassical model or the classical model.

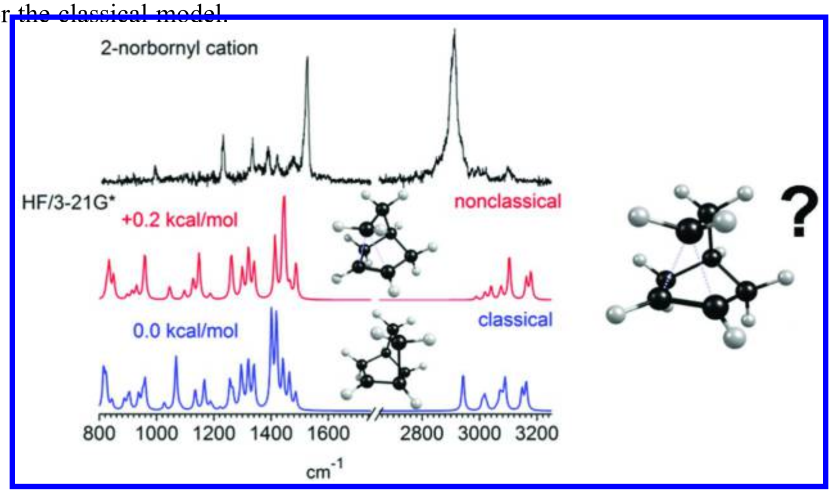

Figure 17. Another potential experiment solution: the gas phase 2NB+ structure could be revealed by infrared photodissociation spectroscopy.

The apparatus that Duncan uses is shown in Figure 18. It is very neat. The cation is generated here and it is standard procedure for him to use H_3^+ as his standard proton source. This proved to be a poor choice, but I have to tell the story the way it happened and this is how he generated it. What you see in the normal mass spectrum, since this is generated in Ar, is not only the various peaks due to hydrocarbon cations, but also Ar tagged species. This is very important because one can use a mass gate in the reflectron mass spectrometer to select this ion or that set of ions. With the mass gate on, you irradiate them with a tunable dye laser and scan the spectrum. And whatever the spectrum absorbs, you knock off the Ar. You then detect the ions on the bottom part of the reflectron. Whenever there is a peak in the infrared you get a peak in this spectrum. By plotting the intensities of the laser vs. the frequency you get a nice IR spectrum.

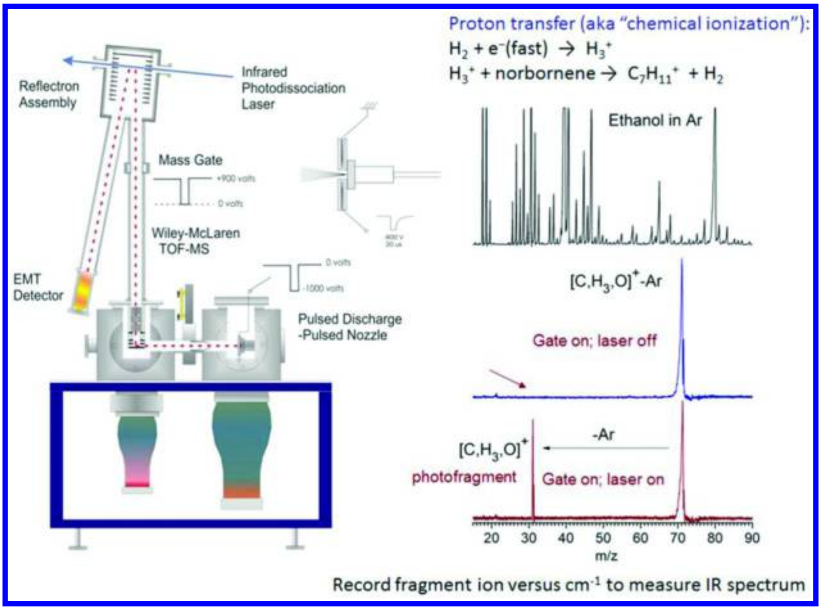

Figure 18. Duncan's IR-PD apparatus and illustration of technique.

The IR spectrum obtained is shown in Figure 19. It is very sharp and very good quality. Duncan has published a number of these. The first thing you do is compare the spectrum with that computed for the 2-norbornyl cation, the bridged form. And much to your horror, it doesn't fit at all. In particular, the peak at 1525 cm-1, one of the strongest peaks in the experimental spectrum, is completely missing in the calculated spectrum. Either you haven't made the norbornyl cation in this experiment or it doesn't have the nonclassical structure.

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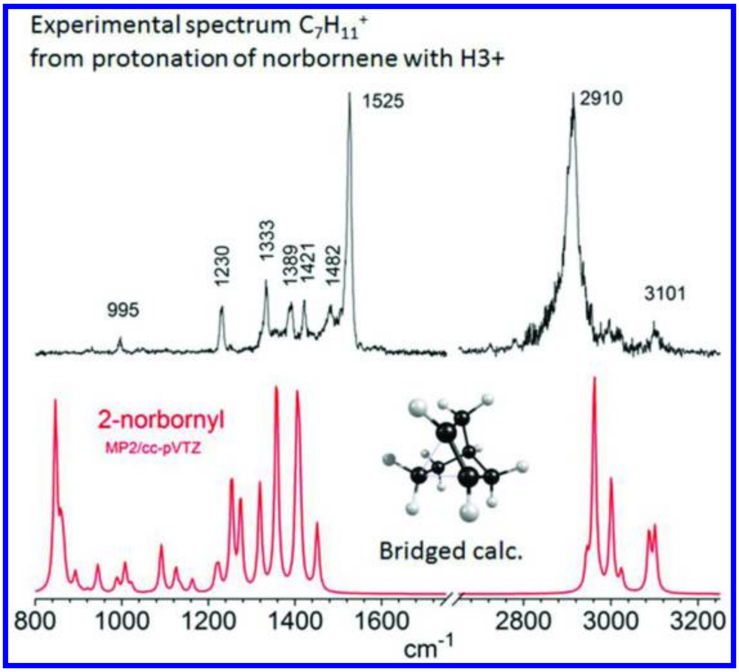

Figure 19. Experimental spectrum of C_7H_{11}+ from protonation of norbornene with H_3^+ vs. calculated nonclassical spectrum.

When you compare the experimental spectrum with the spectrum calculated for the classical 2NB+ cation and it doesn't match either (Figure 20). The conclusion is that this experiment, the protonation of norbornene, did not yield the 2-norbornyl cation. What is this the spectrum of?

People have gotten so used to the 2-norbornyl cation that they may imagine that it must be the global minimum. It isn't. There are other isomers of C_7H_{11}+ that are more stable, and in particular the dimethyl allyl, which is the global minimum (Figure 21).

Let's compare the spectrum computed for the 1,3-dimethylcyclopentenyl cation with the experimental spectrum (Figure 22). These peaks match almost perfectly, and that is what the structure is. Instead of getting the norbornyl cation from norbornene Duncan had gotten the 1,3-dimethylcyclopentenyl cation.

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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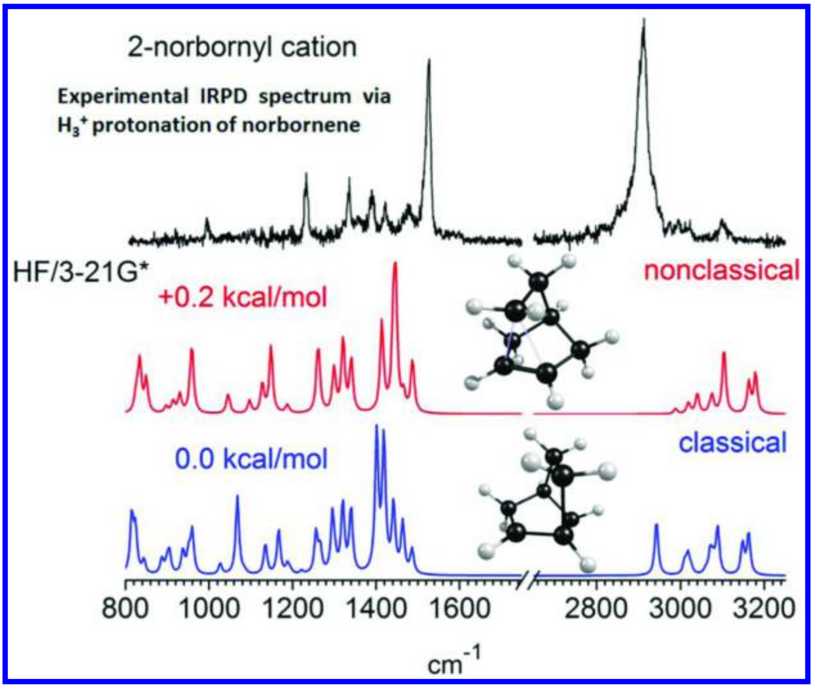

Figure 20. Experimental spectrum of C_7H_{11}+ from protonation of norbornene with H_3^+ compared to the calculated spectrum for the 2-norbornyl cation - both classical and nonclassical models.

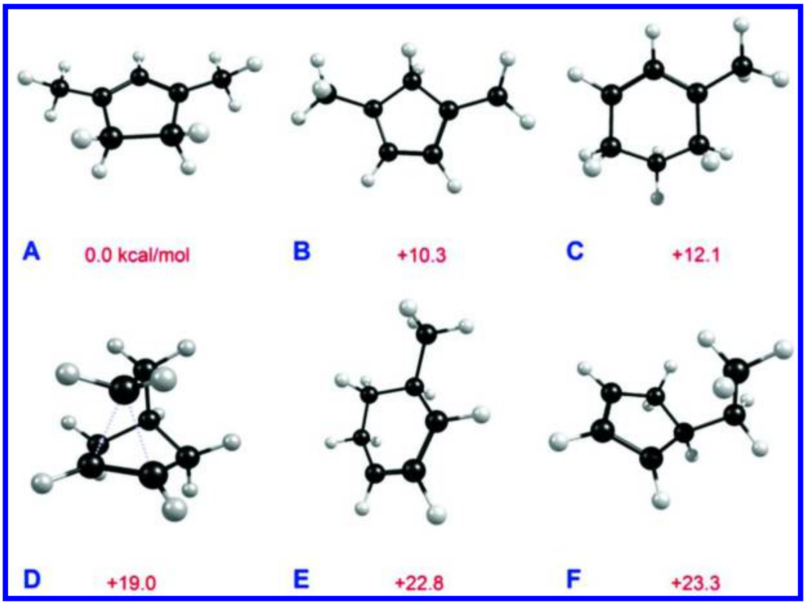

Figure 21. Six low energy isomers, A - F, of C_7H_{11}+ (30). (Reproduced with permission from refn. (30). Copyright (2014) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

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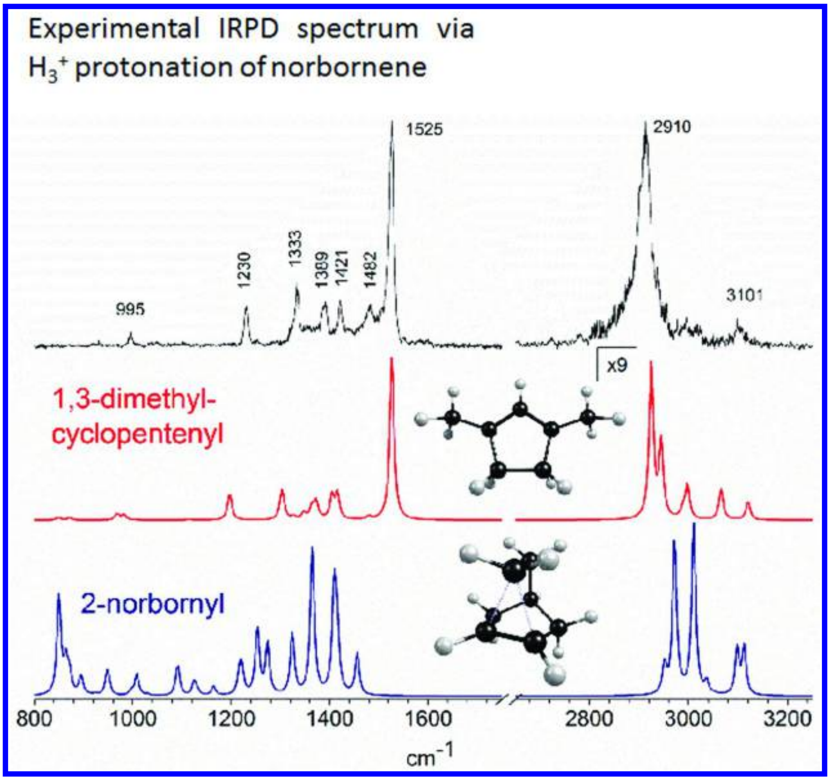

Figure 22. Experimental spectrum (top) vs. computed spectra for 1,3-dimethylcyclopentenyl (middle) and 2-norbornyl (bottom) (31). (Reproduced with permission from refn. (31). Copyright (2014) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

The next question is how on earth do you rearrange the norbornyl cation, which is probably formed first, into this cyclopentenyl cation? Well, I'm sure all of you think you are good carbonium ion pushers – I dare you to try it! You'll see that there is no easy way of doing it and so I enlisted the help of Gabriel Merino in Mexico to help solve this problem.

The question again is how does the norbornyl cation rearrange into the dimethylcyclopentenyl cation (Figure 23)? Merino (*30*) used a Born-Oppenheimer molecular dynamics (BOMD) program that searches for minima, which generates the potential energy surface going from the norbornyl cation bridge going to dimethylcyclopentenyl cation. There are some 16 minima, each corresponding to a different isomer, and a corresponding number of transition states in this process. It is amazing what happens. First, the bicyclic ring opens to a monocycle, and then it goes to an acyclic structure which closes back down to a monocycle, and various shifts occur along this pathway. I won't go into this in any more detail, but it isn't something you develop by trial and error.

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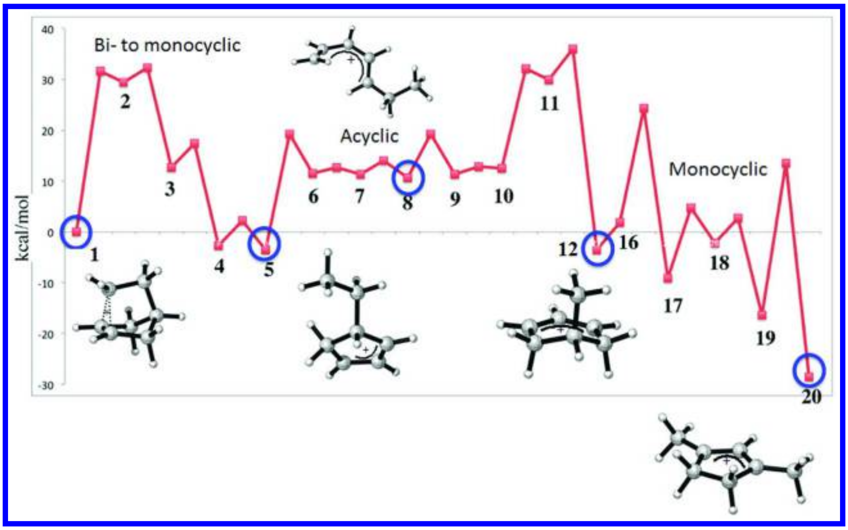

Figure 23. Born-Oppenheimer Molecular Dynamics (BOMD) simulation of the 2-norbornyl cation conversion to the 1,3-dimethylcyclopentenyl cation (30). (Reproduced with permission from refn. (30). Copyright (2014) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

The 2-*Endo*-Norbornyl Cation

The next problem I want to talk about is the nature of the 2-*endo*-norbornyl cation which I believe has gotten lost in the shuffle. It has been assumed that it has a classical structure but if you try to calculate it with a classical geometry you never find a minimum. The new insight is that the 2-*endo*-norbornyl cation also favors a bridged structure. Now, that's hardly new as there has been much evidence hinting at 2-*endo* norbornyl bridging since 1900, but not so interpreted! The problem in finding it experimentally arises because the 2-*endo* bridged ion, which I'll show you in a moment, has a very small transition state to go to the more stable 2-*exo* form. And therefore, what Winstein calls leakage occurs quite easily (Figure 24). For example, bridged ion depictions have been related to 2-bicyclo[3.1.1]heptanes (the norpinane mesonomers) instead. A few examples follow.

This again is Winstein's interpretation (*33*), in which the reaction goes through some sort of species which he didn't try to pin down (Figure 25).

> *"In anchimerically unassisted solvolysis of endo-2-norbornyl-X chemical capture of an unsymmetrical norbornyl cationic species is quite evident, however. While most of the initially formed classical species becomes nonclassical before giving rise to product an appreciable fraction does give optically active inverted product. In the more nucleophilic solvents this amounts to 13%." --- Winstein* (*33*) (Reproduced with permission from refn. (*33*). Copyright (1965) American Chemical Society)

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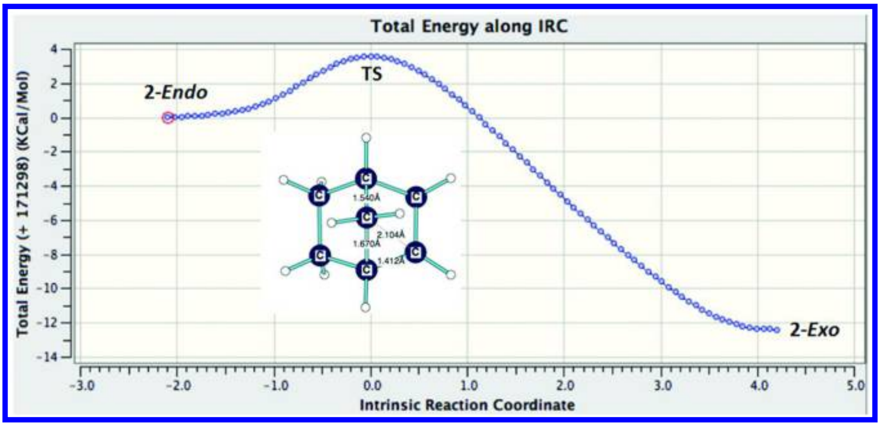

Figure 24. Intrinsic reaction coordinate (IRC) for endo- to exo 2NB+ "leakage." IRC: First computations by MN12L (32).

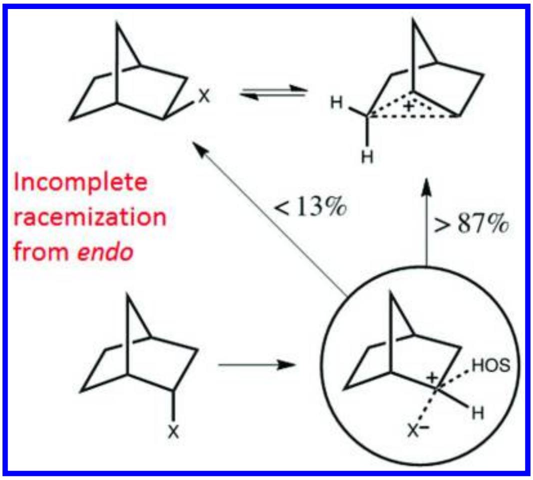

Figure 25. Exo vs. endo 2-norbornyl solvolyses showing endo- product complexities (33). (Reproduced with permission from refn. (33). Copyright (1965) American Chemical Society)

Kirmse has written five or six papers, as well as a review article, on this general topic, which doesn't get much publicity and is summarized in Figure 26.

> *"The ionization of exo-2-norbornyl derivatives occurs with the participation of the C1-C6 bond. (Winstein, 1952) For endo-2-norbornyl derivatives corresponding participation of the C1-C7 bond should likewise be possible. However, the ring strain (Maier/ Schleyer, 1981) thereby increases." --- Kirmse* (*34*). (Reproduced with permission from refn. (*34*). Copyright (1993) Wiley-VCH Verlag GmbH & Co. KGaA)

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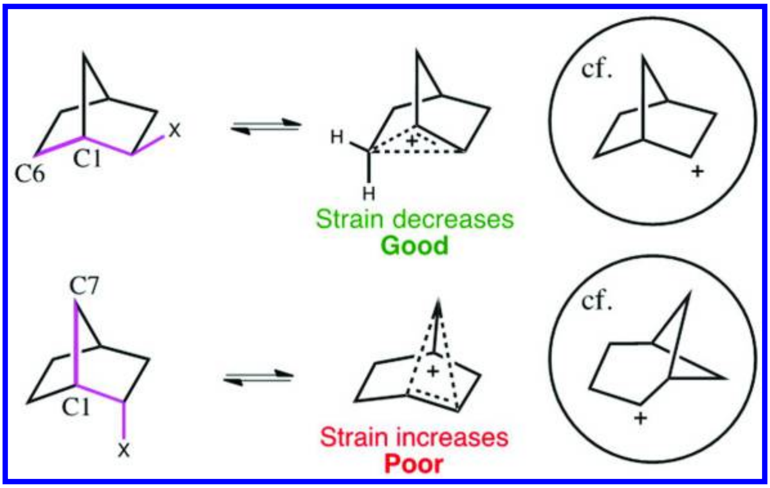

Figure 26. Exo vs. endo 2NB+ solvolysis (34). (Reproduced with permission from refn. (34). Copyright (1993) Wiley-VCH Verlag GmbH & Co. KGaA)

If we invoke trans-anti-peri-planar arrangements, the *exo* would give the bridged cation that we know. But the *endo* should give this bridged cation, which is related to pinene, and has sometimes been called the pinyl cation in the literature.

Figure 27 shows one of Kirmse's reactions, *endo* with a methoxy, where the product is a ketone. You can see the bridged ion in this classical representation.

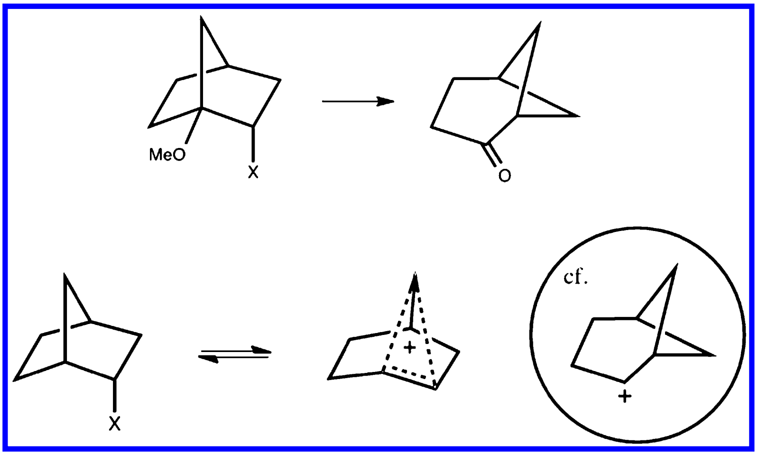

Figure 27. Norpinyl product via an endo-2-norbornyl cation (35). (Reproduced with permission from refn. (35). Copyright (1986) American Chemical Society)

Now, you recall from terpene chemistry, that addition of HCl to camphene gives isobornyl chloride. That's the *exo* product, as seen in the top reaction in Figure 28. That's the reaction that Meerwein (*8*) studied so brilliantly. But if I write it as a classical ion, it looks like the representation in the bottom reaction in Figure 28. The α and β pinenes react with HCl not to give isobornyl but bornyl chloride, stereospecifically *endo*. If you write it as a classical ion and you turn it around, these two are identical. You can't get two different products from the same intermediate ion, so there has to be some difference between these intermediates.

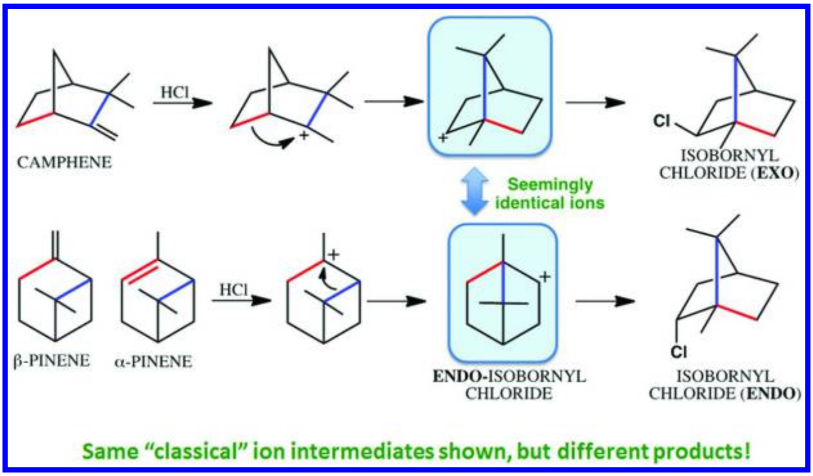

Figure 28. Puzzling Wagner-Meerwein product stereochemistry.

So the difference must be in the nature of the bridging (Figures 29 and 30). Wilson explained the *exo* case first, as I mentioned already. The *exo* case has bridging as shown in Figure 29 and the *endo* case has bridging as shown in Figure 30.

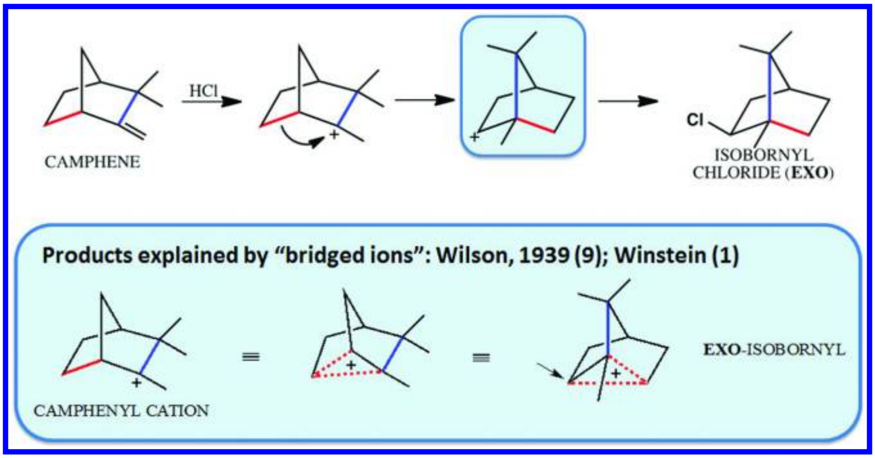

Figure 29. I. Clarifying Wagner-Meerwein reaction products.

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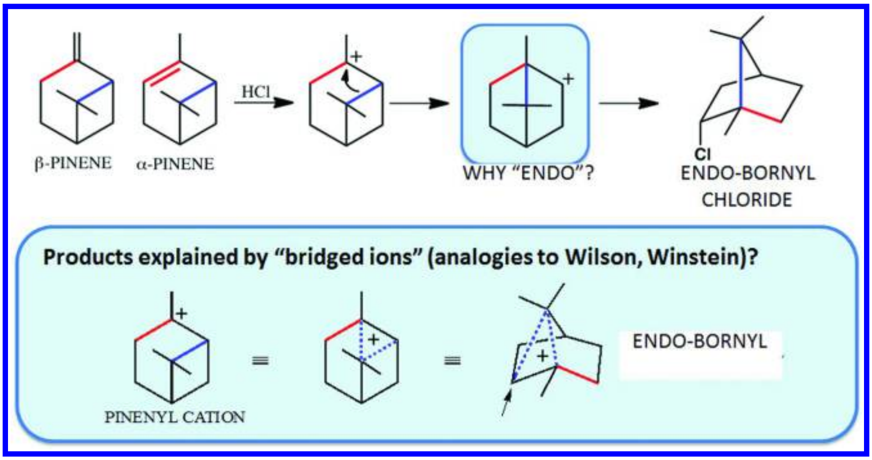

Figure 30. II. Clarifying Wagner-Meerwein reaction products.

Henry Rzepa has looked into this problem (Figure 31). In the reaction of camphene + HCl we need to watch the chlorine. The first thing that happens is that the methyl group rotates and the chlorine moves, giving the transition state. The chlorine then moves to its new position. If both those movements in the counter ion occur simultaneously we end up with bornyl chloride. This was studied by Meerwein in 1922 (*8*).

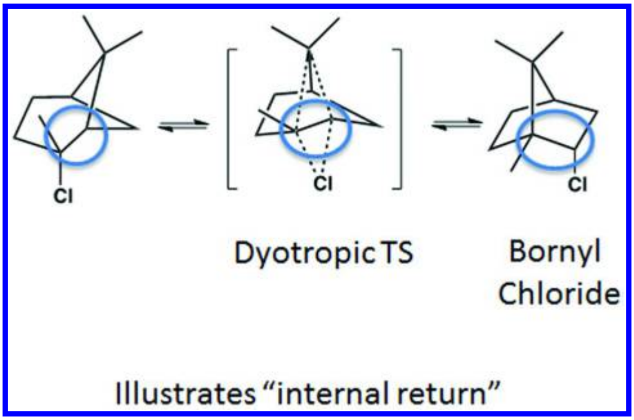

Figure 31. Pinene-HCl to bornyl chloride (endo) rearrangement. (Images courtesy of Prof. Henry Rzepa, 2015)

Henry has looked at some of the other possible transition states, see Figure 32. The barrier values indicated are free energy barriers.

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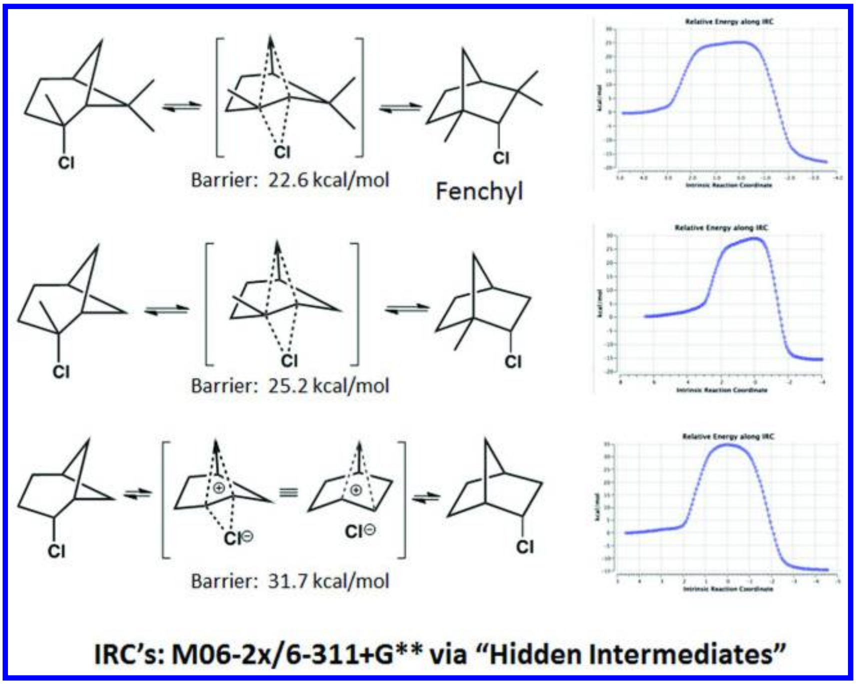

Figure 32. 2-Pinyl to 2-endo-norbornyl dyotropic rearrangement. Barrier values are free energy barriers. DataDOIs for the calculations are rs4, 645 and 646, resolved as e.g. http://doi.org/rs4. (Images courtesy of Prof. Henry Rzepa, 2015)

Interestingly, Winstein found one case like this but didn't realize it (*36*). With Holness he had prepared what he thought were the nopinyl *p*-bromobenzenesulfonates and reported that they reacted anomalously slowly; that is, did not show the expected anchimeric assistance. Expansion of the adjacent four membered ring with relief of ring strain apparently also did not occur. This work was challenged by the Foote-Schleyer relationship, which shows that the rate is anomalously slow. We pointed out that these results would not be anomalous if Winstein's starting structure was wrong. It turned out that Winstein had not studied the nopinyl *p*-bromobenzenesulfonates at all! They had rearranged to dimethylnorbornyl isomers (α-nopinyl reacted with *p*-bromobenzenesulfonyl chloride in pyridine to form *endo*-camphenilyl *p*-bromobenzenesulfonate while β-nopinyl reacted under the same conditions to form apobornyl *p*-bromobenzenesulfonate) by internal return before the rates were measured!

I told Winstein of our results. The compounds from the previous work (*36*) were still available. They were re-examined and spectroscopically were shown to have the structures as reported by Schleyer. In fact, internal return had taken place and what he had solvolyzed was an *endo*- norbornyl derivative instead of the nopinyl derivative that he had imagined. The two papers that resulted from these investigations were published back-to-back (*37*, *38*). The beginning of Winstein's paper (*37*) is shown in Figure 33.

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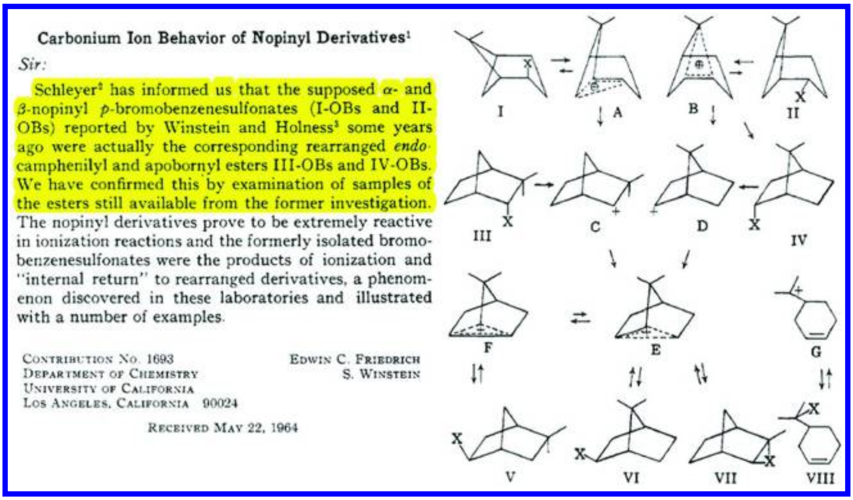

Carbonium Ion Behavior of Nopinyl Derivatives[1]

Sir:

Schleyer[2] has informed us that the supposed α- and β-nopinyl *p*-bromobenzenesulfonates (I-OBs and II-OBs) reported by Winstein and Holness[3] some years ago were actually the corresponding rearranged *endo*-camphenilyl and apobornyl esters III-OBs and IV-OBs. We have confirmed this by examination of samples of the esters still available from the former investigation. The nopinyl derivatives prove to be extremely reactive in ionization reactions and the formerly isolated bromobenzenesulfonates were the products of ionization and "internal return" to rearranged derivatives, a phenomenon discovered in these laboratories and illustrated with a number of examples.

Contribution No. 1693
Department of Chemistry
University of California
Los Angeles, California 90024

Edwin C. Friedrich
S. Winstein

Received May 22, 1964

Figure 33. Excerpts from Friedrich and Winstein, 1964 (37). (Reproduced with permission from refn. (37). Copyright (1964) American Chemical Society)

The first computed structure of the *endo*-norbornyl cation (*39*) is shown in Figure 34. There was an artifact in MINDO-3 which makes it an inadequate theory level. In fact, these authors commented,

> *"Greatly to our surprise, [the bridged 2-endo-norbornyl cation] not only turned out to be a stable species but more stable than any of the other 2-norbornyl isomers." --- Dewar (39).*

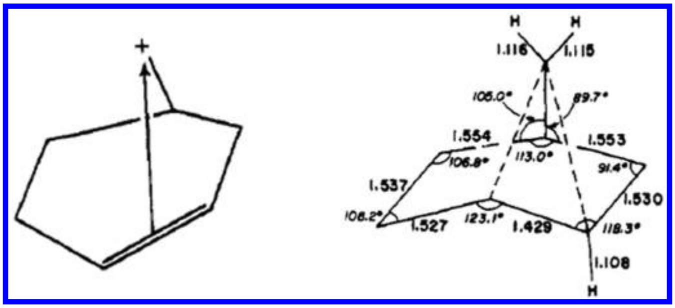

Figure 34. Excerpts from Dewar (39). Computational "discovery" of the bridged 2-endo-norbornyl as a MINDO-3 artifact. (Reproduced with permission from refn. (39). Copyright (1977) American Chemical Society)

The *endo*-norbornyl cation is more stable than the *exo*-norbornyl cation according to this inadequate calculation. But not more stable at refined ab initio levels (*32*), where the minimum structure of the "2-norpinyl cation" was confirmed.

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A paper by Valkanas in 1976 (*40*), studied the reaction of α-pinene with carboxylic acids in order to investigate the transition states necessary to achieve the various products of the reaction (Figure 35).

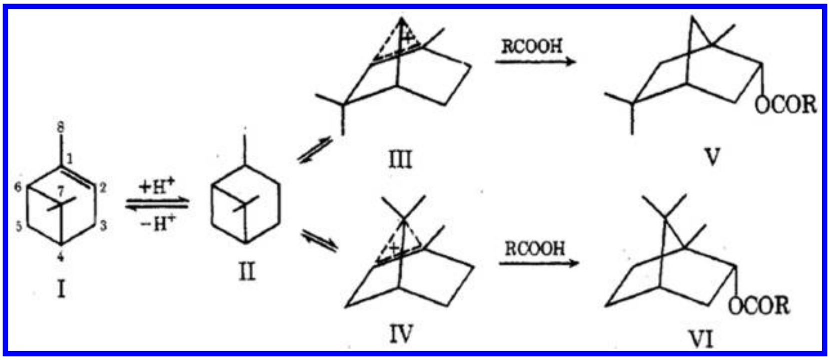

Figure 35. Excerpt from Valkanas (40). 2-Endo bridging explains products from reaction of α-pinene with acetic acid. (Reproduced with permission from refn. (40). Copyright (1976) American Chemical Society)

Figure 36 shows some more *endo*-norbornyl cations that I've calculated. These are the cations with methyl groups in various positions. All of these are minima at good calculational levels, including the *endo*-2-norbornyl cation itself.

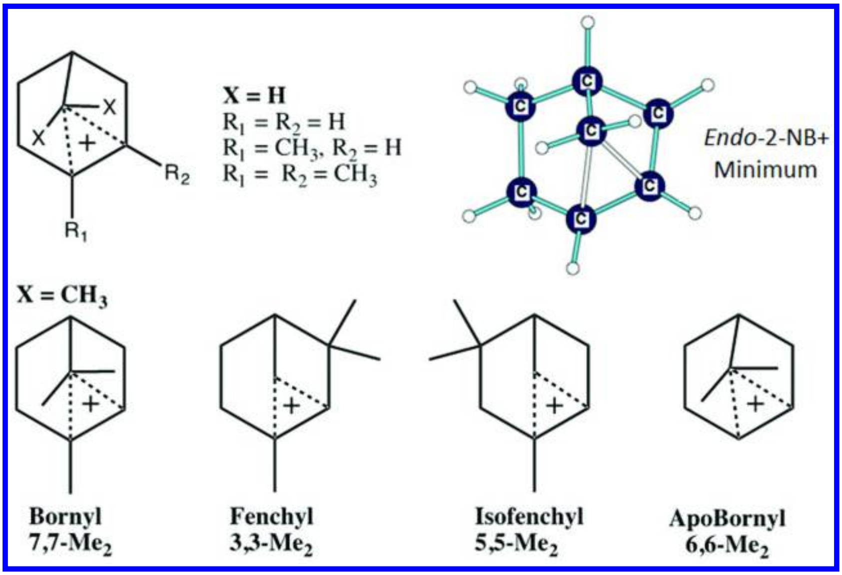

Figure 36. L2-endo-norbornyl (norpinyl) cations with computed bridged minima (also see Kirmse (35).). (Reproduced with permission from refn. (35). Copyright (1986) American Chemical Society)

Again, the reason these *endo* structures have not been found experimentally is that the *endo* bridged ion leaks rapidly to the *exo* bridged ion, as shown in Figure 24, and so you don't detect it very easily.

Conclusions

The structure of the 2-norbornyl cation, the most vituperative controversy of the 20th century involving numerous leading chemists, stimulated many methodological developments and refinements to distinguish single- and double-well potentials. Brown did not "kill physical organic chemistry", but his criticisms pointed to many important, but poorly understood problems.

The verification of sigma-bridging established the validity of "pentavalency" for carbon and its wider acceptance as a bonding possibility. Note that nitrogenase, a rather important enzyme, has a six coordinate carbon!

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Chapter 8

From the Ivy League to the Honey Pot

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[3]Deceased Nov. 21, 2014

Paul Schleyer writes of his early life and research, his use of computational chemistry and his move from Professor at Princeton University to Professor in Germany at the University of Erlangen-Nurnberg. His draft was edited and completed by Andrew Streitwieser.

Introduction

A few decades ago almost two dozen organic chemists were chosen to have their chemical autobiographies published by the American Chemical Society as part of a series, “Profiles, Pathways and Dreams” edited by Jeffrey I. Seeman. Paul Schleyer (Figure 1) was one of those chosen and for this purpose he wrote a draft that he called “From the Ivy League to the Honey Pot”. Jeff Seeman critiqued this early draft and suggested, as he did with everyone in this series, numerous changes, mostly expansions and clarifications. Paul never got back to this project and his autobiography was never published. When I last had dinner with him, a few months before his death, he expressed regret that he never finished this work. After Paul’s death it seemed appropriate, given his extensive contributions to physical oganic chemistry, to include a memorial to him. What better memorial than one in his own words? I’ve taken Paul’s unfinished autobiography, made editorial changes here and there and added appropriate references and figures. I could not respond to all of Jeff Seeman’s queries but I have included some additional clarifying material in brackets. The result emphasizes what Paul thought important and I hope it is a fitting tribute to this remarkable scientist. He and I were friends for many years. He has stayed in my house in Berkeley on a number of occasions and I have stayed at his house in Rangen, a hamlet near Erlangen. One disclaimer:

the opinions expressed are those of Paul Schleyer and do not necessarily reflect my own.

Andrew Streitwieser
University of California, Berkeley

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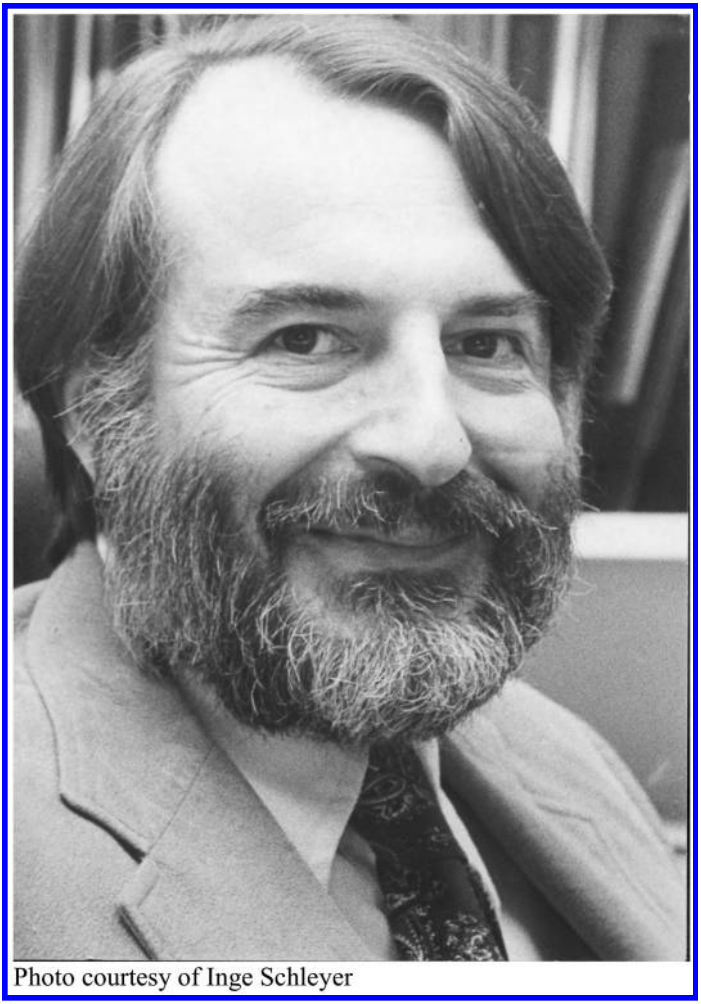
Photo courtesy of Inge Schleyer

Figure 1. Paul Schleyer in 1990 in Erlangen. Photo courtesy of Inge Schleyer

Early Years

I received a small Gilbert chemistry set on my fifth birthday. My mother overestimated my mental abilities but I do remember heating iron filings together with sulfur in a spoon over the kitchen gas range. The fact that the iron sulfide produced was no longer attracted by a magnet interested me less than the blue color and the pungent smell of burning sulfur. Since the experiment was described in the manual, I was delighted to perpetrate this nuisance.

When I was 12, my earnings as a newspaper delivery boy enabled me to buy a larger Chemcraft set. But I was especially intrigued by the catalog, which showed beakers, Erlenmeyer flasks, and similar “real” equipment not supplied with the set. But what could be done with such apparatus? I started reading chemistry books from the public library, one after the other, voraciously. Like the classical novels I had been borrowing from the Cleveland Public Library, I reasoned that the older the book, the better it must be. It soon became obvious, however, that the newer chemistry texts had more information.

My basement laboratory grew and grew. When the time arrived for high school, there was no point in taking the junior-year chemistry course, so my mother arranged for me to try the final examination. My grade of 99.5% annoyed me because I had missed a question. So I started with the senior advanced chemistry course as a sophomore. This Senior chemistry course was intensive, 3 hours for five days a week, much of it laboratory. We were being trained in analytical chemistry, and I suspect that my interest in the quantitative aspects of science originated here. I also graduated from my paper route to jobs in analytical laboratories. The first was with a water testing outfit (I titrated hard water samples with standard soap solution until the suds remained after shaking) and then with a cast iron foundry (I measured the water content of moulding sand by the acetylene gas pressure developed when CaC_2 was added), but I liked the determination of manganese better, because of the lovely purple color produced.

Having taken just about all the academic courses West Tech had to offer, I graduated a semester early in the winter of 1946-47 expecting to enter Oberlin with a scholarship. However, reversion to Fall-only admission led to reconsideration of my choice of college. My mother thought another part of the country would be a good experience for me, and she arranged a last minute interview and application to Princeton (I had never even heard of the “College Boards”). Being high school valedictorian got me into Harvard as well. I was told that Princeton had the better chemistry department (wrong) and paid more attention to undergraduates (right). I decided even then to wait until graduate school for Harvard and set off in the Fall of 1947 for “the happiest years of my life”. This proved to be no exaggeration: The Princeton undergraduate years were wonderful and it was a thrill to be able to return later as an Instructor.

Undergraduate Years at Princeton (1947-1951)

Through some stupidity on the part of my advisor, I did not take chemistry in my Freshman year. The honors section of Freshman chemistry was a “Gut” as a sophomore, but material I knew well bored me. I finished the qualitative analysis laboratory in record time and N.F. Furman awarded me a book as prize. Although elected President of the ACS, he was a tedious lecturer but Clark Bricker made analytical chemistry exciting. He and R. B. Woodward were the two most inspiring teachers that I have had. I did my senior research thesis with Bricker,

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even though the project, which involved the degradation of various hexoses, first to 5-(hydroxymethyl)furfural and then to levulinic acid, had been suggested by Eugene Pacsu, a carbohydrate chemist. Despite Bricker's influence, I saw more future in organic chemistry which I mastered easily, at least at the level then taught in Princeton. Only later at Harvard did I learm about "resonance", that reactions have mechanisms, and that orientation effects in (*1*, *2*) benzene substitutions have a logical explanation.

Hugh Scott Taylor had been called from Glasgow to head Princeton's Chemistry Department in 1923. His leadership built a center of physical chemistry which had an established reputation in the 1930's. Henry Eyring's departure for Utah shortly after WWII, and the aging of an inbred faculty led to a sharp decline. Taylor never had had any use for organic chemistry, and this division was weak. The leading organic chemist, Everett S. Wallis, had extended Lauder Jones' demonstrations that migrating groups in various rearrangements retain their configuration (1,2). He also, as a consultant, contributed to the Merck total synthesis of steroids (carried out by his former student, L. H. Sarrett (*3*)). The discrepancy between his high opinion of himself as a scientist and reality was embarrassingly apparent when I returned to Princeton a few years later. However, that Wallis had not kept up was less important for his academic products. Wallis was impressive as a lecturer and raconteur. His advanced course on "the 25 ways to make a carbon-carbon bond" (although given until the end of his life from the same yellowed note cards) contributed to my decision to become an organic chemist.

My nemesis was physical chemistry. R.N. Pease's dry, cramped lectures spoiled the subject for me. I did well in courses I liked – these required little effort - but relatively poorly in those I didn't. I have never developed the self-discipline to study subjects I don't find interesting.

Besides their written theses Princeton seniors had to take comprehensive examinations in four chemical branches: of these, analytical and organic were easy for me. Although I had not taken a course in inorganic chemistry at Princeton, my youthful background augmented by further reading sufficed. A poor grade in physical chemistry reduced my graduation to "magna cum laude", but I won the prizes in analytical chemistry and for the best Senior Thesis.

The three top Princeton chemistry seniors of the class of 1951 were accepted for graduate work to all of the schools to which we had applied, and all three of us chose Harvard. I was influenced by L.H. Fieser's organic text (*4*) , which was the best of the day, and his book on steroids (*5*) which was also famous. I learned when I arrived in Cambridge in September 1951, that other members of the chemistry faculty were perhaps even more highly regarded by my contemporaries.

Graduate Student at Harvard (1951-1954) and the Return to Princeton as Instructor (1954)

I arrived back in Princeton as Instructor in the Fall of 1954 without my degree in hand, or even my thesis well under way. The Harvard faculty at this time was

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lax requiring theses to be finished before departure, and many candidates took years to complete this task. I did not set the negative record in this respect, but came close. Although I had only spent 3 years at Harvard, it took nearly that long again to produce the six hundred page opus I finally presented to the faculty, essentially a complete review of the bicyclo[2.2.l]heptane literature. I actually think that Bob Woodward, the second reader, perused the entire manuscript judging from the number of his detailed comments and corrections. He paid me the compliment of suggesting that I publish my efforts as a book, but I lacked the self-confidence to even consider this possibility. Years afterwards, people were remarking that I had the thickest thesis on the Harvard Chemistry Library shelves, and I gather that others made good use of my review. Indeed, my only carbon copy (this was long before the days of Xerox machines) was lent to H.C. Brown. He still has it! Although it nearly cost me my job as instructor at Princeton, my thesis and its preparation taught me a lot. I attempted to treat all aspects of norbornane chemistry, terpenes, Diels-Alder reactions, physical studies, etc., in a more general context, as well as emphasizing the behavior of norbornyl cations and the beautiful and often highly complex rerangements they undergo. This was the theme of my research work with Bartlett, a study of the cations associated with dicyclopentadiene in the various possible stereochemistries. I never finished the project he assigned, unfortunately. The reason was partly due to my lack of perseverance, but the project would have been greatly facilitated by gas chromatography and NMR spectroscopy, both of which had not yet been invented. Indeed, years afterward, others, who were not aware of my efforts and those of my predecessor on the problem, published the essential features of what we were investigating. Bartlett had given me considerable latitude in research, and I chose to determine the accelerating effect of 1-methyl substituents on the solvolysis rates of **2**-exo and **2**-endo-norbornyl systems. I wrote up these results after arriving back in Princeton, but I had no experience in the construction of a scientific manuscript. My fellow students at Harvard had the idea that our work was being carried out, not for publication in the ordinary literature, but for a higher authority, namely the Harvard faculty who might deign to complete a manuscript years afterwards. Times were different then. There was less publishing and less perishing.

I submitted the manuscript to *J. Am. Chem. Soc.*; the referees were critical but kind. Nevertheless, I was so discouraged that I never tried to revise the paper and instead I let it die. I now know that getting the paper accepted would have been relatively easy, but I had no experience then. I strongly feel that coworkers should play a direct role in the publication process while they are still in residence and direct discussion is possible. This is necessary training for future scientists, who must write proposals, reports, and primary publications. The first chapter of most of my students' theses give a thorough review of the background of their topic; many of these have appeared in the literature. Professors will read the thesis of their students more carefully, when each chapter is to be submitted as a joint scientific paper!

Although it is nice to be able to start one's academic career at age 24, I was immature and inexperienced. Paul Barlett, rather unwittingly, had gotten me the job at Princeton. As a member of the Chemistry Department Advisory Board, he

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had berated Princeton for its ingrown faculty. But when asked to recommend an instructor candidate in the field of physical organic chemistry, he mentioned my name without remembering my undergraduate Princeton background. Privately, he had told me that Princeton was pretty much in the chemical doldrums and that I should accept a postdoctoral opportunity that had arrived from Cal Tech. I should have. The incumbent of the honorific Fellowship I was offered was given independence, but I would have had much contact with my scientific hero, Jack Roberts, whom I had greatly admired from seeing him in action during his MIT days. But the lure to my alma mater was too great, and I doubted if my car, a rickety MG TC, would have made it across the country with my wife Barbara and my first daughter Betti, who had been born at the beginning of my last year at Harvard. [Paul married Barbara Anne Kinne in 1952. They had three daughters, Betti (b. 1953), Laura (b. 1955) and Karren (b. 1963). They divorced in 1969 shortly before Paul married Inge Venema. Barbara died in 1994.]

The Korean War was also responsible for the chance to return to Princeton. R. K. Hill, the incumbent instructor responsible for running the undergraduate organic laboratory, was about to be drafted. After I was hired, Dick told the good news of his deferment to his chairman, R.N. Pease, A crestfallen face was the reply. What was the faculty going to do with an extra, unnecessary instructor? Dick, with whom I had played tennis when we were both at Harvard, and I always got along well. We never felt that we were in competition for a single slot, despite evidence to the contrary. In fact, we both achieved tenure. The leisurely pace up the academic ladder of the Eastern universities in the 1950’s can hardly be imagined today. After five years as an Instructor, one might be promoted to Assistant Professor, which was expected to last an additional six years. A few selected individuals might then become tenured Associate Professors. Evidently, this was honor enough as many faculty members retired at this rank. Eventual promotion to a Full Professor was not a forgone eventuality. Princeton’s Chemistry Department finally had to give up the luxury of an initial Instructor appointment due to competition from “Middlewestern” universities who actually started people off as Assistant Professors. My early junior colleagues at Princeton, F. C. (Sherry) Rowland and E. C. (Ted) Taylor, were more aggressive than I and applied for research grants even though the senior faculty strongly advised otherwise. Sherry Rowland left Princeton because of this conservatism but Ted Taylor suffered the envy of the tenured staff, who also would have liked to have had postdocs of their own.

Princeton’s Chemistry Department was not an active place in the middle 1950’s. The only outside speakers were supported by the local ACS section, which meant one organic visitor per semester. Dick, Ted, and I instituted an organic seminar program with student speakers and whatever faculty we could get to come without expenses. We regularly attended symposium series held by the North Jersey ACS Section in Seton Hall and in Philadelphia and transported carloads of graduate students with us to experience the prominent chemical personalities of the day. This led to admonishment by the senior faculty whose students complained about this “requirement”.

From Adamantane to Dodecahedrane: Cage Hydrocarbons by Rearrangement

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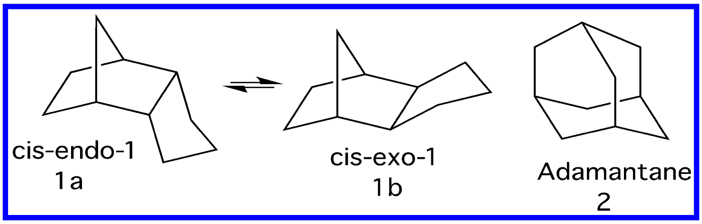
My knowledge of the bicyclo[2.2.l]heptane literature led to an early reward which helped to establish my career. An obscure paper (*6*) published in Dutch in 1903 reported the sulphuric acid isomerization of tetrahydrodicyclopentadiene, **1**. A cis-trans isomerization was proposed but the author used an incorrect structure for **1**. Alder and Stein's elucidation of the structure of dicyclopentadiene in 1931 (*7*) allowed speculation about the nature of the rearrangement. Until Derek Barton's (*8*) "conformational analysis" trained organic chemists to consider the geometrical consequences of molecules even bridged ring systems were all too commonly regarded in the same way they were written: as planar representations. Barton had preceded me at Harvard by only a year, but three-dimensional thinking had taken complete hold by the time I arrived. The new insights into the behavior of molecules were actively discussed and explored during my graduate student days. On the basis of such considerations a cis-endo-**1** (**1a**) to cis-exo-**1** (**1b**) isomerization seemed likely (Scheme 1), and verification of this explanation was one of the first projects I undertook after my arrival at Princeton.



Scheme 1

Sulphuric acid treatment of **1a** gave **1b** just as I had expected, but the isomerization was slow. Aluminum chloride was known to be a much more effective catalyst for alkane transformations, and indeed led to a vigorous reaction when added to **1a**. Although I could hardly have anticipated it at the time, this experiment proved to be the beginning of three decades of involvement with cage hydrocarbon rearrangements.

Princeton's underequipped Chemistry Department did not even possess a gas chromatograph in 1955, and tedious fractional distillation, e.g., through a carefully packed and temperature controlled two meter column, was the only way to analyze hydrocarbon mixtures. It was more convenient to work on a several hundred gram scale, even though this meant that distillations would take over a week and constant supervision was necessary to ensure the maintenance of equilibrium conditions. My garret laboratory-office in Frick (now condemned for this purpose by safety regulations) afforded an ideal arrangement since the column could be set up right next to my desk. At the end of the long run, after the lower boiling isomer **1a** had distilled, a solid formed and clogged the take-off tube. Expecting this material to be the less stable, higher boiling exo-isomer **1b**, I flamed the take-off capillary with a bunsen burner. Nothing happened. More

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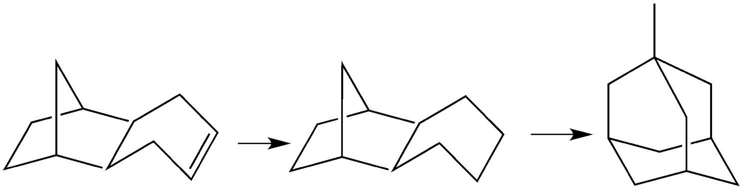
intense heat. Still no results. Direct application of the flame caused the solid to pop in the tube, but it wouid not melt. The distillation pot was essentially empty, but several grams of this high melting substance were obtained by washing the column with ether after it had cooled. I realized that tetrahydrodicyclopentadiene and adamantane (**2**), with its notoriously high melting point of 270°, were isomers, but such a deep-seated rearrangement had no precedent and seemed quite improbable. Transformation into mechanistically closer lying but more symmetrical $C_{10}H_{16}$ isomers seemed much more likely, but how was the structure to be elucidated? I started by determining the melting point of the unknown substance in sealed capillary. Amazingly, at well over 200°, the sample still had not melted, but had sublimed completely onto the cooler upper end of the tube. I had had much experience in working with volatile solids, but this was unique. When the entire sealed part of the capillary was immersed in the heating oil, a melting point could be determined. This approached the literature value for adamantane (**2**) so closely as to constitute a secure identification. But would this suffice for publication purposes?

Adamantane had been discovered in the early 30's by Landa and Machacek (*9*) and assigned the symmetrical structure **2** primarily on the basis of its exceptionally high melting point and the unusual cubic crystalline habit. Their sample was isolated from Czech petroleum. Adamantane is now known to be present, if only in minute quantities, in virtually every petroleum found worldwide, but no adamantane samples were available in 1955. A repetition of Preiog's rather direct but low yield total synthesis (*10*, *11*) was out of the question at this point. Fortunately, I was able to locate infrared (*12*) and mass spectra of authentic adamantane and my brief report on "The Simple Preparation of Adamantane" appeared as my second publication in 1957 (*13*).

I should not really complain about the lack of research facilities at Princeton in the 50's. If we had had a gas chromatograph, the adamantane rearrangement might not have been discovered. Many GC peaks are apparent in the crude product obtained from $A1Cl_3$ and **1**, but none have any guidemarks that would have encouraged further exploration. I take no pride at having been lucky. Many scientists have benefited from chance discoveries! However, I believe chemists should strive to direct and eventually to gain control over what they are doing to an extent which precludes nature springing unexpected surprises. All of my subsequent syntheses in the cage hydrocarbon area were deliberate. The discovery of the antiviral properties of adamantylamine at DuPont was based, for example, on logical extrapolation of existing leads. This compound and its relatives, along with adamantane-based high temperature lubricants, provide the major commercial applications at present. Adamantane is in principle a cheap chemical. Industrial conditions for the quantitative isomerization of **1a** have been developed in Japan. Unfortunately, I never patented the adamantane rearrangement. This possibility had actually been suggested to a consulting firm but their evaluation failed to reveal any reasonable uses, and they declined the offer. I have been rewarded sufficiently. Every fine chemical catalogue now lists numerous adamantane derivatives, all derived from my original synthesis. Perhaps there is an even higher scientific compliment: being taken for granted. Hardly any current paper dealing with adamantane cites even one of my four dozen papers and reviews in the area. The writer of a recent letter wondered if I could be the same Schleyer who had worked on cage molecules a generation ago!

A new graduate student, Robert Nicolas, exploited adamantane chemistry successfully, both physical organic and synthetic aspects. Some physical organic applications will be discussed below. The synthesis of adamantane was quickly generalized. Various $C_{11}H_{18}$ and $C_{12}H_{20}$ precursors provided the next examples of the adamantane rearrangement by leading to methyl- and dimethyl-adamantanes. For example, as summarized in Scheme 2, the Diels-Alder product **3** of norbornene and butadiene (*14*) was hydrogenated to the saturated hydrocarbon **4,** which on standing with aluminum chloride, gave a quantitative yield of substantially pure 1-methyladamantane, **5** (Scheme 2) (*15*).



3 **4** 5

Scheme 2

"Congressane" was our next achievement. The name originated from the 1963 International Congress of Pure and Applied Chemistry held in London which featured 6 as a decoration; e.g., on the covers of abstracts, programs, and publicity material. The foreword to the Handbook explained, "The Congress Emblem 6 represents a beautifully symmetrical molecule which has not, so far, been described in the literature. If adamantane 2 is regarded as an "adamantalog" of cyclohexane then the congress emblem is an adamantalog of adamantane. The hypothetical process of adamantalogous expansion would provide a family of compounds all of which contain part of the diamond lattice. Indeed, diamond is an infinite adamantologue of cyclohexane. The synthesis of the Congress Emblem.... is suggested as a challenging objective for the participants in the Congress."

To meet this challenge, a C_{14} pentacyclic precursor was needed. During a consulting trip to the Union Carbide laboratories in South Charleston, West Virginia, David Trecker described his successful [2+2]photodimerization of norbornene in the presence of a copper catalyst. Although the four-membered ring in this product, 7, was not ideal (too much strain in rearrangement precursors normally leads to ring opening and tar formation), I took a generous sample of 7 back to Princeton and suggested to Chris Cupas that he investigate the rearrangement. The first experiment failed but in the second experiment he noticed sublimed crystals on the cooler portion of the flask that proved to be congressane, 6 (Scheme 3). The simple IR and NMR spectra were indicative, but did not constitute a structure proof. I had heard that Dr. J. Karle and his wife, I. L. Karle had developed a method of **X-ray** analysis that did not require the presence of a heavy atom. They kindly determined the structure of congressane and their report (*16*) appeared simultaneously with our paper (*17*) in **1965.**

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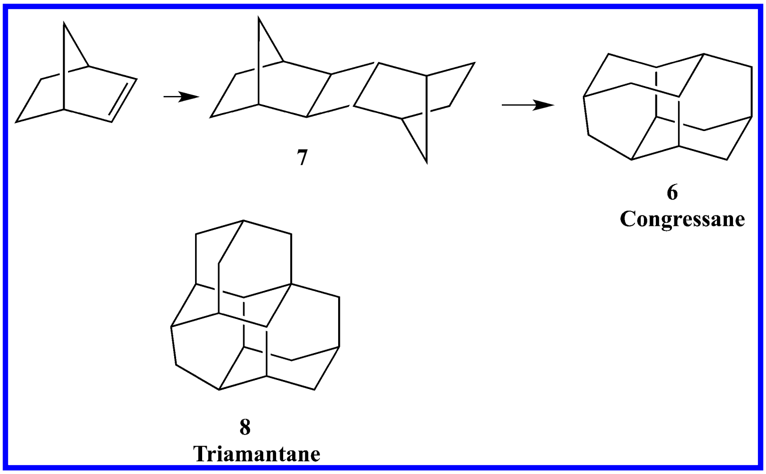

Scheme 3

The synthesis (*18*) of the next homologue, 8, shortly thereafter caused a nomenclature problem. We proposed the trivial name, “triamantane” (Scheme 3), which allowed elaboration to still higher members of the series. Following the same reasoning, “congressane” was redubbed “diamantane”. Sandy Balaban and I later systematized the whole diamond hydrocarbon family (*19*). These studies on diamondoid and related caged systems are just a part of what has turned out to be a whole research area that soon also involved a number of other research groups. The subject has been the topic of many reviews only a few of which are cited here (*20*–*23*).

Carbocation Rearrangement Mechanisms

“Arrow pushing” as a speculative means to describe reaction mechanisms had reached its heyday while I was at Harvard. Some of my contemporaries bragged that they could write a plausible mechanism for any organic reaction. Indeed, we searched for the most complicated examples in the literature to test our friends and to present at the Thursday night Woodward seminars. My speciality was the really wild carbonium ion transformations in cage ring systems, particularly those in terpenes. Later, the adamantane rearrangement afforded a challenge from my own research work. Although, in principle, only three CC bonds have to be broken/made in order to convert **1a** to adamantane, these would involve unlikely 1,3-carbon shifts. The many other mechanisms one could imagine only serve to emphasize the complexities one could expect. At first, it seemed unlikely that the actual mechanism would ever be elucidated, but my early pessimism proved to be unfounded. In a neat application of graph theory, Whitlock and Siefkin at Wisconsin systematized the skeletal rearrangement possibilities in what has been described as a “map of adamantaneland” (*24*). By actual count, there are 2,897 different possible pathways to go from **1a** to adamantane **2**. Some way of narrowing these down to a more manageable number was

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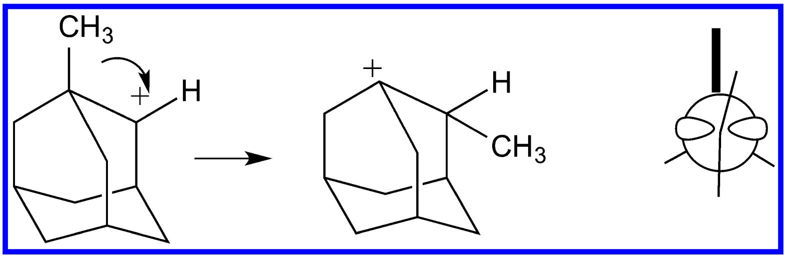
needed. This was accomplished by an early application of empirical force-field (molecular mechanics) calculations. Alkane isomerizations proceed reversibly via intermediate carbocations and, hence, are thermodynamically controlled. By calculating the heats of formation of the possible $C_{10}H_{16}$ isomers on Whitlock and Siefkin's graph, and by considering the strain energies of the carbocation intermediates, we showed that most of the possible pathways are energetically unlikely. We then predicted the most likely routes from the various isomers to adamantane (*25*). Almost all of these routes have now been confirmed by studies of the behavior of the various $C_{10}H_{16}$ isomers synthesized separately. Indeed, all isomerize to adamantane via the isomers postulated as shown, for example, by following the reactions gas chromatographically. More recent investiagtion with carbon labelled materials, carried out by my group and that of the late Prof. Camille Ganter [Deceased 2014], ETH, Zurich (*23*), reveal that the processes are only somewhat more complex than originally envisaged, partly due to degenerate rrearrangements that lead to label scrambling.

Our first attempt to learn something about the adamantane mechanism, by starting with methyl-substitution precursors, failed to give any useful information because of the equilibration of the two possible methyladamantanes under the rearrangement conditions. The 1,2-shift of a methyl group from the 1- to the 2- position of the adamantyl cation appears superficially to be a straightforward carbocation process. As shown in Scheme 4 the rearrangement is accompanied by the change from a secondary to a tertiary carbocation, albeit at a bridgehead (I show below that the bridgehead cation is actually quite stable). However, as also shown in Scheme 4, the dihedral angle between the methyl group (bold bond) and the vacant orbital is highly unfavorable – the methyl bond lies virtually in the nodal plane of the empty p-orbital. Instead, the interconversion of the 1- and 2-methyl carbocations occurs by a skeletal rearrangement in which the methyl and attached carbon move as a unit. Protoadamantane (so named because it is just before adamantane on the Whitlock - Siefkin graph) intermediates were demonstrated to be involved by carbon-labeling experiments. These considerations led to a rather extensive study of protoadamantane chemistry which is enriched by the lack of symmetry and the large number of positions each exhibiting a different chemistry and often degenerate isomerizations (*26*, *27*).



Scheme 4

The advent of superacid chemistry afforded a new way of examining such rearrangements, by viewing the cationic intermediates directly. The

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1-adamantyl cation is a species that George Olah generated as part of our long-lasting collaboration (*28*). The adamantane rearrangement takes place under such stable ion conditions and both the Sorensen (*29*) and my group have observed intermediate ions with different carbon skeletons. Nevertheless, the 1-adamantyl cation refused to undergo even degenerate rrearrangement at the highest temperatures we could use. Thus, Martin Saunders and I found the barrier to 1,2-hydride shifts to be at least as high as 30 kcal/mole (*30*), in sharp contrast to the usual facile rearrangements and neglible barriers of systems that can achieve more favorable orbital overlap.

These results show that not just thermodynamic factors control these reactions. There can be mechanistic bottlenecks. In other words, some of the needed rearrangement steps are inhibited by barriers too high to be overcome under the reaction conditions, even when the overall reaction is favorable thermodynamically.

The Move to Erlangen

I have often been asked, “Why did you move back to Germany?” or “How do you like being back in Germany?” “Back?” Perhaps if my genes had a memory, I could answer these questions. The implication appears to be that no native American would leave a chaired Professorship at Princeton for a post in a little known provincial German university. Although 28% of Americans have predominantly German ancestry, the assumption that I must have been born in the old world rather than in Cleveland, Ohio, seems to have taken a persuasive hold. After my move, I suddenly became “von Schleyer” on both sides of the Atlantic. It is a not uncommon practice in the United States to honor a relative (my grandmother, in my case) by christening a child with a family name as middle name. I never have used “von Rague”, except professionally, but I have been consistent in employing it or an abbreviation on all my publications, from my first onwards. Although the “von Rague” has nothing to do with the “Schleyer”, Germans like titles and it is impossible to convince them to call me simply by my last name. But to my amazement, “Paul Schleyer” became “Paul von Schleyer” also to his American colleagues after his move “back” to Germany. I have complained to my wife, but she responded, “Give the people what they want”. Inge is a genuine Hessian, but emigrated at the age of 26 never expecting to return. I accepted the “call” to Erlangen despite, rather than because of her wishes.

Computer time was the main reason. It was literally impossible to develop my interest in computational chemistry at Princeton because of the restrictive policies of the administration. Computer time was sold, and at high hourly rates, in order to make the computer center as self-supporting as possible. Through grant money, I could perhaps have purchased 10 CPU hours a year. I needed more like 10 hours per day. At the beginning of the computer age, Princeton treated its facility like a library, and computer time was free. But nothing ever seems to be free in American Universities. This meant that costs for the computer were an indirect charge, levied at some percent of every research grant. Government auditors forced a change to direct charging, arguing that libraries can be assumed to be used by every research

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project, but not necessarily computers. Kurt Mislow, while he was Chair, took care of me by allocating a good share of the computer "funny money" allocated to the Chemistry Department. While this sufficed (but only barely!) for molecular mechanics calculations, the entire time could hardly make a dent into my emerging interesting ab initio calculations.

During the 1974-1975 sabbatical year in Munich, many members of my research group were able to accompany me. Although we were only guests, we were able not only to use the University of Munich computer, but also the IBM employed for administrative purposes at the Bavarian Ministry of Culture and Education on nights and weekends. For the first time, we could almost calculate "to our hearts' content" and to use the computer to explore basically new ideas in chemistry, rather than merely calculating what was essentially known already.

It was during this time that the offer to come to Erlangen was made. I am a realist and knew quite well that the inherent advantages of the German system with regard to the positions and research support provided could not be matched even by a wealthy American university. The institutional structures simply are different. My only significant request - two hours of free computer time a week - was turned down flat by the Princeton's Dean of the Faculty, even though it was obvious to my students that the machine was often idle on nights and weekends. What might have been an agonizing decision thus became quite simple. So I left my Alma Mater, where I had spent a quarter century as student and teacher, with little regret, the children from my first marriage, my aged father and a lovely Bucks County farm behind with considerable regret and moved to Erlangen with a very unhappy Inge, several cats, and a few members of my small research group. Mainly due to the elimination of the NIH Postdoctoral Fellowships Program, which had allowed the recipients to work with whom they wished, my group had shrunk from the high of about 30 around 1970 to only a handful. I had reckoned that the research set-up at Erlangen might in its totality be about one and a half times better than at Princeton. I quickly discovered that my estimate was far wrong. The new situation was far, far better than I had expected. The universities in Germany support their Professors rather than vice versa with positions and general funds whereby a rather large group can be supported without need for any outside research grants. The infrastructure of a German institute, with many supporting personnel in permanent state positions, is formidable. The Institute budget should, in principle, cover research as well as teaching costs, although outside grants are now needed to supplement this amount.

I had been promised one shift, 40 hours of computer time a week, on the TR440, albeit that this Telefunken machine was slower than the IBM in use in Princeton. Eight hours a day was possible because the Erlangen computer center was only running their computer during the regular work week, so that someone could always be in attendance. After our shift was added, it was discovered locally that computers really could be allowed to run unattended over night, and eventually it was found that this was also possible on weekends. As a consequence, we soon were using over 70% of .the total University CPU time. We had the lowest priority, but nobody else was using the machine. Computational chemists can never get enough CPU time - their demands are like a black hole - but this seemed pretty near to being in heaven.

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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Inge had hoped that I would be disappointed with Erlangen, and would soon seek to move back to Princeton. But the magnitude of my new set-up was immediately apparent to her. She described the situation to her friends, “He has fallen into a honey pot”. Indeed, a German Professorship (especially in Bavaria) is still a formidable institution. My colleagues complain, but I doubt if they know how well off they are. A recent *Chemical and Engineering News* reported on the “unanimity”, of the “bitterness” and “discouragement” expressed by American chemistry professors with regard to the funding process. It might be harder for younger scientists to build a reputation in Germany, but established Professors can still run substantial research operations without the need for outside funding. German Science Foundation research grants are relatively small, but are also relatively easy to obtain. The proposals are short and can even be drafted (also the reports) by senior associates. The Chemical Industry Fund is like the Petroleum Research Fund in the US, but distributes funds to most chemistry professors automatically, without the need to write any proposals or reports. There are no overhead charges whatsoever! Grants are partly administered by the granting agencies, partly by the Institutes themselves, and only to a small extent by the central university administrations. In Germany, these have not grown out of proportion as in American institutions. Since all German universities are supported, it is felt that charging overhead would only put money from one pocket into another. The German system is too inflexible, but the advantages far outway the deficiencies.

I can actually work in my office creatively for hours during week-days in the middle of the semester without being disturbed. A few Americans have moved to academic positions in Germany but I wonder why more don’t get the idea and apply. It is true that other factors made the move relatively easy in my case. I had spent both my 1964-65 and 1974-75 Sabbatical leaves with Rolf Huisgen in Munich and had been Guest Professor there as well as in Würzburg, Münster and other European universities. I have always taken the opportunity to travel professionally and have given an average of about 25 outside lectures annually over my career. The neat and orderly society of Germany might be boring to some but not to those who enjoy working in a smoothly functioning and well supported environment. My publication rate documents the result. The average over the 21 Princeton years was 11 per year, or 18 in the last decade after I became a Full Professor. The Erlangen average is 25, but I am more proud of the ideas and quality and breadth of these papers than their number.

My transition to Erlangen was remarkably smooth. My predecessor was Prof. Gerhard Hesse, a Meerwein student who had made notable contributions on chromatography during the last part of his career. In the late 1950’s, Hesse had received the call to Cologne to be Alder’s successor. Erlangen was able to keep Hesse by offering him a new building for the Organic Institute, which was finished about a decade before I arrived. Hesse’s carefully thought out design resulted in an attractive laboratory, with a remarkable number of shops just for organic chemistry and instruments. Upon my arrival, I inherited Hesse’s generally well-functioning organisation, and his capable administrator. Dr. Armin Haag. The frictions which had built up between the personnel assigned to the two “chairs” dissipated through friendship with my new organic colleague, Hans

Bestmann, who had played a major role in convincing me to come to Erlangen. I admire Hans for his enthusiasm for research and his interdisciplinary interests. The move was also facilitated by the good advice of another new colleague, Hans Hofmann, and by E.D. Jemmis, a member of my Princeton research group, who had accompanied me to Munich and remained in Germany to set up the computer programs we were using in Erlangen during the Fall of 1975, my last, "lame duck" semester in Princeton. Since 1975, Tim Clark was indispensable, first as a particularly productive member of my research group, and then as a colleague responsible for the rather complex computer operation which had developed over the years. I was additionally helped later when I hired Roswitha Völkner in 1989. With her ability to communicate in German, English and French, she handled much of my correspondence, travel and papers. I was also able when questioned about administrative matters to frequently reply "Ask Rosi".

The Organic Institute benefitted from a rich flow of international and national colleagues most of whom stayed with Inge and me in the "Wagner Villa", a spacious mansion decorated with many pictures of conductors, opera singers, and Wagner family members who appeared annually at the Bayreuth Wagner Festivals. Inge and I were fortunate to be able to rent this house shortly after our arrival in Erlangen. Our visitors helped compensate for the geographical separation of 4 km from our inorganic, physical, and theoretical chemistry colleagues who were housed in a newer campus-like area in the south part of Erlangen but transportation fortunately is quite easy. My group had somewhat different interests than those of my theoretical chemistry colleague, Janos Ladik, but his many visitors, seminar programs, and fine library were considerable assets. Otherwise, the library in Erlangen was pretty bad, especially when compared to Princeton's superb facility. Books and journals were housed in different locations; the budget was inadequate and there was no effective coordination; each Institute decided what to purchase for itself. Indeed, there was no "Chemistry Department" at Erlangen. A "chemistry group" held meetings, but these were informal and were only advisory. The organization consisted essentially of the semi autonomous institutes. Some dechromatization has taken place (less in Bavaria than in Northern Germany), but the Institutes still tend to be dominated by the Full Professors.

When I moved to Erlangen, I noticed that my office, although quite large and pleasant, had a major problem: the door exited directly to the hallway rather than to my secretary's office. Without this buffer, I expected from my American experience that there would be constant traffic into my room and an intolerable number of interruptions. I instisted that a sign, "Nicht storen", be installed, which I could light from a switch at my desk. I never used it. There was no need. Even during semester workdays, hours could pass before someone came to see me, or the telephone rang. On nights and weekends when the laboratory was essentially empty, there is no unwanted interruption at all. The reasons reveal the sociology of the universities as well as German life in general.

German society tends to be family-oriented and immobile. Most students go to the nearest university and then settle in the same area where their parents and earlier ancestors had lived. My foreign colleagues could not believe that there is no "pecking order" of German universities; with the possible exception

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of some of the newest ones all universities are considered to be equally good. There is no competition for undergraduate or graduate students. In fact, there are no undergraduates at all! German secondary education, although essentially exclusively public, generally achieves an average standard rivalled only by the better schools in other countries. Students complete their general education in these Gymnasia at about age 20 having had the equivalent of the first two years of College. Upon entering a University, a German student specializes in his major subject immediately. The first degree, the Diplom (or Master's Degree), is achieved after four years of study. Many students take longer, even much longer, and about a year is devoted to the Master'sThesis. Afterwards, most chemistry students continue to the Doctor's level with the same advisor working on the same topic. Although a German Doctor's Degree is considered to be a higher level than the Ph.D. they are really equivalent. However, it certainly takes longer! Too many students reach 30 before finishing. The system does not force students to complete their studies early, and many take advantage of what was once intended to be intellectual freedom, to draw out the process excessively.

However unfortunate the result may be for a coworker, there are obvious advantages for a Professor's research program in having competent and experienced associates around for a longer time. In addiion, each institute has a number of Instructor positions (Assistantships), a few of them permanent, which can be used to support graduate students, postdocs, or even senior research personnel. In addition, my group benefitted from a number of Habilitation candidates, i.e., aspirants for the teaching profession. These were something like nontenured assistant professors, except that a Habilitation (a "superthesis" with no equivalent in the US) was prepared from independent research results, and no promotion to a tenured position at the same university was possible.

I have always liked to teach, but the first years at Erlangen were pretty awful. I lectured in German from the beginning, but continued to write on the blackboard or on overheads in English to enhance the students' exposure to what has become the common language of science. I have never been any good at languages, and it was a real struggle in the beginning to lecture in German with a limited vocabulary and range of expression. The chemistry courses at Erlangen did not have final examinations and were not graded. (I think this is quite inefficient, since reading assignments are unheeded and most students do not bother taking notes. However, my overheads were xeroxed and circulated to those interested.) Hence, if the lecturer does a poor job and loses attention, students start conversations which creates a background buzz which can become almost intolerable. As a consequence, my German colleagues tended to put a great deal of effort into their lectures and, from a didactic viewpoint these might be better than those of their American colleagues.

Much emphasis was placed on the practical laboratories, which were conducted in inorganic, organic, and physical chemistry with standards and duration that are unknown in the United States. The assistants in charge of these practica had at least a Master's Degree, and the labs were supervised by an Instructor with a Doctor's degree. All of these teaching personnel had their own research work space directly in the laboratory, so as to be generally available to the students, not only to answer questions about the experiments but also

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concerning the Professors' lectures. Although these practica, as well as the accompanying mini-courses on spectra interpretation, mechanisms, etc., received a grade, these were not part of the official record, which consisted exclusively of the marks obtained on set oral hour examinations in the major chemistry divisions at the Master's level. Each student was examined by a Full Professor and a second member of the teaching staff. There was also a similar, but shorter "pre-examination" about two years earlier. This also was not a part of the final record, but did help to orient the student (and the faculty) regarding his level of achievement and promise.

In research, Germany students and the German training system were at their best. By the time they began research, German students had much laboratory experience and considerable self-confidence. Since no differentiation was made until the Master's Thesis, all students were trained equally in organic, physical, and inorganic chemistry. They took pride in solving experimental problems by themselves. Repeating an experiment just to get a higher yield than the literature was typical.

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Applied Spectroscopy and Hydrogen Bonding

Early in his career Woodward formulated rules for the interpretation of UV spectra that enabled the interpretation of chromophores in conjugated systems. Applied infrared spectroscopy, which had its first major success in the penicillin project in WWII, was a more general method, since every organic compound has an infrared spectrum. Detailed structural information could be gleaned from the exact position of stretching vibrations in particular, but what was possible went far beyond the generalities found in the literature.

I actually took my first infrared spectrum while an undergraduate at Princeton, but the cumbersome single channel apparatus was almost useless. It took a day to run. One had to subtract the spectrum of the solvent, determined separately, by hand. By my return, Princeton had acquired a Perkin-Elmer model 21, the standard infrared spectrometer of the day, which, along with a Beckman, I had had much experience in using at Harvard. Every modern inexpensive replica grating spectrometer has better resolution, despite the presence of an impressively large rock salt prism in the older apparatus. In the 3,000 cm^{-1} region, good resolution could be obtained with an LiF prism. Luckily, the Chemical Engineering Department not only possessed such a prism, but also a PE 21 instrument which was hardly used. Daniel Trifan had made some remarkable observations with this machine. The infrared spectrum of a ferrocene derivative having an alcohol side chain showed evidence in the OH stretching region for two new types of hydrogen bonding: to the iron atom and to the π-electrons of the aromatic ring. As was typical of the early post WWII period, Dan had had difficulty in finding a regular academic job, and had settled for a position as an organic chemist in Princeton's "plastics lab". Dan had also obtained his Ph.D. with Paul Bartlett (before my time), and, as a postdoc, did the original work with Saul Winstein on the norbornyl cation. Indeed, it was his discovery (*31*) that the polarimetric racemization rate of the **2-exo** derivative exceeds the solvolysis rate that led to

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Winstein's ion pairing concepts (*32*). We engaged in joint investigations of the extent of OH...π hydrogen bonding. It was possible to show that other polarizable systems, such as cyclopropane rings, also formed hydrogen bonds with proton donors, and to demonstrate the power of this method as a tool for analyzing structural details. This soon became one of my major areas of research interest leading eventually to some 30 papers.

A major contribution was the demonstration that hydrogen bonding was a much more wide-spread phenomenon than had been realized. For example, Pauling's "Nature of the Chemical Bond" states that hydrogen bonds only are possible with the most electronegative elements, nitrogen, oxygen, and fluorine (*33*). Water, ammonia, and HF have abnormally high boiling points whereas their higher molecular weight congeners, PH_3, SH_2, and HC1, are gases. My third scientific paper (*34*), with Bob West of Wisconsin, showed that the elements P, S, Cl, as well as As, Se, Te, Br, and I, as their alkyl derivatives, function perfectly well as *proton acceptors*. It is their inferior *proton donor* ability that differentiates them from their first row counterparts. In a later paper with West's group (*35*), these conclusions were extended by thermochemical hydrogen bonding measurements.

In my group, Adam Allerhand showed that strong hydrogen bonds form to halide anions (*36*), and that carbon can function both as proton acceptor (in isonitriles) and as proton donor (*37*). At the time, the only C-H hydrogen bonding known was with chloroform and with acetylenes. We demonstrated that this phenomenon is much more widespread (*38*); the presence of two or more electronegative atoms or substituents can "activate" phenyl and vinyl derivatives, or heterocyclic rings, for hydrogen bonding. Many implications are still being studied now because of the obvious importance for solvation

Intramolecular hydrogen bonding, typically between hydroxy groups and a second function in the molecule, provide an effective way to study structural details, for example, in the influence of substituents on the populations of different conformers as well as on the ease of ring formation. In many cases the configurations could be assigned readily although this might have been difficult by other methods. The ability to form hydrogen bonds depends on the orientation of the functional groups; "mapping" of proton acceptor sites could be achieved in rigid systems in which the OH probe could only reach certain positions of the proton acceptor (e.g., the π– but not the σ-lone pairs of a carbonyl group). Fine detail is revealed by this method, even the steric environment of free OH (i.e., not hydrogen bonded) groups by the number of stretching vibrations and by their exact frequencies. The "mapping" of proton acceptor sites by means of intramolecular hydrogen bonding is a forerunner of the modern electrostatic potential representations of functional groups. Rather than the tedious and limited experimental procedure of synthesizing many molecules with (more or less) fixed geometries, it would be much simpler and effective today to carry out such hydrogen bonding "mapping" computationally. Furthermore, this would also give information about energies which could be inferred only indirectly from the OH spectral shifts.

In the 1960's NMR became an indispensible spectroscopic tool. One of my best early contributions in this area was with my first post-doctoral coworker, Pierre Laszlo. Our paper on the NMR spectra of norbornene derivatives (*39*) became one of my "citation classics". We were among the first to obtain ^{13}C-H coupling constants from proton spectra on compounds with carbon in natural abundance. This enabled the determination of proton-proton coupling constants between otherwise identical nuclei (which is why the norbornene paper attracted so much attention). We employed this method more widely, e.g., to study the effects of substituents on coupling constants, especially in symmetrical systems.

Solvolysis Reactions

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From the work of Ingold and Hughes on nucleophilic substitution reactions in the 1930's until approximately the death of Saul Winstein in 1969, the solvolysis reaction engaged the attention of many, indeed, most of the leading organic chemists of the day. So many insights concerning mechanism and the nature of electronic interactions in ions and molecules were revealed. It became fashionable in the 1950's and 1960's, particularly in the United States, to introduce a tosylate group onto an interesting carbon skeleton and measure the reaction rate. The remarkable results, an enormous range of reactivities often influenced by seemingly small changes in structure, complicated rearrangements, and the extension of carbon bonding theory to higher coordination, more than justified such widespread interest. Substrates with arylsulfonate leaving groups could be prepared readily from alcohols of known structure. The solvent of choice in the early days, acetic acid, could be purified easily and gives esters as substitution products. These in turn could be converted to alcohols which often were easy to identify.

Although significant work on solvolysis continues today, this area no longer engages the rapt attention of former years. The reasons are several. The first is the natural turn to newer fields of interest, the second is the ability of studying carbocations directly in superacid solution as well as in the gas phase rather than as fleeting intermediates, and the third is an unfortunate aftermath of the "norbornyl ion controversy". If highly regarded chemists could not agree about the interpretation of the behavior of such a seemingly simple system, what was to be learned by further investigation of yet more examples? To these three reasons, a fourth can now be added: the ability of ab initio calculations to provide detailed information about the geometries, energies, and electronic structures not only of carbocation minima, but also of transition structures.

Based on salt effects and the effects of substituents, many solvolysis reactions of sulfonates in acetic acid were thought to have significant carbocation character and to involve carbocation ion pairs as intermediates (*40*). My initial studies in this area were designed to develop criteria for the direct ionization to such carbocation intermedates without involvement of nucleophilic displacement by solvent; i.e., the so-called *limiting* solvolyses. Solvolyses involving phenonium ions appeared to be such systems. Cram's superb early work had established that tosylates with β-aryl groups solvolyze to give substitution products with retention of configuration at the reaction center, but with inversion at the rearrangement site, i.e., exactly the stereochemistry expected on the basis of bridged phenonium ion intermediates (*41*, *42*). While participation of the phenyl group was believed to be simultaneous with ionization, there was a major problem. A participation mechanism requires rate enhancement, but the introduction of a β-phenyl group often led to a decrease in the rate. A "numbers game" developed whereby possible steric and inductive corrections were applied to attempt to explain this discrepancy. Brown (*43*) argued that these corrections were small, whereas Cram (*44*) suggested corrections that proved to be too high.

We solved this problem in a 1969 set of papers in three different ways (*45–48*). The most general approach employed graded Hammett sets of β-aryl groups. But instead of a single straight line, two intersecting straight lines were observed. The one of higher slope clearly corresponded to aryl participation since the charge was brought more into the vicinity of the substituent in the phenyl ring, while the line of lower slope corresponded to the aryl-unassisted reaction with the solvent. The key to the interpretation was provided by the observation that the β-aryl rate enhancement (obtained by subtraction of the extrapolation of the line of lower slope), corresponded exactly to the product distribution. Olefins and inverted substitution products arose from the reaction with the solvent, whereas retention of the configuration indicates phenonium ion intermediates. As there is no cross-over between these mechanisms, no free or weakly solvated carbocations could intervene. Instead, there must be competition between two strongly assisted processes, involving β-aryl group participation on the one hand and nucleophilic solvent participation on the other.

This conclusion provided many new insights, not only with regard to the phenonium ion problem and the interpretation of neighboring group effects in general, but also with regard to the mechanism of solvolysis. It had become apparent that acetic acid is quite far from limiting as a solvent, and that the solvolyses of many secondary and virtually all primary substrates are probably essentially more S_N2 in character rather than S_N1. Interpretations which had assumed carbocation intermediates now required revision. Earlier observations that pointed in this direction, such as Streitwieser's finding of essentially complete inversion of configuration in secondary (*49*) and deuterium-substituted primary solvolyses (*50*), had been reconciled with the S_N1 mechanism by assuming ion pair intermediates. Those might still be present, but it was now apparent that considerable bonding to the solvent must be involved. To demonstrate this directly, a secondary substrate was needed which shows almost no tendency towards participation of any kind. The 2-adamantyl system seemed ideal for this purpose. The backside of the leaving group is strongly hindered, and no participation by neighboring hydrogen (unfavorable torsional angles) or by neigboring carbon (this would lead from an unstrained to a strained skeleton) could be expected. Indeed, the solvolysis behavior of 2-adamantyl tosylate in a variety of solvents paralleled that of tertiary substrates, particularly 1-adamantyl where no solvent participation from the backside is possible. This constancy contrasts sharply with 2-adamantyl/isopropyl rate ratio comparisons, where changes over 10^7 were observed with changes in solvent. The 2-adamantyl system also passed numerous other mechanistic tests. These results were presented as a series of communications in 1970 (*51–53*). Although it has now been joined by

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other similarly-behaving substrates, 2-adamantyl remains the primary mechanistic standard for “limiting” solvolysis in secondary systems.

Another important contribution to solvolysis reactions was a modification of the Grunwald- Winstein solvolysis equation (eq. 1) (*54–56*).

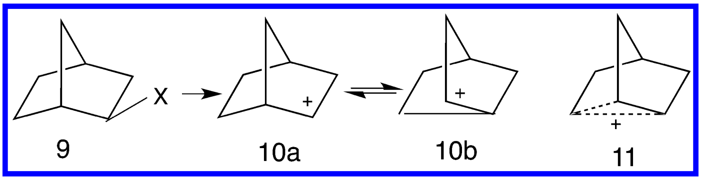
$$\log k/\log k_o = mY + lN \qquad \text{eq. 1}$$

This equation contains both solvent ionizing power (mY) and solvent nucleophilicity (lN) terms, but the latter term was never evaluated. We did so by means of the simple and reasonable assumption that CH_3OTs has m = 0.3 (the value in AcOH and HCOOH), and *1* = 1.0. The resulting scale was published in two full papers in 1976 (*57*, *58*). There is still debate over details, but the importance of nucleophilic solvent participation is firmly established.

The Interminable Norbornyl Controversy

When facts are in dispute, further experimentation can resolve the matter. Even when the facts are clear, debates over interpretation may be considerably more heated. They certainly can be harder to resolve. The recriminating scientific altercations of 19th century chemists are famous. Definitive data was difficult to obtain and professional reputations were considered to be of paramount importance. Even though we pride ourselves on the sophistication of modern science, the norbornyl cation controversy lasted for over a quarter century. At least for some it never ended.

The problem can be stated as follows: In reactions of *exo*-norbornyl compounds **9** (Scheme 5) expected to produce the carbocation **10a**, rearrangement to the enantiomeric cation **10b** takes place presumably via structure **11**. The simple question is then: Is **11** a transition state between **10a** and **10b** or is it an intermediate more stable than **10**? Structures of the type **11** have been proposed for a number of other carbocations and are referred to as σ-bridged or non-classical, the latter because in such structures the number of bonds exceeds the number of electron pairs available. In their initial paper on norbornyl, Winstein and Trifan (*31*) proposed that **11** is relatively stable and explains why **9** is more reactive than the *endo*-isomer, an effect that they called *anchimeric assistance*. H. C. Brown, however, explained the *exo-/endo* ratio on steric grounds. Thus was born the norbornyl controversy that involved a number of chemists and much of the chemical literature.



Scheme 5

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Only part of the norbornyl controversy was exposed to the chemical public (probably more than they were interested in), but this was a modicum relative to the information flood that insiders received, in particular, by H.C. Brown's privately circulated Norbornyl News Letter. This, and my correspondence with him, literally occupied a file cabinet of space. In the next century, historians of science will have a treasure trove of detailed documentation. It is not my intention to write this history here, but I would like to relate some of my own involvement. My scientific experiences with Herb Brown on the phenonium ion were quite positive. He considered my interpretation of the solvolytic behavior of β-arylalkyl arenesulfonates as a competition between solvent and neighboring group participation, and subjected it to further experimental test. This convinced him, and we published the results together (*59*). However, the phenonium ion can be written as a normal covalent intermediate with a tetracoordinate carbon. For Brown, the norbornyl cation is in a different category, since five bonds or, at least partial bonds to carbon are involved. Brown could not really object to such pentacoordination on theoretical grounds. After all, myriad carboranes and metal carbide carbonyl clusters have carbon coordination five, six and even eight, but he was sceptical that such bonding arrangements for hydrocarbon ions could be viable in solution.

Over the years an overwhelming amount of information built up that supports Winstein and Trifan's original contention, but Brown would not concede. In 1975, Brown suggested that we might debate the norbornyl problem not merely by letter, but in the form of a book in which all aspects could be aired. In "The Nonclassical Ion Problem" (*60*), I was given the opportunity to comment on each of the chapters. Earlier reviews of the norbornyl problem had all concluded that the ion is bridged, but Brown not only summarized the data exhaustively, but presented his reasons against coming to such conclusions. In turn, I tried to expose the weaknesses of Brown's arguments and interpretations.

It is not true that Brown locked me into a room next to his office and would not let me out until my "Comments" were completed. But this rumour has some foundation. Since my contribution was making slow progress Herb invited me to come to Purdue to get it done. Herb himself brought me my lunch (a hamburger from McDonalds) so that I could work through undisturbed. The resulting book gives a reasonably complete view of the matter at the time of the mid-1970s; but in the end Brown failed to show that effects other than anchimeric assistance and bridging are responsible for the behavior of the parent 2-norbornyl system. I will not go through the many research results since then but will suffice to refer to some recent reviews of the entire subject (*61–66*) .

I have often heard the opinion that the interminable norbornyl controversy "killed" physical organic chemistry. At least in the USA, funding went elsewhere. But physical organic chemistry merely changed its address and its leading practitioners have become scientists who are formally associated with other disciplines. The negative aftermath of the greatest chemical controversy of our time was outweighed by far by the scientific challenge and stimulation it provided.

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My Beginnings as a Computational Chemist

The structures and energies of molecules have always intrigued me. The appreciation of the relationship between the geometry of a molecule and its behavior is the seminal contribution of “conformational analysis”, but the awareness that “strained” molecules would be more reactive and could exhibit exceptional behavior is now over a century old. For example, nonclassical carbocations are associated, with few exceptions, only with strained systems. My interest in cage molecules obviously required an appreciation of thermodynamic quantities.

By the 1950’s, the heats of combustion of an extensive set of acyclic and many representative cyclic hydrocarbons had been determined as part of an American Petroleum Institute project. However, data for only a few polycyclic hydrocarbons were available. I actually started in my early days at Princeton to prepare large quantities of the carefully purified samples which were needed for measurements in specialized laboratories. It quickly became apparent that less tedious approaches to obtaining thermochemical data would be a blessing. The same thought applied to the elucidation of the detailed structures of molecules. I was particularly intrigued by the exact geometries revealed by microwave spectroscopy, and followed the chemical physics journals where these papers were published. Victor Laurie, a colleague in this area at Princeton, convinced me that no rapid accumulation of data from this source could be expected. I am sure most of my fellow chemists, needing to know a fundamental quantity for their research, have often suffered the frustration of not being able to find the data in the experimental literature. The solution to this problem is now obvious. Basic infomation can now be obtained more readily, and perhaps even more reliably, by computation than by experiment. But this was not the situation in 1965 when my interest in computational chemistry began. Gerald J. Gleicher had joined my group as a postdoc fresh from a similar stay with Michael Dewar in Austin. Molecular mechanics programs were in their infancy, but held considerable promise, especially since digital computers were becoming available. Ken Wiberg kindly gave us his program, the first to include an automatic geometry optimization routine. Gleicher developed it further and parametrized a force-field for carbocations. This led to my first computational paper, published early in 1967 (*67*). The central application was the conformational analysis of bridgehead carbocations and the program was ideal for this purpose. Paul Bartlett had shown that l-halobicyclo[2.2.1]heptane derivatives are essentially inert (*68*), since the carbocation intermediates would be high in energy because the preferred planar geometries could not be achieved. Indeed, the difference in strain energies between a bridged hydrocarbon and the corresponding bridgehead carbocation provides a reactivity index. This gave a nicely linear plot with the experimental rate data for the four systems that then were available.

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Good theories must be able to make difficult predictions and, to be effective in chemistry, must be able to do so quantitatively. I would like to quote my 1967 paper: "Although the calculation scheme presented here is by no means in final form, we have used it to predict the reactivities of other bridgehead systems." Starting with this 1967 paper, I have been confident enough not only to make, but also to publish my predictions. I have tried deliberately to discover examples which violate the accepted and most fundamental rules (or preconceptions) involving structures and bonding. The increasing number of experimental verifications of these predictions has been especially gratifying. The first of these verifications involved several new solvolysis rates of bridgehead systems that Gleicher and I had predicted. By 1971, the experimental data had been extended to 16 bridgehead systems encompassing a relative rate span of nearly 10^{20}. The Princeton molecular mechanics programs had undergone further revision, and Dick Bingham and I showed how well the new data could be correlated (*69*). Further predictions were made and the applicability of the same type of treatment to free radical reactivities was demonstrated. A little later, in collaboration with Willy Parker, we showed that reactivities at bridgeheads could be enhanced, rather than inhibited in middle ring polycyclic systems, since strain could be relieved in going to planar carbocation or radical centers (*70*) . The same reasoning eventually led to our computational discovery of hyperstable bridgehead olefins which, contrary to Bredt's rule, favor placement at bridgehead positions (*71*).

The predictions of bridgehead solvolysis were the first demonstration that empirical force-field calculations could be applied successfully to reactivity problems. This emphasized that chemists eventually would have easy-to-use quantitative computational methods to help solve, and, even more significant, to help find important problems. These predictions of reactivity have had important and interesting sequels. The carbocation force-fields we derived were applicable to secondary, as well as to tertiary systems. But the further development of this approach has been carried out by others.

John Pople and My Introduction to Quantum Chemistry

In 1969, I had my first substantial contact with John Pople at the Mellon Institute during an NSF Lectureship in which I described our work on carbocations. John and his group were just developing the Gaussian 70 program, and carbocation problems were attractive applications. My first participation in ab initio calculations on such species actually had begun at Princeton in collaboration with my colleague L. C. Allen, with Rainer Sustmann, a postdoctoral associate who had carried out semi empirical computations in Michael Dewar's group, and with my first theory graduate student, Jim Williams. However, it soon became apparent that Pople's programs were much more efficient, and he was less limited by computer time restrictions as well. Thus began our 70-paper collaboration which continued until John Pople's untimely death in 2004.

I never had any formal theoretical training. Even physical organic chemists of my day saw little point in learning about quantum mechanics, since this was unlikely to be anything they would ever use. I served largely as "carbonium ion consultant" in the early collaborative work with John Pople. John had always had an especial ability to couch his explanations in terms his discussion partner could understand; high level for some, lower level for me. Unlike many theoreticians, he knew and understood chemistry extremely well. But I was a busy person with a large research group in the early 1970's, and calculations were only one of my interests. Quantum chemistry texts presented masses of equations that quickly defeated my emerging interest. Like all organic chemistry teachers of the day, we had acquired a superficial knowledge of qualitative molecular orbital theory from the Woodward-Hoffmann rules, but these were largely confined to π-systems. The picture book of Jorgensen and Salem (*72*) proved to be a revelation for me. It is said that organic chemists can only understand pictures, rather than equations. I doubt if this is correct, but the visual presentation of MO's made obvious and interesting what seemed obscure before. I spent sleepless nights in extreme excitement literally thinking about molecular orbitals. How might I apply them to problems in which I was interested? As a teacher, how could I provide new explanations which heretofore had been couched in other formalisms? During my sabbatical year in Munich, I developed a course of lectures on qualitative molecular orbital theory for organic chemists based on slides from the Jorgensen-Salem book. Wisdom was overlooked in my enthusiasm. There was a great deal which I should have known, but did not understand.

There was one good way to learn: by calculating. I started to use molecular orbital theory to design new arrangements of atoms, and to use computations as an exploratory tool to discover new chemical structures. Ideas were tested in the computer. If they did not work, there was something I had not understood. A new job was submitted, and the next day a new result emerged that provided further insights. Never in my life had I been able to have such rapid turn-around between an idea and its test. My experience with experimental research was nothing like this. One could wait for months until a student prepared the starting material and the key measurement was carried out. Computational chemistry goes to the heart of the problem directly and provides the key answers almost immediately. The 1974-1975 sabbatical year was the turning point in my professional life. Thereafter, theory and computations came first, and experiment followed. But this is not quite accurate. Computations are also experiments, and I will never lose the experimentalist's insistence that results, from whatever source, be subjected to critical scrutiny and be compared with as many other sources of information as possible.

Roald Hoffmann's ideas provided early inspirations. He had examined the possibility that the electrical effects of substituents might help to stabilize planar tetracoordinate carbon preferentially. He explored a number of possibilities by extended Hückel calculations while recognizing the inherent deficiencies of this method. His work indicated that π-acceptor groups and electropositive substituents would reduce the energy difference between tetrahedral and planar methane, but he did not succeed in locating any system that might violate van't Hoff stereochemistry. This seemed like an ideal problem for ab initio calculations. My research group attacked this problem with excitement! What evolved was the development of an understanding of the best strategies for solving problems by computational means. We started by examining ideas that seemed attractive

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from qualitative MO considerations. Thus, the isomer of cyclopentadiene with all hydrogens in the plane would have six π-electrons which should enjoy aromatic stabilization but it was far from enough to overcome the inherent preference for the tetrahedral arrangement of the methylene group. This anecdotal approach was hit or miss. In contrast, John Pople had been studying the effects of F, OH, NH_2 and CH_3 (as well as other substituents) on basic organic functional groups. We extended this approach for the first time to the more electropositive groups, BH_2, BeH, and Li, in order to complete the “first row sweep” of groups with widely varying electrical properties. This systematic approach was applied to the planar methane problem with startling results. The energy difference between “tetrahedral” (C_{3V}) CH_3Li and the planar C_{2v} arrangement was reduced by over 100 kcal/mol from the value for methane. When two lithiums were present, as in CH_2L_{i2} a practically planar species resulted. Not only that, but the singlet-triplet separation also became quite small. Both results were unprecedented for such a simple methane derivative. We had already ascertained that the planar-tetrahedral energy difference was reduced significantly in strained systems. After all, planar tetracoordinate carbon has 90° rather than 110° bond angles. Combining these effects led to 1,1- dilithiocyclopropane, which was the first molecule actually calculated to prefer a planar tetracoordinate carbon.

John Pople then made a key suggestion. In some respects, he argued, cyclopropane and ethylene behave similarly. Perhaps the preferred geometry of 1,1-dilithioethylene might also be turned around by 90°. Indeed, our calculations showed the perpendicular form to be more stable than the planar, even though both retain the C=C double bond! The calculational demonstration that dilithioacetylene prefers a doubly bridged structure rather than the usual linear geometry completed this basic series of rule-violating simple molecules.

Before these papers were published, Saul Wolfe invited me to lecture at a 1978 stereochemistry conference in Kingston, Ontario, Canada. I thought this would be a splendid opportunity to excite my organic colleagues by our new findings. What could be more dramatic to stereochemists than a planar tetracoordinate carbon, perpendicular ethylene, and doubly bridged acetylene? I expected enormous interest and much discussion, especially as many of the leaders in the field were in attendance. But I have never met with a colder even hostile reception - the response was devastatingly negative. No one believed what I had to say or even seemed interested. A decade later (and after many confirmations of other of our theoretical predictions), the climate of acceptance for computational chemistry is changing, but not completely. While Ph.D.’s trained in computational chemistry are sought after for industrial and national laboratory posts, academic positions are not available. Instead, these are reserved for traditional experimentalists, particularly those working in fashionable areas. Meanwhile, computers have become ever faster and more cost efficient, and quantum mechanical and other chemical programs more effective. It is time to train chemistry students for their future that includes computations, and not just for our non-computational past.

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Epilogue

Paul Schleyer's original manuscript ends at this point, about a quarter century ago. He continued working in computational chemistry and in 1993 became the driving force and director of the Computational Chemistry Center in Erlangen. In 1998 he retired from Erlangen in accordance with German law, but he did not fade away. Instead, he moved to the University of Georgia in Athens, GA, as the Graham Perdue Professor and continued to work with graduate students and post-docs and published prolifically. He collaborated there actively with the theorist H. F. (Fritz) Schaefer. He continued to amass a number of awards but the one he desired most was denied him: he was never elected to the National Academy of Sciences, a fact I consider a discredit to that organization. His sometimes agressive zeal probably turned off too many chemists but I believe they should have separated their personal feelings from an appreciation of his scientific accomplishments. Paul and I had our own deep differences in some interpretations of theory but these did not affect our friendship (*73*). A photograph of the two of us together is shown as Figure 2. Paul's legacy as one of the pioneers in computational organic chemistry is to be found in the now common use of computational results even in papers whose main thrust is the synthesis of natural products.

Paul Schleyer died of a heart problem on November 21, 2014.

Photo from Streitwieser collection

Figure 2. Paul Schleyer and Andrew Streitwieser in 1989.

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Chapter 9

Lost in the Funhouse. Life in the Research Laboratory of William von Eggers Doering

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William von Eggers Doering was one of the most influential organic chemists of the 20th century. In this article, two of his students from the late 50s-early 60s reflect on Doering's research accomplishments, while simultaneously describing the silliness, pranks, and amusements that young adults are wont to engage in.

> *One possible ending would be to have Ambrose come across another person lost in the dark. They'd match their wits together against the funhouse, struggle like Ulysses past obstacle after obstacle, help and encourage each other.*
>
> John Barth (1968), *Lost in the Funhouse*

In many ways, college students of the 1950s were like poor Ambrose, fearful of what lay ahead but, at the same time, eager to take on the challenges. Their apprehension was real, but could be ameliorated by their identifying with others who were in a similar situation. In this memoir, the authors (who have been friends since 1955) relate some of their experiences as undergraduate and graduate students of one of the most brilliant chemists of the 20th century.

William von Eggers Doering, Figure 1, ("Bill," once one got brave enough to call him that) received his undergraduate and graduate degrees at Harvard; in his career, he served as a faculty member at Columbia, at Yale, and at Harvard. Upon the occasion of his 90th birthday, a celebration of some of his major research accomplishments was written by Frank-Gerritt

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

Klärner (with some input by the present authors) and published in 2009 (*1*). Subsequently, Mait Jones and Ron Magid produced two additional documents (http://web.utk.edu/~rmagid/index5.html) to provide some personal insights into what it was like to have been associated with Bill during these incredibly productive years. Those manuscripts (unpublished and, frankly, unpublishable) serve as the basis for the chapter that you are now reading.

Figure 1. Bill Doering at a reunion with students in Cambridge, 2009. Photograph courtesy of Ronald Magid.

For incidents and stories that involved the two of us, the plural pronoun "we" will be used. But for those that involved only one, we will take our guidance from the current practice wherein professional athletes refer to themselves in the third person ... and the most famous of whom are identified by only a first name (LeBron, Peyton, Kareem, etc.). Thus, these sections will be third-person accounts featuring either "Ron" or "Mait."

It is not our intention to use this forum to give detailed accounts of Bill Doering's research accomplishments. Suffice it to say that in addition to the topics covered by Klärner, *et al.* (non-benzenoid aromatic compounds, carbene chemistry, and thermal rearrangements of hydrocarbons), Bill had the knack of doing key experiments that would "open" a field ... and then move on to other interests, leaving these new fields to be explored by others. The breadth of the subjects that intrigued him is astounding. Included are Baeyer-Villiger oxidation; asymmetric induction; the Doering-Zeiss mechanism for solvolysis; [2 +2] and

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[4 + 2] cycloadditions; stabilization of closed-shell dienes, trienes, and polyenes; the behavior of diradicals; and many more.

Mait and Ron are the co-authors of this chapter. Both of us were Yale undergraduates in Bill's introductory organic course in Spring-Fall, 1957, and both did our graduate work under Bill's supervision. Mait knew Bill well before he even knew that chemistry existed, and he worked several summers at Hickrill Chemical Research Laboratory (about which much more, shortly) in Katonah, New York, an easy 40-mile drive north from Columbia's campus. His parents lived nearby, knew Bill socially, and were eager to find a job to keep their son off the street, or at least off the tennis court. Bill was kind enough to take on a totally inexperienced kid in a variety of probably make-work jobs. Much later, during his years on the Princeton faculty, Mait maintained a closer relationship with his mentor.

Most organic chemists will know of the absolutely fabulous work that came from that place – much of it the result of Bill's collaboration with the great, underappreciated Lawrence H. Knox – the tropylium ion and much of the early carbene work are only two examples. Hickrill had an ever-changing staff of postdocs, many of them from Europe, all overseen by Doering and a resident, "permanent" postdoc (the afore-mentioned Larry Knox). How could such a place come into being? When Doering joined Columbia in his first faculty position, there was, of course, a period of time when he was low man on the totem pole. At that time there was an unusual graduate student at Columbia, a middle-aged woman, Ruth Alice Weil, who had gone back to graduate school in chemistry. She found that the world of science didn't exactly embrace such people with open arms, and wound up in the research group of the lowest-ranking person, Bill Doering. At some point, at what we used to call a bull-session (ahem), the question of "what would be the ideal home for research?" came up. When it came Bill's turn to speak, he replied that he thought a smallish institute, with 5-10 postdocs, a resident majordomo, and secure funding would be about right. Some time after the meeting, she came up to him and asked, "Did you mean it? if so, I'll speak to my husband about it." It turned out that they had zillions of dollars and they did it. Now we are not sure what the take-home lesson is here, but we find it delicious to imagine all of the big daddies of the time walking the halls of the Columbia chemistry department smiting their foreheads. It's a wonderful image.

Hickrill certainly was "state of the art" at the time, but seems remarkably primitive now. Instrumentation consisted of a Beckman UV, an early infrared spectrometer, a refractometer, and….that's it. There was a wonderful library, looted, as were some of the labs, during clandestine nighttime raids from the Yale campus in New Haven, CT (just 60 miles from Katonah) after Hickrill closed. Times were changing, though, and one of the early projects that Mait can recall was the construction of a gas chromatograph – a preparative model, with a 2" wide column – and essentially no resolving power at all. It could hardly compete with the two-story fractional distillation column that ran from the basement to the second floor – and was packed by Mait at Doering's command, "One glass helix at a time!" Mait cheated.

The "wet" chemistry at Hickrill – and Yale – was also far different from that of today. For example, the scale of things was vastly larger. Need cycloheptatriene?

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You couldn't buy it in those days, and you needed more than the fractions of milligrams we require today. The solution was to dissolve vast quantities of diazomethane (explosive, carcinogenic, and poisonous) in 12 L of benzene and blaze away with General Electric Sunlamps purchased at the hardware store. Low tech it may have been, but it made the molecule. The occasional fires, fueled by 12 L of burning benzene, are best not mentioned. Diazomethane was made from the notoriously dangerous and carcinogenic *N*-nitroso-*N*-methylurea (NMU) with 50% aqueous KOH (never NaOH, which was rumored to detonate diazomethane – or was it the other way round?). NMU itself was required in kilo amounts, and was synthesized in a metal garbage pail that was stirred with an old baseball bat; the solid NMU would rise to the surface and would be scooped away with a beaker in an ungloved hand. At Hickrill, it was Mait's job to do that, as he seemed not very sensitive to NMU, and he recalls bending over that hideous vat, which was bubbling, spitting, and emitting who knows what noxious molecules. At Yale, every new grad student was given this opportunity to achieve fame. Can you imagine that today? Everyone would be in jail.

Mait's role at Hickrill was something less than gopher, and he owes those folks, Larry Knox in particular, a great deal for putting up with him. The effect on a young person is easy to imagine. He didn't know what anyone was really doing, and he vividly recalls looking at the blackboard and trying to work out all the crossing lines of norbornanes and what they meant. Nonetheless, the effect on him was enormous – literally life-determining, and that may stand as a metaphor for the impact Hickrill had on many people and, indeed, for the impact Bill Doering has had on so many of his students and associates.

The "miracle that was Hickrill, alas, came to an ignominious end. At about the time that Mait and Ron entered grad school, Ruth Alice Weil died and her husband at that time decided that the community would be better served if the lab were sold to *The Harvey School*, a local private school. (One is reminded of the French judge's comment as he denied Lavoisier's appeal of his death sentence, "The Republic has no use for savants." But we digress.) We were participants in one raid (of several) to see what could be "liberated" from the lab so that it might serve a higher purpose than as a playground for the benefit of rich kids. One of the items taken was the Perkin-Elmer Vapor Fractometer which had, if one recalls correctly, serial number 0001. Our memory on this is fuzzy, but we remember switching its serial number with one from a machine at Yale so that the new owners would mistakenly believe that this instrument did not belong to them. (We assume that the statute of limitations has long passed. At least we hope it has.) We don't recall what other mischief we did that day or what we might have loaded into the back of Bill's big Mercedes, but Ron has a very vivid recollection of being petrified, not by our having skirted the law, but of riding "shotgun" in the front seat (no seat belts, of course) with Bill driving on back-country roads, holding a hamburger in one hand and a beer in the other, steering with his knees. Obviously we survived, but there were definitely moments of doubt.

Like Hickrill, and of much broader impact in that it affected hundreds of students, Doering's sophomore organic course at Yale was another powerful magnet attracting young people to organic chemistry, even those who were somewhat turned off by their previous experiences with chemistry. Ron, for example, was definitely put off by Yale's introductory freshman course for chem majors – it was classical, descriptive, lacking in any theory, and *dull* – there was no excitement, no sense of passion whatsoever. He had been juggling the possibility of majoring in physics or math or chemistry – by the end of his freshman year, he was ready to commit to one of the first two, but Mait convinced him to defer his decision for another semester or two. The first term of our sophomore year featured quantitative analysis; as Yale had (and still has) no analytical chemists on the faculty, the teaching of this course fell to the youngest physical chemist on the staff, who enjoyed being in the classroom and lab almost as little as we did. That solidified Ron's decision to get out, but Mait, who knew that Ron would be enthralled by Doering's course the following semester, urged him to stick it out. And so he did. And he fell in love – with the subject matter and with the man who let it unfold in glorious technicolor (at least five different colored pieces of chalk, along with an extra-long eraser, were employed every lecture) with witty dialog and extraordinary insights. We think that Bill loved teaching the undergrads as much as we loved being in his class. We soaked up the lessons and stories, bordering in many cases on the libelous. We were treated to remarkably candid comments about some famous organic chemists: "His head is filled with homogenized goose feathers" was said about one chemist and "Thank goodness he's dead" referred to another, whom Doering also disparaged as "the maker of the last of the nonanes." We don't recall who the lucky person was whom Bill described as "a throw-back to a Neanderthal" and perhaps it's just as well. We ate it up, as undergrads will, and as it was intended to be. Many alumni of Doering's Chem 29/35 went on to become professors of chemistry themselves; it is a near-certainty that their lecture notes, style of delivery, and blackboard technique are patterned so closely after Doering's that the fine line between flattery and plagiarism may well have been breached.

As for Ron's reluctance to choose to major in chemistry, it was the prodding of Mait that convinced him: first, to endure the quantitative analysis semester in Fall 1956 and second, to get past the required textbook (Fieser's *Organic Chemistry*) for Bill's Spring semester course. After a general chemistry course that had been more engineering than science (who can forget the Bessemer steel process or the Frasch process for extracting sulfur from the ground?), Ron recalls having opened the organic text while at the bookstore and seeing pictures of industrial distillation towers and chemical processing plants. Once again, he wanted to bail out. But Mait was persistent and so both of us enrolled in Chem. 29 in Spring 1957. (It was not the Yale chemistry department's soundest pedagogical decision to split the two-semester organic sequence between Spring and Fall semesters with a summer term in between, but that's what was done. So it goes.) Ron recalls the first class meeting: a short, dark-complected, rather young man wearing a tie that was much too long for him began to lecture without having introduced himself to the class. Ron wondered, "This is Doering? Surely not." It wasn't until the second class meeting that the lecturer sought approval from a somewhat older man, whose presence I had not earlier noted, in the back of the room and asked, "Isn't that right, Bill?" Mait, of course, knew all along that the lecturer was not Doering. In fact, it was a new assistant professor, Martin Saunders. At the third lecture, Bill took over and led us the rest of the way. (When he told us that he would take a mechanistic approach, Ron's juvenile mind registered "mechanistic = mechanics = industrial processes = engineering" and he almost bailed out again.) He regrets that he no longer has his notes from that class – in their stead, he has the notes that he took as a grad student, sitting in on that same undergraduate class, that became the basis for his own organic chemistry lectures when he became a professor.

As for the Fieser text, it proved to be of more value as a reference work than as a guide to learning. In truth, we have used it many times whenever we needed a key fact about a compound or reaction. Bill's rationale for requiring it was "Usually the only thing that students get out of their organic course is the textbook." The book was irrelevant simply because Bill's Chem. 29/35 courses were purely lecture and 100% mechanisms-based. It wasn't until Ron began teaching Rice University's introductory organic course, in 1966, that he discovered that the textbook by Morrison and Boyd mirrored many of Bill's approaches to topics – is it possible that he had a clandestine pre-publication copy that he never shared with us?

Did we know that even in his late 30's he was already one of the leading organic chemists of the world? (Figure 2) Like other undergrads, most of us had very little understanding of the nature of academic research. And, in striking contrast to the open-door policy that Mait and Ron employed throughout their teaching careers, we don't recall ever having visited Doering in his office to ask questions. We suppose that he had office hours, but for some reason none of us (so far as we knew) took advantage of them. Ron doubts that Doering knew his name or those of most of his classmates by the time the course ended.

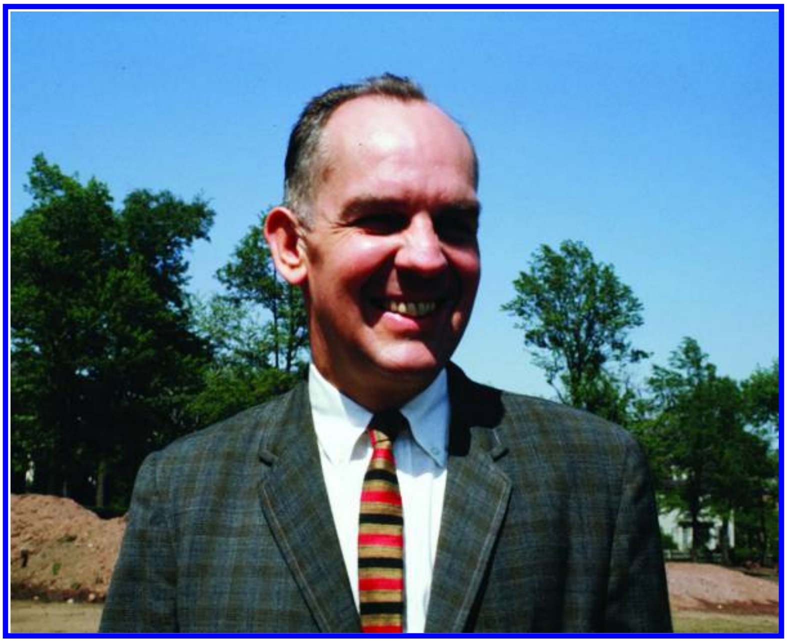

Figure 2. The young Bill Doering in 1963. Photograph courtesy of Ruth Haines Doering Zeiss.

Ron's other major interaction with him, prior to grad school, came during a semester of senior research. In retrospect, he realizes that the project that Doering entrusted to him (and that he was too inexperienced and inept to execute) was not only very sophisticated but also significant – it was to produce the parent cyclopropenylium ion, $C_3H_3^+$, as a test of the Hückel prediction that a 2π-electron system would be aromatic. (At that time, no such compound had been made.) The synthetic design was straight-forward: Diels-Alder reaction of dimethyl acetylenedicarboxylate with 7-cyanotropilidene (reacting *via* its norcaradiene valence tautomer) would produce a tricyclic adduct whose retro Diels-Alder cleavage of different bonds would yield dimethyl phthalate and 3-cyanocyclopropene; reaction of the latter with silver ion should produce AgCN and the desired ion. Ron writes, "I encountered several significant hang-ups. Neither Bill nor our TA (Tony Vellturo, a member of Gary Griffin's group) told me that the acetylenic diester was commercially available, so I synthesized it from fumaric acid by (1) bromination, (2) double dehydrobromination, and (3) methylation. According to the literature procedure that I had found, the bromination was to be carried out in a round-bottomed flask using a Herschberg stirrer – little did I know that the twisted Nichrome wire paddle would be consumed by bromine, thus precluding any stirring action. Furthermore, although I did not know it ahead of time, I soon discovered that the acetylenic diester was a *nasty* lachrymator. But I soldiered on. Next, I was to beg the legendary Horst Prinzbach, the first of Bill's brilliant German post-docs at Yale, for a sample of precious tropylium ion that I was to treat with cyanide ion to make the cyanotropilidene; somehow (memory fails me on this) I was unsuccessful here, so the project ground to a halt, but still I managed to get my B.S. degree."

Mait recalls his own senior research project, "Does methylene react with the carbon-carbon bonds of spiropentane?" Answer, "No." But he would not like to revisit the experiments he did to show that! Spiropentane was made by the zinc-dust mediated debromination of pentaerythrityl tetrabromide (look it up), and that process inevitably yields zinc bromide, which is Lewis acidic enough to rearrange spiropentane to methylenecyclobutane, a sure precursor of the putative insertion product of reaction of methylene with spiropentane. He supposes the fact that he found no reaction is comforting. Years later, he went back and did this work better in several respects. There was a special issue of *Tetrahedon* (July, 1997) dedicated to Bill, and it seemed appropriate to revisit this reaction in a proper way. First of all, spiropentane is not the best molecule to use as there is little strain relief in expanding the three-membered ring to a four (well, there are those bent bonds....); in its favor, however, spiropentane does possess the virtue of having the highest ratio of C-C to C-H bonds of any hydrocarbon. Anyway Mait persuaded Guoxian Wu to look at the reaction of methylene with spiro[3.3]heptane. He did the whole reaction in a few weeks, and we put Bill's name and the late Larry Knox's on the paper (*2*). Mait still feels good about that: "I owe Knox the world and was proud to have another paper with him, even if he couldn't know about it."

In 1959, Mait and Ron moved on to graduate school, but the questions that we had as undergrads could still be asked: What do graduate students know about their advisor, their co-workers, or even their research projects? Answer: A lot and not a lot. And much of what they "know" is wrong or on the fringes of the

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ridiculous. We knew that Doering was a very important person in the world of organic chemistry – his publications, his many absences to give symposia, his friends in the scientific community, etc. told us that. We also knew about some of our chemical “ancestors,” for example his earlier spectacularly outstanding group of graduate students at Columbia, among whom were people whose publications we were reading: Jerry Berson, Andy Streitwieser, Ken Wiberg, and Chuck DePuy, among others. And we were surrounded by an extraordinary group of post-doctorals, most of them German, who would go on to brilliant independent careers when they left Yale; among these were Horst Prinzbach, Gerhard Schröder, Wolfgang Roth, Wolfgang Kirmse, Wolfram Grimme, and Gerhard Klumpp.

Our research group was far more homogeneous than those of today. True, there were European – mostly German – postdocs, but very few from Asia, and almost no women. In truth, the situation was little different from that encountered by Ruth Alice Weil at Columbia! There were some exceptions: postdoc Ray Okamoto came from Japan and gave his name to a unit used in the group. He was such a wizard at fractional crystallization, that laborious and time-consuming technique, that Peter Gaspar coined a term “the okamoto” to refer to the number of such operations that Ray could accomplish in one day. The rest of us could aspire, on our good days, to accomplish, at best, a milli- or a micro-okamoto. Jean Day Lassila was the only female graduate student in our group, a couple of years ahead of us, and not only married but pregnant. She delivered her daughter, Kathrin Day Lassila, on a Saturday, immediately after passing her seventh cumulative exam, and was rapidly back in the lab. There seems to have been no deleterious effect on that daughter – she is now, four decades later, the editor of the Yale Alumni Magazine. She wrote to Ron, “Now that I have two children of my own and a full-time job, I often wonder how in earth she managed it. She always insisted I was no trouble at all.” Jean would bring her infant daughter to departmental seminars; the child would awaken and scream only when the speaker was notoriously bad.

We knew of Doering’s close friendships with R. B. Woodward, dating from the quinine synthesis in the 1940s, and with Saul Winstein. Here are a few personal memories. In the undergraduate course, Doering devoted a couple of lectures to the story of the synthesis of quinine. We reveled in the personal touches, such as “Woodward ran exactly one reaction” and “When I reported that a key compound had the wrong melting point, Woodward went directly to bed; this was on Good Friday. Purification by crystallization led to the right melting point, which I reported to Woodward on Easter Sunday.” Woodward was probably the only person about whom Doering never said a bad word. He was in awe of Woodward’s encyclopedic knowledge and his imagination in synthetic design. Ron recalls that Woodward came to Yale to give a lecture on his recently completed synthesis of chlorophyll: “I happened to be walking down a hallway when I glanced to my left and saw the great man, standing at the blackboard of the room where the seminar was to be, painstakingly and meticulously drawing the target structure on the board – chalk in one hand, wet sponge in the other (to expunge any bond or group that was not perfect), cigarette dangling from his lower lip.”

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At the 1966 Sheffield Symposium on aromaticity, Woodward reported that Doering had told him that heptafulvalene undergoes cycloaddition with TCNE. “Now, when he called to tell me about the result, Doering, who is a very playful fellow, said: ‘Of course it adds at the 2 and 2′ positions!’ Those of you who like to count will have observed already that addition in that sense represents a [14 + 2] combination, and at first sight you will stigmatize that as bad. ... The important fact which Doering withheld (until I had discerned the solution of the dilemma) is that the adduct (*3*)” is formed by antara addition to the 14-electron component, an allowed process.

Winstein spent a semester at Yale (Fall, 1960) and gave two lectures per week: one on organic chemical topics (solvolysis mechanisms, non-classical ions, and homoaromaticity – do any of these topics appear in today’s courses?) alternating with one about the physical chemistry of ionic solutions. Yale’s faculty happened to have some of the world’s leaders in this latter subject, most notably Lars Onsager. At one point, someone asked Winstein a question, causing him to go to the board to carry out a calculation. Just as he began, Lars (who had probably been dozing) sprung to life and said “Vell, I tink de answer is 6,221.” Some minutes later, Winstein (not having heard Onsager) finished his calculation and announced, “There it is - 6,221!” Two memorable quotations from Winstein, uttered more than once during that semester were, “Heh, heh – of course the only lab work I do now-a-days is in my bar at home” and (speaking about the modest exo/endo rate ratio for 2-norbornyl tosylate) “These are not the factors of 10^6 that we like, but we have to take what we get.” A final vignette: at one of the weekly departmental organic chemistry seminars (given by postdocs and by grad students in their 2nd, 3rd, ... nth years) the speaker was our post-doctoral colleague Gerhard Schröder. I don’t recall the topic, but Winstein asked a question at the end of the talk. Schröder walked over to a portable blackboard and turned it back to front – there was the answer in full. Said Winstein to Doering, “You set me up for this, didn’t you?”

A personally painful moment came when Ron was giving one of those weekly departmental seminars – his topic was “The Benzilic Acid Rearrangement,” for which he had read every pertinent article and review. As he was presenting the arguments of some very prominent chemists, Doering interrupted and asked, pointedly, “Haven’t you ever heard of the Curtin-Hammett Principle?” “The WHAT?” “The Curtin-Hammett Principle!” Silence. “Perhaps someone in the audience could inform Mr. Magid what it says?” Dead silence. Bill’s behavior, harsh on its face, had its designed pedagogic value, because Ron made it a point to learn this principle and, when he became a professor, to pound it into the heads of the students in his graduate courses. And, of course, he had the smug satisfaction of finding occasional Curtin-Hammett errors in published work and of putting them on exams.

We organic grad students had only limited contact with Onsager, but stories about him were spread throughout the department. It would be a few years before he would win the Nobel Prize, but that mattered not. Onsager and John Gamble Kirkwood, his good friend and fellow physical chemist, are buried side-by-side in the Grove Street Cemetery on the Yale campus. Kirkwood’s tombstone has some twenty lines of print about his accomplishments. As the ultimate example

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of "one-upsmanship," Onsager's has only three lines: • Gibbs Professor • Nobel Laureate • Etc.

What else did we "know"? We knew very little about Bill's personal life, although rumors circulated widely and wildly. We knew that he drove a big Mercedes, always. We knew that he would attend our weekly group seminars *if* he was in town – and that when he wasn't, the seminar would go on anyway, often under the guidance of one of the postdocs. Those meetings were remarkable for their range and power – and for their robustness. They did not flag when Doering wasn't there, as in later days he often was not. Perhaps this strength is not too surprising, given the presence of such major intellects as Horst Prinzbach, Wolfgang Kirmse, and Wolfgang Roth, but the staying power of these meetings is also surely a tribute to their originator. When Bill did attend, he did not suffer fools gladly (an understatement!) – if one of us was less than fully prepared to give his/her talk, Bill made it abundantly clear that that was never to happen again. And, of course, it didn't. His insistence on careful preparation was a hallmark of his research style, imparted to all of us in the clearest of terms: do a thorough literature search; give credit to others where credit is due; make certain that the facts are as you report them; check and check again before making any claims; re-do the measurements without any prejudice about how you "want" them to come out; establish the identity of a compound by an IR spectrum that is within a pen's width of the spectrum of the known material; and so on.

Given that he was one of the founders of physical organic chemistry, it's ironic that he spent much of his academic career in the study of "no-mechanism reactions" – but his justification of this seeming "absurdity" makes all the sense in the world: " 'No-mechanism' is the designation given, half in jest, half in desperation, to 'thermo-reorganization' reactions ... in which modern, mechanistic scrutiny discloses insensitivity to catalysis, little response to changes in medium and no involvement of common intermediates, such as carbanions, free radicals, carbonium ions, and carbenes (*4*)."

Through his behavior, more than through his words, he conveyed to us that the most important quality that a research scientist possesses is integrity. If we lose our trust in one another, then we have lost everything. When one publishes a paper, the expectation is that a chemist anywhere in the world will be able to reproduce the result. When one draws conclusions from the data, they must be sound and within the bounds of the reasonable – but if the result demands a novel explanation or a new theory, then the experimentalist must be triply sure that the results are as claimed. We knew of feuds that he had with two well-known chemists concerning primacy in one instance (the synthesis of tropylium ion) and probity in another (the validity of experiments on the stereochemistry of dihalocarbene addition). Even worse, there were two instances of falsified results within our laboratory: one occurred before our time at Yale (but was still whispered about) but the other occurred while we were there; for the latter, Doering had to publish (*5*) an embarrassing retraction some years later: "W.v.E.D. belatedly takes an opportunity to accept the evidence for the irreproducibility of the alleged realization ... and apologizes to those whose careful work has made the case."

Doering could wield a poison pen, but he could also be "playful" when criticizing others. Consider these statements: in 1955, "It seemed most surprising

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to us (although not to Johnson or Nozoe and Sato) ... (*6*)," in 1990, "The values obtained by Dewar and Wade from 'two measurements' ... are in spectacular agreement – 'wondrous strange (*7*).' " and "Humbled, WvED apologizes to Dewar and Wade for ever having had doubts, but not without admitting to speculation that the sage of Austin is on-line to the Delphic oracle; possesses the ultimate computational program, which a secretive US Air Force has requested not be revealed; and is a deserved beneficiary of Pasteur's Postulate 'Chance favors the prepared mind.' (*7*) "

Let us elaborate on Bill's seemingly innocuous barbs (*7*) directed at Michael James Steuart Dewar. The rather witty retort (above) was actually a fiendish (one of Bill's favorite words) scheme for discrediting the work and its authors. Doering quotes a passage from a 1987 paper by Dewar and Jie: "However, there are in fact good reasons for regarding the published experimental values with suspicion. The activation parameters ... were derived from just two measurements at two temperatures ...." and uses it to cast doubts on experimental work published in 1972 by Dewar and Wade. Thus, Bill sets the stage for what is to follow by letting Dewar criticize his own work. Bill concludes the paragraph with "Prudence called for a repetition." [No, whatever you're thinking, Prudence was not one of Bill's adoring harem.] And he couldn't resist plunging and twisting the knife a little more by inserting, as a footnote, an exact quotation from Wade's dissertation with a relatively minor grammatical error highlighted by *sic*: "In his defense, Wade's comment should be heard: 'No claim as to the accuracy of these values is made since only two rate measurements were used to calculate them .... The standard deviations for these rates was (*sic*) reasonably good.' " In fact, when Bill and his coworkers measured the rate at *five* different temperatures, they obtained precise values for the activation parameters, leading to this already-cited passage "The values obtained by Dewar and Wade from 'two measurements' ... are in spectacular agreement – 'wondrous strange'." To this is appended the footnote "Humbled, WvED apologizes ..." that was quoted in full above.

Often he wrote with elegance and style, as in 1956: "Although the word 'carbene' has been defined ('A bitumen soluble in carbon disulfide but not in carbon tetrachloride') ... one appears justified in assuming the innoxious risk that the new meaning become known in the same, presumably chemical, circle presently aware of the old. In its new meaning (collaboratively conceived by W. von E. Doering, S. Winstein and R. B. Woodward in a nocturnal Chicago taxi and later delivered diurnally in Boston) 'carbene' is synonymous with one of the several definitions of 'methylene' ... (*8*)"; and in 2001: "Theoretical efforts to elucidate the thermal behavior of the pristinely unsubstituted archetypal cyclobutane in the gas phase have been extensive. At the experimental level, intrepid purists have explored these questions with deuterium as a minimal perturbation, while soldiering pragmatists have introduced more drastic perturbations in the hope of achieving answers (*9*)."

Yale used a cume (cumulative exam) system, modeled after Harvard's, to assess the progress of the grad students. These exams, on unannounced topics in synthesis, mechanism, whatever were given once a month on Saturday mornings throughout the academic year. The requirement was to pass eight exams, which most of us did by the end of our second years. One exam, however, sticks in our

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collective memories like a rotten apple. The cume on December, 5, 1959 (the third in our first semester of graduate work) was clearly written by Doering: no other faculty member used this font (in those electric typewriter days) nor did any other draw such precise structures. A polycyclic structure with a plethora of oxygenated functional groups was shown to undergo a fairly extensive cleavage with ethanolic KOH. Further, the keto group of the reactant could be reduced to a pair of epimeric alcohols, each of which also reacted with ethanolic KOH in ways entirely different from each other and from the original ketone. The challenge was to write mechanisms for the three reactions that would also explain why they differed so dramatically when only a small change had been made. Fair enough, except ... The formula given for the reactant, $C_{26}H_{28}O_8$, did not correspond to the structure drawn so elegantly on the exam page. That is, if the dashed lines on the structure corresponded to methyls, the carbon count was wrong; and if they referred to hydrogens, the count was still wrong. Only one person passed the exam, a man who was spending only his first year at Yale before going to CalTech for his degree. Over the years, Mait and Ron would try to solve the exam – and although we probably got close enough that our answers would have given us a passing grade, we never were satisfied with our attempts. Then, in 1977, Ron received a hand-scrawled note from Mait: “See, instantly, *Experientia* ....” Mait had found the very article on which the question had been based! He also wrote “Note that not only was the formula wrong, but the structure as well.” Thanks a hell of a lot, Bill! In 2008, we made this paragraph available to him and thought, “You may be reading this story for the first time, but had you known about it we think that you would have been pleased with the turmoil you created.” [This cume problem also had a life in the classroom. On a final exam in his Princeton undergraduate course, Mait prefaced a question thus: “The first section of this question graced last year’s final, and is part of a series of reactions that the legendary R. M. Magid and I have been thinking about – not constantly, we are not obsessive – for decades.”]

As we’ve said, our weekly group seminars were amazing institutions. We numbered 20-25 (grad students and post-docs) and were divided into groups of four or five. Each week, on a rotating basis, one of the groups would read the set of journals assigned to it and write abstracts of those articles that would interest the rest of us; one member of the group would pose some mechanistic or synthesis problems; and two or three members of the group would prepare talks. It was at these sessions that we believe that we learned most of our chemistry. [A frightening event, the Cuban missile crisis, was unfolding in October, 1962, and became the sub-text of one evening’s seminar at which it was very difficult to concentrate on chemistry.] Bill made it a point to attend these gatherings, but when he couldn’t one of the post-docs or older grad students would keep things in line. In our fourth year, however, Mait and Ron noted that the spirit of the group was waning, that there wasn’t much enthusiasm at the seminars, and that attendance was sporadic. So with the assistance of Phil Shevlin (a second-year student whom we recruited to add a semblance of respectability to our nefarious plan) we decided to prepare a totally *fake* seminar! *Everything* was wrong: the date on the abstract sheet; the spelling of Phil’s last name; the quotation by Christine Keeler (who was much in the news at the time and who *might* well have said “There are times in a man’s life when he must subvert truth to the pursuits of pleasure”). The abstracts reported some barely plausible results, authored by such luminaries as a journeyman catcher for the Cincinnati Reds, various characters from “Catch-22,” and the real Russian names of Lenin, Trotsky, and Stalin. The concluding abstract reported on a rat sex attractant whose structure looked remarkably like ... well, a rat. Phil gave some invented problems and Mait reported on some nonsensical carbene work. For Ron’s talk, a letter from his soon-to-be postdoctoral advisor, Eugene van Tamelen, ostensibly “arrived” that very morning – “he” described some work then going on in his lab as a prelude to what Ron would be working on. According to what “he” wrote (all of it imaginary), his student had isolated a compound, $C_{10}H_{10}$, whose melting point and spectral properties immediately told us it was bullvalene but which the Stanford chemists had misidentified because Schröder’s paper had not yet been published. Of course, we chose a day for our charade when Doering would be out of town. To our horror, he announced in the morning that he *would* be in attendance, so Mait and Ron (clothed in trepidation) went to his office to alert him as to what we were planning to do. And, of course, he never showed! The good news (or bad news, depending on one’s perspective) is that we pulled it off without a hitch. A few days later, one of our fellow graduate students told Mait that he was unable to find one of the references in the library, so Mait gave him a “corrected” page number and sent him off again. A few days later, we revealed what we had done. Many of our colleagues were quite unhappy with us.

Doering would have preferred that all of us live monastic lives, tethered to our laboratory benches, leaving only when hunger or sleep became compelling. But times were changing and, if memory serves correctly, more than half of us were married and some of us even had children. So it goes.

The bullvalene story is an amazing one. Doering had just returned from a European trip in time to come to the group seminar on October 9, 1961. It was unusual for him to preempt someone who had planned to speak, but this time he took chalk in hand and outlined for us the nature of his thinking. He began by reviewing the work that he had done with Wolfgang Roth on the degenerate Cope rearrangement of 3,4-homotropilidene. (An aside – many of us suspected that he loved to use the phrase “degenerate Cope” because of its alternate meaning.) This led him to speculate about what would happen if the molecule were locked in its unfavorable cisoid conformation, the one needed for Cope reaction, by a bridge linking the two methylene carbons, as in barbaralane (named for post-doc Barbara Ferrier, who made it). And if that bridge were a -CH=CH- unit, then the resulting $C_{10}H_{10}$ would have some spectacular properties – not only would all three of its degenerate Copes lead to the same structure, but through a series of such reactions every carbon would become like every other, every hydrogen like every other. The prediction: if the Copes were fast enough, there would be a single peak in the ^1H and ^{13}C NMR spectra! Doering showed how 1,2-carbon interchanges and 1,3-carbon interchanges could occur. And he confessed that the man sitting next to him on the return flight, watching his wild scribblings, was convinced that he must be mad. Well ...

Ron doesn’t recall (nor do his notes reveal) if Doering had already decided that a single peak, if it occurred, would indicate that 1,209,600 identical structures were in equilibrium, although he did ponder the question of whether a single peak

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would indicate fast degenerate Copes or, just as interesting, a single averaged structure. Lars Onsager provided a simple answer: it would have to be the former because, "as everybody knows," one cannot put 10 points symmetrically about the surface of a sphere (i.e., there are only five "Platonic Solids" and the 10-vertex structure is not one of them.) It was at this group seminar (or maybe a day or two later – memories are cloudy on this) that either Ron or Mait blurted out the name *bullvalene* for this hypothetical molecule. As related by Nickon and Silversmith, "Which of the two students was the *blurtor* and which was the *blurtee* remains unsettled; but their term caught on with the research group. And everyone was surprised when Doering and Roth formally adopted it in their seminal publications in 1963 (*10*)."

Fact: everyone was not just "surprised" but *astonished* that Doering knew the name we had given it. In a 1967 article, he inserted a footnote: "The precise origin of this ignoble name, at the hands of incredulous graduate students, is lost, but their initial response to its conception and the possibility of its existence is suggested in E. Partridge, *A Dictionary of Slang and Unconventional English* p. 104 (*11*)." This is what one calls a red herring – Doering knew that this was not the origin and, as fate would have it, Mait had the opportunity to publish his own footnote in 1970: "As one of those quoted in Footnote 15 of ref 5, it is perhaps not out of order to suggest that the source of this 'ignoble name' is neither lost nor contained in E. Partridge... (*12*)." And there the matter remained until Nickon and Silversmith published a full explanation: "It seems that during Professor Doering's early days on the faculty at Columbia University, his research students nicknamed him 'The Bull' ... Perhaps it was because 'Bill Doering' sounds like 'Bull Durham,' a popular brand of tobacco; but other explanations can be found. Dr. Doering and his nickname subsequently transferred to Yale University, and it was there at a group seminar on October 9, 1961 ... (*10*)" (The second part of the name was chosen so that bullvalene would rhyme with fulvalene, a molecule of great interest to our research group in those days of non-benzenoid aromatic compounds.)

Well, what about Doering's nickname? As recently as June of 2007, Bill professed (or pretended) not to know the origin. In an email to a German colleague, he wrote that Fred Chang, a graduate student in Louis Fieser's group, in the early 1940s, had nicknamed him " 'Ole Bool', the meaning behind which escapes me." And yet ... We never knew if he knew that we called him "the bull" (which is why we were so shocked by his adopting the moniker bullvalene), although there was an occasion on which he cautioned us about something or other with the words *Cave Taurum* (we may have butchered the declension). And, in fact, there was a pouch of Bull Durham tobacco in the lab that had been handed down from generation to generation. We wonder what's become of it.

Bill told the undergrads a story from his own years as a grad student. Many of his friends (including Fred Chang whom he nicknamed Red Fang) were in Louis Fieser's group. One summer, Mary and Louis Fieser decided that they wanted to have an outdoor barbeque pit and so they requisitioned slave labor (i.e., Louis's grad students) to build it. Bill, who was not in Fieser's research group, joined in the "fun." Throughout the hot summer days that they labored, never once were they invited inside the great man's house. Finally, when the construction was finished,

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Mary said "Louis, invite the boys inside for a glass of water." Bill told us, "I was so mad that I peed all over the barbeque!"

So, back to the bullvalene story. Bill recruited some grad students and postdocs for a crash program to synthesize the compound by a rational path. Ron once asked him why he published the idea of the molecule before he had made it – he answered that so many people were then doing hydrocarbon chemistry that he feared that someone would stumble across it. And that's precisely what happened (as is related in the article by Klärner, *et al.* (*1*)) when Gerhard Schröder, at that time an independent researcher in Belgium, irradiated a cyclooctatetraene dimer (of then unknown structure), which cleaved to produce benzene and bullvalene. Ron had the good or bad fortune to have been in Bill's office one day in May, 1963, desperately trying to conclude his research and to schedule his orals, when Doering's secretary brought in the day's mail. "Oh, good, a letter from Gerhard," he said as he opened it and proceeded to ignore his anxious grad student. It would be an exaggeration to say that steam poured from his ears and that his facial colors went from red to purple but he finally composed himself, smiled, and said, "Gerhard has made bullvalene. And it has one peak in the NMR." Nevertheless, he couldn't resist (no he couldn't!) publishing part of that letter as evidence of Schröder's "contrition" at having made this legendary compound. Here is a loose translation from the German (italics added for emphasis): "For the last weeks and months, I have been busy with the structure determination of fluxional molecules $C_{16}H_{16}$ and $C_{12}H_{12}$. Thereby, it was *completely unwanted and unexpected* that 'Your Bullvalene' fell into my hands (*11*)."

In the 1950s, modern instrumentation was making its way into the organic research lab. Yale had a Cary UV spectrometer and a plodding Perkin-Elmer Model 221 IR spectrometer, to be supplemented by a speedier model, the 421. We also had one of the first commercial NMR spectrometers: the 60 MHz Varian V-4300 that nearly required an electrical engineering degree to operate; maintenance of a homogenous magnetic field was controlled by a galvanometer (called a "super-stabilizer") that sat atop the machine and that would go haywire on the least provocation: a truck entering the city, a bird flapping its wings, etc. Later, we got a Varian A60, so all of us were able to run our own NMR spectra routinely. (That the spectrometers were in the only room in the building, aside from Bill's office, to be air-conditioned, made their use an all-day project in the hot summer months.) In the research laboratory, we had a Varian Aerograph A90 and other gas chromatographs (or g.l.p.c., gas-liquid partition chromatographs, as Bill insisted we call them). There was a Perkin-Elmer 154 "Vapor Fractometer" for preparative separations, the commercial descendent of that home-made GC at Hickrill that had 2" wide columns! In one of the hoods was an acid bath, heated with a Meeker burner – woe unto the person who put a piece of glassware coated with silicone grease into that fuming cauldron. The recipe for this monster was: fill the bath with sulfuric acid, add a few mL of nitric acid, and throw in a penny. Heat till boiling. There was a melting point apparatus with a series of very precise Anschütz thermometers (each covering a range of only 25 °C). And there was a locked cabinet filled with specialized ground-glass equipment, much of it (or so it was rumored) constructed by Bill in his guise as Master Glassblower. Money was alleged to be short, so we all had to sign out "exotic" glassware as needed.

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Naturally, someone had to keep the books and act as policeman – not an enviable task, at least for Mait! Because many of us worked with volatile materials, there was not only an elaborate vacuum line with diffusion pump but also a series of portable pump tables, shared by two or three students, based on a design in Wiberg's "Laboratory Technique in Organic Chemistry" (an essential source, published in 1960, for all sorts of experimental insights).

Doering made very few visits to the research lab, but when he did "miracles" would occur (some good, some bad). Ron was carrying out a five-step literature prep and he recalls having had a terrible time trying to crystallize one of the products; Doering wandered by, took the flask in hand, said some magic words, and crystals rained down. He then set Ron the task of crystallizing 1 mg of benzoic acid from diethyl ether, a task made fiendishly difficult by the small quantity, by its high solubility, and by the narrow range between boiling and room temperature for this solvent; after much practice (and using a micro filtration device that someone showed him how to make) he succeeded. A "bad miracle" occurred when Ron's lab bench neighbor, Marty Pomerantz, having mistranslated a German language procedure to read "all at once" (instead of "little by little"), added a huge slug of concentrated sulfuric acid to a reaction mixture; he happened to have walked away from his bench when Doering passed by the apparatus at the very moment that acidic green noxious clouds emanated from the top of the condenser.

Doering could get "bees in his bonnet" during those visits and the results were nearly always dire. For example, the sight of an unattended GC would set off the "Helium is a precious natural resource!" reflex in Doering and he would demand that we all switch to hydrogen as carrier gas. Never mind that all our previous data would become worthless, we had to do it. Solution? Wait a while and clandestinely switch back.

"Meerwein Ponndorf," a mythical postdoc, figures in many of the stories from the Yale years. One of our favorite reactions, partly because Doering had elucidated its mechanism but mostly because of its exotic name, was the *Meerwein-Ponndorf-Verley Reduction* a.k.a. the *Oppenauer Oxidation* a.k.a. the *MPVO Equilibration*. Mait and Ron were the instigators of a prank that we played on one of Bill's well-meaning but terribly gullible secretaries. Whenever the great man would leave town (which was often), Meerwein Ponndorf (for whom Ron provided the German accent) would telephone and demand to speak to him. When told that Doering was away, Ponndorf would get angry and promise to call back later. This went on for some time. At one point, we decided that Meerwein had to make a personal appearance, so we recruited a grad student from another group (Lebanese, not German, but at least he had an accent) to appear at the office door, announce his presence, click his heels, and storm off. We also contrived to have a crate delivered to the office – it contained (if you'll pardon the false Italian) an *Equilibrazioni Apparazioni*. Inside was a wooden board – attached at one end was a vial marked *ketoni* and at the other end another vial labeled *alcoholi*. In the middle was a vial containing *hydridio* and, if we recall correctly, a light bulb that would flash on/off when plugged into an outlet. (Meerwein will make another appearance, shortly.)

One of the most dramatic and frightening events, even for a group of students who were "accustomed" to explosions, was the violent detonation that Wolfgang

Roth had one evening. He was generating gaseous diazomethane in one flask and passing it into a second flask that contained *Z*-1,3,5-hexatriene and CuCl. The idea was to determine at how low a temperature *cis*-1,2-divinylcyclopropane would undergo Cope rearrangement to 1,4-cycloheptadiene. By cooling the reaction flask to lower and lower temperatures, Roth found that the Cope was rapid at around 0 °C and even at -20 °C. It was when he cooled the flask to -55 °C that all hell broke loose. Because the reaction flask had frosted over, he squirted a small stream of acetone to clear a window. What he saw must have frightened him out of his wits – the contents of the flask were bright yellow, an indication that diazomethane had accumulated but had not decomposed. And so there was a fearsome explosion. Fortunately, most of the force was up and down, but there was not a recognizable piece of glassware afterwards, and the magnetic stirring motor was reduced to half its height and was driven into the base of the ring stand. Doering has written, in typical Doering style, a warning that below -50 °C, "... diazomethane is not decomposed, accumulates in the reaction vessel, and eventually explodes with singularly dangerous and destructive violence ... Accumulations of diazomethane are then indicated by the turning yellow of the drops of condensate on the tip of the reflux condenser. Experienced operators normally withdraw and continue flushing the apparatus with nitrogen in the occasionally vain hope that the diazomethane will thus be removed without event (*13*)."

Roth was hospitalized but, aside from a few pieces of glass in his face, escaped pretty much unscathed. An article in *The New Haven Register* described the incident. Alas, it contained errors: it identified Roth as a grad student and it said that the explosion occurred in Room 203 (Doering's office!). What it got right was that the supervisor was Doering, that the compound was "diazomethane (which is used as a methylating agent)" but then it concluded "Except for a test tube, which was destroyed, there was no damage to the laboratory." Some test tube! Some "no damage"! The next day, a similar article appeared with this additional information: "The experiment reportedly called for an explosion, but the force of it was greater than anticipated." This demanded the attention of Meerwein Ponndorf, so "he" (Ron) called the reporter to set the record straight: (1) Roth was a post-doc, not a grad student [true enough]; (2) he was not working in Room 203 but in 150 [also true]; (3) he was not working with diazomethane (a harmless, yellow solid [well, it is yellow]) but with isopropane [this stemmed from the time when one of Marty Saunders's students interrupted his boss, who was conversing with some full professors in the hallway, and asked, "Marty, how would you distinguish propane from isopropane by NMR?" and, much to his delight, got an answer!]; (4) he was not working for Prof. William Doering but for *me,* Prof. Meerwein Ponndorf; (6) he was not using a "test tube" but rather an "equilibration apparatus"; and (7) he was in this country on a Deuterium-Exchange Fellowship.

Even the staff at *The New Haven Register* had enough journalistic acumen to be suspicious, and so the reporter called the phone in Sterling Lab 150 and asked to speak to Meerwein Ponndorf. And who should have been making one of his *rare* visits to the laboratory, but none other than Prof. William von E. Doering who answered the phone and, without missing a beat but breaking out in a wide grin, handed the phone to Ron and said, "I think it's for you." And so, German

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accent intact, "Meerwein" proceeded to confirm all of the "corrections" that had already been given. The next day, a third article appeared. Roth was still described as a graduate student, but was now working in Room 105 (close enough) with isopropane! The article concluded "An *equilibration apparatus*, which contained the chemical, was destroyed." Alas, neither Ponndorf's name nor the Deuterium-Exchange Fellowship made it into print.

Explosions were a way of life in Room 150, but generally – not quite always – we were careful. In fact, a benign explosion was regarded as a good thing – it kept us on our toes, and kept us putting those blast shields up. There were, however, those whom nature seemed to favor who could get away with anything (not Roth, apparently, nor Wolfgang Kirmse who had three diazomethane explosions in a single day. One can only admire Kirmse's tenacity, not to mention courage!). John Munro, a postdoc from Scotland, distilled diazocyclopentadiene on the desktop in multigram lots. Insane! – but nothing ever happened. Nonetheless, we tended to absent ourselves from the lab when John was at the still. One of the iconic stories of our group, from before our time, concerned the time Chuck DePuy had an explosion that knocked him senseless; he awoke to find himself in a room filled with dense white smoke. Doering, in re-telling this story, reported that DePuy thought he was dead and that it took all of the boss's powers to persuade him he was not in heaven. On the other hand, Barbara Ferrier quipped that DePuy should have known that he was not in heaven when he saw Doering there! Peter Leermakers, an American post-doc, walked the halls of Sterling lab with 5-L flasks yellow with gaseous diazomethane. Worse than insane! Doering remarked, after chewing us all out: "I hope he was wearing a lead-lined jockstrap!"

Though most of Bill's post-docs were German, there were a couple from Great Britain and a notable one from the U.S., the afore-mentioned Peter Leermakers, who had completed his Ph.D. with George Hammond at CalTech and was just a year away from taking a faculty position at Wesleyan. He came to our lab with all the confidence and bravado of one who is, probably, very insecure. His boastful manner resulted in a not unexpected negative reaction from his new colleagues. Peter was a dreadful experimentalist, but he must have had a guardian angel who protected him from injury when he performed such terrifying acts as a closed-system distillation or the diazomethane stroll. R. Srinivasan (from IBM) came to Yale for a seminar and described some of his photochemical work on what would come to be called, once Woodward and Hoffmann arrived on the scene, [2+2] cycloadditions of alkenes and electrocyclic ring-openings of cyclobutenes. There was one particular reaction that Doering challenged and refused to believe, but Peter argued that it was probably correct. So Bill made a bet with him: "$50 says that you can't reproduce the result in less than a month." Peter, of course, accepted the challenge and, to everyone's surprise but his own, won the bet, which Bill paid off with a great flourish at an organic seminar. (Stu Staley remembers the wager somewhat differently: "The bet was $10 at 10:1 odds – and Bill actually paid off with a new $100 bill, after saying he was willing to accept 10 g of 95 or 97% pure material in lieu of the specified 1 g of 99% pure material.")

And we ourselves also did some awfully dumb things. Nighttimes would sometimes find us (and others whom we shall not name in order to protect the guilty) outside Sterling Lab trying to observe the blue flash that, legend had it, occurs an instant before diazomethane explodes. Here, for those foolish enough to repeat our experiment, are the details of one of our attempts. On a dark night, on the lawn behind Sterling Lab, Mait was the principal instigator (others of us in the group were his fearful unindicted co-conspirators) for what we were convinced was a brilliantly conceived experiment. Imagine a large Erlenmeyer flask into which was placed decalin over aqueous KOH. The idea, then, was to add solid NMU to the flask, then cover the opening with a New York Mets trading card onto which had been sprinkled $KMnO_4$. Sulfuric acid was then poured onto the permanganate. This combination of chemicals was supposed to catch fire after about 20 seconds, giving the NMU/KOH reaction time to generate a vast quantity of gaseous diazomethane. The result should have been an explosion that we could all witness to see if there was, indeed, a blue flash. So the brave Mait added the NMU, set the card over the opening in the flask, poured acid onto it, and ran like hell to hide behind the nearest tree with the rest of us. Yes, it was a "brilliantly conceived experiment" except for one variable that we failed to factor in: a gust of wind blew the card and its chemical cargo several feet from the flask – and when it did burst into flames, it was too far from the flask to set off the yellow gas. What to do? The smart, but cowardly, solution would have been to leave the flask until morning – surely no other idiots would be crossing this dark expanse of grass at night, and the diazo compound would have dissipated in a few hours. But Mait had a sense of responsibility and would have none of it. Calling upon his outstanding athletic skills he threw a rock at the flask ... and missed. So he inched closer and threw another rock ... same result. And then before he could throw the third rock, the contents of the flask exploded. He claims to still bear the scars from this adventure. Oh, yes, although none of us observed the blue flash Mait has written in Volume 1 of *Carbenes*, his monograph with Bob Moss, "the failure of the Yale workers should not deter other investigators."

As we related previously, much of our knowledge and understanding were acquired in the weekly group seminars. It became our practice, when seminar ended, to repair to a restaurant/bar called The Old Heidelberg (familiarly known as "The OH"), where we proceeded to "get hydrolyzed." In 2008, the Yale Alumni Magazine published several tributes to the recently-deceased William F. Buckley. One was by David Frum (famous right-wing zealot, although we usually hesitate to apply such sweeping labels) in which he described an invitation that the Yale Political Union had sent to Mr. B.: "For dinner, we students booked a restaurant on Chapel Street called The Old Heidelberg (long-ago, and *deservedly extinct*)." Alumni of the Doering seminars (Peter Gaspar, Marty Pomerantz, Stu Staley, Mait, and Ron) reacted strongly to Frum's ugly characterization, although in retrospect The OH might not have been the most wholesome of places. Gaspar even recalls that Bill attended one of these post-seminar sessions and paid for the evening's festivities by throwing a $50 bill on the table.

What we remember most vividly about The OH was a table populated by graduate students in Spanish who were shouting "*Viva, la guardia*." (In today's climate, they would have been arrested, labeled as enemy combatants, and sent to Guantanamo.) We also recall that we conspired to have Stu Staley (he of some 1000 sheep jokes and, also, affectionately nicknamed "mouse bladder") sit at the center position on the bench so that he'd have to exit under the table

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for his numerous trips to the bathroom. Many of us have fond memories of two lunchtime venues: the internationally famous Louis' Lunch (original home of the hamburger) and the totally ignored (but wonderful in its own way) Tony's Apizza, which served the universe's best meatball sandwiches and which, according to Mait, is now "dead as a smelt" (as Bill was wont to say).

The second-year chemistry grad students, by tradition, would host a beer party for the department. As part of the festivities, they would put on a play about the faculty: one (typically terribly boring and poorly written) by the physical chemistry grad students, the other (brilliant!) by the organic chemists. In the spring of 1961, we reserved a wonderful conference room on the top floor of Gibbs Lab. (That some rowdies, almost certainly the physical chemistry grad students, threw beer kegs off the roof guaranteed that future classes would never be allowed to use that venue again.)

Mait and Ron wrote the organic chemists' play, based on the horrific events then unfolding in Belgian Congo. Set in the capital city of Sterlingville, the principal characters, modeled after Doering and Saunders, were Patrice von Eggers Lubullba and Martin Tschaunbe, roles played with distinction, pathos, and libelous intent by Mait and Ron, respectively. We conspired to skewer every member of the organic faculty in our not so subtle satire – hell, we even killed off Lubullba in a people's riot, led by Jungle Jim! Other characters were Harold Cassidivubu, Richard Gebairdu, Gary W. Griffutu, Equus Wassenga, and Count Lwalter Lwowski; these were the *noms de scènes*, respectively, for Jim English, Harold Cassidy, Dick Baird, Gary Griffin, Harry Wasserman, and Walter Lwowski). Most faculty, wisely, stayed away, but one who didn't was visiting professor Melvin Calvin (who had not yet won the Nobel Prize, although he was sure that he deserved it). Tom Mattingly (from the Griffin research group) dressed up in a bald wig and suspenders, to mimic Calvin's appearance, and played the role of "Malvin Kelvin." Every word uttered by "Kelvin" in the play came from the lecture series that Calvin was giving. Examples: "Having published most of the excellent work in this field myself" and "It is a real tribute to your Department Chairman that I am here today." Saul Winstein, who had been a visiting professor the previous semester, was portrayed as Saul Hammerstjein from the U.N. – this character, also, spouted authentic Winsteinisms, such as attaching "-wise" to words, as in "reaction mechanismwise."

We mentioned the course that Winstein taught in Fall, 1960. It was toward the end of the semester that Winstein discovered, to his great dismay, that a student had mistakenly registered to take the course for credit. That student, Stu Staley, to his even greater dismay, was required to meet with Winstein for an oral exam. As it turned out, the exam was easy and Stu received an A, even though he claimed to have answered none of the questions correctly.

The next semester, Calvin lectured twice a week in the late afternoon. It was his habit to look up at the clock, note that it was close to the 5:30 ending time, and say, "I have a few more minutes, so let me continue" (which he did for more than a "few more minutes"). At his final lecture, we noticed (but Calvin didn't) that the wall clock had stopped at 5:25. Calvin glanced at it, noted the time, and said "I have a few more minutes, so let me continue." And when he looked up again and saw the clock at 5:25, he repeated that sentence. We don't remember how long this went on, but he eventually recognized his error and let us go. A few weeks later, Doering said, “Wasn’t it great what the assistant professors did to Calvin?” Huh? We didn’t know, until that very moment, that some of the younger faculty had conspired with a custodian to stop the clock at 5:25. (It was hinted that a bottle of booze was the price that they had to pay.)

Speaking of Stu Staley, as we did earlier when discussing The Old Heidelberg, he achieved great fame as a recipient of the “coveted” Emil Fischer award. The award was given for notable chemical indiscretions (i.e., monumental screw-ups) and was, for some time, the permanent property of various hacks in the Saunders research group. Stu received the honor for having isolated a compound by gc, taking its IR spectrum within salt plates(!), discovering that it was water, and leaving the spectrum on his desk for all to see. The award, itself, consisted of three layers of liquid in a bottle: CCl_4 on the bottom, water in the middle, and decalin on top. A blue compound (azulene?) was dissolved in the lowest layer and a red compound in the top. When Ron decided that such an award was needed during his first teaching position at Rice University, he named it after Arthur Rudolph Hantzsch, an early 20th century German chemist, who was wont to propose brilliant ideas but was unable to realize them experimentally. Sad to say, one day a custodian saw the three-layered-liquid, was intrigued, shook the bottle, and destroyed the beautiful red-white-blue pattern. Mait also stole the idea. At Princeton, the “Lead Star” was awarded for many years for “conspicuous acts contributing to the decline of chemistry.”

We return, again, to the weekly group seminars where we learned to write concise abstracts of literature articles, to present cogent talks, and to hone our skills for solving problems in mechanism and synthesis. As we began to recognize patterns in these problems, Ron developed a facetious set of guidelines that Mait nicknamed “Magid’s Rules.” Not only did he teach these rules to his undergraduates, but he immortalized them by including them in his popular [“Not popular enough!” according to Mait] textbook. First Rule: “All neutral products are lactones” applied to road-map problems in which, typically, a carboxylic acid (whose molecular formula, but not its structure, was given) was transformed into a “neutral product” – more often than not, such a compound turned out to be a lactone. Second Rule: “Always try the Michael first” referred to “fun-in-base” mechanism questions that might involve sequences of aldol condensations and Michael additions (the Robinson annulation being a typical example). Third Rule: “When all else fails and desperation is setting in, look for the hydride shift” often proved to be the key element in a mechanism problem that might have involved an oxidation/reduction at some stage.

We will close with short descriptions of two other chapters in Doering’s life: his Chinese connection and his work with the Council for a Livable World.

In the early 1980s, Doering was the American designer of the Chinese Graduate Program (CGP) through which the best young Chinese graduate students in chemistry were to be educated at a consortium of Western universities. Special examinations were held, unusual language training applied, and, at least at the start, precious hard currency exchanged. Eventually 240 extraordinary young people came to this country and others. The program was a spectacular success on this side, as anyone close to one or more of these students will attest.

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However politics and fate intervened to make it a failure from the Chinese side. Returning students were not met with open arms. Far from it: they were greeted with suspicion and the anticipated junior-faculty positions were clearly not about to materialize. Word got back to those still abroad who swiftly went into postdoctoral parking orbits as a result. After Tiananmen in 1989, it became clear that there were few who would go back.

Mait attended a reunion of CGP students in Los Angeles in 1994. About 50 attended and nearly 25 gave talks on what they were doing. They came from the U.S. and Canada, from Hong Kong and other places. They were in academia and in industry. Still others had moved quite far from chemistry and were in the world of commerce. He remembers the day as “one of the most inspiring I have ever had in chemistry. The energy and excitement were palpable ... It was a glorious day. I think that Doering thought that the CGP program would contribute to the rebirth of Chinese chemistry. That it did not do, or at least has not done yet. But I am certain that when some future Ph.D. student in sociology writes her thesis on this subject, she will conclude that Western chemistry profited immensely ... Doering has much to be proud of in his professional life, certainly in the number of scientific ‘children’ he has produced. This group of CGP ‘kids’ may prove to be the most remarkable in the long run.”

In 1962, nuclear physicist Leo Szilard founded the *Council for a Livable World*, a non-profit group dedicated to the goal of reducing the spread of nuclear weapons. Doering chaired the Board of Directors from 1962 to 1973; and from 1973 to 1978 he served as president of the association. Mait and Ron’s tenure as graduate students coincided, in part, with Doering’s increasing involvement with this organization. When he was out of town, it seemed that it was as often for Council meetings as to give a research seminar at a U.S. or European university. The Council is still active in lobbying Congress, endorsing electoral candidates, and holding symposia on how to achieve nuclear non-proliferation.

In the preceding pages, we’ve described what life was like as students in Doering’s lab. We’ve related serious incidents as well many that produced only amusement. What was the point of all this japery and foolishness – and of now writing about it? We were a dedicated lot in Sterling Chemistry Laboratory’s Room 150 (and we knew it), but at the same time, we were having an enormous amount of fun. We suspect that the atmosphere in contemporaneous research labs was similar. Some of those pranks and silly behavior reflected the fact that we just loved what we were doing. We wonder if the same is true today – it seems awfully serious and intense out there.

We were also very goal-directed – we wanted to make those molecules and see what they were like. But there was more to it. The atmosphere in the Doering research lab was deeply intellectual, despite practical issues and all the tomfoolery. That attitude came right from the top, as we have tried to make clear. In a sense we were being instructed, by words and deeds, to emulate Rainer Maria Rilke, who wrote (in “Letters to a Young Poet”) “... be patient towards all that is unsolved in your heart, and try to love *the questions themselves*.”

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Chapter 10

60 Years of Research on Free Radical Physical Organic Chemistry

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In this Chapter the reader is conducted on a gentle cruise through the green and pleasant land of mechanistic radical chemistry. My love of chemistry arrived with a bang (potassium metal + water) and I was already enamored by "how fast?". These two loves combined at the NRC as I helped to convert radical chemistry from a tarry, black art, into clean, practical, useful, predictable and comprehensible chemistry.

My father, Christopher Kelk Ingold, Professor and Head of the Chemistry Department at University College London (UCL, 1930-61), was the first recipient of the James Flack Norris Award for Physical Organic Chemistry (1965). This was a great honor and one that he very much appreciated. (To both of us, this was a very personal example of Americans' generosity of spirit, particularly since it was a very distinguished American, Louis Hammett, who coined the words "Physical Organic Chemistry". Hammett's seminal role in this subject was honored by his receipt of the second J. F. Norris Award in 1966).

I went to the ACS meeting in Atlantic City to see the Award presented and then drove my father, and two chemists from UC Santa Barbara, Clifford Bunton (ex-UCL) and Tom Bruice (Norris Award winner in 1996), back to my home in Ottawa. I live on the Rideau River which is at the bottom of my garden (in Summer, in Spring the garden is at the bottom of the river!) and had a ski boat (woefully underpowered relative to later boats). My father surprised all of us by expressing a wish to water ski though he'd never done it before. With many misgivings I agreed and even drove the boat. To our joint surprise, my father got up the first time he tried, but then he had always kept fit. He used to do, and encouraged me

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to do, a lot of walking, rock climbing (Wales), and mountaineering (Alps), sports he continued into his late 50s (Figures 1-4).

Figure 1. Getting ready for the great water-ski caper: (right to left) John Ingold (age 5), Bruice, Bunton, CKI, and KUI.

Figure 2. CKI skiing for first time at age 72

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Figure 3. KUI skiing at 85. One of the advantages of living with a river!

Figure 4. Other than the first two pictures in this Chapter, this is the only known snap of myself and my father together. We are sitting with Lionel Jones, husband of my sister, Dilys, in their garden in Sussex.

C. K. Ingold was chosen to be the 1st recipient of the Norris Award largely for his pioneering mechanistic and kinetic studies of heterolytic chemical reactions. The statement: "*I should tell you that in this Department, homolysis, even between consenting adults, is grounds for instant dismissal*." was not made by CKI but by Peter de la Mare as comment on Alwyn Davies' wish to start work on peroxide homolysis (*1*).

That I would also become a research chemist, like my father (and mother) was unsurprising, as was my very conscious decision to steer well clear of heterolytic chemistry. Emigration to Canada (with a freshly minted D.Phil from Oxford) in 1951 at the age of 22 may have been one of my wiser decisions since my father and I had, perhaps, too much in common to get on as well as we actually did if we'd lived closer to one another, cf., pictures of the two of us through the years (Figures 5 and 6).

I believe my love of chemistry was sparked by an event in 1941-2. World War II disrupted everyone's life. My father and mother were evacuated with half of UCL's Chemistry Department to Aberystwyth (Aber), Wales. Eventually, (summer 1940) they were joined by me and my two sisters. I had attended at least 3 schools after evacuation and before my arrival in Aber in June, 1940. While living in Aber I attended 3 more schools (and went to yet another upon our return to London in 1944) before my entry as a chemistry undergraduate into UCL. My frequent school changes were not due to (sometimes well-deserved) expulsion, they were just a consequence of Hitler's disruptions. In Aber there was little to do on a weekend. In a forlorn attempt to keep me out of trouble, my father arranged for the Department's glass blower to teach me some of his skills on Saturday mornings (which proved very useful later). However, time hung heavy (until I discovered the joys of rock climbing). One Sunday my father took me into the labs and, after finishing whatever work had dragged him there, he decided to show me some interesting chemistry. Interesting was an understatement! He wanted to show me what happened when a small piece of sodium was dropped into water. Fortunately for me, he didn't know where the sodium was kept. However, he found the potassium and, being a bit rattled by his failure to find the sodium in "his" new-to-him lab, cut off several grams of potassium and threw it straight into a sink prefilled with water. Spectacular! There was an enormous bang, far louder than any I later heard from V2 rockets landing in London. The sink was instantly dehydrated, small puddles by the hundred appeared on the floor, the bench-tops, everywhere, each one with little bits of purple-burning potassium speeding around on its surface. We were not wearing safety glasses, but survived unharmed. Even though we had to clean the entire lab (to keep all others in the Department ignorant of the Professor's sins) I was instantly and totally hooked on chemistry.

Hooked on chemistry, yes, but I'd been hooked on kinetics almost a decade earlier. Well before I was a teenager, I overheard some adults describing a lady who lived near us as a "fast woman". I'd seen the lady in question and she didn't look fast to me, though I did consider the possibility that high-heels gave speed on the running track. Since this seemed a mite unreasonable, I decided that when I grew up I would adopt an experimental approach and find out what made a woman fast. The results of these experiments were so rewarding that I've remained an

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experimentalist who measures how fast things go, though today it is only chemical reactions, unfortunately.

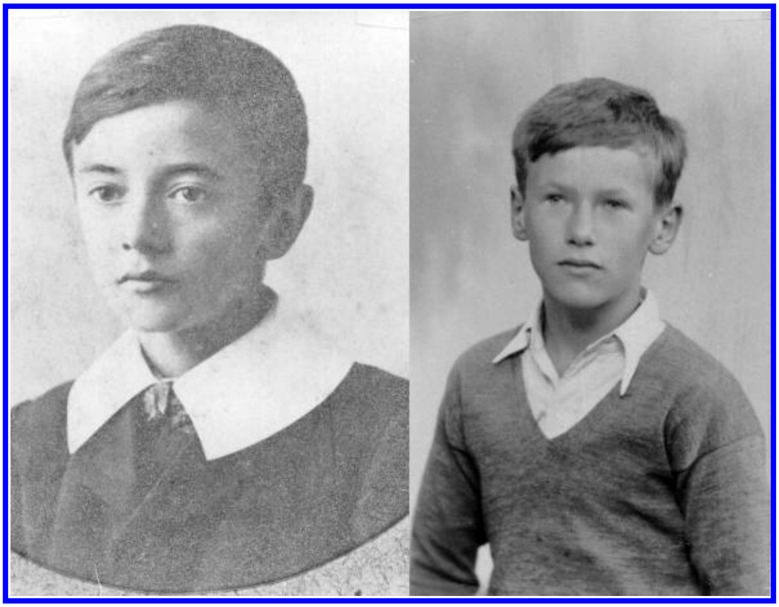

Figure 5. CKI and KUI as ca. 12 year olds.

Figure 6. CKI and KUI in their 70s.

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Four years (and 2 Post-Docs) after I arrived in Canada, I abandoned gas phase chemistry to accept a position in the Division of Applied Chemistry at the National Research Council in Ottawa (despite snide comments from many of my ‘pure’ chemistry friends). I wanted to work in the liquid phase because there is so much more interesting chemistry there than there is in the gas phase (witness, the entire field of biochemistry). I was hired to investigate the mechanism of oxidative degradation of automobile engine oils and to try to find ways to retard such degradation. A few years of glacially slow progress as a “real” applied chemist working on “real” engine oils convinced me to go back to basics. To this end, during 1960 I wrote my first *Chemical Review*, *Inhibition of the Autoxidation of Organic Substrates in the Liquid Phase*, in order to acquaint myself fully with the current state of knowledge (*2*). My career is now “book-ended” by my second *Chemical Review* (2014): *Advances in Radical-Trapping Antioxidant Chemistry in the 21st Century. A Kinetic and Mechanistic Perspective* (*3*). Although antioxidants remain my “first love”, the present Norris Chapter will show that my research has extended into a few other areas of physical organic chemistry.

Mechanism of Inhibition of Hydrocarbon Oxidation by Phenols

In the early 1960s I started work on this topic. Literature results were very confusing. Controlled oxidation of a hydrocarbon, RH, is achieved by thermal decomposition of an azo-initiator, iN=Ni, and occurs by a two-step chain reaction:

$$\textit{Initiation} \qquad \text{iN=Ni} \rightarrow 2\text{i}\bullet + \text{N}_2 \quad \textit{Rate} = R_\text{i} \qquad (1)$$

$$\textit{Propagation} \qquad \text{ROO}\bullet + \text{RH} \rightarrow \text{ROOH} + \text{R}\bullet \qquad (2)$$

$$\text{R}\bullet + \text{O}_2 \rightarrow \text{ROO}\bullet \qquad (3)$$

$$\textit{Termination} \qquad \text{ROO}\bullet + \text{ROO}\bullet \rightarrow \text{non-radical products} \qquad (4)$$

$$\textit{Uninhibited Rate} = -\text{d}[\text{O}_2]/\text{dt} = \text{d}[\text{ROOH}]/\text{dt} = k_2[\text{RH}](R_\text{i}/2k_4)^{1/2} \qquad (\text{I})$$

Such oxidations are retarded by phenols, ArOH, but not by anisole, PhOMe. This implied that the phenolic OH group was required for inhibition. The obvious inhibition step is an H-atom transfer by which a chain carrying peroxyl radical is converted into a non-chain carrying phenoxyl radical:

$$\text{ROO}\bullet + \text{ArOH} \rightarrow \text{ROOH} + \text{ArO}\bullet \qquad (5)$$

However, if this reaction was responsible for the inhibiting effect of ArOH, it would be expected to show a deuterium kinetic isotope effect, DKIE, but none had been found. The DKIE experiments involved measuring the rates of azo-initiated oxygen uptake by some readily oxidizable hydrocarbon (e. g., cumene or Tetralin) under an atmosphere of O_2. To the hydrocarbon was added, in mM concentrations, a phenol, ArOH, and in a matched experiment, the same concentration of the corresponding pre-formed O-deuterated phenol, ArOD. In such experiments the reduction in the rate of oxygen uptake induced by the ArOH and ArOD were identical, indicating that there was no DKIE for inhibition. This negative result was confirmed by many authors (myself included) and it led to some extraordinary mechanistic suggestions in the literature. During the writing of my first *Chemical Review*, I realized one evening that these inhibition experiments actually had **no** chance whatever of uncovering a DKIE (if there really was one). Rates of oxidation were followed in sealed systems under pure O_2 by measuring the consumption of O_2. What I belatedly realized was that to measure such a rate required the absorption of an appreciable amount of O_2. In the equipment of the day, this measurement required the uptake into the hydrocarbon of a higher concentration of O_2 than the concentration of ArOH or ArOD that had been added. This meant that in order to measure the rate of O_2 uptake it was necessary to make a higher concentration of the substrate's hydroperoxide, ROOH, than the concentration of added ArOD. I had recently completed some IR studies on phenols, incidentally demonstrating (contrary to then accepted wisdom) that the O-H bond in 2,6-di-*tert*-butyl phenols lay in the aromatic ring plane and that 2-*tert*-butylphenols existed as an equilibrium mixture of *syn* and *anti* structures. This work had taught me that OH-containing compounds underwent proton exchange with ArOD extremely rapidly. I concluded, therefore, that in all the experiments searching for a DKIE in reaction 5, essentially all ArOD had been converted to ArOH before the rate could be properly measured.

$$\mathrm{ROOH + ArOD \leftrightarrows ROOD + ArOH} \qquad (6)$$

These thoughts led me to suggest to my first Post-Doc, J. A. (Tony) Howard, that he add a drop of D_2O to a hydrocarbon oxidation retarded by 2,6-di-*tert*-butyl-4-methylphenol (BHT, the major phenolic antioxidant used commercially) so as to make sure that the BHT remained fully deuterated during the reaction. I also suggested using styrene as the oxidizable substrate because it was known to yield a polyperoxide (with no exchangeable H-atoms) rather than a hydroperoxide. Tony's results (*4*) were a game changer in antioxidant research. He found a DKIE of 10.6 at 65 °C, thus demonstrating that phenols are antioxidants because they donate their phenolic H-atom to an attacking peroxyl radical.

$$\textit{Phenol Inhibited Rate} = -\mathrm{d}[O_2]/\mathrm{dt} = k_2[\mathrm{RH}]R_\mathrm{i} \,/\, 2k_5[\mathrm{ArOH}] \qquad (\mathrm{II})$$

The length of time the oxidation is retarded by the phenol, known as the induction period, τ, is given by:

$$\textit{Induction Period}\ (\mathrm{sec}) = \tau = 2[\mathrm{ArOH}] \,/\, R_\mathrm{i} \qquad (\mathrm{III})$$

Work on phenolic antioxidants was continued by an examination of the effect of ring substituents on the abilities of phenols to retard the autoxidation of styrene. Electron donating (ED) para and meta substituents improved antioxidant activity while electron withdrawing (EW) substituents reduced activity. In these experiments, the rates we were measuring only allowed us to determine the rate constant ratio, k_2/k_5. A Hammett plot of $\log(k_2/k_5)$ against Brown and Okamoto's σ^+ values for the substituents yielded a straight line. This was completely unexpected because σ^+ substituent constants had been derived from the relative

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rates of a *heterolytic* reaction, the ionization (solvolyses) of m- and p-substituted cumyl chlorides in aqueous acetone.

$$XC_6H_4CMe_2Cl \rightarrow XC_6H_4C^+Me_2 + Cl^- \qquad (7)$$

The reason for the linear free energy relationship between $\log(k_2/k_5)$ and σ^+ was only uncovered many years later. It arises because the XC_6H_4O-H bond dissociation enthalpies (BDEs) also correlate with σ^+. This last correlation was recognized (by an outstanding Post-Doc, Gino DiLabio) to arise because the O• moiety is, like the $^+CMe_2$ group, an extremely powerful EW substituent. As a consequence of the EW effect of O•, ED substituents weaken and EW substituents strengthen the ArO-H BDE, making the antioxidant reaction 5 thermodynamically more and less favorable and, hence, faster and slower, respectively. In fact, the O-H BDEs in substituted phenols and the N-H BDEs in substituted aromatic amines trend with σ^+ due to the electron-poor nature of O• and N• as discussed in a 2004 *Account*: *Bond Strengths of Toluenes, Anilines, and Phenols. To Hammett or Not* (*5*). The mechanism of retardation of hydrocarbon oxidation by diarylamines, Ar_2NH, was also contentious until we demonstrated an NH/ND antioxidant DKIE. This class of industrially important antioxidants therefore owed their activity to donation of their amino H-atom to ROO• radicals. Thus both phenols and aromatic amines are *Radical Trapping Antioxidants*, RTAs.

If further progress in antioxidant chemistry was to be made it was necessary to know the magnitude of k_5 rather than k_2/k_5 rate constant ratios. After all, my ultimate goal was to see whether a phenolic antioxidant could be designed that reacted with the first peroxyl radical it encountered! This Holy Grail was achieved several decades later by Derek Pratt, who had worked with me in 1998-99 as a NRC summer student, and there caught "grail fever", see reference (*3*) for the full story. Such an antioxidant could not be bettered since reaction 5 would be diffusion-controlled (with $k_5 \sim 10^9$ $M^{-1}s^{-1}$). It had already been shown that absolute rate constants could be determined for a number of free radical polymerization chain reactions. The main focus of research in my lab therefore shifted to the measurement of absolute rate constants for radical reactions, a subject that looked boundless and a subject to which I have (mainly) stayed faithful.

Absolute Rate Constants for Hydrocarbon Oxidation

Some polymer chemists had been using photolysis to initiate their reactions and wanted to know how the rate of polymerization varied with the light intensity. Since no instrument was available to measure light intensities they inserted a metal disc, from which a 90° sector had been removed, between the light source and the reaction vessel. Rotation of this disc would block the light for 75% of the time and so the rate was expected to be 25% of the rate with full illumination. This was the case when the disc was rotated slowly but as the rotation rate was increased the rate of polymerization also increased up to a limit of 50% of the full-light rate. This odd behavior arose because chain termination in these polymerizations was a second-order process, $P_n\bullet + P_m\bullet \rightarrow P_{n+m}$. Provided the rate of chain initiation, R_i, was known, the rate constant for chain termination could be calculated from the

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duration of the flash at rotation speeds where the rate was >25% but <50% of the full-light rate.

The transfer of this rotating sector technology to hydrocarbon oxidation was surprisingly easy. The experimental temperature was decreased as far as possible (30 °C) to minimize any thermal formation of radicals. UV photolysis of an azo compound provided a steady rate of initiation, R_i, and the magnitude of R_i was determined from the length of the induction period induced by addition of a known concentration of BHT. Product studies by George Hammond (Norris Award, 1968) had shown that each molecule of BHT traps two ROO• radicals (hence the $2k_5$ term in equation II). With R_i known, the measured uninhibited rate yields the rate constant ratio, $k_2/(2k_4)^{½}$, the rotating sector yields $2k_4$ and hence k_2, and finally the inhibited rate yields k_2/k_5 and hence k_5. This may seem a long road, but in the 1960s it was the only road available for obtaining the desired absolute rate constants. Measurements on some 40 alkyl-aromatic and olefin hydrocarbons (*6*) laid the foundation for all subsequent quantitative work on autoxidation and inhibition by radical trapping antioxidants. It was found that k_2 was highly dependent on the RH structure, mainly for enthalpic reasons (R-H BDEs), for example, k_2 / $M^{-1}s^{-1}$ = 0.18 for isopropylbenzene (cumene), 60 for methyl linoleate (MeLin), and 1500 for 1,4-cyclohexadiene (CHD) for which the chain carrying peroxyl is hydroperoxyl, HOO•. {Note that work from Alwyn Davies' lab has shown that there is an analogous propagation step in the oxidation of organoboranes, i.e., $ROO• + R_3B \rightarrow ROOBR_2 + R•$, and that this step is many orders of magnitude faster than any ROO• + RH reaction.} The values of $2k_4$ varied just as dramatically, with values for tertiary alkylperoxyls being very much lower than for secondary and primary alkylperoxyls, e.g., 10^{-6} x $2k_4$ / $M^{-1}s^{-1}$ = 0.015 for cumene, 9 for MeLin, and 1300 for CHD. For this uninhibited termination reaction, tertiary and secondary alkylperoxyls almost certainly react by different mechanisms but, despite the efforts of many physical organic chemists (notably, Paul Bartlett, Norris Award, 1969, and Glen Russell, Norris Award, 1983), only the mechanism for *tert*-alkylperoxyls can be said to be fully understood. Chain propagation for styrene autoxidation involves the addition:

$$ROO• + PhCH{=}CH_2 \rightarrow ROOCH_2C•HPh \qquad (8)$$

for which k_8 was determined to be 41 $M^{-1}s^{-1}$ at 30 °C (*6*). This allowed the values of k_5 for BHT and diphenylamine to be calculated. Both of these radical trapping antioxidants had $k_5 \sim 2 \times 10^4$ $M^{-1}s^{-1}$, some 4 to 5 orders of magnitude below the diffusion limit, leaving much room for later (huge) improvements (*3*).

Absolute Rate Constants for Reduction of Alkyl Halides by Tin Hydrides

In the mid-60s I had the good fortune to hear Cheves Walling (Norris Award, 1971) give a wonderful lecture on the radical chain reduction of organo-halides by tri-*n*-butyltin hydride, reactions 9 – 14. This was brand new chemistry to me. Walling described the reduction of 5-hexenyl bromide because he was investigating cyclization of the 5-hexenyl radical (chemistry later studied in detail

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by Athel Beckwith). The main products were 1-hexene and methylcyclopentane which are formed in a ratio dependent on [Bu_3SnH] and on the rate constant ratio, k_{15}/k_{16}. I decided, while Walling was speaking, to investigate the kinetics and measure the absolute rate constants for these reactions. Walling was supportive of my decision and a friendship developed that survived his becoming Editor of *J. Am. Chem. Soc.* and quite a few arguments over the suitability for *JACS* of some of my later submissions! Indeed friendly relations were maintained with subsequent *JACS* Editors, all the way to the present day (Peter Stang, Norris Award, 1998).

Initiation $\rightarrow R\bullet$ (Rate R_i) (9)

Propagation $R\bullet + Bu_3SnH \rightarrow RH + Bu_3Sn\bullet$ (10)

$Bu_3Sn\bullet + RX \rightarrow R\bullet + Bu_3SnX$ (11)

Termination $R\bullet + R\bullet \rightarrow$ non-radical products (12)

$R\bullet + Bu_3Sn\bullet \rightarrow$ non-radical products (13)

$Bu_3Sn\bullet + Bu_3Sn\bullet \rightarrow$ non-radical products (14)

5-Hexenyl Radical: Reduction by Bu_3SnH vs Cyclization

$\bullet CH_2(CH_2)_3CH{=}CH_2 + Bu_3SnH \rightarrow$ 1-hexene (15)

$\bullet CH_2(CH_2)_3CH{=}CH_2 \rightarrow c\text{-}C_5H_9CH_2\bullet$ (16)

$c\text{-}C_5H_9CH_2\bullet + Bu_3SnH \rightarrow$ methylcyclopentane (17)

An easy decision to make, but how to monitor these, necessarily photo-initiated, reactions? Another excellent Post-Doc, Dave Carlsson, took up the challenge. We decided to measure the heat evolved in these exothermic reactions using a Pt / Pt-10%Rh thermocouple mounted at the center of a Pyrex cell that was, in its first incarnation, about 1.5 cm long and 3 cm in diameter. The design of the system evolved, the cell shrunk and the problem of direct photo-heating of the thermocouple was evaded by using twin cells side-by-side in the light beam with the full slate of reactants in cyclohexane present in only one of these cells, the other contained the reference thermocouple and cyclohexane. Conditions in the reactant cell remained adiabatic for ca 10-15 s, i.e., the temperature rise was linear, and the rate of temperature increase could be converted to a rate of reaction after some separate (essentially classical) calorimetric experiments. After each rate measurement, the system was allowed to return to thermal equilibrium (10-15 min).

The kinetics were fascinating. For RCl the rates were proportional to [chloride] and independent of [Bu_3SnH], but for RBr and RI the rates were independent of [halide] and proportional to [Bu_3SnH] (*7*). Thus, with chlorides,

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chlorine atom abstraction was rate controlling and termination was by the bimolecular self-reaction of the tin-centered radical, reactions 11 and 14, respectively. However with bromides and iodides, hydrogen atom abstraction was rate controlling and termination was by the bimolecular self-reaction of the alkyl radicals, reactions 10 and 12, respectively. Simple competition experiments with chlorides gave rate constants for bromine and iodine abstraction by $Bu_3Sn•$. As we wrote in 1968 (*7*): *The evaluation of the rate constants for both propagation reactions and two out of the three possible termination reactions means that these processes are now among the best understood two-step chain reactions.*

The advantage of synthesis via a chain reaction with a long chain length is that by-products (e.g., from initiation and termination) become no more than very minor impurities. Although tin hydride reductions are of no interest industrially (because of the toxicity of tin), these reactions are of immense value to academics exploring free radical-based syntheses. With all these rate constants now available to synthetic chemists some, most notably Dennis Curran, made use of them to plan complex syntheses in which the reagent concentrations and other conditions could be pre-selected for success.

From the physical organic chemist's viewpoint, there were two especially interesting results in this work (*7*).

[i] Since the rate constant for cyclization of the 5-hexenyl radical was now available, this rearrangement could be employed to time, i.e., to determine the rate constants, for other reactions involving primary alkyl radicals using kinetic competition methods and product analyses. This was the birth of the *Free Radical Clocks* concept, as described in an *Account* (*8*) with this title, and later exploited with great elegance by Marty Newcomb (Norris Award, 2000). This was another step on our way to a full quantitative understanding of free radical chemistry. However, it is the peroxyl radical clocks, developed in the lab of Ned Porter (Norris Award, 2013), that have proved the most helpful to the physical organic chemistry of highly reactive RTAs (*3*). Porter had demonstrated that the complex mixtures of isomeric hydroperoxides formed during the autoxidation of polyunsaturated fatty acids, arose because O_2 addition to pentadienyl radicals is reversible, see Scheme 1 (reaction 18). The initial pentadienyl radical adds O_2 to give a cis-trans peroxyl radical which may be trapped by an H-atom donor to give a cis-trans hydroperoxide or may undergo a bond rotation followed by a β-scission with loss of O_2 to form a new trans-trans pentadienyl radical. Addition of O_2 to this new pentadienyl yields the thermodynamically favored trans-trans peroxyl and hence the corresponding trans-trans hydroperoxide. The rate constants for β-scission were determined by competition with H-atom donation from 1,4-cyclohexadiene and hence can be traced back to much earlier measurements of the absolute rate constants for 1,4-cyclohexadiene autoxidation (*6*). A variety of peroxyl radical clocks have been calibrated and have proved invaluable for determining rate constants for the near diffusion-controlled radical trapping antioxidants developed in recent years (*3*).

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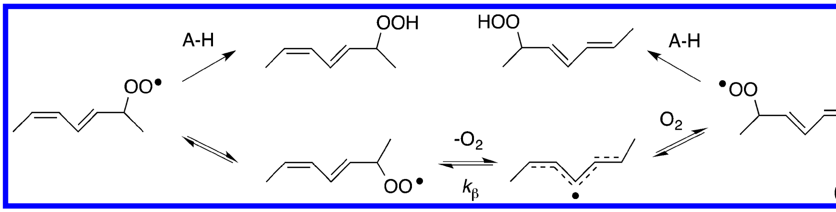

(18)

Scheme 1

[ii] The rate constants for chain termination via bimolecular self-reactions of the radicals: n-hexyl, c-hexyl, t-butyl, Bu_3Sn• (and various other R_3Sn•), were all ca. 2 x 10^9 $M^{-1}s^{-1}$. That these reactions must all be diffusion-controlled was demonstrated by showing that $2k_{12}$ for one of the radicals, *t*-Bu•, was larger in the less viscous solvent n-pentane, and smaller in the more viscous n-tridecane, than in cyclohexane. {Amusingly, some gas-phase chemists claimed years later that the *t*-Bu• + *t*-Bu• rate constant was only ca. 10^6 $M^{-1}s^{-1}$, although by that time we had confirmed the 10^9 $M^{-1}s^{-1}$ value using EPR spectroscopy, a technique later brought to perfection by Hanns Fischer. Complex mixtures of reagents were used to generate *t*-Bu• in our EP(ara*magnetic*)R (e.g., *t*-BuOOBu-*t*, Me_3SiH, *t*-BuCl, in *c*-C_3H_6) which led to the following (Paris bar) exchange with the adamant 10^6 $M^{-1}s^{-1}$ proposer, as recorded in a footnote to a 1974 *JACS* paper: Sceptic, "*Getting reliable radical decay rate constants out of that mixture mustbe like trying to find a needle in compost heap*." Author, "*It would be if we did not use a magnet*."}

The tin hydride work induced me to purchase an Electron Paramagnetic Resonance (EPR/ESR) spectrometer in the late 1960's. I expected this would become an important instrument for a lab devoted to measuring the kinetics and absolute rate constants for radical reactions, particularly since Jay Kochi (Norris Award, 1981) had just developed several novel ways to photo-generate radicals in an EPR. My expectations were fully realized. The new EPR turned out to be ideal for studying the kinetics of radical decay whether this occurred by a bimolecular process (combination and/or disproportionation, *cf.*, reactions 4, 12, and 14), or by some unimolecular process such as isomerization into a different radical (of the same molecular weight) by an intramolecular rearrangement, e. g., reaction 16, or by a bond-scission to form an unsaturated molecule and a smaller radical. Measurements of the decay kinetics of a very wide structural range of radicals having the unpaired electron (formally) centered on C, O, N, Si, etc. led to the crystallization of some ideas I'd long been mulling over.

Persistent Carbon-Centered Radicals

Is the title of an *Account* (*9*) in which these ideas were presented. The problem addressed was centered around the meaning of "*stable radical*". These words were being used throughout the literature to refer two very different radical properties. Consider the benzyl and ethyl radicals, the former is obviously "more

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stable" than the latter, but both radicals decay by bimolecular self-reactions with the same rate constant, viz. 25% (the doublet-doublet spin correction) of the diffusion-controlled limit. Indeed, nearly a decade of careful kinetic work by several Post-Docs, notably David Griller, demonstrated that sterically non-congested and EPR-visible radicals of all types (note that RO• and RS• have degenerate SOMOs and are invisible by EPR.) underwent their self-reactions with this rate constant provided they could combine to give thermodynamically stable dimers or disproportionate, e.g., 2 $R_2CHX• \rightarrow R_2C{=}X + R_2CHXH$.

The need to separate thermodynamic stabilities from kinetic stabilities was met in this *Account* (*9*). Thermodynamic stabilities are normally defined by R-H BDEs. Thus, for C-centered radicals, thermodynamic stabilities are normally referenced to the [CH_3-H] BDE or, with a nod to obvious structural effects, to the [CH_3CH_2-H] BDE for primary alkyls, the [$(CH_3)_2CH$-H] BDE for secondary alkyls, etc. The *Account* dealt with thermodynamic stability in the conventional manner (*9*). However, to describe kinetic stabilities, or lack thereof, this *Account* formally introduced the words *Transient* to describe radicals that decayed at (1/4) of the diffusion-controlled rate, and *Persistent* to describe radicals that decayed more slowly. Thus, benzyl, $PhCH_2•$, is a stabilized transient radical, but the sterically crowded benzyl, $PhC(Me_3C)_2•$, is a stabilized persistent radical. Similarly, Ph• is a destabilized transient radical, but the sterically encumbered phenyl, 2,4,6-tri-*t*-butylphenyl, is a destabilized persistent radical. The words *stable radical* were restricted to radicals that could be "*put in a bottle*" such as 2,2-diphenyl-1-picrylhydrazyl (dpph•), di-*t*-alkyl nitroxides (e.g., TEMPO), and di-1-adamantylketiminoxyl. Di-*sec*-alkyl nitroxides and all alkylperoxyls do undergo bimolecular self-reactions but with rate constants well below the diffusion limit, they are therefore stabilized, but mildly persistent radicals. Interestingly, even the secondary alkyl radical, (t-Bu)$_2$CH•, is persistent, but it slowly dimerizes to form (t-Bu)$_2$CHCH(t-Bu)$_2$. This compound was the most sterically crowded molecule made to that time. A fact that reminded me of a fictional molecule, thiotimoline, that was so crowded that it pushed a part of itself into the future and another part into the past! In 1977, I celebrated steric crowding in *JACS* (thanks to Editor Walling, who ruled in my favor over a mirthless reviewer) with two footnotes:

[21]Despite severe crowding ((t-Bu)$_2$CHCH(t-Bu)$_2$) does not appear to show the unusual properties reported[22] for the "super" sterically hindered molecule, thiotimoline.

[22]I. Asimov, *J. Astound. Sci. Fict.* **50**, 120, (1948).

Today, the persistent / transient nomenclature is widely employed in both radical and non-radical chemistry (but thiotimoline has still to be synthesized).

Electron Paramagnetic Resonance and the Art of Physical Organic Chemistry

Is the title of an *Account* (*10*) which summarizes highlights from a decade or so of lovely work by several Post-Docs, notably David Griller. I acquired my first EPR spectrometer in the late 1960's because it was obviously an important

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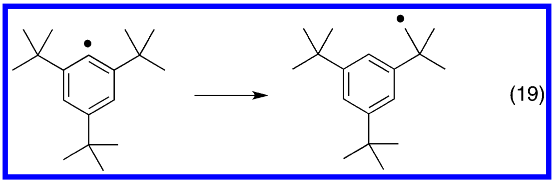
instrument to have in a lab devoted to measuring the kinetics and rate constants for radical reactions. A rich research vein was soon tapped, some 42 papers being published between 1971 and 1983 in *J. Am. Chem. Soc.* under the title: *Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy* and even more EPR-based research appeared that was not a part of this series.

Quantum Mechanical Tunneling

A kinetic EPR study showed that the persistent 2,4,6-tri-*tert*-butylphenyl radical (generated by UV photolysis from the corresponding bromide and a source of tin- or silicon-centered radicals) decayed with first-order kinetics. Decay was shown to involve a 5-center intramolecular H-atom transfer from one of the ortho *tert*-butyl groups to the vacant position on the ring so as to form a transient primary alkyl (neophyl) radical, reaction 19. Both of these radicals could be observed and, on shuttering the UV light, the phenyl decayed with first-order kinetics and the neophyl with second order kinetics. The temperature dependence for phenyl radical decay (183–243 K) showed an unexpectedly small Arrhenius pre-exponential factor (A_{19} = 2 x 10^5 s^{-1}). I commented to my two coworkers (Griller and Ross Barclay) that this H-atom transfer must involve Quantum Mechanical Tunneling (QMT)! Both laughed heartily and said some less than complimentary things about my intelligence. Quite understandable, the year was 1974 and R. P. Bell had spent the past couple of decades looking for an unequivocal example of QMT in proton transfer reactions with little or no success. The subject of QMT was virtually "off limits" for serious chemists. However, in my mid-teens I had read the physicist, George Gamow's wonderful "*Mr. Tomkins*" books. I had been particularly taken by the short story "*Quantum Billi*ards" and the accompanying cartoons, particularly that of Mr. Tomkins' car tunneling out of his closed garage. In this story one reads: "*It is impossible to hold anything inside an enclosure provided there is enough energy for running away after crossing the wall. Sooner or later the object will just* '*leak through*' *and go away.*" A bit of a stand-off ensued but eventually I got my way and my two 'doubting Thomas' colleagues synthesized a bromide with three per-deuterio-*tert*-butyl groups, the phenyl radical from which also decayed with first order kinetics but much more slowly than the non-deuterated phenyl, k_{19}^{H}/k_{19}^{D} = 50 at 243 K, a result that quieted my two doubters.



Work on reaction 19 (and on its deuterated analogue) was later extended. QMT was firmly established by demonstrating that at temperatures below ca. 100 K, k_{19}^{H}

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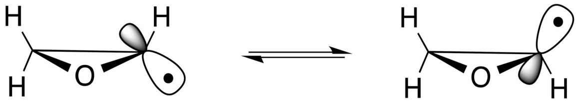
(and k_{19}^{D}) became independent of the temperature, with $k_{19}^{H}/k_{19}^{D} \sim 100{,}000$! The decay of phenyl radicals having related *rigid* and *crowded* structures also occurred by intramolecular 1,5-H-atom isomerizations in which QMT is dominant.

A number of other H-atom transfers were also demonstrated to occur exclusively by QMT at low temperatures. In all cases, these reactions involved *rigid* systems. Some of these reactions were exothermic, e.g., reaction 20 at very low temperatures in rigid methanol glasses where k_{20}^{H} becoming constant at temperatures below ~45 K and exhibits a very large DKIE. At temperatures above 45 K but below the glass' softening temperature, this reaction was particularly interesting because $CH_3\bullet$ decay followed a "stretched exponential", i.e., each half-life was longer than the preceding half-life. The reason for this behavior is that the $CH_3\bullet$ radicals occupy an array of sites within the methanol glass, each with its characteristic first-order rate constant. Rates of QMT are highly dependent on the "jump" distance with the smaller jumps occurring far more rapidly than the longer jumps. A detailed treatment of the kinetic data was utilized to derive jump distances (no variables and no assumptions) and gave a structure for the rigid methanol glass that was fully consistent with that deduced by other (non-kinetic) methods.

$$[CH_3\bullet + CH_3OH \rightarrow CH_4 + \bullet CH_2OH]_{glass} \qquad (20)$$

QMT was also explored in a number of thermoneutral "reactions", e.g., inversion of the oxyranyl radical, reaction 21, for which the occurrence of QMT had been denied. However, the rate constant for inversion, k_{21}^{H}, became temperature independent below 140 K and again there was a huge DKIE.



(21)

Serious attempts to obtain evidence by EPR for QMT in exothermic intermolecular H-atom transfers in solution were made in my lab, but all were inconclusive (low A-factors, but 'normal' DKIEs and no rate constants independent of temperature). All of this QMT work has been summarized (*11*). My conclusion is that while QMT must always play a role in H-atom (and proton) transfers, it only becomes dominant, and hence obvious, in reactions where the H-atom source and sink are physically prevented from achieving a close (optimum) separation. The large DKIEs reported by J. P. Klinman and others for certain enzyme-catalyzed reactions are consistent with this idea. Shamefully, I had overlooked a lovely example of QMT in what is, formally, an intermolecular H-atom transfer. This example had been right under my nose for decades! I'm referring to a recent report from the Porter group that reaction 2, with RH = tetralin, has a primary DKIE at 65 °C that is at least twice the classical maximum (~6-7). These results indicate, to me, that this apparently 'simple' H-atom transfer involves QMT in a pre-reaction ROO•/RH complex.

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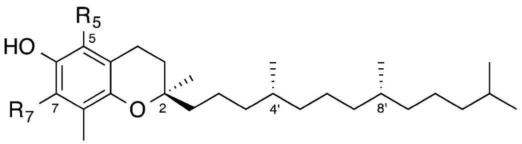
The Return to My First Love, Peroxyl Radical Trapping Antioxidants

After a separation of many years, I was enticed back to antioxidant research in 1980 by the ending of a long running controversy in the biochemical literature, a controversy that, in my opinion, the "wrong" side had won, pretty much by default. The question at issue had been: *Does Vitamin E owe its bioactivity to its ability to trap radicals?* I "knew" the answer should have been "*Yes"* simply because "*Vitamin E*" is any one of, or is any mixture of, four phenols, the tocopherols (see Chart 1). Since Howard and I had shown that every one of the 50-odd phenols we had examined were RTAs, Vitamin E just had to be one. However, numerous reports in bio-oriented journals claimed that the tocopherols were not RTAs and some quite extraordinary explanations for this dichotomy were published. Furthermore, there were also reports that γ-tocopherol was a better antioxidant than α-tocopherol. Since it was well established that α-tocopherol had a stronger Vitamin E activity than γ-tocopherol, Vitamin E could not, therefore, owe its activity to radical trapping (or so the argument went). When I finally forced myself to read these papers I was amazed to discover that the oxidizable substrate was most commonly the homogenized organ from a rat, generally its liver. Apparently, this made the experiments *biologically relevant*, though I know of no animal that can survive if its liver is homogenized! In my view, both then and today, the oxidation of the lipids in a homogenized organ would be a metal ion-catalyzed (mainly $Fe^{II/III}$) oxidation, with an unknown, uncontrolled, high, and highly variable, R_i. The stronger antioxidant action of γ-tocopherol relative to α-tocopherol in these systems was, in my view, irrelevant to the question of whether or not Vitamin E owed its activity to peroxyl radical trapping. γ-Tocopherol would obviously be oxidized to an ortho-quinone and, of course, ortho-quinones are metal ion chelators. Such an oxidation product would not be formed from α-tocopherol since it lacks a non-methylated ortho-position on its aromatic ring. Thus, γ-tocopherol would not only be able to trap peroxyl radicals, its (main) oxidation product would chelate some of the catalytic metal ions present in the liver homogenate and so reduce R_i. No wonder γ-tocopherol was a "better" antioxidant than α-tocopherol in tissue homogenates! However, living animals keep a very tight control of catalytic ions via storage (e. g., ferritin) and transport (e. g., transferrin) proteins, so the observed "better" antioxidant activity of γ-tocopherol compared with α-tocopherol reveals nothing of chemical significance and does not translate to the living.



Congener	R_5	R_7
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
δ	H	H

Chart 1

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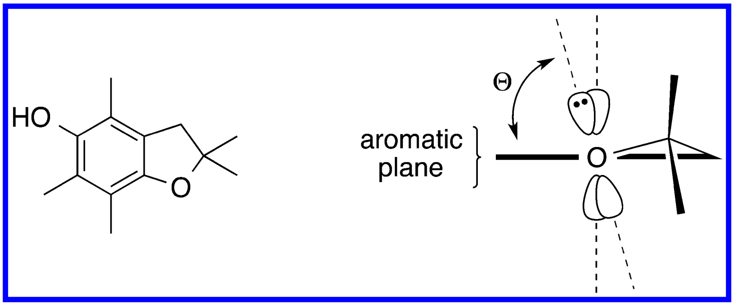
The problem remained as to whether or not the tocopherols were RTAs. Another excellent Post-Doc, Graham Burton, agreed to explore this matter, starting with the building of a much more sensitive apparatus for measuring oxygen uptake than our original. This work, and much more, is reported in the *Account*: *Vitamin E. Application of the Principles of Physical Organic Chemistry to the Exploration of its Structure and Function* (*12*). Graham discovered that all four tocopherols were excellent ROO•-trapping antioxidants, with activities increasing in the order: $\delta<\gamma\sim\beta<\alpha$, an order that is the same as the order of their bio-activities (as judged by their abilities to cure animals of Vitamin E deficiency symptoms). Furthermore, α-tocopherol was far and away the best trap for peroxyl radicals yet reported, e. g., $k_5 = 320 \times 10^4$ $M^{-1}s^{-1}$ for α-tocopherol vs. 1.4×10^4 $M^{-1}s^{-1}$ for BHT. Extensive experiments (applying Physical Organic Chemistry principles) demonstrated that the high activity of α-tocopherol was related to the extent of overlap of the (rehybridized) 2p-type lone pair on the para-oxygen with the π-electrons on the aromatic ring. In α-tocopherol the heterocyclic ring ensures that orbital overlap is high. However, it is not perfect (the dihedral angle, Θ, between the orientation of this lone pair and the ring plane is ca. 73° while the optimum angle would be 90°). Indeed, flattening the heterocyclic ring by reducing the number of its carbon atoms from 3 to 2 increased Θ to 84° and, as expected, also increased antioxidant activity (*cf.* Scheme 2). This phenol had $k_5 = 570 \times 10^4$ $M^{-1}s^{-1}$. Although k_5 is still two or three orders of magnitude below the diffusion limit, for many years I thought it represented the best phenolic RTA that could ever be made. I was wrong, see reference (*3*). Perhaps more interesting than my own short sightedness, was that when this compound was "decorated" with the C_{16} phytyl "tail" of the tocopherols, the resultant compound showed roughly twice the biopotency of Vitamin E in one animal model (the rat curative myopathy assay). This last result was one of the two final blows to the powerful "Vitamin E is not an antioxidant" movement. The other was our demolition of the highly popular Diplock-Lucy theory that Vitamin E stabilized bio-membranes by some (unprecedented) physical interaction of the methyl groups on its phytyl 'tail' with cis-ene 'pockets' in the polyunsaturated fatty acid 'tails' of the phosphoplipids. However, when we replaced the phytyl group in α-tocopherol by an unbranched C11 or C13 paraffinic tail the resulting compounds showed (rat curative myopathy test) the same bioactivity as α-tocopherol!



Scheme 2

Having established that the tocopherols were superb peroxyl radical trapping antioxidants, the obvious question became: *Is Vitamin E the sole lipid-soluble RTA in humans?* To answer this question my lab had to become bio-oriented. We learned how to draw blood from one another. (No worries about AIDS in those days.) We learned how to separate red blood cells and lipoproteins, and how to remove the interior content of the red cells to leave behind “ghost” membranes (to get rid of hemoglobin and so prevent iron catalysis of the planned oxidations). We also invested in a very early liquid chromatograph – mass spectrometer (LC/MS) instrument to enable us to quantify the tocopherols (mainly α) in our samples. Then we exploited a procedure, pioneered by Lee Mahoney and Stefan Korcek at the Ford Motor Company, that “titrates” for all RTAs in an (oxidizable) sample by providing a steady supply of ROO• at a known rate, R_i, from the thermal decomposition of an azo-initiator (the reason we had to eliminate the hemoglobin). The length of the induction period, τ (see Equation III), then yields the concentration of the unknown RTA via:

$$[\text{unknown RTAs}] = [\text{ArOH}] = \tau \times R_i / 2 \qquad \text{(IV)}$$

When we finally felt confident that our protocols covered all foreseeable eventualities, we took samples of blood plasma and ghost membranes, divided each sample into two portions, one portion for the measurement of [tocopherols] by LC/MS, the other for [unknown RTAs] by oxidation (equation IV, adding a readily oxidized hydrocarbon when necessary). Within our limits of accuracy, [tocopherols] = [unknown RTAs] for all the chemists in my lab. This was also the case for an individual with very severe Vitamin E deficiency. So Vitamin E must certainly be the major lipid-soluble RTA in humans. (Later work by others showed that the hydroquinones, ubiquinol-9 and -10, can also function as RTAs in low density lipoproteins. In general, hydroquinones are poor RTAs because they yield semiquinone radicals and these can react with O_2 to form the chain carrier, HOO•.)

“Antioxidants” were as popular 30 years ago as they are today. Then, as now, the word was frequently employed indiscriminately to describe (bio)-molecules having structures that precluded *any* ability to trap ROO• radicals or to reduce R_i by interfering with redox reactions that can lead to free radicals (e.g., $Fe^{II} + H_2O_2 \rightarrow Fe^{III} + HO^- + HO•$) and hence to an increase in lipid peroxidation. All kinds of ‘natural’ products were (and are) promoted because they contained reducing agents that have been mislabeled as ‘antioxidants’. I have generally ignored even the wildest of such claims because they generally harm only the wallets of unscientific, but health conscious, consumers. However, on half-a-dozen occasions I’ve been sufficiently annoyed to react. Two of my ‘reactions’ to Vitamin E nonsense are described below.

α-Tocopherol is sold to consumers as Vitamin E (*d,l*-α-tocopheryl acetate, or all-*rac*-α-tocopheryl acetate) and (a bit more expensively) as Vitamin E “*from natural sources*” (*d*-α-tocopheryl acetate). The former is synthetic and is correctly 2*RS*, 4′*RS*, 8′*RS*-α-tocopheryl acetate. The latter is made from a mixture of natural tocopherols (mainly γ-tocopherol) distilled from soy beans, then fully methylated on its aromatic rings, and finally acetylated, it has the 2*R*,4′*R*,8′*R* configuration. (Note: animals, including man, have a tocopherol transport protein, TTP, which

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discriminates strongly in favor of α- over γ-tocopherol. This protein is responsible for the inter- and intra-cellular distribution of the water-insoluble tocopherols and protection from cytochrome P450-mediated oxidation.) The actetate is the preferred vehicle for human and animal consumption because (ex-*vivo*) the free phenol is fairly rapidly oxidized in air. The then accepted answers to two questions posed below "got my goat".

1) *What is the* '*cost*' *in Vitamin E uptake when taking the acetate rather than the free phenol?* Remember that only the free phenol can capture ROO• radicals. Furthermore, the acetate is not absorbed from the gut, it must first be hydrolyzed to the free phenol and it is the free phenol that is absorbed. *Accepted answer*: The acetate has *twice* the bioactivity of the phenol!!
2) What is the activity of 'natural' Vitamin E (as acetate) vs. synthetic α-tocopheryl acetate (the Vitamin E standard)? *Accepted answer*: 1.36 / 1.00!

To answer these (and a host of other physiological) questions correctly, and in the hope of obtaining information more acceptable to rational, unbiased observers, Graham and I applied the competitive kinetic methods of Physical Organic Chemistry. Building on commercial practices, pure γ- and δ-tocopherol were methylated with CD_3 groups to give 2*R*,4′*R*,8′*R*-α-tocopherol with masses 3 and 6 Daltons, respectively, greater than the unlabelled material. Traditional bioassays for Vitamin E involve dissolving the material to be assayed in a large excess of tocopherol-stripped corn oil and administering this oil directly (intubation) into the stomachs of several Vitamin E deficient rats (several rats because bio-scientists love statistics, while most chemists are content with Avagadro's 6 x 10^{23}). We followed this procedure using tocopherol-stripped corn oil to which was added equimolar concentrations d_3-α-tocopheryl acetate and d_6-α-tocopherol. Some rats were E-deficient (traditional bioassay) and some that were not E-deficient. Later, the rats were "sacrificed" (killed, in English), divided into bits (dissected), and the ratios of α-tocopherol from phenol to α-tocopherol from acetate (d_6-/d_3-α-tocopherol) were measured in about ten different tissues. In the blood and tissues of all the rats, the d_6/d_3 ratio was about 0.5, supporting earlier conclusions that the acetate was a better source of Vitamin E than Vitamin E! Since this was a senseless result, one evening I took my courage in both hands, used another hand to grab and then swallow a capsule containing equimolar d_6-α-tocopherol and d_3-α-tocopheryl acetate, and yet another hand to pick up a large glass of red wine as a 'chaser'. Supper continued very pleasantly, in part because I didn't tell my wife that what I'd been doing might make it my last. The next morning I was bled at work and the LC/MS analysis of α-tocopherol gave d_6/d_3 ratio of 1.0. This proof that "*Man is not a rat*" was confirmed by other '*volunteers*' in my lab, but was disputed by my secretary: "*All men are rats*". Upon reflection, I decided she might be partly correct! However, I was not willing to swallow a huge dose of corn oil on an empty stomach, so the rats were again called into play. This time the rats were given the two d-labeled Vitamin Es with their food (no wine). All these new results gave a d_6/d_3 ratio of 1.0, proving that

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my secretary understood the world better than I. Apparently, when following the long-approved protocol, about 50% of the free α-tocopherol given to the rats is oxidatively destroyed in their stomachs, whereas the acetate passes safely through the stomach into the small intestine where it is hydrolyzed and absorbed. Clearly, the long-accepted test for Vitamin E activity had been sacrificing rats on the altar of stupidity, not science.

Far more contentious (because of its financial implications for the manufacturers of synthetic Vitamin E) was a ratio Graham and I obtained by application of the same d-labeling/competitive kinetic technique to the second question. We found that the 2*R* stereoisomer of α-tocopherol was absorbed and retained in the human body twice as effectively as the racemic material, meaning that Vitamin E "*from natural sources*" is twice as good a source of this Vitamin for humans as is plain, i.e., synthetic, "Vitamin E"! This result was contested (futilely) but is fully consistent with TTP only binding (accepting) the "*natural*" stereoisomer, as was later proven by others using recombinant human TTP. If you are into 'antioxidants' just remember to read the label and the mnemonic: "To hell with the l", when purchasing Vitamin E.

Our pioneering work on the "biokinetics" of α-tocopherol uptake and loss in animals and in humans (both healthy and with certain genetic diseases such as an inability to synthesize TTP), was interesting and exciting. Uptake (and loss) rates differ dramatically between tissues with the brain and nerves being the most determined to hang on to their supply when 'new' α-tocopherol from food was not available. Under such conditions, TTP is up-regulated, and lipoproteins in the blood shuffle α-tocopherol from less important tissues, such as the liver, to the brain. The kinetics of these processes follow "stretched exponentials", like the $[CH_3\bullet + CH_3OH]_{glass}$ reaction described above. In this case, the stretched exponentials are due to the presence of many organelles within each tissue, each of which will have its characteristic first-order uptake/loss kinetics. This is an interesting area, but one I thought unlikely to be scientifically, or intellectually, rewarding (except in terms of publication numbers!).

Vitamin E as a Pro-Oxidant!

About the time that I finally gave up Vitamin E biokinetics I was seduced into studying the oxidation of Low Density Lipoproteins (LDL). There was some evidence that (per)oxidized LDL was a causative factor in the development of atherosclerosis. Most work was qualitative and of little value. However, eventually Australian researchers (Roland Stocker and Vince Bowry, an ex-PDF of mine) undertook quantitative studies that used (mainly) water-soluble azo-initiators, iN=Ni. Their studies allowed the number of ROO• radicals generated / LDL particle to be calculated and led to the amazing discovery that α-tocopherol was a *pro-oxidant* in LDL particles dispersed in saline at physiological pH. I was able to explain at least a part of this astonishing result to the Australians and a very fruitful collaboration ensued. In brief, there are two reasons that α-tocopherol is a pro-oxidant in LDL:

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(i) The water soluble iOO• radicals can only pass their radical character into an LDL particle by abstracting the phenolic H-atom from an α-tocopherol molecule which, we had demonstrated by NMR methods, has its OH group at the surface of LDL-mimicing phospholipid liposomes dispersed in water.

(ii) The α-tocopheroxyl radical formed in this initiation event, actually can abstract a bis-allylic H-atom from a polyunsaturated fatty acid moiety in the LDL. (This reaction is very slow, but the tocopheroxyl radical is "stuck" in the LDL by its insolubility in water and the pentadienyl radical it produces is very rapidly trapped by O_2.) Moreover, two radicals cannot coexist in such small particles which means that LDL particles contain either no radical centers (and are not oxidizing), or a single radical center (and are oxidizing). The kinetics are virtually identical to those for emulsion polymerization, as described by Walling (*vide supra*) in his book *Free Radicals in Solution* (Wiley, 1957). This similarity was celebrated by a joint 1993 *PNAS* publication with the two Australians and Walling, as described in the *Account*: *The Unexpected Role of Vitamin E (α-Tocopherol) in the Peroxidation of Human Low Density Lipoprotein* (*13*).

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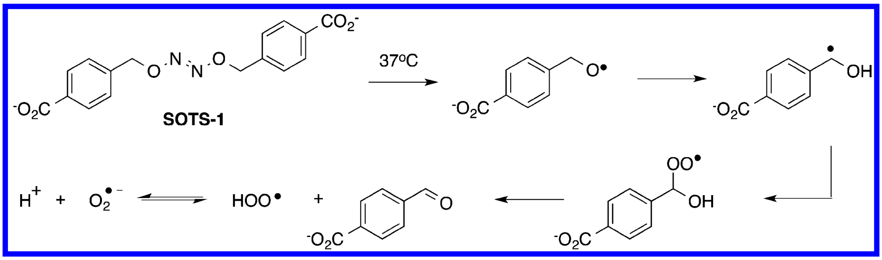
Invention of the First Superoxide Thermal Source, SOTS-1

During my lab's bio-era, we were naturally interested in DNA, particularly in quantitative studies on peroxyl radical-induced DNA damage. The only existing work of this kind involved a commercially available, water-soluble, positively charged, azo-initiator, $^{+}$iN=Ni^{+}. Plasmid DNA was cleaved, but the number of double strand breaks per $^{+}$iOO• radical generated was not reported. Moreover, this result was simply assumed to be true for all peroxyl radicals. I was unwilling to accept this assumption because DNA bears a negative surface charge that would attract and hold $^{+}$iOO• and because the electron-withdrawing effect of the positive charge would be expected to make these $^{+}$iOO• radicals far more reactive than neutral peroxyls, *cf.*, the reactivities of Cl_3COO• *vs.* Me_3COO•. Physical organic chemists must be able to synthesize the molecules they wish to study. We did exactly that and found that neither water-soluble neutral iOO•, nor negatively charged $^{-}$iOO•, cleaved DNA to any significant extent. These results made me doubt reports that superoxide ($O_2^{\bullet -}$) readily cleaved DNA. Superoxide is the major radical formed *in vivo*. It generally functions as a reducing agent (despite its name), but its conjugate acid, HOO•, pK_a 4.6, is present at ca. 1% of the [superoxide] at physiological pH (7.4). (The peroxyl radical, HOO•, is slightly more reactive than alkylperoxyls.) So we had to synthesize a superoxide thermal source that would produce superoxide at a known and useful rate in water at 37 °C and pH 7.4. This was achieved by means of the chemistry shown in Scheme 3. Plasmid DNA was not cleaved by superoxide!



Scheme 3

Invention of a Nitric Oxide Cheleotropic Trap, NOCT

A second small inorganic radical, nitric oxide (•NO), is also of large biological importance. It is synthesized *in vivo* both as an antibacterial agent in macrophages and as an important signaling molecule (e.g., for blood pressure control). When •NO is generated together with O_2•- in the vacuole of a white blood cell that has engulfed a bacterium, these two rather unreactive radicals combine to form peroxynitrite, $ONOO^-$. We demonstrated (contrary claims notwithstanding) that peroxynitrite's conjugate acid undergoes a fast homolysis under physiological conditions to produce nitrogen dioxide and the very reactive hydroxyl radical, ONOOH → NO_2• + HO•. Under physiological conditions, most peroxynitrite will react with CO_2 to give $ONOOCO_2^-$. This ion (with the lovely empirical formula CNO_5) also undergoes a fast homolysis to NO_2• + CO_3•-, both of which are also powerful oxidizing radicals. The engulfed bacterium does not have a chance! Nor did early workers in this field who were unaware of: (i) the reaction of $ONOO^-$ with CO_2, and (ii) the reaction of •NO_2 with O_2•- to form peroxynitrate, O_2NOO^- which, confusingly, absorbs at 302 nm, the wavelength normally employed to monitor peroxynitite decay! My lab had lots of fun helping to sort out some of this 'messy' chemistry.

Since nitric oxide was so 'hot' in 1990, I thought it would be nice to have a method for monitoring its production in time and space *in vivo*. It seemed possible that •NO might add to a suitably constrained diene to form a stable nitroxide radical that would be easy to monitor by EPR spectroscopy. However, •NO is very unreactive so addition to the diene would require a strong driving force. This driving force might be provided by aromatization of a 1,3-cyclohexadiene moiety. All of which suggested that 1,2-bis(exo-isopropylidene)cyclohexa-3,5-diene (Scheme 4) might be suitable. This (somewhat transient) compound can be synthesized by the photo-decarbonylation of 1,1,3,3-tetramethyl-2-indanone and, if the diene trapped •NO as hoped, it would yield a known stable nitroxide radical, see Scheme 4, Since I was going on a Humboldt Fellowship to Germany, I collaborated with Hans Korth, an EPR expert at U. Essen (and several other organic and medicinal chemists), to explore this reaction. To my surprise, the chemistry worked like a charm, first time! However, this and related •NO trapping reactions were later shown by my German collaborators to be too slow to be of much use for monitoring •NO *in vivo*.

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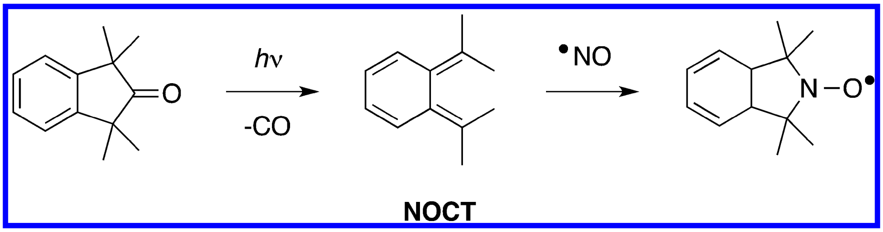


Scheme 4

Nanosecond Laser Flash Photolysis (LFP) and Solvent Effects

The wonderful LFP technique proved ideal for measuring the rate constants for reactions involving reactive free radicals. It was brought to my lab by another great Post-Doc, J. C. (Tito) Scaiano, and quickly replaced EPR spectroscopy as our main research tool. This technique was more versatile than EPR and, most importantly, LFP made it simple to study the kinetics of alkoxyl radical, RO•, reactions, particularly H-atom abstractions. Such studies took on increased vigor when we discovered that benzyloxyl and related radicals, ArCRR′O•, had a fairly strong absorption in the visible (unlike $Me_3CO\bullet$). This meant that the reactions of ArCRR′O• radicals could be monitored directly (rather than indirectly via the "*probe*" method).

The ease and speed with which LFP measurements could be made encouraged me to investigate the effect of solvents on the rate "constants" of radical reactions. The prevailing wisdom among synthetic organic chemists was that radical reactions did not exhibit any significant solvent effects. Physical organic chemists knew this was not true for two good reasons:

First, in the 1950's Glen Russell (*vide supra*) had discovered that the free radical chain chlorination of 2,3-dimethylbutane using Cl_2 gave a higher tertiary/primary chloride product ratio, $[Me_2CHCMe_2Cl]/[Me_2CHCHMeCH_2Cl]$, in benzene than in CCl_4. Russell attributed this result to formation of a chlorine atom-benzene π-complex that was less reactive and more selective in H-atom abstractions than a 'free' Cl• atom in CCl_4. Russell's interpretation was challenged some 30 years later and his two H-atom abstractors, Cl• and $\pi\text{-}(ClC_6H_6)\bullet$, were increased to three by the addition of a third abstractor, a Cl• atom-benzene σ-complex. Our LFP and spectroscopic studies soon demonstrated that all the facts could be fully and most simply (Occam's razor) explained with Russell's two original abstractors. This work is summarized in an *Account*: *The Unusual and the Unexpected in an Old Reaction. The Photochlorination of Alkanes with Molecular Chlorine in Solution* (*14*).

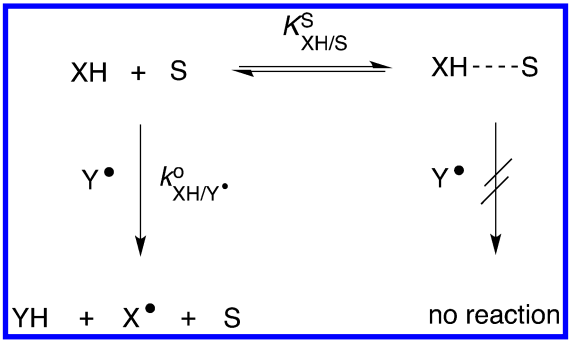
Second, and of more relevance to organic chemists, roughly a decade later Cheves Walling (*vide supra*) had reported dramatic solvent effects on *tert*-butanol / acetone ratios in competitions between H-atom abstraction from cyclohexane by *tert*-butoxyl and its β-scission, reactions 22 and 23.

$$Me_3CO\bullet + C_6H_{12} \rightarrow Me_3COH + C_6H_{11}\bullet \tag{22}$$

$$Me_3CO\bullet \rightarrow Me_2CO + Me\bullet \qquad (23)$$

For example, with 0.1 M cyclohexane at 40 °C the [*tert*-butanol] / [actone] ratios were 7.5, 3.5, 1.6, and 1.4 in $CFCl_2CF_2Cl$, C_6H_6, MeCN, and MeCOOH, respectively. Walling pointed out that "*solvent effects on competitive radical reactions must reflect different degrees of solvent interaction with the transition states rather than with the radicals*" and that "*Solvent interactions with the transition state for β-scission presented no difficulties, but in the transition state involving an alkoxy(l) radical and a substrate such as cyclohexane, solvent molecule should be sterically excluded from close vicinity to the alkoxy(l) radical.*" Solvent effects on the [Me_3COH] / [Me_2CO] ratio were therefore ascribed "*chiefly to solvation of the transition state for the β-scission process".* Roughly 30 years later, our LFP measurements proved that this was correct. That is, $k_{PhCMe2O\bullet/C6H12}$ was 1.2 x 10^6 $M^{-1}s^{-1}$ in six solvents of widely different polarity, whereas the rate constants for β-scission of $PhCMe_2O\bullet$ (to acetophenone and $Me\bullet$) varied substantially. When we reported these results, we naturally added the footnote: "*Hats off to Cheves Walling*".

Two years later, in 1995, we discovered (thanks to LFP) some very much more dramatic solvent effects on the rate "constant" for H-atom abstractions by the cumyloxyl radical, $PhCMe_2O\bullet$. The substrates were not hydrocarbons, but were phenol and *tert*-butyl hydroperoxide. It was clear from our earlier studies that these kinetic solvent effects (KSEs) could not be due to effects on the cumyloxyl radical but must, instead, be due to effects on these hydroxylic substrates. A simple reaction Scheme was proposed for H-atom abstraction from a hydrogen bond donor (HBD), XH, by radical Y• in a hydrogen bond acceptor (HBA) solvent, S:



Scheme 5

From this Scheme, the measured rate constant in solvent S is given by,

$$k^{S}_{XH/Y\bullet} = k^{0}_{XH/Y\bullet} / (1 + K^{S}_{XH/S}\,[S]) \qquad (V)$$

where $k^0_{XH/Y\bullet}$ represents the rate constant in a non-HBA solvent (i. e., an alkane).

Scheme 5 was based on three assumptions:

(1) Each XH can act as an HBD to only one single HBA molecule, S, at any one time.

(2) The magnitude of the equilibrium constant, $K^{S}_{XH/S}$, for formation of the HB complex, XH---S, was independent of the nature of the surrounding medium (e. g., its dielectric constant).
(3) Cumyloxyl radicals cannot abstract the hydroxylic H-atom from the XH---S complex (for steric reasons).

The magnitude of the KSE for these cumyloxyl radical reactions was greater for phenol than for *tert*-butyl hydroperoxide, e. g., k^{CCl4}/k^{Me3COH} was 240 for phenol but only 37 for the hydroperoxide. It took another six years and a lot of LFP measurements before I could provide a quantitative explanation for our observations. However, in the interim, two predictions that come directly from Scheme 5 were quickly put to the test.

(i) It was predicted that equilibrium constants for HB formation could be determined by kinetic measurements. This was readily demonstrated by comparison of $K^{S}_{PhOH/S}$ calculated for phenol from $k^{S}_{PhOH/RO•}$ values measured for several S at different phenol concentrations in CCl_4, with PhOH/S equilibrium constants determined by infrared spectroscopy in CCl_4.
(ii) It was predicted that KSEs should be independent of the attacking radical (since they depend only on the strength of the HB between the substrate and a solvent molecule). This was verified by a visting chemical dynamo, Luca Valgimigli (U. Bologna), using phenol (8 solvents) and α-tocopherol (13 solvents) and two H-atom abstracting radicals having very different reactivities, *tert*-alkoxyl (RO•) and 2,2-diphenylpicrylhydrazyl (dpph•). Rate constants in alkane solvents were about two orders of magnitude faster than those in the 'slowest' solvents used. Plots of log $k^{S}_{RO•}$ vs log $k^{S}_{dpph•}$ gave excellent straight lines with the predicted slope of 1.0 despite the RO• rate constant in any particular solvent being faster than that for dpph• by factors of more than 10^6 for α-tocopherol and more than 10^{10} for phenol! A new and most important principle for physical organic chemistry was presented: "*Provided rate constants have been measured for the reaction of one radical with a substrate in a range of solvents, the measurement of the rate constant for reaction of the same substrate with some different radical need be made in only one of these solvents for values in all the other solvents to be predicted accurately.*"

Each of these early KSE experiments produced one similar anomaly in the plots of log $k^{S}_{RO•}$ vs log $k^{S}_{dpph•}$ for phenol and α-tocopherol. For both substrates, the values of k^{S}_{RO*} were "normal" for S = *tert*-butanol, but the values of $k^{S}_{dpph•}$ in this solvent were "too large". The reason for these abnormally fast "hydrogen atom transfers" from phenols to the dpph• radical in *tert*-butanol were eventually traced, thanks to some great detective work by Grzegorz Litwinienko (U. Warsaw), to a solvent-dependent difference in mechanism. The mechanism is a (slow) H-atom transfer from the phenol to dpph• in most solvents, but a (fast) electron transfer from even traces of the phenoxide anion to the (very electron-deficient)

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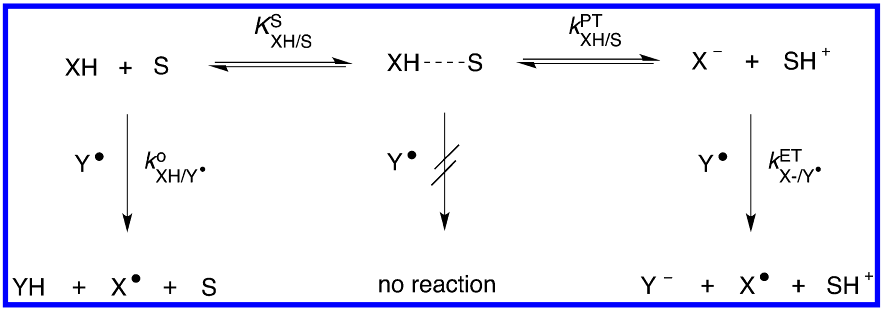
dpph• radical in solvents that could support at least some ionization of the phenol, i.e., alcohols and water, Scheme 6. This (new) mechanism, christened Sequential Proton Loss Electron Transfer (in part because of its lovely acronym, SPLET), is described together with the development of the standard H-bond quantitative model of KSEs that is based on Scheme 5 (*vide infra*), in the *Account*: "*Solvent Effects on the Rates and Mechanisms of Reaction of of Phenols with Free Radicals*" (*15*).



Scheme 6

During our long struggles to accumulate enough data to quantify KSEs for H-atom transfers, Mike Abraham (University College London) was struggling to develop two reliable, quantitative, thermodynamic scales relating to 1:1 HBD/HBA complex formation. One scale gave the HBD activities of many molecules, symbol $\alpha^{H}{}_{2}$ (range 0.00 for alkanes, to ca. 1.0 for carboxylic acids) and the other a parallel thermodynamic scale of HBA activities of an equally huge number of molecules, symbol $\beta^{H}{}_{2}$ (range 0.00 for alkanes to 1.00 for hexamethylphosphorustriamide, HMPA, the strongest organic HBA). Both scales rely on 1:1 HBA/HBD equilibrium constants in CCl_4 that can be easily and precisely determined by infrared spectroscopy. To cut a very long story short, I found that the KSEs for all H-atom abstractions examined (that had no significant SPLET chemistry) gave linear plots when log $k^{S}{}_{Y\bullet/XH}$ values (in roughly a dozen solvents) were plotted against the $\beta^{H}{}_{2}$ value for the solvent. Furthermore, the slopes of these linear free energy plots (which were, of course, independent of Y•) varied from 0.00 for cyclohexane (which has no KSE), through -3.0 for α-tocopherol, -3.5 for *tert*-butyl hydroperoxide, -5.1 for phenol, to -6.0 for 3,5-dichlorophenol. These (and many other) slopes in *neat* solvents were proportional to Abraham's $\alpha^{H}{}_{2}$ values for the substrates. Not only did these results confirm our earlier assumption #2 (*vide supra*), but also, and more importantly, they led to a simple equation for the quantitative description, and prediction, of kinetic solvent effects on any H-atom transfer in solution, Equation VI. This equation implies that for an XH having $\alpha^{H}{}_{2} = 1.0$, $k^{S}{}_{XH/Y*}$ would decrease by just over *eight* orders of magnitude on changing S from an alkane to HMPA! When I'd started work on KSEs I'd hoped that we might *eventually* learn how to describe their cause in some quantitative and predictive manner. When I finally discovered the answer, I was flabbergasted by its simplicity. Equation VI stands, in my mind, as a fitting monument to the rationalizing power of Physical Organic

Chemistry, to the hard work and dedication of the many kineticists who have worked in my lab, to the totally separate efforts of Mike Abraham at UCL to provide quantitative hydrogen bonding scales, and (as always) to serendipity.

$$\log (k^{S}_{XH/Y}\bullet / M^{-1}s^{-1}) = \log (k^{0}_{XH/Y}\bullet / M^{-1}s^{-1}) - 8.3\ \alpha^{H}{}_{2}\ \beta^{H}{}_{2} \qquad \text{(VI)}$$

Over some 60 years I have been privileged to work with a great many brilliant chemists: students, Post-Docs, NRC colleagues, and Professors from Academia. Unfortunately, only a few of these individuals could be named in this Chapter, but I recognize that everything I know about Physical Organic Chemistry, I owe to them. Thank you. I also express my love and gratitude to my late wife, Cairine, who not only put up with my enthusiasm for chemistry, but also "mothered" each and every one of my coworkers (Figure 7).

Figure 7. Cairine and Keith Ingold as I receive the 1998 NSERC medal. I "hold the gold", but it was Cairine who earned it.

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Chapter 11

Diradicals – A Fifty Year Fascination

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Diradicals are molecules in which two electrons occupy two molecular orbitals that have the same or nearly the same energies. This chapter describes the author's half century of fascination with this class of molecules and the theoretical and experimental research on diradicals that he has done during this period.

Introduction

Diradicals/Biradicals

Diradicals are molecules in which two electrons occupy two molecular orbitals (MOs) that have the same or nearly the same energies (*1*, *2*). Some authors call such molecules "biradicals." However, molecules with two positive charges are called "dications" (not "bications"); molecules with two negative charges "dianions" (not "bianions"); and molecules with two unpaired electrons are called "diyls" (not "biyls"). It follows, therefore, that the correct name for molecules in which two electrons occupy two MOs that are degenerate or nearly degenerate in energy should be "diradicals", not "biradicals" (*3*). "Diradicals" will be used exclusively throughout this chapter.

The Contents of This Chapter

In 1982 a book entitled *Diradicals,* which was edited by me and to which I contributed a chapter, was published (*2*). A huge amount of new research about diradicals has been published during the past 33 years; and, were I to edit a similar book now, it would have to be a multivolume series. Therefore, within the confines of this book chapter, I cannot possibly provide anything approaching an encyclopedic coverage of diradicals.

Three years ago Professior Carl Lineberger and I coauthored a review entitled, "The Synergy Between Qualitative Theory, Quantitative Calculations, and Precise Experiments in Understanding, Calculating, and Measuring the Energy Differences Between the Lowest Singlet and Triplet States of Organic Diradicals" (*4*). I knew that the chapter I wrote for this book would wind up discussing some of the diradicals that were covered in that review. However, I certainly wanted to avoid duplicating in this chapter the review that I published with Carl.

Tom Strom, the Co-Editor of this book, had requested that I include some biographical information in this chapter. As I began to think about how I would write this biographical section, I realized that one way of describing some of what is now known about diradicals would be to describe the history of how I learned it.

Recounting the evolution of the author's understanding of an area of science is not the traditional way to write a book chapter about that area. Nevertheless, I thought that my taking this opportunity to give an account of how my own understanding of diradicals has developed over the past 50 years might be a useful contribution to the history of this area of chemistry. In addition, I thought that reading about the slow pace of the evolution of my understanding of diradicals may be encouraging to those readers, who, like me, take a long time to figure things out (*5*).

Having decided that the first part of this chapter would be a description of the electronic structures of diradicals, organized around the history of how my own understanding of this area of theoretical chemistry developed, it seemed appropriate that the second major part of this chapter should recount how some of my theoretical predictions about diradicals have been tested experimentally. I believe very strongly that providing experimentalists with explanations is only part of a theoretical chemist's job. Even more important is using one's understanding to make clear predictions about the outcomes of experiments that have not yet been performed.

Making experimentally testable predictions is usually a very good way to motivate experimentalists to perform the experiments that are necessary, in order to test those predictions. Occasionally, I have even designed the necessary experiments myself and then collaborated with the chemists who performed the experiments on interpreting the results..

The second part of the chapter begins with a description of the experimental techniques for measuring the singlet-triplet energy differences (ΔE_{ST}), in diradicals. I have focused on negative ion photoelectron spectroscopy (NIPES), because it can, in principle, provide very accurate values of ΔE_{ST}, no matter how large or small ΔE_{ST} is.

This introductory section on experimental methodology is followed by descriptions of the results of measurements by NIPES of the values of ΔE_{ST} in several different types of diradicals. The experimental results on the effects on ΔE_{ST} of the replacement of methylene groups in trimethylenemethane (**TMM**) and in *meta*-benzoquinodimethane (**MBQDM**) by oxygens are described. The predictions, published prior to any experiments, were that this substitution would

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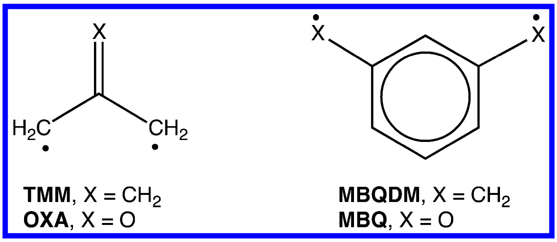
have a huge effect on ΔE_{ST} in **TMM** → oxallyl **(OXA)** (*6*), but very little effect in *meta*-benzoquinodimethane (**MBQDM**) → *meta*-benzoquinone (**MBQ**) (*7*). My group's collaborations with Professor Carl Lineberger on the experimental verification of the first prediction (*8*, *9*) and with Dr. Xuebin Wang on the experimental verification of the second (*10*, *11*) are described.



When one thinks singlet-triplet energy differences in diradicals, one thinks of Hund's rule and its prediction that the triplet should be the ground state of any diradical in which the two partially occupied MOs have exactly the same energies (*12*, *13*). One of the aspects of diradicals that has interested me most over the past half century is the possibility that some diradicals might be found to violate Hund's rule. Therefore, I have included in this chapter a discussion of predicted Hund's rule violations and the experimental testing of these predictions in several diradicals (*14*).

One of these experiments involved obtaining the NIPE spectrum of the radical anion of cyclooctatetraene (**COT**$^{\bullet-}$) (*15*). This experiment, which was done in a collaboration with Paul Wenthold and Carl Lineberger, resulted in the observation of not only the D_{4h} transition structure (TS) for ring inversion in D_{2d} **COT** but also the D_{8h} TS for π–bond shifting in singlet **COT** (Figure 1). The NIPE spectrum of **COT**$^{\bullet-}$ showed that, as had been predicted (*16*, *17*), the D_{8h} TS for bond shifting in singlet **COT** is lower in energy than the D_{8h} equilibrium geometry of the lowest triplet state, thus providing a clear violation of the strictest version of Hund's rule (*15*).

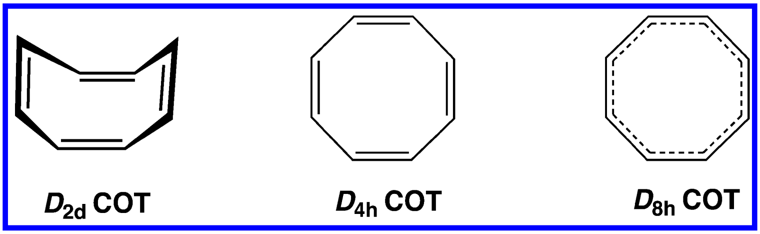


*Figure 1. The D_{4h} transition structure (TS) for ring inversion of D_{2d} cyclooctatetraene (**COT**), and the D_{8h} TS for bond shifting.*

The next-to-last section of this chapter describes my group's very recent research on the $(CO)_n$ series of molecules. The discussion focuses on the very surprising prediction that $(CO)_4$ has a triplet ground state (*18*), and on the experimental confirmation of this prediction by NIPES experiments, carried out

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by Dr. Xuebin Wang (*19*, *20*). The chapter concludes with a brief description of some of the future collaborations that Xuebin Wang and I have planned.

A Brief History of Diradicals and of My Interest in Them

A Brief History of the First Fifty Years of Diradicals

The history of diradicals extends back over a century to the preparation of Chichibabin's (*21*), Thiele's (*22*), and Schlenck's (*23*) hydrocarbons, respectively **1**-**3** in Figure 2. Although resonance structures with two unpaired electrons can be written for **1** and **2**, the dominant resonance structure for each of these derivatives of *para*-benzoquinodimethane is that shown in Figure 2, with all of the π electrons paired and occupying bonding MOs. Neither **1** nor **2** is actually a diradical (*24*).

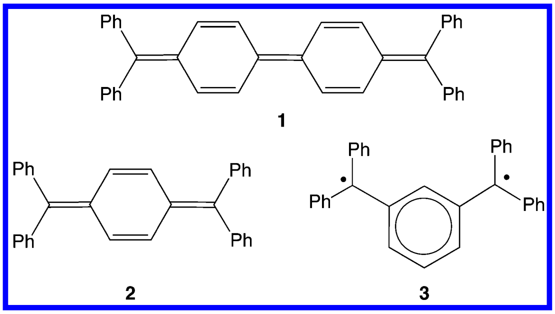

*Figure 2. Chichibabin's (**1**) (21), Thiele's (**2**) (22), and Schlenck's (**3**) (23) hydrocarbons.*

In contrast, **3** is a derivative of *meta*-benzoquinodimethane (**MBQDM**), a hydrocarbon for which it is impossible to write any Kekulé structures in which all of the electrons are paired. Longuet-Higgins showed that in such non-Kekulé hydrocarbons two electrons occupy a pair of non-bonding MOs that have the same Hückel energy, α (*25*). Therefore, **3** is a true diradical, and 2015 marks the 100th anniversary of its preparation (*23*).

In 1966 two landmark publications ushered in the modern era of diradical chemistry. First, Rowland Pettit reported the generation of cyclobutadiene (**CBD**) by oxidation of its $Fe(CO)_3$ complex. Pettit did not isolate **CBD**; instead, as shown in Figure 3, he trapped it by Diels-Alder reactions (*26*). The stereospecific Diels-Alder reaction of **CBD** with fumarate and maleate diesters was taken as evidence that the reactive state of **CBD** is a singlet, rather than a triplet.

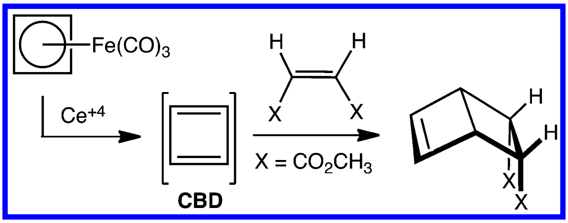

*Figure 3. The generation and stereospecific, Diels-Alder trapping of **CBD** (26).*

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Second, Paul Dowd reported the preparation of the simplest non-Kekulé hydrocarbon, trimethylemethane (**TMM**), by photolysis of 4-methylenepyrazoline (Figure 4) (*27–29*). The triplet state of **TMM** was characterized by its EPR spectrum, and Dowd subsequently showed the triplet to be the ground state of **TMM** (*30*).

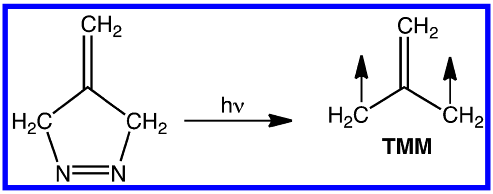

Figure 4. The generation of triplet ***TMM*** *by photolysis of 4-methylenepyrazoline (27).*

CBD and **TMM** each contain four π electrons. In each molecule one pair of electrons occupies a bonding π MO, leaving the remaining two π electrons to be distributed between two MOs. In both square (D_{4h}) **CBD** and in trigonal (D_{3h}) **TMM** these two MOs are nonbonding and are degenerate by symmetry. Therefore, square **CBD** and trigonal **TMM** are both diradicals; and according to Hund's rule, at these high-symmetry geometries, both diradicals should have triplet ground states (*12*, *13*). Dowd's EPR experiments did, in fact show that **TMM** does have a triplet ground state (*30*), but Pettit's trapping experiments (*26*) at least raise the question of whether **CBD** might actually have a singlet ground state.

How I Became Interested in Diradicals

In 1966 I was a graduate student at Harvard; and I had several late-night talks about **TMM** with Paul Dowd, who was a Junior Faculty member in the Chemistry Department at the time. However, my interest in diradicals actually began four years earlier, when I was an undergraduate at Harvard.

In the autumn of 1962 I borrowed my roommate, Bob Joffe's, copy of Andy Streitwieser's book, *Molecular Orbital Theory for Organic Chemists* (*31*). At the end of that academic year, Bob decided to give up chemistry, in order to become a lawyer. In fact, he attended Harvard Law School and went on to become the Managing Partner of Cravath, Swain, and Moore, a very prestigious New York City law firm. Bob and I remained friends until he died, much too young, of pancreatic cancer in 2010 at age 66.

I kept Bob Joffe's copy of Streitwieser's book, and I still occasionally consult it. It was, in fact, this book which first sparked my interest in **CBD** and in **TMM;** and my fascination with diradicals has now persisted for over half a century (*32*).

During the autumn semester of 1962 Bob Joffe and I were both enrolled in an undergraduate organic chemistry course at Harvard, which was taught by E.J. Corey. On night, at the end of the semester, I went to E.J.'s office to pick up my final exam. I had done well enough on the exam that E.J. asked me about my future career plans.

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I explained to E.J. that my first chemistry Professor at Harvard had been Bill Lipscomb, who convinced me that all of chemistry could be understood through chemical theory. My second chemistry Professor had been Frank Westheimer, who emphasized the importance of experimental research in chemistry. In fact, although Professor Westheimer was arguably the father of molecular mechanics calculations, he at least pretended to be very skeptical that theoretical chemistry could predict anything worth measuring. I told E.J. that, having been influenced by both Professors Lipscomb and Westheimer, I planned to become a physical-organic chemist and to combine doing theory with performing experiments, in order to test my own predictions.

On hearing this Professor Corey pulled down his copy of Streitwieser's book from his bookshelf. I expected that he was going to tell me that, if I wanted to do research in theoretical chemistry, I would have to read Streitwieser's book. Having just finished working my way through Bob Joffe's copy of this book, I could barely prevent myself from visibly glowing with pride. However, to my utter dismay, E. J. said, "Well if you are going to do theoretical chemistry, you will have to do much better than the Hückel theory in this book."

Crestfallen, I asked, "So what should I do?" E.J. thought for a moment and then said. "If I were you, I would go to study with H. C. Longuet-Higgins in Cambridge, England."

And that is exactly what I did do, immediately after I received my B.A. degree. I applied for and won a Fulbright Fellowship; and in the early fall of 1964, together with all of the other Fulbright Fellows who were going to England that year I boarded a ship that was bound for Southampton. (It is hard to believe that, only half a century ago, people frequently crossed the Atlantic by ship, rather than by airplane).

In a biography of Professor H. C. Longuet-Higgins that I wrote for another ACS book, which was co-edited by Tom Strom (*33*), I have described some aspects of my year in Cambridge. I recounted how, at least once during each of my weekly tutorials with Christopher Longuet-Higgins, he would exclaim, "Weston, stop talking nonsense!"

Despite his impatience with me, I learned a great deal from Christopher that year about how to solve scientific problems. Mostly I learned by watching how he worked out the answers to the questions that I asked him. Perhaps the most important thing I saw in witnessing Christopher solve problems was that he had complete confidence that he would eventually find the correct answer to any problem, even if he did not know the answer when he began. It took me decades to develop that type of confidence (*5*).

During my year in Cambridge, I learned a great deal about many things from Christopher; however, I did not learn anything about diradicals from him. Nevertheless, Christopher did encourage me to invest some of my time in working through Robert Parr's book on Pariser-Parr-Pople (PPP) calculations (*34*). I was anxious to learn how to do PPP calculations, because they explicitly include in the Hamiltonian operator the Coulombic repulsion between electrons. Therefore, PPP calculations take an important step beyond Hückel theory. As I would learn, understanding the effects of electron-electron repulsion in diradicals is the key to understanding diradicals.

When I was in Cambridge in 1964-65, I do not think that Christopher Longuet-Higgins knew how to write a computer program. Nor did I. Therefore, I did all of my PPP calculations with pencil and paper. In retrospect, this was very fortunate, because I had the opportunity to work through and really understand the nuts and bolts of doing PPP calculations on diradicals.

The Results of PPP Calculations on Diradicals

What I Learned about Diradicals from Doing PPP Calculations

In Cambridge, England in 1964-65, by doing PPP calculations, I started learning about the wave functions for diradicals and how to calculate their energies. For example, I came to understand that

$$\Psi(1,2) = |\psi_i^{\alpha}(1)\ \psi_j^{\beta}(2)> \qquad (1)$$

is not a proper wave function for an open-shell, singlet diradical, in which one electron occupies MO ψ_i and another occupies MO ψ_j. I learned that the wave function in eqn. 1 is actually a 50:50 mixture of the wave functions for an open-shell singlet state and the $S_z = 0$ component of the triplet state with the same orbital occupancy. The correct wave functions for an open-shell singlet and the $S_z = 0$ component of a triplet state are, in fact,

$$\Psi_{S,T}(1,2) = (|\psi_i^{\alpha}(1)\ \psi_j^{\beta}(2)> \pm |\psi_j^{\alpha}(1)\ \psi_i^{\beta}(2)>)/\sqrt{2} \qquad (2)$$

where the positive sign is for the singlet wave function and the negative sign is for the triplet.

The symbol |….> in eqns. 1 and 2 is called a “ket”. It denotes that the many-electron wave function inside the ket has been properly antisymmetrized, so that the wave function changes sign on exchanging the labels on any pair of electrons.

Expanding the kets in eqn. 2 gives, for the singlet,

$$\Psi_S(1,2) = [\psi_i(1)\ \psi_j(2) + \psi_j(1)\ \psi_i(2)][\alpha(1)\beta(2) - \beta(1)\alpha(2)]/2 \qquad (3)$$

and for the triplet,

$$\Psi_T(1,2) = [\psi_i(1)\ \psi_j(2) - \psi_j(1)\ \psi_i(2)][\alpha(1)\beta(2) + \beta(1)\alpha(2)]/2 \qquad (4)$$

It is easy to see that the wave functions in eqns. 3 and 4 are both antisymmetrized. The negative sign in each wave function causes it to change sign on switching the labels on the electrons. However, the singlet wave function in eqn. 3 and the triplet wave function in eqn. 4 differ in an important way. The singlet wave function has a symmetrical spatial part but an antisymmetrical spin part; whereas, the triplet wave function has an antisymmetrical spatial part but a symmetrical spin part.

Because the spatial wave function for the triplet is antisymmetrized, it is easy to see that it gives zero for $\psi_i = \psi_j$. Therefore, two electrons with the same spin – $\alpha(1)\alpha(2)$, $\beta(1)\beta(2)$, or $[\alpha(1)\beta(2) + \beta(1)\alpha(2)]/\sqrt{2}$ – cannot occupy the same orbital, because, if they do, the triplet wave function vanishes. Thus, the

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antisymmetrization of the spatial part of a triplet wave function results in its obeying the Pauli exclusion principle.

Antisymmetrization of the spatial part of a triplet wave function does more than just keep electrons of the same spin from occupying the same MO. Eqn. 4 shows that two electrons of the same spin in different MOs cannot appear simultaneously in the same region of space (for instance in the same AO); or the triplet wave function again vanishes. However, the spatial part of the singlet wave function in eqn. 3 is not antisymmetrized; so there is some probability that the electrons of opposite spin in a singlet state will simultaneously appear in the same region of space. Consequently, triplet wave functions usually have smaller Coulombic repulsion energies than their singlet counterparts.

This gives rise to Hund's rule: If ψ_i and ψ_j have the same energy, then the electronic state of lowest energy is the triplet, in which the two electrons minimize their Coulombic repulsion energy by occupying different orbitals with the same spin (*12*, *13*).

In order to obtain the probability distributions for the electrons in the singlet and triplet wave functions in eqns 3 and 4, the wave functions must be squared. The lower Coulombic repulsion energy of the electrons in the triplet than in the singlet arises mathematically from the signs of the cross terms in the spatial parts of Ψ_S and Ψ_T, when Ψ_S and Ψ_T are squared. The different signs of the cross terms make the electrostatic repulsion energy between an electron in ψ_i and another in ψ_j $J_{ij} + K_{ij}$ in the singlet and J_{ij} - K_{ij} in the triplet, where

$$J_{ij} = \int \psi_i^{\alpha}(1)\ \psi_i^{\alpha}(1)\ [e^2/r_{12}]\ \psi_j^{\beta}(2)\ \psi_j^{\beta}(2) \qquad (5)$$

and

$$K_{ij} = \int \psi_i^{\alpha}(1)\ \psi_j^{\alpha}(1)\ [e^2/r_{12}]\psi_i^{\beta}(2)\ \psi_j^{\beta}(2) \qquad (6)$$

The Coulomb integral, J_{ij}, in eqn. 5 gives the electrostatic repulsion energy between a spinless electron in ψ_i and another in ψ_j. As shown in eqn. 5, this Coulombic repulsion energy is calculated from $\psi_i(1)^2$ and $\psi_j(2)^2$, the probability distributions for these two, spinless electrons.

Of course, electrons do have spin. For all three components of a triplet state, the exchange integral provides a correction, $-K_{ij}$, to the Coulomb integral, J_{ij}. The physical reason why J_{ij} is corrected by $-K_{ij}$ for a triplet state is that, as is evident from eqn. 4, two electrons of the same spin are prevented by the Pauli exclusion principle from simultaneously appearing in the regions of space that ψ_i and ψ_j have in common. Therefore, for electrons of the same spin, J_{ij} for spinless electrons must be corrected by $-K_{ij}$.

In contrast, doing the math for the Coulombic repulsion between the electrons in ψ_i and ψ_j in the open-shell singlet state shows that J_{ij} is corrected by $+K_{ij}$. The physical reason for this correction is that, in an open-shell singlet state, the motions of the electrons in ψ_i and ψ_j are, actually anti-correlated. What this means is that, in an open-shell singlet, the pair of electrons in the singly-occupied MOs tend to simultaneously appear in the same region of space with a higher probability than that predicted by J_{ij} for spinless electrons.

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Since the Coulomb repulsion energy between the two electrons is $J_{ij} + K_{ij}$ in the open-shell singlet state and $J_{ij} - K_{ij}$ in the triplet state, the energy difference between these two states is

$$E_S - E_T = \Delta E_{ST} = 2K_{ij} \qquad (7)$$

However, it should be noted that eqn. 7 assumes that the optimal MOs for an open-shell singlet state and the corresponding triplet state are the same. Many years after I left Cambridge, England and returned to Cambridge, MA, I would learn that in some diradicals, including **TMM**, the optimal sets of MOs for a singlet and a triplet state, and even for two singlet states, are not the same.

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PPP Calculations Show that TMM and CBD Are Very Different Types of Diradicals

Having learned the rudiments of how to compute the energies of wave functions, such as those in eqns 3 and 4, for molecules with open shells of electrons, I moved on to performing PPP calculations on two diradicals, D_{3h} **TMM** and D_{4h} **CBD**. As already noted, each of these diradicals has four π electrons; and in each of these diradicals two of these electrons occupy a bonding π MO, ψ_1, and the two remaining electrons are distributed between a pair of non-bonding π MOs, ψ_2 and ψ_3. Despite these similarities, the PPP calculations I performed revealed that there are some major differences between **TMM** and **CBD**.

In the lowest singlet state of D_{3h} **TMM**, group theory predicts that there are two wave functions, Ψ_x and Ψ_y, that form the two components of a degenerate, singlet (^{1}E′) electronic state. These two wave functions are:

$$\Psi_x = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_2^{\alpha}(3)\ \psi_3^{\beta}(4)\rangle + |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_3^{\alpha}(3)\ \psi_2^{\beta}(4)\rangle/\sqrt{2} \qquad (8)$$

and

$$\Psi_y = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_2^{\alpha}(3)\ \psi_2^{\beta}(4)\rangle - |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_3^{\alpha}(3)\ \psi_3^{\beta}(4)\rangle/\sqrt{2} \qquad (9)$$

The manner in which the bonding π MO, ψ_1, and the degenerate pair of nonbonding π MOs, ψ_2 and ψ_3, are occupied by electrons in Ψ_x and Ψ_y is depicted graphically in Figure 5. As shown symbolically in eqns 8 and 9 and graphically in Figure 5, both singlet wave functions consist of two different configurations.

Since Ψ_x and Ψ_y are the two components of the degenerate, singlet (^{1}E′) electronic state in D_{3h} **TMM**, Ψ_x and Ψ_y must, of course, have exactly the same energies. However, as shown graphically in Figure 5, the MOs ψ_2 and ψ_3 are occupied very differently in Ψ_x and Ψ_y. Therefore, I set out to convince myself that Ψ_x and Ψ_y really do have the same energies.

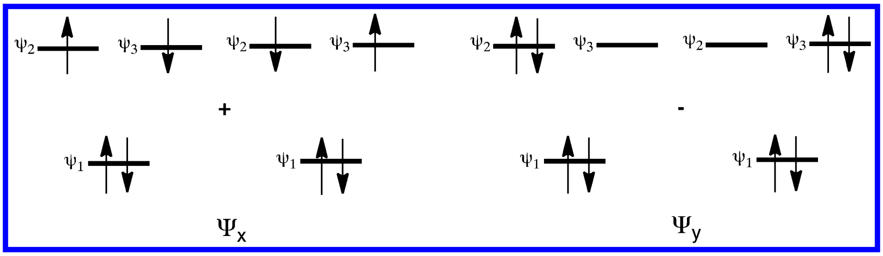

*Figure 5. Schematic depiction of the two components, Ψ_x and Ψ_y, of the $^1E'$ state of **TMM**. Each component consists of two configurations.*

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When I worked through the math, it appeared that there actually is a difference between the energies of Ψ_x and Ψ_y. This energy difference is equal to

$$E(\Psi_x) - E(\Psi_y) = J_{23} + K_{23} - [(J_{22} + J_{33})/2 - K_{23}] \\ = J_{23} - (J_{22} + J_{33})/2 + 2K_{23} \qquad (10)$$

where J_{23} is the Coulombic repulsion between one electron in ψ_2 and one in ψ_3; $J_{22} = J_{33}$ is the Coulombic repulsion between a pair of electrons in the same, degenerate, non-bonding MO in **TMM**, and K_{23} is the exchange integral between ψ_2 and ψ_3.

In order to use PPP theory to compute the Coulomb and exchange integrals in eqn. 10, I wrote out the expressions for the non-bonding MOs, ψ_2 and ψ_3, in **TMM** as the e″ combinations of the 2p-π AOs on the three peripheral carbons, ϕ_1 - ϕ_3.

$$\psi_2 = (\phi_2 - \phi_3)/\sqrt{2} \qquad (11)$$

and

$$\psi_3 = (2\phi_1 - \phi_2 - \phi_3)/\sqrt{6} \qquad (12)$$

I then used these MOs to compute the Coulomb and exchange integrals in eqns. 5 and 6 in terms of the Coulomb repulsion energies between two electrons in the same 2p-π AO (γ_{aa}) and in 2p-π AOs on two different CH_2 groups (γ_{ac}). I found that in **TMM**

$$J_{22} = J_{33} = (\gamma_{aa} + \gamma_{ac})/2 \qquad (13)$$

$$J_{23} = (\gamma_{aa} + 5\gamma_{ac})/6 \qquad (14)$$

$$2K_{23} = 2(\gamma_{aa} - \gamma_{ac})/6 \qquad (15)$$

Therefore, in eqn. 10

$$E(\Psi_x) - E(\Psi_y) = J_{23} - (J_{22} + J_{33})/2 + 2K_{23} \\ = (\gamma_{aa} + 5\gamma_{ac})/6 - (\gamma_{aa} + \gamma_{ac})/2 + 2(\gamma_{aa} - \gamma_{ac})/6 \\ = 0 \qquad (16)$$

In The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award; Strom, et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2015.

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proving that $E\ (\Psi_x) = E\ (\Psi_y)$ in **TMM**. Group theory told me that this had to be true, but proving that it actually is true gave me the satisfaction of knowing that I really did understand how to do PPP calculations correctly.

According to eqn. 7, the energy difference between the lowest triplet state ($^3A_2'$) and the open-shell singlet state (Ψ_x) of **TMM** is $2K_{23}$. Since Ψ_x and Ψ_y, have the same energy in D_{3h} **TMM**, $2\ K_{23}$ is the energy difference between $^3A_2'$ and both components of the $^1E'$ state. Because $^1E'$ is the lowest singlet state of D_{3h} **TMM**, from eqn. 15 the triplet is predicted to be the ground state of **TMM** by $(\gamma_{aa} - \gamma_{ac})/3$. Consequently, **TMM** is predicted to follow Hund's rule (*12*, *13*), which is, of course, what Paul Dowd found experimentally (*30*).

I also did PPP calculations on **CBD**. I discovered that, due to the difference between the three-fold symmetry of the nonbonding MOs in D_{3h} **TMM** and the four-fold symmetry of these MOs in D_{4h} **CBD**, these two diradicals differ in several ways.

In the rectangular geometry of **CBD** in which C1-C2 and C3-C4 are shorter bonds than C1-C4 and C2-C3, the MO,

$$\psi_2 = (\phi_1 + \phi_2 - \phi_3 - \phi_4)/2 \qquad (17)$$

is lower in energy than the MO,

$$\psi_3 = (\phi_1 - \phi_2 - \phi_3 + \phi_4)/2 \qquad (18)$$

Consequently, at such a rectangular geometry, the wave function, Ψ_S, for the lowest singlet state can be written as

$$\Psi_S = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_2^{\alpha}(3)\ \psi_2^{\beta}(4) > \qquad (19)$$

However, at the rectangular geometry where C1-C4 and C2-C3 are shorter C-C bonds than C1-C2 and C3-C4, then ψ_3 is lower in energy than ψ_2. Consequently, at such a geometry, the wave function for the lowest singlet state can be written as

$$\Psi_S = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_3^{\alpha}(3)\ \psi_3^{\beta}(4) > \qquad (20)$$

At a square geometry, which is the transition structure for the interconversion of the two rectangular geometries of **CBD**, ψ_2 and ψ_3 have the same energies; and the lowest singlet wave function, Ψ_S is a linear combination of the two one-configuration wave functions in equations 19 and 20.

$$\Psi_S = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_2^{\alpha}(3)\ \psi_2^{\beta}(4) > - |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_3^{\alpha}(3)\ \psi_3^{\beta}(4) >/\sqrt{2} \qquad (21)$$

The lowest singlet wave function for square **CBD**, Ψ_S in eqn. 21, has the same form as Ψ_y in eqn. 9 for one of the two degenerate singlet wave functions in **TMM**. However, group theory predicts that the lowest singlet state of square **CBD** is non-degenerate. In fact, it is easy to use PPP theory to show that in square **CBD**, the wave function

$$\Psi_S' = |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_2^{\alpha}(3)\ \psi_3^{\beta}(4)> + |\psi_1^{\alpha}(1)\ \psi_1^{\beta}(2)\ \psi_3^{\alpha}(3)\ \psi_2^{\beta}(4)>/\sqrt{2} \qquad (22)$$

which is of the same form as Ψ_x in eqn. 8, is higher in energy than Ψ_S.

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As in **TMM**, where the energy difference between Ψ_x and Ψ_y is given by eqn. 10, in **CBD**

$$E\,(\Psi_S') - E\,(\Psi_S) = J_{23} - (J_{22} + J_{33})/2 + 2K_{23} \qquad (23)$$

However, using the **CBD** MOs in eqns 17 and 18, rather than the **TMM** MOs in eqns 11 and 12 to evaluate J_{22}, J_{33}, J_{23}, and K_{23}, PPP theory finds that in square **CBD**

$$J_{22} = J_{33} = J_{23} = (\gamma_{aa} + 2\gamma_{ab} + \gamma_{ac})/4 \qquad (24)$$

$$K_{23} = (\gamma_{aa} - 2\gamma_{ab} + \gamma_{ac})/4 \qquad (25)$$

Therefore, according to PPP theory, in **CBD**

$$J_{23} - (J_{22} + J_{33})/2 = 0 \qquad (26)$$

so that eqn. 23 becomes

$$E\,(\Psi_S') - E\,(\Psi_S) = 2K_{23} \neq 0 \qquad (27)$$

As predicted by group theory, eqn. 27 shows that the energies of Ψ_S' and Ψ_S are not the same in square **CBD**.

In square **CBD** (as in **TMM**) the wave functions for the open-shell singlet, Ψ_S', and the triplet state Ψ_T are given by eqn. 2; and, according to eqn. 7, their energies differ by $2K_{23}$,

$$E\,(\Psi_S') - E(\Psi_T) = 2K_{23} \qquad (28)$$

Subtracting eqn. 28 from eqn. 27 shows that in **CBD**

$$E\,(\Psi_S) = E(\Psi_T) \qquad (29)$$

Thus, in contrast to the case in **TMM**, where the triplet is calculated to be $2K_{23}$ lower in energy than both components of the lowest singlet state, in square **CBD** the lowest singlet state and the triplet are predicted by PPP calculations to have the same energies (*35*). This difference between **TMM** and **CBD** is shown in Figure 6, in which the symmetries of the low-lying electronic states in each of these two diradicals are given and the relative PPP energies of these states are shown schematically.

In 2015 I am amazed that in 1965 I was apparently not interested in delving into the physical reason why PPP calculations predict a large singlet-triplet energy separation in **TMM**, but not in **CBD**. However, attempting to get some physical insight into computational results is something that I only began to do around 1968, inspired by the papers that Roald Hoffmann started publishing after he had joined the Faculty at Cornell.

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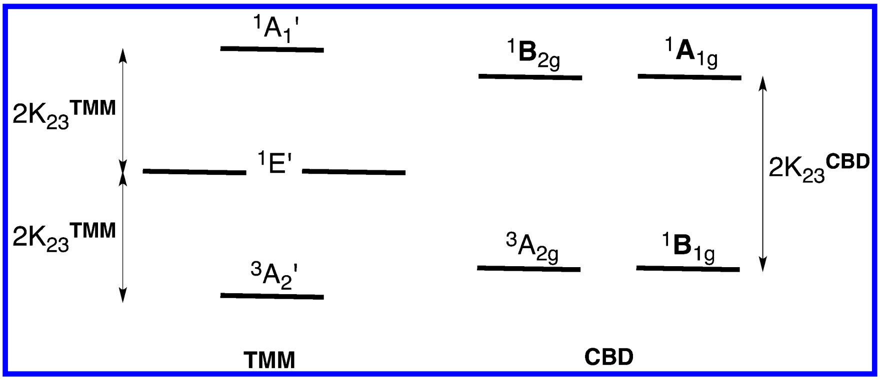

Figure 6. Schematic depiction of the relative PPP energies of the low-lying electronic states of ***TMM*** *and* ***CBD****.*

Roald had been a lab instructor in the first chemistry course that I had taken in 1961 as a freshman at Harvard; and my roommate, Bob Joffe, had done undergraduate research with both Roald and Lionel Salem. In 1965, I learned from H. C. Longuet-Higgins that Roald was working with Bob Woodward on what would eventually become the Woodward-Hoffmann rules (*36*). Therefore, when Roald started publishing independent papers on organic chemistry in 1968, I paid close attention to them; and they have had a huge influence on my approach to theoretical chemistry throughout the remainder of my career.

Planar Allene and Its Similarity to CBD

As my time in Cambridge, UK was drawing to a close, I decided that, before I returned to Cambridge, MA, I would like to use what I had learned about performing PPP calculations, in order to make a prediction that might turn out to be publishable. I thought it was possible that the lowest triplet state of allene would prefer a planar equilibrium geometry to the non-planar equilibrium geometry of the singlet; so I did PPP calculations to see if this was, in fact, the case. The calculations predicted that triplet allene should, indeed, have a planar equilibrium geometry.

What I had not realized when I began these calculations was that the planar → non-planar allene transformation is very similar to the transformation of rectangular → square **CBD**. In both cases a geometry that has two bonding π MOs is transformed into a geometry that has one bonding and two non-bonding orbitals (NBMOs). Therefore, what I learned from doing PPP calculations on planar allene, I was subsequently able to apply to understanding the PPP results for **CBD**.

As shown in Figure 7, in planar allene the singly occupied MOs are a σ AO that is confined to the central carbon and an allyl non-bonding π MO that is confined to the two terminal carbons. Although in 1965 I was not thinking much about the shapes of MOs, it was clear to me even then that the overlap between these two NBMOs in planar allene must be very close to zero. Therefore, the exchange integral between electrons in these two NBMOs must also be close to zero, so that the energy difference between the lowest singlet and triplet states, in which each of these MOs is singly occupied, must also be close to zero. This is what my PPP calculations found for planar allene.

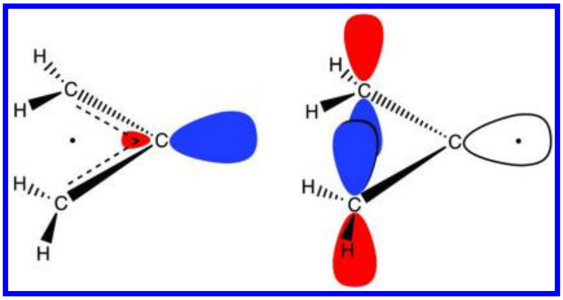

Figure 7. The two nonbonding (NB)MOs of planar allene are a σ AO on the central carbon and an allyl π NBMO on the two terminal σcarbon atoms.

When I returned to Harvard as a first year graduate student in the fall of 1965, I decided to work for E.J. Corey. He seemed quite interested in the results of my PPP calculations on allene. In fact, he said, "We should do an experimental test of your prediction, that triplet allene has a planar equilibrium geometry."

However, before beginning to work in the lab on the photoracemization of an optically active allene, I decided to write a manuscript about my computational prediction, that triplet allene has a planar equilibrium geometry. When I had completed a first draft, I sent it to Professor Longuet-Higgins and asked him if he would like to have his name on the manuscript that I planned to submit for publication. He declined. At the time I chose to believe that he was being gracious; but now I think that he probably did not want his name on a paper that fell below his very high standards.

Like Square CBD, Planar Allene Is Calculated To Violate Hund's Rule

My paper on planar allene was my first publication on electronic structure theory (*37*, *38*). Probably the most interesting finding in it appeared in a footnote, which read, "Carrying out complete configuration interaction to resolve the degeneracy [between the lowest singlet and triplet states], one finds that the singlet lies 0.05 eV below the triplet" (*37*, *39*). In other words, my PPP configuration interaction calculation predicted that Hund's rule (*12*, *13*) is violated in planar allene.

Unfortunately, I did not believe my own computational result. In fact, I devoted the rest of the footnote to explaining that, "Quite possibly, the triplet lies lowest" (*37*). Nevertheless, as I subsequently discovered, my finding that in planar allene the singlet state is calculated to be lower in energy than the triplet state was not the first predicted violation of Hund's rule in a diradical.

The first prediction of a violation of Hund's rule in a diradical seems have been made by Craig in 1950 (*40*). Interestingly, he found that, with inclusion of

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configuration interaction (CI), square **CBD** has a singlet ground state. In 1968 Buenker and Peyerimhoff made the same prediction about square **CBD**, based on the results of their *ab initio* CI calculations (*41*).

Thus, square **CBD** and planar allene have more in common than just a lowest singlet and triplet state that have the same energies in PPP theory. In addition, with inclusion of CI, the singlet is predicted to fall below the triplet state in both diradicals, in violation of Hund's rule.

It took me nearly ten years, but eventually I realized that the reason for the predicted violation of Hund's rule in square **CBD** is essentially the same as that in planar allene. However, rather than asking the reader to wait for a description of the next ten years of my career in chemistry, let me skip ahead from 1965 to 1975, with a brief stop in 1969.

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Why the Lowest Singlet and Triplet States Are Calculated To Have the Same PPP Energies Not Only in Planar Allene but Also in Square CBD

It was not until 1969 that I first realized that the lowest singlet and triplet states of **CBD** have the same energies in PPP theory for the same reason that the lowest singlet and triplet states of planar allene do. In **CBD**, as in planar allene, the degenerate MOs can be chosen so that they have no atoms in common (*35*). Therefore, since the exchange integral, K_{ij} in eqn. 6 involves the overlap of the two degenerate MOs, ψ_i and ψ_j, if these MOs are confined to different regions of space, $K_{ij} \approx 0$. Then, according to eqn. 7, if $K_{ij} \approx 0$, $\Delta E_{ST} \approx 0$.

As already noted, the nonbonding (NB)MOs in planar allene – the σ NBMO on the central carbon and the allyl π NBMO, which is confined to the two terminal carbons – are disjoint (i.e., they have no atoms in common). On the other hand, the **CBD** NBMOs in eqns. 17 and 18 are clearly not disjoint. In fact, they span exactly the same set of 2p-π AOs; and the exchange integral, K_{23}, between them in eqn. 25 is certainly not zero. Consequently, the energy separation of $2K_{23}$ between the open-shell singlet, Ψ_S', and the triplet Ψ_T is quite large in **CBD**.

This was confusing, until I realized that it is not the open-shell singlet, Ψ_S' in eqn. 22, but the two-configuration singlet, Ψ_S in eqn. 21, that is calculated to have the same PPP energy as the triplet state in square **CBD** (eqn. 29). Eqn. 21 shows that Ψ_S consists of two configurations, in each of which one of the NBMOs is doubly occupied. One configuration places both of the nonbonding electrons in ψ_2; the other places both nonbonding electrons in ψ_3.

Such a two-configuration wave function is hard to interpret physically. However, it can be factored into

$$\Psi({}^1A_{\square}) = |\psi_2{}^{\alpha}(1)\ \psi_2{}^{\beta}(2)> - |\psi_3{}^{\alpha}(1)\ \psi_3{}^{\beta}(2)>/\sqrt{2} = \\ |[(\psi_2 + \psi_3)(1)(\psi_2 - \psi_3)(2)][\alpha(1)\beta(2) - \beta(1)\alpha(2)]/2\sqrt{2} \qquad (30)$$

The sum and difference MOs on the right-hand side of eqn. 30 are called Generalized Valence Bond (GVB) MOs (*42*). GVB MOs provide a useful physical interpretation of two-configuration wave functions, because the wave function on the right hand side of eqn. 30 is that for an open-shell singlet, in which each GVB MO is occupied by one electron.

Using eqns 17 and 18 for the non-bonding MOs of **CBD**, the GVB orbitals for singlet **CBD** are

$$\psi_2^{\mathrm{GVB}} = (\psi_2 + \psi_3)/\sqrt{2} = (\phi_1 - \phi_3)/\sqrt{2} \tag{31}$$

and

$$\psi_3^{\mathrm{GVB}} (\psi_2 - \psi_3)/\sqrt{2} = (\phi_2 - \phi_4)/\sqrt{2} \tag{32}$$

It should be noted that ψ_2^{GVB} for **CBD** in eqn. 31 has no 2p-π AOs in common with ψ_3^{GVB} in eqn. 32. Therefore, like the two non-bonding MOs in planar allene, ψ_2^{GVB} and ψ_3^{GVB} in **CBD** are disjoint. It is the disjoint nature of these singly occupied MOs of planar allene and of square **CBD** that result in the calculated PPP energies of the lowest singlet and triplet states to be the same in both of these diradicals.

In 1969 I published a communication on why the disjoint nature of the NBMOs of square **CBD** make this diradical different from cyclopentadienyl cations and benzene dianions, which have singly-occupied MOs that are not disjoint (*35*). In reading this communication I am struck by the fact that I opted for mathematical elegance, rather than physical clarity (*35*). I used MOs with complex coefficients in my proof that the PPP energies of the lowest singlet and triplet of **CBD** are the same; and nowhere in this communication is there a single drawing of an MO. It is interesting and sometimes a little embarrassing to read the papers that one published early in one's career and to see how much the way one writes manuscripts has evolved with the passage of time.

Why Do CI Calculations Predict that Hund's Rule Is Violated in Planar Allene and in Square CBD?

I did not find the answer to this question until I started writing Chapter 9 of my textbook, *Modern Molecular Orbital Theory for Organic Chemists* (*43*) (the same title that Professor Andrew Streitwieser used for his book (*31*), except for the addition of the word "Modern" to my title). Chapter 9 discussed calculations on open-shell π systems in general and on the allyl radical in particular. I described how a small configuration interaction (CI) calculation, involving the three possible configurations that can be generated by exciting an electron from the bonding π MO in allyl radical into the antibonding π MO, generates the negative spin density at the central carbon of allyl that is seen experimentally (*44*).

Of course, planar allene has an allylic π system. The reader will also recall that it is only with inclusion of CI, involving the same configurations that produce the negative spin density in allyl radical, that planar allene is calculated to have a singlet ground state (*37*, *39*). Therefore, it is the negative spin density at the central carbon of the allylic π system of planar allene that produces the predicted violation of Hund's rule in this diradical.

Including the negative spin density at the central carbon of the allylic π system, the singlet and triplet states of planar allene can be depicted schematically as in Figure 8. The component of the triplet state, in which the electrons in the σ and π NBMOs both have α spin is shown on the left. It can be seen that the negative spin density in the 2p-π AO at the central carbon in the triplet is β, opposite to the α spin in the σ NBMO that is localized at this carbon.

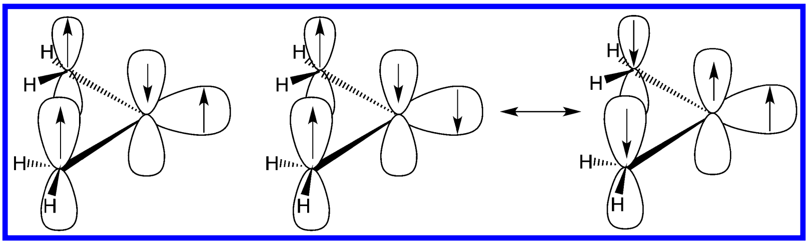

Figure 8. Schematic depiction of one component of the triplet state (left) and of the two configurations that comprise the open-shell singlet state of planar allene (right). The negative spin density in the 2p-π AO of the central carbon is shown in both electronic states. In the triplet state the negative spin in the 2p-π AO of the central carbon is antiparallel to the spin in the σ AO on this carbon, However, in the singlet these two spins in the AOs on the central carbon are parallel, so that these two electrons cannot simultaneously appear in the regions of space that these two AOs have in common.

Shown at the right of Figure 8 is the open-shell singlet state of planar allene. Figure 8 shows that in both configurations of the open-shell singlet state the spin of the electron in the σ NBMO is the same as that of the electron that gives rise to the negative spin density in the 2p-π AO at the central carbon. Since electrons of the same spin are prevented from appearing in the regions of space that the σ and π AOs at the central carbon have in common, the Coulombic repulsion between these two electrons is smaller in the open-shell singlet state than in the triplet state, where the spins of these two electrons are antiparallel. Therefore, the origin of the predicted violation of Hund's rule in planar allene is easy to understand as an effect that arises from the presence of negative spin density in the 2p-π AO at the central carbon.

The predicted violation of Hund's rule in square **CBD** has a similar origin (*45*). When a CI calculation is performed, the triplet and lowest energy singlet state each have two nonbonding π electrons that can affect the distribution of the two electrons of opposite spin in the lowest π MO. Using the GVB orbitals for square **CBD** in eqns. 31 and 32, each of these nonbonding π electrons is confined to two carbons of the four membered ring.

As shown schematically in Figure 9, in the singlet state the asymmetric distribution of spin in the NBMOs, ψ_2 and ψ_3, allows the α spin electron in the lowest π MO, ψ, to become partially localized at the two carbons at which an α spin electron is localized in one of the NBMOs. Similarly, the β spin electron in the lowest MO can become partially localized at the two carbons at which a β spin electron is localized in the other NBMO. Even partially confining electrons of the same spin to two carbons and electrons of opposite spin to the other two carbons reduces the Coulombic repulsion energy between the electrons in ψ and those in ψ_2 and ψ_3 in the lowest singlet state of square **CBD**.

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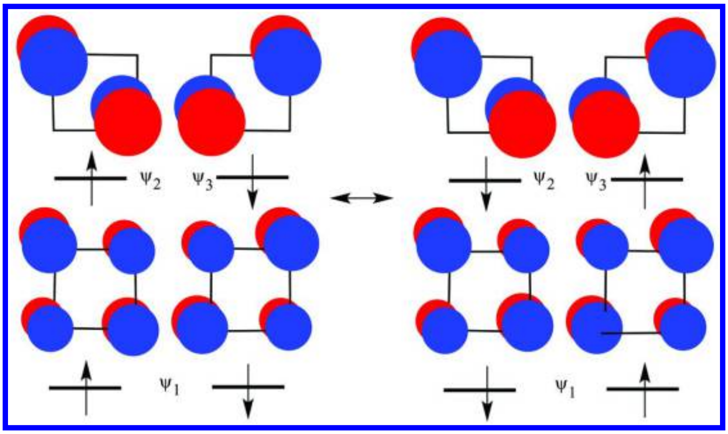

Figure 9. Schematic depiction of dynamic spin polarization in the lowest singlet state of square ***CBD****. The spins of the electrons in the nonbonding π GVB MOs,* ψ_2^{GVB} *and* ψ_3^{GVB}*, favor partial localization of the electrons in the bonding π MO,* ψ_1*, so that electrons of opposite spin in these three π MOs are found predominantly at different sets of carbons. This partial localization makes the Coulombic repulsion between the electrons in* ψ_2 *and* ψ_3 *and those in* ψ_1 *lower in the singlet state than in the triplet, which leads to the violation of Hund's rule that is predicted to occur in square* ***CBD*** *(40, 41, 45).*

It should be noted once again that the wave function for an open-shell singlet state consists of two configurations, which differ from each other by reversal of the spins of the electrons in the singly occupied MOs. Consequently, the spin polarization depicted in the left- and right-hand sides of Figure 9 is not static, but dynamic. The name "dynamic spin polarization" has, in fact, been given to the type of spin polarization shown in Figure 9 (*46*), and this name also describes the type of spin polarization shown in Figure 8.

In the triplet state of square **CBD** electrons of the same spin occupy the nonbonding MOs, ψ_2 and ψ_3. Consequently, there is a uniform distribution of the same type of spin (e.g. α) at all four carbons. As a result, no polarization of the spins of the electrons in the lowest π MO is possible; and this is the reason that the triplet state of **CBD** is calculated to be higher in energy than the singlet state, not only at rectangular geometries but also at the square geometry.

The Singlet and Triplet States of Trimethylenemethane

In 1966 I was in my first year of graduate school at Harvard when Paul Dowd, who was a junior faculty member in the Chemistry Department, succeeded in generating **TMM** and obtaining the EPR spectrum of its triplet state (*27*, *29*). I was very interested in Paul's experiments, and he took the time to talk to me about them. We discussed why photolysis of 4-methylenepyrazoline leads to the formation of triplet trimethylenemethane, which then dimerizes to form 1,4-dimethylene-cyclohexane; whereas, pyrolysis of 4-methylenepyrazoline leads to the quantitative formation of methylenecyclopropane (*28*).

I conjectured that, although both of these two different modes of deazatizing of 4-methylenepyrazoline lead to formation of **TMM**, the thermal reaction produces the lowest singlet state. The singlet closes to methylenecyclopropane faster than it undergoes intersystem crossing to the triplet ground state. With Paul's encouragement, I wrote a communication that contained this conjecture; and I was very pleased when it was accepted for publication in *Tetrahedron Letters* (*47*).

Personally, I think that the only reason that such a lightweight manuscript was accepted was that it contained some correlation diagrams for conrotatory and disrotatory deazatization of 4-methylenepyrazoline. 1966 was the heyday of the Woodward-Hoffmann rules (*36*); and Longuet-Higgins (*48*), as well as Woodward and Hoffmann (*49*) had used correlation diagrams to understand, respectively, electrocyclic and cycloaddition reactions.

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The Geometry of the Lowest Singlet State of TMM

By 1970, there were several lines of experimental evidence which indicated that, although triplet **TMM** is planar (*27*, *29*), singlet **TMM** prefers a non-planar geometry with one CH_2 group twisted out of conjugation (*50–52*). Indeed, in 1971 Dewar and Wasson had published the results of MINDO/2 calculations which confirmed that this interpretation of the experimental results is correct (*53*).

I decided to perform PPP calculations of my own, to test this conclusion. My calculations found that the MOs of D_{3h} **TMM** give a Coulombic repulsion energy for the planar singlet state that is higher by $3(\gamma_{aa} - \gamma_{ac})/8$ than the Coulombic repulsion energy for twisted TMM, which consists of an allyl radical plus an electron localized in a non-conjugated 2p AO on the third CH_2 group. Although the Hückel energy of **TMM** is lower than that of allyl plus 2p by $2(\sqrt{3} - \sqrt{2})\beta = 0.6\beta$, any reasonable values of γ_{aa}, γ_{ac}, and β confirm the MINDO 2 conclusion, that allyl plus 2p has a lower energy than planar singlet **TMM**.

In fact, eqns. 14 and 15 can be used to show that the Coulombic repulsion energy between the two nonbonding electrons in the open-shell singlet state of planar **TMM** is $J_{23} + K_{23} = (\gamma_{aa} + 2\gamma_{ac})/3$; whereas the Coulombic repulsion energy between the two nonbonding electrons in twisted **TMM** (i.e., allyl + 2p) is just γ_{ac}. The difference of $(\gamma_{aa} - \gamma_{ac})/3$ is almost 90% of the total difference of $3(\gamma_{aa} - \gamma_{ac})/8$ between the total Coulombic repulsion energies of planar singlet **TMM** and allyl plus 2p.

The reason for the lower energy of the allyl plus 2p NBMOs is evident in Figure 10. It shows that the NBMOs of allyl plus 2p in Figure 10b are disjoint; whereas those of planar **TMM** in Figure 10a are not. The disjoint NBMOs of allyl + 2p in Figure 10b make the singlet wave function for twisted **TMM** much lower in energy than the singlet wave function that employs the non-disjoint NBMOs for planar **TMM**, which are shown graphically in Figure 10a.

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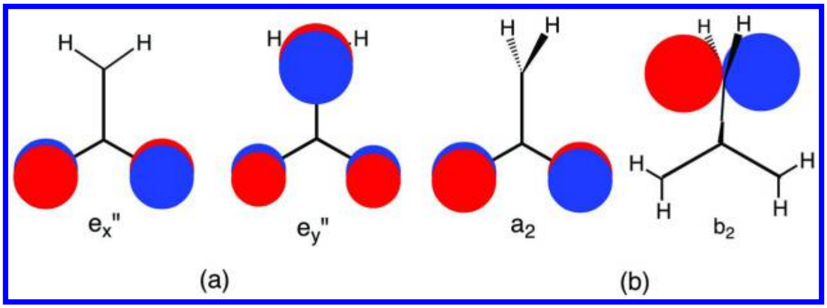

*Figure 10. NBMOs in (a) planar **TMM** and (b) in **TMM** with one CH_2 group twisted out of conjugation, giving the MOs for allyl radical and a 2p AO.*

Singlet TMM versus Singlet CBD

Having published a paper on **TMM** in 1966 (*47*), of which I was less than proud, I had not planned to publish the results of my PPP calculations on **TMM**; and I had, instead, made them the subject of Problem 7.18 in my book on MO theory (*43*). However, Lionel Salem changed my mind; and the manuscript on **TMM** that I had not wanted to submit for publication wound up appearing as a Communication in *JACS* (*54*).

As I have recounted elsewhere (*32*), in 1973 Lionel was a visiting Professor at Harvard, where I was in the terminal year of being an Assistant Professor. Lionel was one of my heroes at the time. He had not only been one of Christopher Longuet-Higgins' most successful graduate students; but also, in 1962, I had attended, together with my roommate Bob Joffe, a most extraordinary party at Lionel's apartment in Cambridge.

In 1973 Lionel was interested in modeling the effects of electron repulsion on the different possible geometries for sigmatropic reactions, a subject about which he had just published a paper with Jerry Berson (*55*). Therefore, Lionel wanted to compare planar singlet **TMM** with allyl + 2p as two models for the transition structure in methylenecyclopropane rearrangement. In addition, he also wanted to compare singlet **CBD** with allyl + 2p, as models for the transition structures, in, respectively, a forbidden but concerted [1,3]sigmatropic shift (*36*) and a stepwise reaction.

My PPP calculations showed that electron repulsion disfavors planar singlet **TMM**, relative to allyl + 2p, by $3(\gamma_{aa} - \gamma_{ac})/8$; but electron repulsion disfavors singlet **CBD**, relative to allyl + 2p by only $(\gamma_{aa} - \gamma_{ac})/8$ – one third as much as singlet **TMM** is disfavored, relative to allyl + 2p. As Lionel and I pointed out in the conclusion to our *JACS* Communication (*54*), the difference between singlet **CBD** and planar singlet **TMM** is that in singlet **CBD** the NBMOs can be chosen so that they have no atoms in common (see Figure 9); whereas in planar singlet **TMM**, the NBMOs do have atoms in common (see Figure 10a).

Four years later, in 1977, I would use the words “disjoint” to describe the NBMOs in **CBD** and “non-disjoint” to describe the NBMOs in planar **TMM**. This difference between the NBMOs in these two diradicals would subsequently provide a paradigm for making general predictions about the ground states of diradicals (*56*).

The Wave Functions for Planar Singlet TMM

The rules for predicting the ground states of diradicals came about in a collaboration with Professor Ernest R. Davidson. We began to collaborate after I moved from Harvard to the University of Washington in 1973, and my collaborations with Ernest on multiple projects began with our mutual interest in the wave functions for the lowest singlet state of planar **TMM**.

Based on the Communication that I had published with Lionel Salem, it seemed that their must be a very large energy difference between a planar geometry and a twisted allyl + 2p geometry for singlet **TMM**. However, Bill Doering, with whom I talked frequently at Harvard, told me that, based on the results of his experiments (*50*), this could not be correct. His experiments showed that, for singlet **TMM,** a twisted allyl + 2p geometry is preferred to a planar geometry but only by a small amount of energy.

A paper published in 1974 by Yarkony and Schaefer (*57*) convinced me that Bill Doering was right. They found that the energy of the wave function for *planar* singlet **TMM** is much lower in energy if only C_{2v}, rather than D_{3h} symmetry, is imposed upon its MOs. With the imposition of D_{3h} symmetry the NBMOs for planar **TMM** are those given in eqs. 11 and 12 and depicted in Figure 10a. However, if only C_{2v} symmetry is imposed on the MOs, then, even at a planar geometry, the NBMOs for singlet **TMM** can be those for an allyl radical plus an electron localized in a 2p AO. Fritz Schaefer was kind enough to send me the MOs for the planar singlet **TMM** in C_{2v} symmetry; and, as I had guessed, the MOs he sent me were those for an allyl radical plus an electron localized in a 2p AO.

Until I saw Fritz’s C_{2v} MOs for planar singlet **TMM**, I had believed that MOs belonged to molecules. For example, I had thought that, at a D_{3h} geometry, the MOs for singlet and triplet **TMM** are the same. Fritz’s result taught me that the MOs for different electronic states of a molecule, even at the same geometry, can be very different (*58*).

This is true not only in **TMM** but also in other diradicals in which the singly occupied MOs in the triplet have atoms in common (i.e., are non-disjoint). The wave functions for the lowest singlet states of such diradicals are comprised of MOs that are more disjoint than their triplet counterparts. In fact, a hallmark of diradicals with NBMOs that are non-disjoint is that the MOs for different electronic states are different (*59*).

However, there is a problem with singlet **TMM** having C_{2v} MOs at a D_{3h} geometry, because at a D_{3h} geometry, the MOs for any state must have D_{3h} symmetry. Nevertheless, I was able to show that, by mixing different D_{3h} electronic configurations that contain e″ MOs, $^1E'$ wave functions that have

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only C_{2v} symmetry can be obtained. I showed that this is the case by carrying out both PPP CI calculations (*62*) and *ab initio* CI calculations (*63*) on planar singlet **TMM**. The latter calculations were performed in collaboration with Ernest Davidson, and that was the first of many projects on which we collaborated.

The CI calculations with Ernest on **TMM** eventually spawned a review on real and artifactual symmetry breaking that Ernest and I coauthored (*64*). We also carried out *ab initio* calculations on the potential surfaces for singlet **TMM** (*65*) and for singlet **CBD** (*66*). However, the most important paper that Ernest and I coauthored was probably a paper on the prediction of the ground states of diradicals, according to whether they do or do not have disjoint NBMOs (*56*).

A Simple Way To Predict the Ground State of a Diradical

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As already discussed, eqn. 4 shows that in an antisymmetrized wave function the probability of two electrons of the same spin simultaneously appearing in the same region of space is zero. Thus, if the two singly occupied MOs in a diradical have atoms in common, the triplet state will have a lower Coulombic repulsion energy than the open-shell singlet state that has the same orbital occupancy.

However, this does not necessarily mean that the triplet is the ground state of such a diradical. In addition to the open-shell singlet state, which has the same orbital occupancy as the triplet, there is another low-energy singlet state that consists of two configurations. As shown in eqn. 30, this two-configuration wave function can be factored into a wave function in which orbitals, that are the sum and difference of the original MOs, are each occupied by one electron. As already noted, the sum and difference orbitals are called the GVB orbitals.

The original set of MOs may have atoms in common, as do the **CBD** MOs in eqns 17 and 18; but the GVB MOs formed from them may be disjoint. Indeed, the GVB MOs for **CBD** in eqns 31 and 32 have no atoms in common. Therefore, before deciding whether the degenerate MOs for a diradical can or cannot be confined to different sets of atoms, one has to check not only the orginal pair of degenerate MOs but also the GVB orbitals derived from them.

If in a diradical there is no combination of the degenerate MOs that is disjoint, then the ground state of the diradical is the triplet. One example of such a diradical is **TMM**; but there are many other diradicals that also have triplet ground states, because all of the possible choices of the degenerate MOs have atoms in common. Another of these diradicals, *meta*-benzoquinodimethane (**MBQDM**) is discussed later in this chapter.

However, if in a diradical, a pair of degenerate MOs can be found that are disjoint (i.e., have no atoms in common), then electrons that singly occupy these two MOs will not appear in the same region of space, no matter whether the spins of the two electrons are parallel or anti-parallel. Consequently, in such a diradical, to a first approximation, the singlet and triplet states will have the same energies.

Under these circumstances, it is possible for the effect of the non-uniform distribution of spin in the singlet state to make the singlet the ground state. As discussed above, dynamic spin polarization (*46*) makes a singlet the ground state of both planar allene (*37*, *39*) and square **CBD** (*40*, *41*, *45*). Since Hund's rule predicts that the triplet state of a diradical is always the ground state (*12*, *13*), planar allene and square **CBD** are both predicted to violate Hunds rule.

Determining Whether the Degenerate Nonbonding MOs of a Diradical Are Disjoint or Non-Disjoint

In order to determine whether the singly occupied MOs of a diradical are disjoint or non-disjoint, it might seem that one would have to obtain these MOs by performing DFT or *ab initio* electronic structure calculations. However, there is one class of diradicals for which it is trivial to obtain the singly-occupied MOs, by performing a back-of-the-envelope calculation (*25*). Members of this class are called alternant hydrocarbon (AH) diradicals.

In an AH it is possible to separate the carbon atoms into two sets – traditionally called the starred set and the unstarred set, such that no two atoms of the same set are nearest neighbors (*43*, *67*). Figures 11 and 12 show that the diradicals – **TMM**, *meta*-benzoquinodimethane (**MBQDM**), **CBD**, and tetramethyleneethane (**TME**) are all AHs.

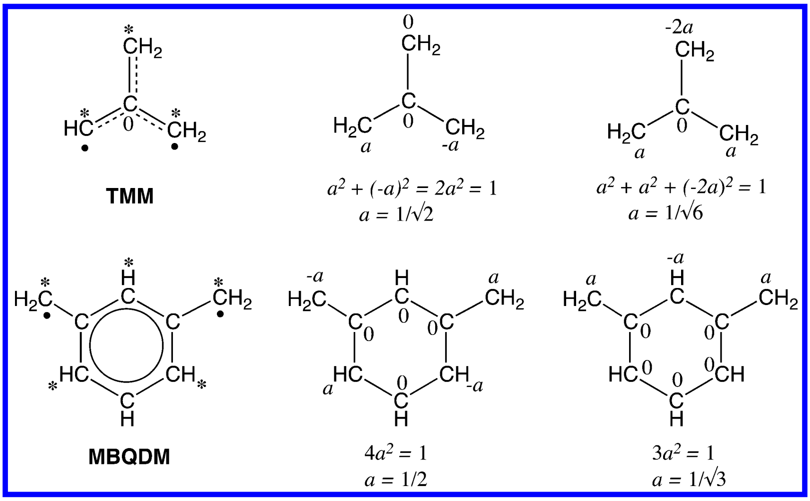

*Figure 11. NBMOs of **TMM** and of meta-benzoquinodimethane (**MBQDM**), derived from use of the zero-sum rule (25). In both of these diradicals the number of starred atoms (n*) minus the number of unstarred atoms (n) is equal to two. Consequently, the NBMOs are both confined to just the starred set of carbon atoms and have carbons in common. Therefore a triplet ground state is predicted for both of these diradicals (56).*

The nonbonding (NB)MOs of an AH diradical can be found from Longuet-Higgins' zero sum rule (*25*). It states that in both NBMOs the coefficients of the starred atoms must sum to zero about each unstarred atom; and the coefficients of the unstarred atoms are either zero or sum to zero about each starred atom.

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Figure 11 shows how the NBMOs of **TMM** and of **MBQDM** can be found from the zero-sum rule. In order for the coefficients of the unstarred atoms to sum to zero about each starred atom in these two AH diradicals, the coefficients of the unstarred atoms must all be zero. This is generally the case when the number of starred exceeds the number of unstarred atom by 2 (*56*).

To find the coefficients of the starred atoms, one starts by assigning a coefficient of *a* to one starred atom and then determines how the zero-sum rule can be satisfied by assigning ±*a,* multiples thereof, or zero to the other starred atoms. The magnitude of *a* can be determined from the requirement that the NBMO be normalized. Therefore *a* must be equal to 1, divided by the square root of the sum of the squares of all of the coefficients of *a* in the MO.

If, unlike the case in **TMM** and **MBQDM**, the number of starred and unstarred carbons is the same in an AH diradical, then one NBMO can be chosen to be confined to the starred set of carbon atoms, while the other NMBO can be chosen to be confined to the unstarred set of carbons (*56*). This is illustrated in Figure 12 for **CBD** and **TME.**

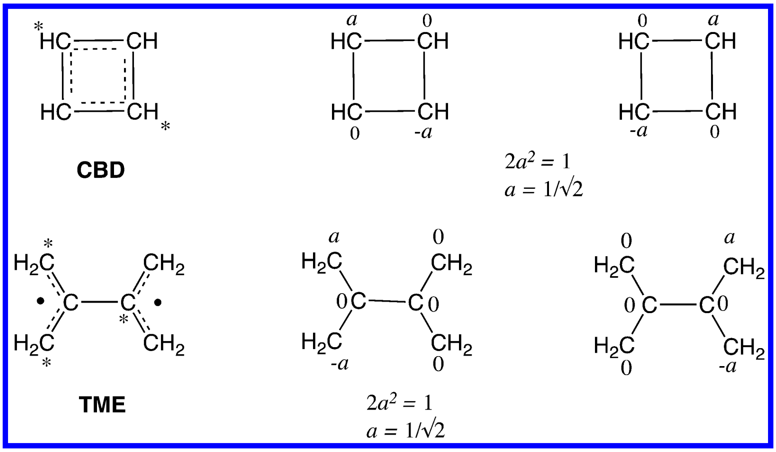

*Figure 12. NBMOs of square **CBD** and tetramethyleneethane (**TME**), derived from use of the zero-sum rule (25). In both of these diradicals the number of starred atoms (n*) and unstarred atoms (n) is the same; so one NBMO is confined to the starred set of atoms and the other to the unstarred set (56). Therefore the NBMOs are disjoint; and, with inclusion of dynamic spin ploarization (45, 46), a singlet ground state is predicted for both of these diradicals (56).*

The NBMOs in Fig. 12 do not have the full molecular symmetry. For example, the **CBD** NBMOs in Fig. 12 are the GVB MOs in eqns. 31 and 32, which are linear combinations of more delocalized sets of **CBD** NBMOs in eqns 17 and 18. Taking the sum and difference of the MOs in Figure 12 gives the more delocalized set of NBMOs for **CBD** and for **TME**, which do have the full molecular symmetry.

Although using MOs that have the full molecular symmetry is advantageous for actually doing calculations, the orbitals in Figure 12 have the virtue of showing that the NBMOs of **CBD** and **TME** can be chosen to be disjoint. Therefore, based on the disjoint topology of their NBMOs, it can be predicted that dynamic spin polarization is likely to lead to a singlet ground state for **CBD** and **TME**.

Although it is easy to use the zero-sum rule to find the singly-occupied, nonbonding (NB)MOs in AH diradicals, Ernest Davidson proved that it is possible to discover whether or not these NBMOs are disjoint (i.e. have no atoms in common) or non-disjoint, just by counting the numbers of starred and unstarred atoms (*56*). Ernest proved that, if the number of starred carbons (n^*) exceeds the number of unstarred carbons (n) by two in an AH diradical, the two NBMOs are both confined to the starred set of atoms. Hence, they are, in general, non-disjoint. Consequently, $n^* - n = 2$ in an AH diradical predicts non-disjoint NBMOs and, hence, a triplet ground state.

Ernest also showed that if $n^* = n$, then one NBMO is confined to the starred set of atoms, and the other NBMO is confined to the unstarred set of atoms. Therefore, the NBMOs are disjoint. Consequently, $n^* - n = 0$ predicts a singlet ground state for a diradical.

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Ovchinnikov's Equation

Another qualitative method for predicting the ground state of a diradical is due to Ovchinnikov (*68*). He used valence-bond (VB) theory to derive the formula in equation 33 for the spin quantum number, S, of the ground state of any AH.

$$S = |n^* - n|/2 \tag{33}$$

This method is also based on the difference, $n^* - n$, between the number of starred and unstarred carbons in an AH diradical. However, instead of using $n^* - n$ to determine whether the NBMOs are disjoint or non-disjoint, in the Ovchinnikov method $n^* - n$ provides information about π bonding in a molecule, using VB theory. If $S = 1$ in eqn. 33, a triplet ground state is predicted; but, if $S = 0$, the ground state is predicted to be a singlet.

For example, in **TMM**, $|n^* - n| = 2$, so eqn. 33 gives $S = 1$; and the ground state is predicted to be a triplet. In contrast, in **CBD** $n^* = n$; so the ground state is predicted to have $S = 0$ and to be a singlet. It can be seen that the predictions made from Ovchinnikov's formula, which is based on VB theory, are the same as those made on the basis of the disjoint/non-disjoint topologies of the singly-occupied π MOs in a diradical.

Why do these two different approaches lead to the same set of predictions? The MO approach to predicting ground state of a diradical starts by finding the orbitals that maximize bonding and then determining whether or not the singly occupied MOs in the diradical are disjoint or non-disjoint. In contrast, VB theory starts by assuming that an AH has one electron in the 2p-π MO of each carbon and then determining how many of these π electrons are involved in forming bonds. It is gratifying that either starting point leads to the same prediction about the ground state of an AH diradical.

However, the classification of the MOs in diradicals as being disjoint or non-disjoint does have the advantage over Ovchinnikov's equation of being applicable

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to antiaromatic ions, containing 4*n* electrons in rings of 4*n* ± 1 or 4*n* ± 2 carbons (*35*). In addition, although, neither method, by itself, provides any information about the size of ΔE_{ST} in a diradical, using the zero-sum rule to actually find the Hückel NBMOs and then inspecting the degree to which they overlap can provide some qualitative information.

Inspecting the Hückel NBMOs of a non-disjoint diradical has the additional advantage of providing a good indication of the ways in which these delocalized NBMOs for the triplet state are likely to become localized in the lowest singlet states, in order to reduce the Coulombic repulsion between the nonbonding electrons. For example, from inspection of the NBMOs of triplet **TMM** in Figure 10a, it is easy to deduce that the Coulombic repulsion in the corresponding singlet state will be reduced by localization of the e_y'' MO on the unique carbon atom, where the e_x'' MO has a node. This localization should make twisting of this carbon out of conjugation, as shown in Figure 10b, very likely in the lowest singlet state of **TMM**; and, as already discussed, this non-planar geometry actually is favored by the lowest singlet state of **TMM** (*50–54*).

Computing Not Just the Sign but Also the Size of ΔE_{ST}

The previous section discussed how the ground state of an AH diradical can be predicted, just by counting the number of starred and unstarred carbons. Of course, one wants to do more than just predict the sign of the singlet-triplet energy difference ($\Delta E_{ST} > 0$ for a triplet, and $\Delta E_{ST} < 0$ for a singlet); one also wants to predict the size of ΔE_{ST}. For this purpose, the software to perform high-quality electronic structure calculations is now readily available.

However, calculations, based on one-configuration wave functions, will usually prove inadequate for calculations on diradicals. As already noted in the discussion of eqns. 1 and 2, a one-configuration wave function for an open-shell "singlet" diradical furnishes MOs and energies that are 1:1 averages of those for the actual open-shell singlet state with $S^2 = 0$ and the triplet state with $S^2 = S(S + 1) = 2$. Such a one-configuration "singlet" wave function has $S^2 \approx 1$.

From the energy and calculated S^2 value of a one-configuration, open-shell, "singlet" state it is possible to estimate the energy of the actual two-configuration ($S^2 = 0$) singlet state, using the energy of the triplet state, calculated at the same geometry (*69*). However, the MOs on which the energy of a one-configuration, "singlet" is based will, unfortunately, be an average of the MOs for the triplet and for the two-configuration $S^2 = 0$ open-shell singlet state. Therefore, the MOs for the one-configuration, $S^2 \approx 1$, "singlet" state will, in general, not be the optimal MOs for the two-configuration, ($S^2 = 0$) singlet state.

This can be a very serious problem when the triplet NBMOs are non-disjoint, as is the case in **TMM**. As discussed above, the allyl + 2p MOs, which are optimal for the open-shell ($S^2 = 0$) singlet state of planar **TMM** are very different from the MOs for the triplet. Therefore, an average of these two sets of MOs will not be very useful for accurately computing the energy of the $S^2 = 0$ singlet state.

Coupled-cluster calculations with single and double excitations and a perturbative correction for triplet excitations [CCDSD(T)] are currently the "gold standard" of computational chemistry (*70*). However, garden variety CCSD(T) calculations are based on one-configuration wave functions for singlet states. Therefore, although CCSD(T) calculations may provide a very accurate value for ΔE_{ST}, when the singlet can be well-represented by just one reference configuration, the CCSD(T) value of ΔE_{ST} will, in general, not be reliable if the singlet is open-shell and thus requires a two-configuration, reference wave function.

When I began doing *ab initio* calculations on diradiucals, I started by performing configuration interaction (CI) calculations. With small basis sets, full π CI calculations were possible, and it was even possible to include some single σ excitations. However, as faster computers made calculations with larger basis sets practical, I began doing complete active space (CAS)SCF calculations. In a CASSCF calculation, not only are the weights of the most important configurations in a limited CI wave function determined, but the MOs in those configurations are also optimized.

However, CASSCF calculations ignore the effects of dynamic correlation – how the electrons outside of the active space respond dynamically to all of the electrons that are included in the active space. I learned through experience that the effects of dynamic electron correlation can be quite important (*71*). Therefore, about 20 years ago my group started doing CASPT2 calculations (*72*). CASPT2 uses second-order perturbation theory (PT2) to provide dynamic electron correlation for a CASSSCF wave function; and for the past 20 years, my research group has mostly used the MOLCAS suite of programs (most recently MOLCAS 7) (*73*) to perform CASPT2 calculations on diradicals.

My own interest in calculations has always been largely directed toward using them to make new, experimentally testable predictions. Therefore, I try to publish the results of my group's calculations, *before* the experiments to test them have been performed. Consequently, in the subsequent sections of this chapter on the values of ΔE_{ST} in different diradicals, I have mostly chosen to reference the calculations that were published by my research group, *before* the experimental values of ΔE_{ST} were measured.

I owe an apology to those computational chemists who have published the results of their calculations of ΔE_{ST} in different diradicals, after the experimental values of ΔE_{ST} were measured, for not discussing their calculations in this chapter. Comparing calculated values with known experimental values is important for benchmarking different computational methods; but predicting, rather than benchmarking, has almost always been the goal of the calculations carried out by my research group.

Measurements of ΔE_{ST} in Diradicals

Measuring the Sign and Size of ΔE_{ST} with Curie Plots

If the triplet is the ground state of a diradical, a Curie plot of its EPR signal intensity versus 1/T should give a straight line (*74*). It was through the linearity of Curie plots that a triplet ground state was established for Schlenck's hydrocarbon (*75*, *76*), the parent **MBQDM** (*77*), and **TMM** (*30*).

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There are two different circumstances under which a curved Curie plot will be observed. If a plot of signal intensity curves upward with decreasing temperature, it means that more molecules in the triplet state are being populated as the temperature is reduced. This implies that the triplet is the ground state, but that there is a thermally accessible singlet state which is being depopulated as the temperature is reduced.

On the other hand, if the Curie plot curves downward, it means that the triplet is being depopulated as the temperature is lowered, The triplet is then a thermally accessible excited state, and the ground state must be a singlet.

A linear Curie plot will be obtained if a triplet ground state is well below the lowest singlet excited state in energy; but if the triplet state and a singlet state have exactly the same enthalpy, then a linear Curie plot will also be obtained. In other words, a Curie plot cannot distinguish between $\Delta E_{ST} = 0$ and $\Delta E_{ST} >> 0$. This ambiguity actually makes it incorrect to claim, unequivocally, that a linear Curie plot establishes that a molecule has a triplet ground state.

A curved Curie plot has the virtue of establishing whether the triplet is slightly above or slightly below the lowest singlet state. However, as emphasized by Platz and by Berson, curvature will only be detectable if the triplet and lowest singlet state are very close in energy (*74*). Particularly if the triplet is the ground state, the presence of a low-lying singlet state will be very hard to detect.

Making predictions is a less than satisfying activity, unless the predictions can, at least in principle, be tested experimentally. The severe limitations of Curie plots in providing accurate values of ΔE_{ST} in diradicals sometimes made me feel that I was wasting my time in calculating ΔE_{ST} values, since it seemed that none of them would ever be measured.

Measuring the Sign and Size of ΔE_{ST} by Negative Ion Photoelectron Spectroscopy (NIPES)

This feeling of futility vanished entirely with the publication of the negative ion photoelectron (NIPE) spectrum of the radical anion of **TMM** by Wenthold, Hu, Squires, and Lineberger in 1996 (*78*). It then became clear that, at least in principle, NIPES could provide a very accurate experimental value of ΔE_{ST} in any diradical on which I performed calculations (*4*).

As shown schematically in Figure 13, in a NIPES experiment a beam of radical anion molecules ($\mathbf{D}^{\bullet -}$) is crossed by a laser, whose energy is sufficient to ionize any of the electrons in the highest energy MOs of the radical anion. The kinetic energies of the photoelectrons, ejected by absorption of the laser light by the molecules of the radical anion, are measured. From conservation of energy, the energy of each electronic state of the neutral diradical, minus the energy of the radical anion, must be equal to the energy of the laser, minus the kinetic energy of the electron that is ejected.

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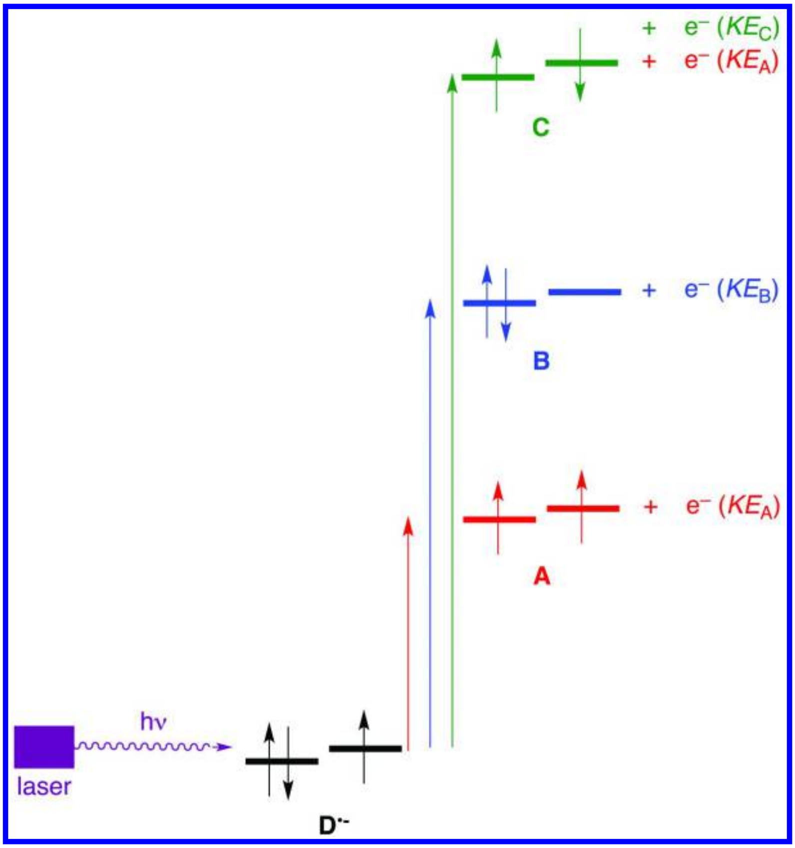

*Figure 13. Schematic depiction of a NIPES experiment in which a laser detaches a photoelectron from a radical anion, **D•⁻**, forming three different electronic configurations of the neutral diradical. Each configuration is accompanied by a photoelectron with a different kinetic energy. Configuration **C** is part of both the $S_z = 0$ component of the triplet and the open-shell singlet state. Formation of the triplet state produces a photoelectron with the same kinetic energy (KE_A) as the photoelectron produced by formation of state **A**, the $S_z = 1$ component of the triplet. However, formation of the open-shell singlet state produces a photoelectron with a different kinetic energy (KE_C).*

Of course the energy of the laser is the same for each of the electronic states that is formed in a NIPES experiment. Therefore, the relative energies of the electronic states of a neutral diradical are given by the differences between the kinetic energies of the electrons that are ejected in forming each of these states from the radical anion. As discussed below, it is usually possible to identify each of the electronic states of a diradical, whose formation accompanies the ejection of a photoelectron with a particular kinetic energy.

As shown schematically in Figure 13, a radical anion can give rise to three, low-lying, electronic configurations of the neutral diradical, formed from the radical anion. Configuration **A** is the $S_z = 1$ component of the triplet state. Configuration **B** is a singlet state in which both electrons occupy the same MO. In configuration **C**, electrons with opposite spins are found, one each, in each of the two MOs.

As discussed in connection with eqns.1 and 2, configuration C is not a proper spin state. It is, instead a 1:1 mixture of the $S_z = 0$ component of the triplet state and the open-shell singlet state. Formation of the $S_z = 0$ component of the triplet produces a photoelectron with the same kinetic energy as formation of the $S_z = 1$ component of the triplet; whereas formation of the open-shell singlet state produces a photoelectron with a different kinetic energy.

In the absence of a strong magnetic field, radical anions in which the unpaired electron has spin up, (i.e., radical anions with $S_z = ½$), should be accompanied by an equal number of radical anions in which the unpaired electron has spin down (i.e., radical anions with $S_z = -½$). Loss of an electron from an $S_z = -½$ radical anion again gives rise to three configurations. In this case they are: the $S_z = -1$ component of the triplet state, closed-shell configuration B again, and a variant of configuration C, with the spins of the electrons in the two singly occupied MOs reversed

Starting with a radical anion in which the unpaired electron is found in only one MO, there is one way to form each of the three components of the triplet state, two ways to form the singlet state in which one MO is doubly occupied, and one way to form the open-shell singlet state. Thus, on a purely statistical basis, the peak in a NIPE spectrum for formation of the triplet should be 50% more intense than the peak for formation of the closed-shell singlet state and three times more intense than the peak for the formation of the open-shell singlet state.

Differences in Franck-Condon factors (*79*) (*vide infra*) can cause the relative intensities of the peaks in a NIPE spectrum to deviate from the expectations based on the above statistics for formation of the triplet and the two low-lying singlet states of a diradical. However, it generally seems to be the case that the peaks for formation of the triplet are the most intense peaks in a NIPE spectrum (*4*).

On this basis, in the NIPE spectrum of $(CO)_5^{\bullet-}$ in Figure 14 (*80*), it is possible to assign the group of peaks marked A to the triplet state and the group of lines marked X to the lowest singlet state. The onsets of these two groups of peaks are at 3.830 ± 0.005 eV (X), and 4.680 ± 0.010 eV (A), giving the singlet-triplet energy difference in $(CO)_5$ as $\Delta E_{ST} = -0.85$ eV = -19.6 kcal/mol. The negative sign indicates that the singlet is lower in energy than the triplet.

Assignment of the Peaks in a NIPE Spectrum by Vibrational Progressions and by Calculations of Franck-Condon Factors

The NIPE spectrum in Figure 14 obviously does not consist of one peak for formation of the singlet state and one peak for formation of the triplet state, but, instead, of groups of peaks for formation of each state. The multiple peaks are

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the result of vibrational progressions in each state. These vibrational progressions are seen because the geometries of both the singlet and triplet states of the neutral molecule are different from the geometry of the radical anion, from which the singlet and triplet states of the neutral are formed.

Intensities of electronic transitions depend on the squares of the overlaps of the vibrational wave functions for the ground and excited states. The squares of these overlaps are called the Franck-Condon factors (*79*). If there is no difference between the geometry of the ground and excited state, then, as shown in Figure 15a, a single peak is observed, because the lowest vibrational wave function of the ground state has a non-zero overlap with only the lowest vibrational wave function of the excited state.

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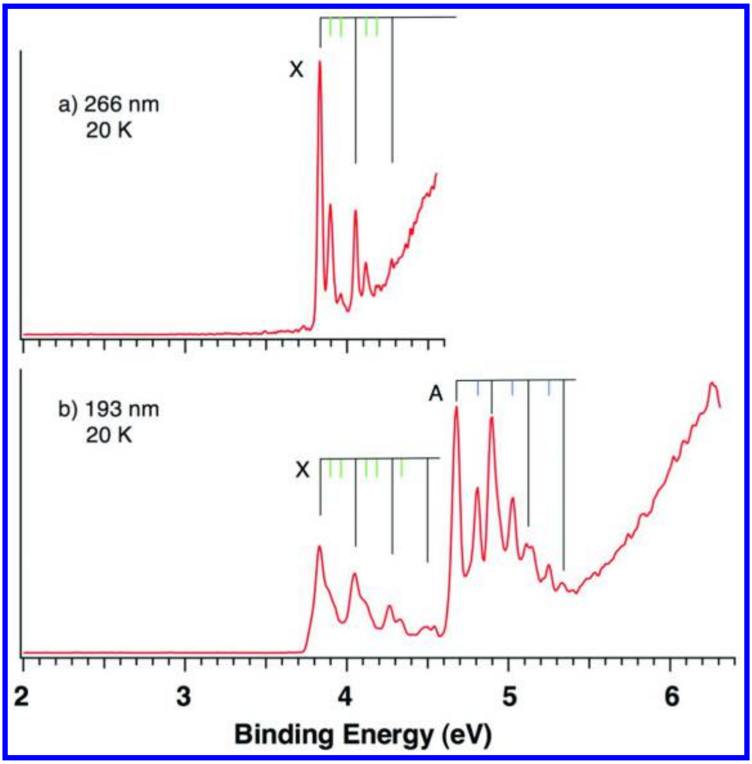

Figure 14. NIPE spectrum of (CO)$_5^{\bullet-}$ (80). The greater intensity of band A than of band X indicates that band A should be assigned to formation of the triplet state of (CO)$_5$. Reprinted with permission from Bao, X.; Hrovat, D. A.; Borden, W. T.; Wang, X.-B. J. Am. Chem. Soc. ***2013****, 135, 4291. Copyright 2013 American Chemical Society.*

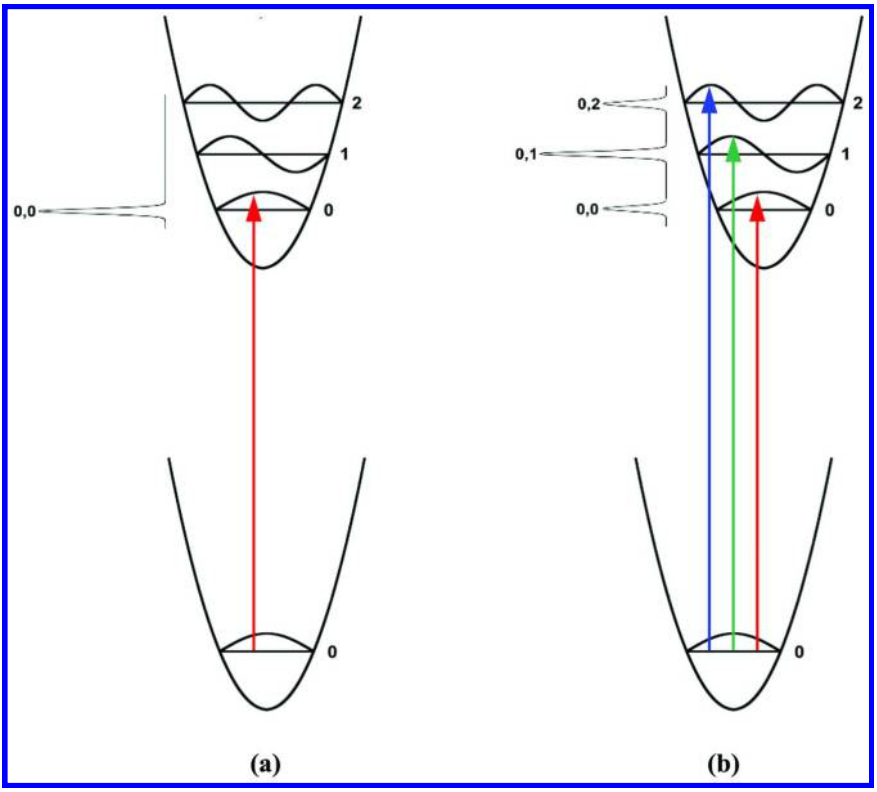

Figure 15. Vibrational wave functions with non-zero overlaps when (a) the geometries of the ground excited states are the same and (b) the geometries are different in a particular coordinate. In (a) only the (0,0) peak is seen in the electronic excitation spectrum; but, in (b) several peaks – for example (0,0), (0,1), and (0,2) – may be observed. The frequency of the vibrational progression seen in (b) is the frequency of the vibration in the excited state that affects the internal coordinates along which the ground and excited state geometries differ.

However, as shown in Figure 15b, if there is a geometry change upon excitation, the lowest vibrational wave function of the ground state may have non-zero overlaps with the wave functions for several vibrational levels of the excited state. As a result, several vibrational levels of the excited state may be populated; and a vibrational progression will then be seen. The peaks in this progression are separated by the frequency of the vibration in the excited state that affects the internal coordinates along which the geometries of the ground and the excited state differ.

In NIPES the ground state is the radical anion and the excited states are the electronic states of the neutral molecule that is formed by ejection of a photoelectron from the radical anion. Therefore, in a NIPE spectrum vibrational progessions are seen when the geometries of the radical anion and the neutral

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species formed from it differ. The frequencies in these progressions are those in the neutral species for vibrations that affect the internal coordinates along which the geometries of the radical anion and the neutral differ.

Consequently, from calculations of the optimized geometries of a radical anion and those of different low-lying electronic states of the neutral molecule formed from it, one can qualitatively predict what types of vibrations are likely to appear in the NIPE spectrum of the radical anion. From vibrational analyses on the electronic states of the neutral, one can also predict what the frequencies of these vibrations are likely to be. Finally, one can use a program, such as ezSpectrum (*81*), to compute the Franck-Condon factors for formation of different electronic states of the neutral and thus provide a quantitatively reliable simulation of the NIPE spectrum. From comparison of the observed and simulated NIPE spectra, all of the peaks in the experimental spectrum can usually be assigned. Some examples will be provided in the sections that follow.

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The NIPE Spectra of Some Radical Anions

The NIPE Spectrum of TMM$^{•-}$

TMM is the simplest and the best-studied of the Non-Kekulé, AH diradicals (*82*). As shown in Figure 11, n^* - n = 2 in **TMM**; so the NBMOs of **TMM** are non-disjoint. As can be seen in both Figures 10 and 11, the D_{3h} NBMOs of **TMM** do, in fact, have two carbon atoms in common. Consequently, **TMM** should have a triplet ground state.

The linear Curie plot obtained for **TMM** (*30*) is, of course consistent with this prediction. Unfortunately, the Curie plot provides no information about the size of ΔE_{ST} in **TMM**. However, this information is available from the NIPE spectrum of the radical anion of **TMM** (**TMM$^{•-}$**) (*78*).

TMM$^{•-}$ was generated by treatment of 1,3-bis(trimethylsilyl)-2-methylenepropane with a mixture of F_2 and F– in the gas-phase (the Squires' reaction) (*83*). As expected, the lowest energy peak in the NIPE spectrum of **TMM$^{•-}$** is for formation of the $^3A_2'$ state (*78*). This peak is followed by a second peak for formation of a singlet state of **TMM**. From the energy separation between these peaks, ΔE_{ST} = 16.1 ± 0.2 kcal mol^{-1} in **TMM**.

The lowest energy singlet state of **TMM** has one CH_2 group twisted out of conjugation, as shown in Figure 10b. However, the Franck-Condon factors for formation of this twisted geometry of neutral **TMM** from the planar geometry of the **TMM$^{•-}$** radical anion are zero. Therefore, the singlet state that is formed by photo-detachment of an electron from **TMM$^{•-}$** is not the lowest singlet state of **TMM**, but the lowest energy singlet state that can be accessed by photo-detachment of an electron from the planar radical anion.

The planar singlet state of lowest energy in **TMM** is $^1A_1$, which is depicted in Figure 16 (*65*). The value of ΔE_{ST} = 16.1 ± 0.2 kcal/mol from the NIPE spectrum of **TMM$^{•-}$** presumably corresponds to the energy difference between the $^1A_1$ and $^3A_2'$ states of planar **TMM** (*78*).

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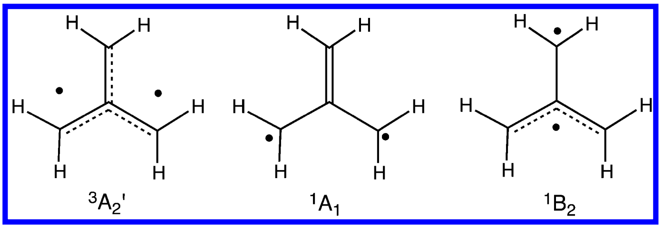

*Figure 16. Three electronic states of planar **TMM**. $^3A_2'$ is the ground state, with $^1A_1$ predicted to be slightly lower in energy than $^1B_2$. The three equivalent $^1A_1$ structures are the minima on the Jahn-Teller potential surface for pseudorotation of the lowest singlet state of planar **TMM** around the $^1E'$ cusp that exists at D_{3h} geometries, and the three equivalent $^1B_2$ states are the transition structures that connect the minima (65).*

An early *ab initio* calculation on **TMM** predicted ΔE_{ST} = 18.2 kcal/mol as the energy difference between the $^1A_1$ and $^3A_2'$ states of planar **TMM** (*84*). This calculated value is about 13% higher than the experimental value of ΔE_{ST} = 16.1 ± 0.2 kcal/mol (*78*). More recent calculations, performed at higher levels of theory (*85*, *86*), are in slightly better agreement with the experimental value. However, the results of these calculations were published after the experimental value of ΔE_{ST} = 16.1 ± 0.2 kcal/mol had been measured. In contrast, the calculated value of ΔE_{ST} = 18.2 kcal/mol (*84*) was truly a prediction, since it was published 14 years before the NIPE spectrum of **TMM**$^{\bullet-}$ had been obtained (*78*).

The NIPE Spectrum of MBQDM$^{\bullet-}$

Like **TMM**, **MBQDM** is a non-Kekulé AH diradical (*82*). The Hückel NBMOs of **MBQDM**, $3b_1$ and $2a_2$, are shown in Figure 17. As demonstrated in Figure 11, they can easily be found using the zero-sum rule (*25*). However, since $n^* - n = 2$ in **MBQDM**, the conclusion that the NBMOs are non-disjoint can be made without actually finding them (*56*).

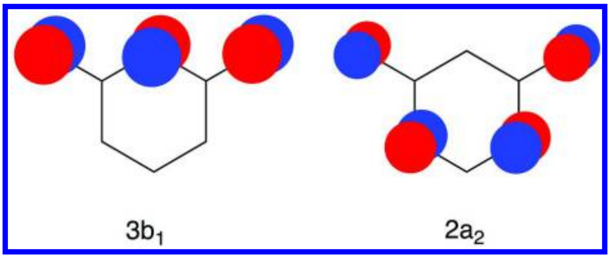

*Figure 17. Schematic depiction of the Hückel NBMOs of **MBQDM**.*

Because the NBMOs of **MBQDM** are non-disjoint, it is easy to predict that the ground state of **MBQDM** is a triplet. Indeed, as already noted, the triplet EPR signal of **MBQDM** gives a linear Curie plot, strongly suggesting that **MBQDM** does, in fact, have a triplet ground state (*77*). This conclusion is confirmed by the NIPE spectrum (*87*), which not only provides the value of ΔE_{ST} = 9.6 kcal/mol, but also provides the relative energies of both of the low-lying singlet states of **MBQDM**.

The radical anion of **MBQDM** was generated by allowing *m*-xylene to react with $O^{\bullet-}$ in the gas-phase. The NIPE spectrum shown in Figure 18 was obtained (*87*). As expected, the lowest energy peak is for formation of the $^3B_2$ state of neutral **MBQDM,** followed by a peak that is assigned to the $^1A_1$ state and then by another that is assigned to formation of the open-shell $^1B_2$ state. What is the nature of these two singlet states, and what determines their relative energies?

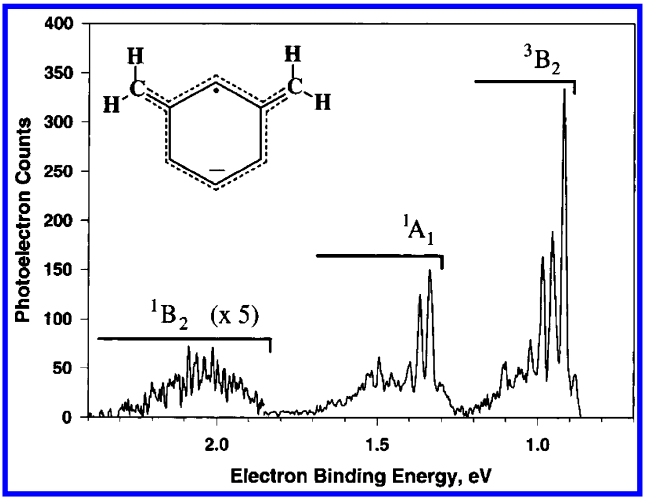

*Figure 18. The NIPE spectrum of **MBQDM**$^{\bullet-}$. Reprinted with permission from Wenthold, P. G.; Kim, J. B. Lineberger, W. C. J. Am. Chem. Soc., **1997**, 119, 1354. Copyright 1997 American Chemical Society.*

The non-disjoint nature of the Hückel NBMOs of **MBQDM** in Figure 17 means that although these NBMOs may be optimal for the triplet, they will not be optimal for either singlet state. Nevertheless, from the NBMOs for the triplet, it is possible to guess what the NBMOs will be like in both low-lying singlet states. Hence, the nature of the bonding in each singlet state can be qualitatively predicted.

For example, in the open-shell $^1B_2$ state, the electrons of opposite spin each singly occupy the $3b_1$ and $2a_2$ π MOs. These opposite-spin electrons minimize their Coulombic repulsion by tending to localize at different carbon atoms. This can be accomplished by localization of the $2a_2$ NBMO at just two ring carbons and partial localization of the $3b_1$ NBMO at a third ring carbon. The bonding in the $^1B_2$ state of **MBQDM** is depicted schematically in Figure 19.

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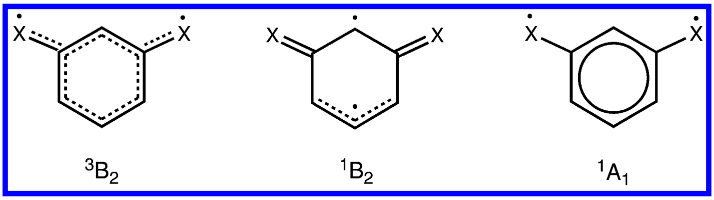

Figure 19. Schematic depiction of the bonding in the three lowest electronic states of ***MBQDM*** *($X = CH_2$) and in* ***MBQ*** *($X = O$). In order to avoid the high Coulombic repulsion that is associated with two electrons of opposite spin appearing in the same region of space, the nonbonding electrons are more localized in the singlet states, $^1B_2$ and $^1A_1$, than in the triplet state, $^3B_2$, of* ***MBQDM*** *and of* ***MBQ****.*

The way that the **MBQDM** NBMOs in Figure 17 localize in the $^1A_1$ state is a little harder to understand, because the $^1A_1$ state has a two-configuration wave function of the form,

$$\Psi(^1A_1) = |\ldots 3b_1^2> - |\ldots 2a_2^2> \qquad (34)$$

The two GVB orbitals derived from it are, therefore, the sum and difference of the $3b_1$ and $2a_2$ NBMOs in Figure 17.

It seems paradoxical; but, in order for the GVB orbitals to be as disjoint as possible, the two NBMOs in Figure 17 need to both localize at the same set of carbons, specifically, at the carbons of the exocyclic methylene groups. Then the two GVB MOs, which are the sum and difference of the $3b_1$ and $2a_2$ NBMOs, will each be localized at a different CH_2 group, thus minimizing the Coulombic repulsion between this pair of electrons. The bonding in the $^1A_1$ state of **MBQDM** is depicted in Figure 19.

The depictions in Figure 19 of the bonding in the $^1B_2$ and $^1A_1$ states of **MBQDM**, as well as the optimized bond lengths in these two states (*7*, *88*), indicate that $^1A_1$ preserves the aromaticity of the benzene ring in **MBQDM**, whereas the $^1B_2$ state destroys it. It is for this reason that, in the NIPE spectrum of **MBQDM**$^{\bullet-}$ in Figure 18 (*87*), the $^1A_1$ state is found to lie about 12.5 kcal/mol below the $^1B_2$ state, with the $^3B_2$ state 9.6 kcal/mol below $^1A_1$. Calculations performed both before (*7*) and after (*88*) the NIPE spectrum of **MBQDM**$^{\bullet-}$ was published are in good agreement with these relative energies of the $^3B_2$, $^1A_1$, and $^1B_2$ states of **MBQDM**.

The Effect of the Substitution of O for CH_2 on ΔE_{ST} in Going from TMM to OXA

Substitution of O for one CH_2 group in **TMM** gives the oxallyl diradical (**OXA**). The results of calculations on ΔE_{ST} in **OXA** were published (*6*) nearly

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20 years before the NIPE spectrum of the **OXA**$^{\bullet-}$ radical anion was obtained (*8*, *9*). These calculations predicted $\Delta E_{\mathrm{ST}} \approx 0$ (*6*).

Two decades later, more sophisticated calculations found the singlet actually to be the ground state of **OXA**. One set of calculations found ΔE_{ST} = -1.3 kcal/mol (*8*, *9*), and the other ΔE_{ST} = -1.5 kcal/mol (*89*). Perhaps fortuitously, ΔE_{ST} = -1.3 kcal/mol is the same as the value obtained experimentally from Lineberger's NIPE spectrum of **OXA**$^{\bullet-}$ (*8*, *9*).

Based on Lineberger's experimental values of ΔE_{ST} = 16.2 kcal/mol in **TMM** (*74*) and -1.3 kcal/mol in **OXA** (*8*, *9*), the substitution of the O in **OXA** for one CH_2 group in **TMM** stabilizes the $^1A_1$ state, relative to the $^3B_2$ state, by 17.5 kcal/mol. At least part of this large, selective, stabilization of the singlet can be ascribed to the greater electronegativity of oxygen, relative to carbon. The greater electronegativity of oxygen lowers the energy of the $2b_1$ π NBMO of **OXA** (e_y'' in **TMM** in Figure 10a), which has a large coefficient on oxygen, relative to the a_2 π MO (e_x'' in **TMM** in Figure 10a), which has a node at the oxygen atom.

Since the $2b_1$ and a_2 MOs do not have the same energies in **OXA**, the form of the two-configuration wave function in eqn. 30 must be modified, so that the two configurations are allowed to have different weights. The form of a more generally useful two-configuration wave function is

$$\Psi(^1A) = c_1^2|\psi_1^{\alpha}(1)\,\psi_1^{\beta}(2)> - c_2^2\,|\psi_2^{\alpha}(1)\,\psi_2^{\beta}(2)> =$$
$$|[(c_1\psi_1 + c_2\psi_2)(1)(c_1\psi_1 - c_2\psi_2)(2)][\alpha(1)\beta(2) - \beta(1)\alpha(2)]/\sqrt{2} \quad (35)$$

The ratio, c_1/c_2, as well as the MOs, ψ_1 and ψ_2, can be optimized computationally; and the magnitudes of c_1 and c_2 in eqn. 35 can be chosen, so that the wave function is normalized.

In **OXA** use of a two-configuration wave function, like that in eqn. 35, with $\psi_1 = \psi(2b_1)$ and $\psi_2 = \psi(a_2)$, allows the occupation of the lower energy $2b_1$ MO to be significantly greater than that of the a_2 MO in the $^1A_1$ state. In contrast, in both the triplet ($^3B_2$) and the open-shell singlet states ($^1B_2$) one π electron occupies the $2b_1$ MO and another π electron occupies the a_2 MO. Therefore, neither of these states can take full advantage of the lower energy of the $2b_1$ MO, relative to the a_2 MO in **OXA**. That is why substitution of O in **OXA** for CH_2 in **TMM** is computed to stabilize the $^1A_1$ state, relative to the $^3B_2$, state by 17.5 kcal/mol.

One way to represent the greater contribution of the $|\ldots 2b_1^2>$ configuration, relative to that of $|\ldots a_2^2>$, to the wave function for the singlet ground state of **OXA** is by writing the zwitterionic resonance structure **b** in Figure 20 as a contributor to this $^1A_1$ wave function. However, the NIPE spectrum shows a C=O progession of 1680 ± 50 cm^{-1} in the $^1A_1$ state (*8*, *9*), indicating that resonance structure **b** in Figure 20 is not a significantly greater contributor to the singlet ground state of **OXA** than similar resonance structures are to the singlet ground states of ordinary ketones. The high C=O stretching frequency in the $^1A_1$ state, found in the NIPE spectrum of OXA (*8*, *9*), provides experimental confirmation for predictions, made 15 (*90*), 19 (*6*), and 25 (*91*) years earlier, that the dominant contributor to the lowest singlet state of **OXA** is resonance structure **a** in Figure 20, not resonance structure **b**.

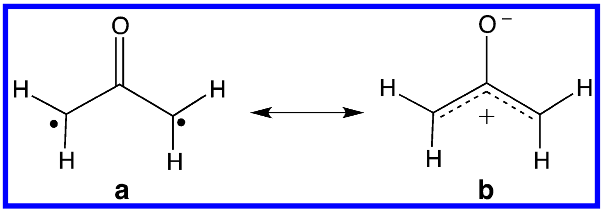

*Figure 20. Two possible resonance contributors to the structure of the singlet ground state of **OXA**. The high C=O stretching frequency in this state, seen in the NIPE spectrum of **OXA**$^{\bullet-}$, indicates that structure **a** is dominant and that the contribution of structure **b** is not significantly greater in the singlet ground state of **OXA** than in the singlet ground states of other ketones.*

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Nevertheless, structure **b** suggests that the lowest singlet state of **OXA** might undergo an orbital symmetry-allowed (*36*), disrotatory ring closure to cyclopropanone, with only a modest barrier. Indeed, calculations found this mode of ring closure actually to be barrierless (*8*, *9*, *89*). Therefore, the $^1A_1$ state of **OXA** is actually the transition structure for ring opening of cyclopropanone. Specifically, it is the C_s transition structure by which optically active *trans*-cyclopropanone-2,3-d_2 would racemize.

The fact that the $^1A_1$ state of **OXA** is a transition structure explains why the bands for formation of this state in the NIPE spectrum of **OXA**$^{\bullet-}$ are so broad. The Heisenberg uncertainty principle can be written

$$\Delta E \Delta t \geq h/2\pi \qquad (36)$$

Therefore, if the lifetime of a state is very short (i.e., Δt is very small), the uncertainty in the energy of the state (ΔE) must be large. Consquently, it can be said the lines in the NIPE spectrum for the formation of the $^1A_1$ state of **OXA** are "uncertainty broadened."

Despite the very short lifetime of the $^1A_1$ transition structure, as already noted, a progression of 1680 ± 50 cm^{-1} for C=O stretching can be seen in this state in the NIPE spectrum of **OXA**$^{\bullet-}$**.** In fact, NIPES makes it possible to obtain spectroscopic information about not only transition structures (*8*, *9*, *15*, *92*) but also mountain tops (*93*) on potential energy surfaces.

The Effect of the Substitution of O for CH$_2$ on ΔE_{ST} in Going from MBQDM to MBQ

If the substitution of the oxygen in **OXA** for a CH$_2$ group in **TMM** reduces the value of ΔE_{ST} by 17.5 kcal/mol, one night expect an even larger reduction when the two oxygens in **MBQ** are substituted for the two methylene groups in **MBQDM**. However, from the NIPE spectra of **MBQDM** and **MBQ**, the actual change in ΔE_{ST} is only 0.6 kcal/mol, from ΔE_{ST} = 9.6 kcal/mol in **MBQDM** (*87*) to ΔE_{ST} = 9.0 kcal/mol in **MBQ** (*10*, *11*).

Interestingly, the prediction, that this would be found to be the case (*7*), was published more than 20 years before the NIPE spectrum of **MBQ**$^{\bullet-}$ was first reported by Xuebin Wang and coworkers (*10*). They prepared this radical anion by electrospraying the dianion of *m*-cresol into the gas phase. When stripped of a sufficient number of solvent molecules, the dianion loses an electron and forms the **MBQ**$^{\bullet-}$ radical anion.

As shown in Figure 21, the NIPE spectrum of **MBQ**$^{\bullet-}$ is complicated, consisting of many peaks (*10*). Hence, it is not amenable to easy interpretation. However, Dr. Bo Chen in my research group was able to use electrionic structure and Franck-Condon calculations, in order to provide the simulation, also shown in Figure 21, of the experimental NIPE spectrum (*11*).

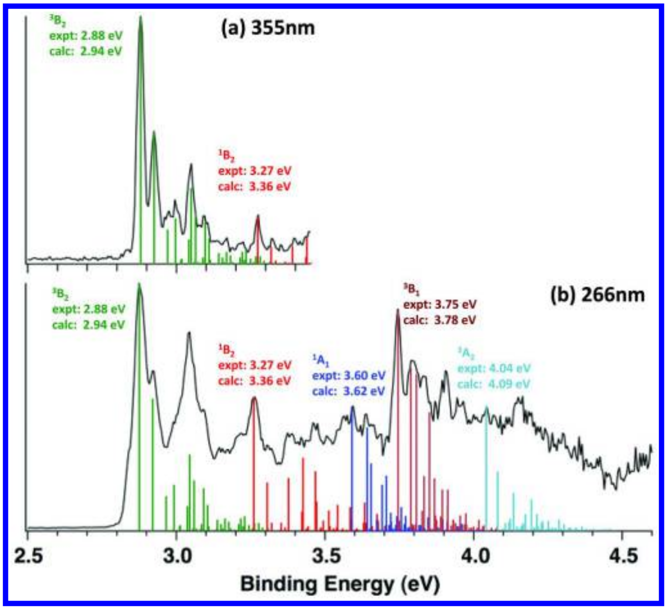

Figure 21. The NIPE spectra of ***MBQ***$^{\bullet-}$ *(10). Shown under the experimental spectra are the predicted spectra, obtained by using ezSpectrum (81) to calculate the Franck-Condon factors for the vibrational progressions in the formation of each electronic state of* ***MBQ*** *from* ***MBQ***$^{\bullet-}$ *(11). Reprinted with permission from Chen, B.; Hrovat, D. A.; Deng, S. H. M.; Zhang, J.; Wang, X.-B.; Borden, W. T. J. Am. Chem. Soc.* ***2014****, 136, 3589.. Copyright 2014 American Chemical Society.*

Comparison of the NIPE Spectra in Figures 18 and 21 shows that the lowest singlet state changes from being $^1A_1$ in **MBQDM** to $^1B_2$ in **MBQ**. The reason for this change is easy to see from the depictions of the bonding in these two singlet states in Figure 19. As already discussed, in the hydrocarbon the aromaticity of the π system of the benzene ring in the $^1A_1$ state of **MBQDM** makes this the lowest singlet state. However, on substitution of oxygen for CH_2, the strengths of the C=O π bonds in the $^1B_2$ state of **MBQ** apparently overcome the aromaticity of the benzene ring in the $^1A_1$ state; so $^1B_2$ becomes the ground state of **MBQ**.

Consequently, despite the change in ΔE_{ST} of only 0.6 kcal/mol on going from **MBQDM** to **MBQ**, the substitution of O for CH_2 actually has a very large effect on the relative energies of the $^1A_1$ and $^1B_2$ states. As shown schematically in Figure 22 and in the NIPE spectrum of **MBQDM**$^{\bullet-}$ in Figure 18, $^1B_2$ is found to be 12.5 kcal/mol higher in energy than $^1A_1$ (*87*). However, on going from **MBQDM** to **MBQ** there is a 20.1 kcal/mol stabilization of $^1B_2$, relative to $^1A_1$, so that in the NIPE spectrum of **MBQ**$^{\bullet-}$ in Figure 21, $^1B_2$ is lower in energy than $^1A_1$ by 7.6 kcal/mol (*11*). Nevertheless, as shown in Figure 18, despite the huge change in the relative energies of these two singlet states, the energy difference between the lower of these two states and the $^3B_2$ ground state changes by only 0.6 kcal/mol on going from **MBQDM** to **MBQ**.

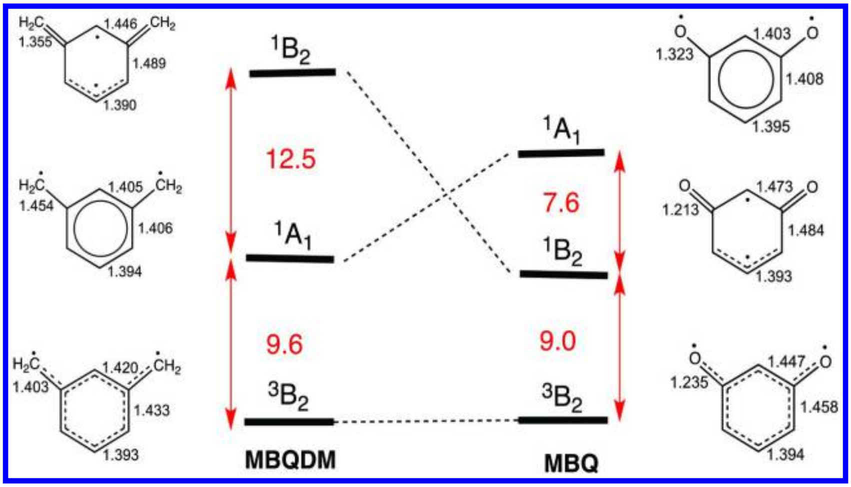

*Figure 22. Relative energies (kcal/mol) of the low-lying electronic states of **MBQDM** (87) and **MBQ** (11), obtained from their NIPE spectra. Calculated C-C bond lengths (Å) for each state are also shown.*

Electronic structure calculations were not only essential for deconvoluting the NIPE spectrum of **MBQ**$^{\bullet-}$ (*11*), but also for understanding why the substitutition of the oxygens in **MBQ** for the CH_2 groups in **MBQDM** has almost no effect on ΔE_{ST}. As already mentioned, the prediction, that this would be found to be the case (*7*), was published more than 20 years before the NIPE spectrum of **MBQ** provided experimental confirmation of this prediction (*11*).

Violations of Hund's Rule in Diradicals (*14*)

Fifty years ago, when I first began doing calculations on diradicals, one of the things that most interested me was the PPP prediction that in square **CBD** and in planar allene, $\Delta E_{ST} = 0$. When I subsequently discovered that, with inclusion of dynamic electron correlation, the singlet is actually predicted to be the ground state of both diradicals (*37*, *40*, *41*, *45*), I began to think about how these predicted violations of Hund's rule might be confirmed experimentally.

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Unfortunately, square **CBD** and planar allene are both transition structures, the former for interconversion of the two rectangular minina on the potential energy surface for singlet **CBD** and the latter for racemization of an optically active allene. Therefore, measuring the energy difference between these two singlet transition structures and the corresponding triplet energy minima would pose a formidable challenge.

ΔE_{ST} in TME

Of course, in addition to **CBD** and planar allene, there are other diradicals that have disjoint NBMOs. For example, the NBMOs of tetramethyleneethane (**TME**), which are shown in Figure 12, can be chosen to have no atoms in common. Consequently, to a first approximation, the singlet and the triplet have the same energies. Inclusion of dynamic spin polarization, which creates some weak π bonding between the central carbons of the two allylic radical subsystems, results in the lowest singlet state of planar **TME** being predicted to be lower in energy than the triplet state (*94*).

However, the conformational flexibility of **TME** complicates calculating ΔE_{ST} in this diradical (*94*, *95*). The relative energies of the in-phase and out-of-phase combinations of the localized allyl NBMOs in Figure 12 depend on the dihedral angle between the allyl groups in **TME**, as does the π bonding between the two central carbons, which results from dynamic spin polarization in the lowest singlet state.

The conformational flexibility of **TME** may be at least partly responsible for the apparently contradictory experimental findings about whether a singlet or the triplet is the ground state of **TME**. A linear Curie plot of the intensity of the EPR signal versus 1/T indicates that the triplet is the ground state (*96*), but the NIPE spectrum of **TME**$^{\bullet-}$ shows that the singlet is the ground state (*97*). A possible resolution of this apparent paradox has been proposed (*4*, *82*).

ΔE_{ST} in TMB

If **TME** is viewed as being created by joining the nodal carbons of two allyl radicals, 1,2,4,5-tetramethylenebenzene (**TMB**) can be seen to result from joining the two pair of nodal carbons in two pentadienyl radicals. The two C-C single bonds that join the pentadienyl radicals in **TMB** make it far less conformationally flexible than **TME**, where the two allyl radicals are connected by just one, single, C-C bond.

As shown in Figure 23, in **TMB** $n^* = n$. Therefore, each of the two NBMOs of **TMB** can be taken to be the NBMO of one of the two pentadienyl radicals. These localized, non-bonding orbitals are, of course, disjoint; and, with inclusion of dynamic spin polarization, **TMB** has been predicted to have a singlet ground state (*98*).

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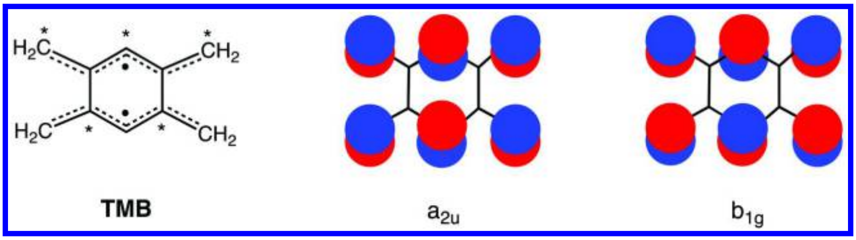

*Figure 23. Starred and unstarred carbons in 1,2,4,5-tetramethylenebenzene (**TMB**) and its a_{2u} and b_{1g} NBMOs. The GVB orbitals of **TMB** are the sum and difference of the a_{2u} and b_{1g} NBMOs, Therefore, each GVB orbital is the non-bonding π orbital of one of the two pentadienyl radicals, of which **TMB** is comprised. Therefore, the GVB MOs are disjoint, as can be predicted from the fact that $n^* = n$ in **TMB**.*

The localized pair of pentadienyl NBMOs of **TMB** are the GVB orbitals of TMB. These GVB orbitals are the sum and the difference of the a_{2u} and b_{1g} **TMB** NBMOs in Figure 23, which have the full D_{2h} molecular symmetry. However, the a_{2u} and b_{1g} MOs are not degenerate. With inclusion of the effects of 1,4-interactions between the 2p-π AOs, a_{2u} is slightly lower in energy than b_{1g}.

In a two-configuration wave function for singlet **TMB**, which takes the form of the wave function in eqn. 34, the coefficient of $|\ldots a_{2u}{}^2\rangle$ will be larger than that of $|\ldots b_{1g}{}^2\rangle$. Therefore, the wave function for the lowest singlet state of **TMB** will have a larger contribution from the lower energy of these two NBMOs. In contrast, in the triplet state, one electron occupies each of these NBMOs. The greater occupancy of the lower-energy, a_{2u} MO in the singlet than in the triplet should tend to make the singlet the ground state of **TMB**.

Thus, there are two different effects that contribute to the prediction that **TMB** should have a singlet ground state. The first is the effect of dynamic spin polarization, which creates some additional π bonding in the singlet between the pairs of pentadienyl nodal carbons (C1-C2, and C4-C5) at which negative spin density appears. The second is the effect of the 1,4-π interactions between C3 and C6 and between pairs of methylene carbons.

The relative sizes of these two effects can be estimated by first computing ΔE_{ST} with a two-configuration wave function, like that in eqn. 34, and then recomputing ΔE_{ST} with a multi-configurational wave function. In the former wave function. the effects of the 1,4-π interactions are captured, but in the latter the effects of dynamic spin polarization are also included. Such a comparison shows that 1,4-π interactions contribute about 30% to the calculated value of $\Delta E_{ST} = 6.0$ kcal/mol in **TMB**, and dynamic spin polarization contributes the rest (*98*). Experiments by Jerry Berson and coworkers have confirmed the prediction that **TMB** has a singlet ground state (*99*, *100*).

However, since the a_{2u} and b_{1g} NBMOs of **TMB** have slightly different energies, can **TMB** really be claimed to violate Hund's rule? A violation of the strictest form of Hund's rule can only be really claimed if (a) the two half-occupied MOs in a molecule have *exactly* the same energies; and (b) the ground state of the molecule is, nevertheless, a singlet.

The only way to ensure that two MOs have *exactly* the same energies is if symmetry makes them degenerate. That is what would make measurement of ΔE_{ST} at the square (D_{4h}) geometry of **CBD** very interesting; the two half-filled MOs would be guaranteed to have the same energy. Unfortunately, I could not think of an experiment that would allow ΔE_{ST} at the D_{4h} geometry of **CBD** to be measured.

The NIPE Spectrum of COT$^{•-}$

However, I was able to design an experiment that would measure ΔE_{ST} at the D_{8h} geometry of cyclooctatetraene (**COT**) (*15*). Like the D_{4h} geometry of singlet **CBD**, the D_{8h} geometry of **COT** is the transition structure (TS) for bond shifting in singlet **COT**. As is the case at the D_{4h} geometry of **CBD**, at the D_{8h} geometry of **COT** dynamic spin polarization results in the singlet state being calculated to be lower in energy than the triplet state (*16*, *17*), in violation of Hund's rule (*14*).

However, there is an important difference between **CBD** and **COT**. The equilibrium geometry of singlet **CBD** is a highly reactive, planar D_{2h} rectangle, but the equilibrium geometry of singlet **COT** is the kinetically stable, non-planar, D_{2d} tub, which is shown in Figure 1.

The reaction path down from the D_{8h} TS for bond shifting in **COT** to the D_{2d} equilibrium geometry bifurcates at the D_{4h} TS for ring inversion, since either of two tub geometries can be formed after bond shifting. In fact, the reaction path from the D_{8h} TS for bond shifting to the D_{4h} TS for ring inversion contains a valley-ridge inflection point, where the force constant for maintaining planarity in singlet **COT** changes from positive to negative (*101*). Therefore, in descending from the D_{8h} geometry of the TS for bond shifting to the D_{2d} equilibrium geometry, a **COT** molecule need not stay on the reaction path that leads to the D_{4h} TS for ring inversion. Instead, a planar, D_{4h} COT molecule can fall off the D_{4h} ridgeline into either of the D_{2d} valleys below.

Conversely, a D_{2d} **COT** molecule that undergoes bond shifting need not pass through the D_{4h} transition structure for ring inversion but can begin shifting its four double bonds before complete planarity is reached. Nevertheless, one can rigorously divide the energy required for bond shifting in D_{2d} **COT** into the energy required for passage through the D_{4h} TS for ring inversion plus the energy required for bond shifting, starting from the D_{4h} TS for ring inversion. No D_{2d} **COT** molecules may undergo bond shifting by exactly this pathway. However, it is convenient to think about the energy that is necessary to reach the D_{8h} TS for bond shifting as being the sum of the energy that is necessary to planarize the eight-membered ring, plus the energy that is necessary to shift the double bonds in the planarized, D_{4h} **COT** ring.

In fact, in separate NMR experiments, Anet elegantly measured the activation energy that is necessary, starting from D_{2d} **COT**, to reach both the D_{8h} transition structure for double bond shifting (*102*) and the D_{4h} transition structure for ring inversion (*103*, *104*). The difference of *ca.* 4 kcal/mol between these two activation energies is, of course, equal to the barrier for double bond shifting in planar D_{4h} COT. Therefore, if one could measure the difference between the energy of the singlet at the D_{4h} TS for ring inversion and the energy of the triplet at its D_{8h} equilibrium geometry, addition of 4 kcal/mol to the energy of the singlet

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would give the energy difference between the D_{8h} singlet and the D_{8h} triplet states of **COT**.

I thought that it should be possible to use NIPES to measure the energy difference between the D_{4h} singlet and the D_{8h} triplet. The **COT** radical anion (**COT**$^{\bullet-}$) is known to be planar (*105*); so the Franck-Condon factors for formation of non-planar singlet geometries from the planar radical anion should be zero. Of course, planar COT•– could not only lose a photoelectron to form the D_{4h} singlet, it could also lose a photoelectron to form the D_{8h} equilibrium geometry of the triplet. The difference between the kinetic energies of these two photoelectrons would be exactly equal to the energy difference between D_{4h} singlet **COT** and D_{8h} triplet **COT**.

At a Gordon conference I told Paul Wenthold, who was then a post-doc in Carl Lineberger's research group, about my proposed NIPES experiment on **COT**$^{\bullet-}$; and he agreed to try it when he returned to Boulder. He did the experiment, and it worked (*15*). In fact, it worked even better than I had expected.

As I had hoped, the NIPE spectrum of **COT**$^{\bullet-}$ showed a peak for formation of the equilibrium geometry of the planar triplet state and another peak for formation of the D_{4h} TS for ring inversion in the lowest singlet state of **COT**. However, in addition, 4.4 kcal/mol above the peak for formation of the D_{4h} TS for ring inversion was a pair of peaks. Their energy was in good agreement with the energy, expected from Anet's experiments (*102–104*), for the D_{8h} TS for double bond shifting (*16*, *17*). In addition, as Carl Lineberger pointed out, at energies near or above that of this D_{8h} TS, there should actually be two vibrational wave functions for antisymmetric C-C stretching, with slightly different energies (*15*). Thus, the NIPE spectrum provided direct measurements of the energies of not only the D_{8h} equilibrioum geometry of the triplet state and the D_{4h} TS for ring inversion of the singlet state, but also of the D_{8h} TS for double bond shifting in the singlet state.

From the separation of 0.36 eV between the lower energy of the two peaks for the D_{8h} TS for double bond shifting and the 0→0 peak for formation of the D_{8h} triplet state, the NIPE spectrum of **COT**$^{\bullet-}$ gives ΔE_{ST} = -8.3 kcal/mol in D_{8h} **COT**. The negative sign indicates that the singlet lies below the triplet in D_{8h} **COT**. At this geometry the NBMOs of COT are degenerate in energy. Therefore, the strictest version of Hund's rule is violated in D_{8h} **COT**, and it is violated by a very substantial amount of energy, > 8 kcal/mol (*15*).

$(CO)_4$ – An Apparently Closed-Shell Molecule with a Triplet Ground State

The story of how I became interested in cyclobutane-1,2,3,4-tetraone, $(CO)_4$ (*106*), starts with the finding by Dr. Xin Zhou, a post-doc in my research group, of a *very* large imaginary frequency in a molecule on which she was carrying out calculations. The explanation of her observation led to her performing calculations on other molecules that we expected would have very high-lying, highest-occupied (HO)MOs and very low-lying, lowest unoccupied (LU)MOs (*107*, *108*).

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Our papers on these molecules were read by Professor Rolf Gleiter. Rolf had been my host in Heidelberg, when I spent three, three-month sabbaticals there, as a Humboldt Senior Scientist. Rolf had published the results of some calculations on $(CO)_4$, which he had also found to have a very high-lying HOMO and a low-lying LUMO (*109*). He had also found $(CO)_4$ to be a computationally challenging molecule; and he, therefore, suggested that my group might consider performing some higher level calculations on it.

Professor Haijun Jiao had also carried out calculations on $(CO)_4$, and the results of his calculations were very surprising in predicting that this very ordinary-looking tetraketone might have a triplet ground state (*110*). The results of our own calculations, at several different levels of theory, also predicted a triplet ground state for $(CO)_4$ (*111*). However, like the results of Rolf (*109*) and Haijun (*110*), the lower-level calculations performed by us gave such widely different results that we were skeptical of whether the results of our highest-level calculations [CCSD(T)] could be trusted. Therefore, we took a different approach.

$(CO)_4$ has a very high-lying σ HOMO (b_{2g}) and a low-lying π LUMO (a_{2u}). These are shown in Figure 24. The singlet electronic state, in which a_{2u} is doubly occupied, is only slightly higher in energy than the singlet state in which b_{2g} is doubly occupied. Thus, it is understandable that some calculations predict a triplet ground state in which b_{2g} and a_{2u} are each singly occupied.

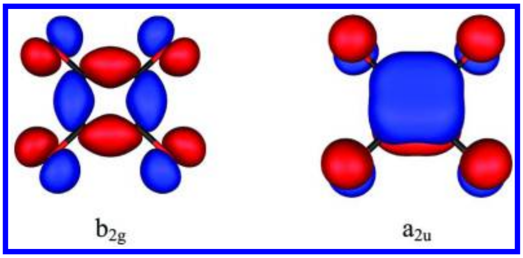

Figure 24. The two MOs that are singly occupied in the triplet ground state of $(CO)_4$. Reprinted with permission from Bao, X.; Zhou, X.; Lovitt, C. F.; Venkatraman, A.; Hrovat, D. A.; Gleiter, R.; Hoffmann, R.; Borden, W. T. J. Am. Chem. Soc. ***2012****, 134, 10259. Copyright 2012, American Chemical Society.*

The b_{2g} and a_{2u} MOs obviously have atoms in common. Therefore, if b_{2g} and a_{2u} had exactly the same energy, then Hund's rule should be obeyed (*12*, *13*); and the ground state of $(CO)_4$ should be the triplet. We calculated the energies of these orbitals in several different ways. For instance, we computed the *IEs* of the singly occupied MOs in the triplet at two different levels of theory. Based on the results of our calculations, our conclusion was that the triplet is the ground state of $(CO)_4$ (*18*).

Our paper was apparently read by Dr. Xuebin Wang, who tested our prediction by obtaining the NIPE spectrum of $(CO)_4^{\bullet-}$ (*19*). He generated the radical anion by electrospraying a solution of the dianion of the commercially available squaric acid $[C_4O_2(OH)_2]$ into the gas phase. In the gas-phase, the squarate dianion $(CO)_4^{-2}$ loses an electron and forms $(CO)_4^{\bullet-}$.

The NIPE spectrum of the radical anion is shown in Fig. 25 (*19*, *20*). Based on the large intensity of the lowest energy peak, Xuebin assigned it as belonging to the triplet, giving a value of ΔE_{ST} = 2.5 kcal/mol, with the triplet state lower than the singlet state. A value of this size was consistent with the results of high-level calculations, done by ourselves (*111*)and by others (*112*).

Unlike $(CO)_4$, $(CO)_3$, $(CO)_5$, and $(CO)_6$ are all calculated to have singlet ground states (*113*), as is $(CS)_4$ (*114*). Xuebin obtained the NIPE spectra of $(CO)_3$ (*115*), $(CO)_5$ and $(CO)_6$ (*79*), and $(CS)_4$ (*116*), and the spectra confirmed our prediction that each of these molecules has a singlet ground state. We collaborated with Xuebin on assigning all of the peaks in his NIPE spectra by computing the positions of the band origins and the frequencies and the Franck-Condon intensities of the peaks in the vibrational progressions in each band. The results of our calculations on the vibronic peaks in $(CO)_4$ are shown in Figure 25, under the experimental spectrum (*20*). They confirm Xuebin's original assignment of the triplet as the ground state of $(CO)_4$ (*19*).

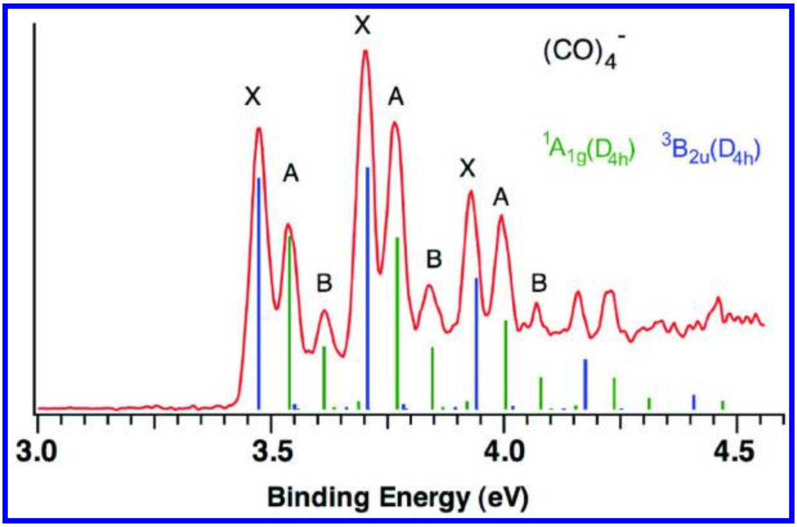

Figure 25. The NIPE spectrum of $(CO)_4^{\bullet-}$, with the simulated vibrational structure superimposed onto the experimental spectrum. Note that only two electronic transitions, i.e., to the $^3B_{2u}$ ground state (blue lines) and to the low-lying $^1A_{1g}$ excited state (green lines) were used in the simulation. The simulation shows that the B peaks are not due to a third electronic state (19), but are part of a vibrational progression in the symmetrical C-C stretching mode in the closed-shell, $^1A_{1g}$ state. Reprinted with permission from Bao, X.; Hrovat, D. A.; Borden, W. T.; Wang, X. B. J. Am. Chem. Soc. ***2013****, 135, 4291. Copyright 2013, American Chemical Society.*

Asking why the ground state of $(CO)_4$ is the triplet is equivalent to asking why the b_{1g} and a_{2u} MOs are accidentally degenerate in energy (*18*). Both MOs can be viewed as being the in-phase combinations of the C-O π* orbitals of four

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CO molecules (*113*). Normally, one would expect the σ overlaps of the 2p-π AOs in b_{1g} to provide more C-C bonding than the π overlaps of 2p-π AOs in a_{2u}; and this probably is the case in $(CO)_4$ too.

However, in $(CO)_4$, in addition to the 1,2 interactions between AOs on adjacent carbons, there are also substantial 1,3-interactions between 2p AOs on pairs of carbons across the diagonals of the four-membered ring. As can be seen in Figure 24, these 1,3-interactions are bonding in a_{2u}, but antibonding in b_{2g}. It appears that the difference between the favorable 1,3-interactions in a_{2u} and the unfavorable 1,3-interactions in b_{2g} almost exactly balances the greater strength of the 1,2-σ interactions in b_{2g}, compared to the 1,2-π interactions in a_{2u}. It is this accidental balance between the sizes of two different types of C-C interactions that leads to the b_{2g} and a_{2u} MOs of $(CO)_4$ having almost exactly the same energy (*113*) and, hence, to this molecule being both predicted (*18*) and found (*19*, *20*) to have a triplet ground state.

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Future Research on Diradicals

It is traditional to end a scholarly treatise on a field of chemistry with some predictions about the future evolution of the field. However, there is a Danish saying, "It is difficult to make predictions, especially about the future."

These words of wisdom have been attributed to a diverse group of famous people, including Nostradamus, Mark Twain, Niels Bohr, Samuel Goldwyn, and Yogi Berra (*117*). I believe in the truth of this saying, even if none of these wise men ever said it. In fact, I just authored a journal article entitled, "The Unpredictability of Research Directions… in Physical-Organic Chemistry" (*106*). Therefore, I would not only be foolish, but also hypocritical, if I ventured to make any predictions about the future evolution of the field of diradicals.

However, I do feel secure in making some predictions about the near-term future of my own research in this area of chemistry. These predictions involve collaborative projects with Xuebin Wang that we have either discussed or have already begun.

By electrospraying solutions of the dianions into the gas-phase, Xuebin has the ability to generate the corresponding radical anions and to obtain their NIPE spectra. He has successfully generated the following radical anions in this manner: $(CO)_n^{\bullet-}$, with n = 3 (*115*), 4 (*19*), 5 and 6 (*20*), $(CS)_4^{\bullet-}$ (*116*), and **MBQ**$^{\bullet}$- (*10*, *11*). Adding to this list of organic radical anions is easy; one has only to think of acids that are strong enough to form dianions. Three that come to mind immediately are the bis-enol of 1,2,4,5-cyclohexanetetraone, oxalic acid, and carbonic acid.

Electrospraying the corresponding dianions into the gas-phase, should result in electron loss, leading to formation of **TOTMB**$^{\bullet-}$, **TOTME**$^{\bullet-}$ and **TrOTMM**$^{\bullet-}$. Ejection of a photoelectron from the radical anions thus formed, would give the oxygen containing diradicals shown in Figure 26. They are, respectively the tetraoxo (**TO**) derivatives of **TMB**, **TME**, and the trioxo (**TrO**) derivative of **TMM**.

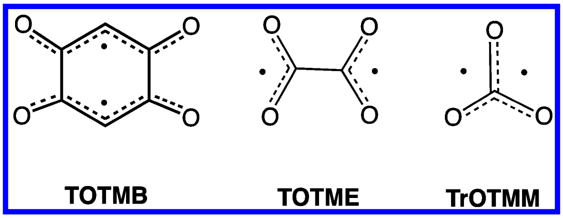

Figure 26. Three diradicals in which oxygens replace the CH_2 groups of, respectively, ***TMB****,* ***TME****, and* ***TMM****.*

Xuebin has already obtained the first NIPE spectra of **TOTMB**$^{\bullet -}$ and **TrOTMM**$^{\bullet -}$ radical anions, and my group has completed calculations on both the **TOTMB** and **TrOTMM** diradicals. The results of our calculations and Xuebin's experiments may have already been published by the time that this chapter appears.

Acknowledgments

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Subject Index

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