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A Perspective Distilled from Seventy Years of Research

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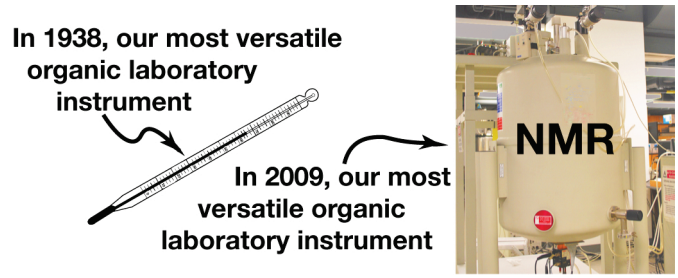

Physical organic chemistry might be regarded as officially recognized as a distinct discipline through the publication of L. P. Hammett's book of that title, although substantial earlier work can be traced back to the turn of the 20th century. Many of the instrumental tools that helped the discipline develop in so many different ways began to appear in the late thirties and during World War II and were soon built to be increasingly operated in the "hands-on" mode. This development became very popular in academia, where instruments are not operated for you by an expert, but even if you are an undergraduate, you can more or less be the expert yourself and take many varieties of data on instruments usually available on a 24 h basis. It has been my privilege and joy to begin research in chemistry just as these waves of change began to grow and to savor the great contribution that the new methods, such as measurement of ^{14}C, UV−vis, IR, NMR, and hands-on use of computers, made in facilitating our research programs at MIT and later at Caltech. Among those programs, which will be discussed, were ^{14}C tracing of carbocation rearrangements and benzyne formation, electrical effects of substituents, Grignard reagents, synthesis of small-ring compounds, (2 + 2) cycloaddition reactions of halogenated ethylenes, assisting in development of ^{19}F, ^{13}C, and ^{15}N NMR for conformational analysis, other structural, kinetic, and tracer studies, as well as helping through textbooks to bring Hückel MO theory and the elements of NMR to familiarity for organic chemists. From the very beginning of my research career, I have been the beneficiary of personal mentoring which has been very crucial to my success in research and is an important theme in what follows.

Introduction

The hundred years since the founding of the American Chemical Society's Division of Organic Chemistry has constituted an extraordinary period of progress in our science.

The prior hundred years was largely characterized by the slow, but intellectually very challenging, exercises of deducing structures of organic compounds from analysis of products of degradation reactions. No help was available in those years from the instruments and theoretical tools developed in the subsequent hundred years, which ushered in what we might call the modern era, in which extraordinary rapid progress has been made in all areas of chemistry.

My life of 90 years has spanned much of the past 100 years, and so much has been written already about the modern era that it may seem fatuous to believe there would be sufficient interest for someone to write about their personal experiences of living through the extraordinary changes, which took place

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with almost dizzying acceleration beginning in the years not much before when I started research in 1938. In the first 30 or so years of our 100-year period of interest from 1908 to the present, much of organic chemistry continued to develop relatively slowly in synthesis and structural determination essentially in the same way as in the previous hundred years. However, new and very important approaches to chemistry were germinating in this period: applications of quantum mechanics to molecules, development of X-ray diffraction of crystals to determine molecular structures, early explorations of molecular spectroscopy, and studies of kinetics and mechanisms of chemical reactions.

However, few, if any, of those important beginnings were really available for what could be called "hands-on" use by organic chemists. Instead, one had to find a specialist and have him or her (seldom her in those years) carry out the desired experiments and interpret the results, if any.

In what follows, I will try to explain how my early interest in chemistry developed and how it was greatly enhanced over many years by a series of wonderful mentors. Indeed, I believe that my example shows how mentoring, especially in research, can be vitally important to the development of enthusiasm and breadth of interest for undergraduates. On the one hand, mentoring can help keep them from becoming too narrow and specialized in their subsequent careers and, on the other hand, help to develop their research talents, independently of deficiencies in academic excellence as defined by course grades.

Reflections on Life before University

I was born June 8, 1918 in Los Angeles. At the time, my father was a diary farmer near the town of Puente, a life he enjoyed but was not very attractive to my mother who was the daughter of a prominent and successful physician in Peoria, IL. My father was also from Peoria, and I believe they may have first met at popular picnics held periodically in the Los Angeles area for expatriates from Illinois. My parents (Figure 1S, Supporting Information) were very strong for education, and my father attended Bradley College in Peoria where he had some renown as a basketball player. One of the features of my early life was to go with my parents, brother, and sister to the local public library and stock up with a week's worth of books. Time for reading in the evenings came easily in an era of no TV, minimal radio, and no computers. Reading library books brought in many ideas of the wonders of general science around the start of junior high school, heightened by the then immense public interest in Albert Einstein and his ideas of relativity, particularly associated with his three-month stay at Caltech in 1931. I suffered some personal depression about 1928 as a result of an infection that permanently destroyed much of my hearing. However, to a degree the depression was ameliorated by my immersion in books like Paul de Kruif's *Microbe Hunters*, published in 1926.[1] My first real encounter with organic chemistry came in 1933−34 from Edwin Slosson's 1919 *Creative Chemistry*. Of the various Slosson chapters, my favorites covered much on organic structures, coal-tar products, perfumes and flavors, carbohydrates, cellulose, rubber, polymers, and medicines in a knowledgeable, interesting, and understandable way.[2]

A large factor in my interest in chemistry also came from the Porter series of Chemcraft sets, and despite the financial stresses of the Great Depression, my parents indulged my working up to near the top level of Porter's sets (Figure 2S, Supporting Information), which were actually quite safe and sane. The Porter sets were quite different from the later dumbed-down chemistry sets, dictated by a fervor of litigation fears, namely to be sure no possible harm could be done. My parents helped and encouraged me in the study of chemistry, although as I progressed, my mechanically skilled father occasionally admonished me, "Why don't you invent something?"

During this period in the early thirties, one of my maiden aunts would chauffeur me about 20 miles to take in Caltech's annual all-day open-house sessions for anyone interested. The exhibits featured their new wind tunnel, liquid−air demonstrations, and a high-voltage lab with displays of million-volt discharges of direct and alternating currents, but best of all for me were the vivid demonstrations of Caltech's breadth and depth of its program in organic chemistry.

Undergraduate Work at UCLA

My scientific interests led to my being involved as a laboratory and teaching assistant in a beginning science course in junior high school and for classes in physics in a Los Angeles high school. Despite these activities, I was generally a B student and was worried about admission to college. My mother wanted me to apply to Caltech and wrote a letter to R. A. Milliken, who replied, "Send him over", but I knew I would not be able to survive Caltech's math and physics and applied instead to UCLA. My parents were supportive of this decision and my understanding with them was that I could live and eat at home, but I was expected to work and earn all of my other living and college expenses. For two years, I did that through employment at night as a salesperson in the stores of a large bakery chain. After that, I worked for UCLA as a teaching assistant and in the chemistry stock room.

I was admitted to UCLA in 1936, but at the time it was far from the UCLA of today. With a new campus in 1932, it had just a few buildings; one for chemistry and geology combined, probably no more than 5000 undergraduates, and no Ph.D. programs, although a smallish M.S. program was operating. One of the chemistry M.S. candidates was Jerome Vinograd, my Teaching Assistant (TA) in general chemistry, later a very well-known researcher on DNA structure, a faculty colleague at Caltech, and a member of the National Academy of Science (NAS).

Of course, Berkeley was then the kingpin of the University of California system and not eager to cede a Ph.D. program to UCLA. Nonetheless, the junior branch had a number of excellent younger chemistry faculty who were eagerly awaiting the setting up of a Ph.D. program, which finally arrived about 1943. Actually for me, the status of UCLA in 1936 could not have been better, as will be seen later.

Chemistry at the university level started for me with General Chemistry, and with the knowledge I had already accumulated, it was rather easy in the first semester. The second semester was a different story with the laboratory work directed to qualitative inorganic analysis, with separations of metal ions based largely on hydrogen sulfide precipitations. These required gaining some expertise in acid−base equilibria and solubility−product calculations, for which I was not prepared. They did not come easily, which helped to knock out the overconfidence characterized by my first semester's work.

In moving on to the second year of Analytical Chemistry, I got off to an inauspicious late start; laid up for 10 days by a flu attack and having missed the knowledge provided in the opening

lectures, I was not ready to achieve an acceptably precise value in an acid titration of a base solution supplied as an unknown. The professor, William R. Crowell (Figure 3S), closely monitored each student's progress with care and, when he came by and inspected the erratic values in my laboratory notebook, he said, "You note that this titration was done with a buret, I could do better with a graduated cylinder!" But he took time then and later to assist me and became the first of several mentors at UCLA to help advance my career. A highlight near the end of Crowell's course was to choose from a list of research-like experiments. Mine involved a titration requiring an oxygen-free atmosphere. Because the nitrogen in cylinders of those days was not oxygen-free, the gas had to be purified, and in Crowell's lab that meant being passed through chromous solution in a spiral bubbler. When I asked him where I could get a spiral bubbler, he replied, "I don't have one now, but you could make one in the glass-blowing shop, I will get you a key if you are willing." I was more than willing, indeed eager, and spent every spare moment afterward learning how to make spirals out of soft glass tubing, joining different sizes of tubing and making ring seals. And I got a rather crude bubbler made, but too late to use in the desired experiment.

This was a crucial turning point in my career, because I realized that for once I could do something that none of the fellow students in my class had learned to do. Crowell seemed impressed and asked if I wanted to do research with him in the summer on potentiometric titrations. Then, at the end of the summer, he invited me to be a TA for the next year's analytical course for which there were no available M.S. candidates to help. At that point, I became a professional chemist earning $10/month, and with the ever-present need for TA assistance, I had the privilege to be a TA in four different courses by the time I graduated, which helped solidify a firm ambition to sometime become associated with an academic institution.

The goal of the potentiometric titration research in the summer of 1938 was to distinguish bromide and chloride in water using silver nitrate solution. It did not work because of the extreme insolubilities of the silver halides. So in the fall of that school year, Crowell put me to work on the kinetics of osmium catalysis of the reaction of perchloric acid with bromide ion at 100 °C in sealed glass tubes. This project worked out well and was the subject of my first paper, of course written by Crowell.[3] Caltech's Don Yost was a coauthor because he had suggested that Crowell work on osmium after a prior cooperative effort on ruthenium catalysis of the same reaction.

Another UCLA mentor of note was Charles Coryell (Figure 4S), Instructor of Physical Chemistry, who was coming off a 1935 Ph.D. with Linus Pauling at Caltech, with whom he established the paramagnetism of oxyhemoglobin. Coryell was a truly inspiring teacher; always looking for ways so that eager undergraduate students could break out of the routine physical chemistry lab work. My laboratory partner in the course was Bill McMillan (Figure 5S); we were eager, and the result was that, over a semester of Coryell's lab course, McMillan and I did only one of the regular experiments.

Our first foray was to determine the thermodynamics of dithionite ion, and Coryell wanted us to do that by measuring the heat evolved in its reaction in a Dewar flask with ammoniacal silver nitrate. The educational purpose was to learn to use the Beckmann thermometer, which could be read to 0.01°. The result of Coryell's exuberance, with a Dewar flask named as a "vacuum-jacketed calorimeter", was a small but nice JACS paper with McMillan and me as coauthors.[4] Later in the lab course, Coryell suggested we construct an apparatus for measuring dielectric constants so we could determine the dipole moments of a series of alkyl acetylenic ethers prepared by his UCLA colleague, Tom Jacobs (Figure 6S). This was a tough assignment, but McMillan knew how to set up the needed electronics, while I used my glassblowing skills to craft the measuring cell. We got it to work, and the results were also published in JACS.[5]

A very important mentor for me was Professor of Organic Chemistry G. Ross Robertson (Figure 7S). Robertson was quite unusual among chemistry professors I have known. Rather than promoting his synthetic and laboratory expertise, he gave simple, very clear, but quite self-effacing lectures that led to student confidence that they not only understood what was presented and, even more, imparted the feeling that they could actually be ahead of him on what he was going to say next. Robertson wrote a very excellent organic chemistry laboratory manual,[6] which besides being clear with well-tested experiments introduced physical principles for understanding topics such as phase problems encountered in crystallization, vapor pressure, drying agents, and azeotropes. Robertson seemed almost always available for consultation and spent hours criticizing my early scientific writing, as well as demonstrating very helpful techniques for making clear scientific illustrations. However, best of all, rather than accepting my request to undertake undergraduate research with him, he insisted I should aim for higher level organic research with William G. Young (Figure 8S) and Saul Winstein (Figure 9S).

In looking for an undergraduate research project, I met with Young and Winstein together. Young suggested working on the butenyl Grignard reagent, which up to then was a structural enigma, best known for giving a mixture of butenes with water.[7] The tough question was whether the mixture of butenes was formed by rearrangement reactions from a single static Grignard reagent or without rearrangement from the individual members of an equilibrating mixture of 1-(2-butenyl)- and 3-(1-butenyl)-magnesium halides, where the composition of the butene mixture depended on the relative reaction rates of water with each of the two isomeric forms. However, Winstein wanted me to finish off and extend his earlier ideas on the mechanism for displacement reactions of butenyl chlorides.[8] Young deferred to Winstein, and this was fortunate because I could then use much of what I learned of kinetics and running reactions in sealed tubes while studying osmium catalysis with Crowell. As I found out later, I did not really have enough organic laboratory experience to work on the Grignard problem at that time. Looking for the S_N2' mechanism through correlation of kinetics and reaction−product-investigations turned out to be a full-year project, and it was a great experience to be exposed to Winstein's thoroughness and rigor. At the time the project started, Bill Young became department chairman and he invited me and Bill McMillan to use his personal laboratory, day and night, for our respective projects with him and our joint physical chemistry laboratory research. The solvolysis project turned out very well, with no S_N2' involvement under the chosen conditions and solvents. It was very rewarding in that, while I would only receive my B.A. degree in June, Young and Winstein invited me to present a paper covering my work at the 1941 ACS Fall Meeting in Atlantic City.[9]

In the spring of 1941, Robertson and I spent some mentoring time discussing possible graduate schools. "Columbia is too

physical, the right school for McMillan", "Harvard won't take you", "Illinois is too synthetic", "Wisconsin might be OK", but "Penn State with F. C. Whitmore, a carbonium-ion researcher sounds good." Applications were made to both Wisconsin and Penn State, but as stated, while my research record was good, my grades were hardly breathtaking. Ultimately, Wisconsin said NO, Penn State, YES! So off to Penn State I went, by train via the ACS Meeting in September 1941, but never having been out of California before and with winter coming! At the time, I did not even own a winter coat, but I did have the advantage of taking with me UCLA 's extensive mentoring in both research and teaching.

Graduate work at Pennsylvania State College

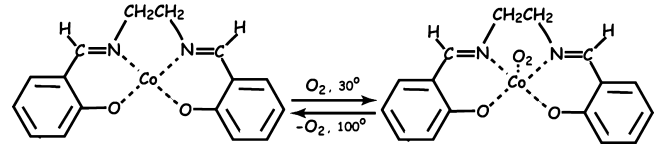
Penn State and Frank C. Whitmore (Figure 10S) were wonderful on all accounts, even though at first, Whitmore would not take me a as a graduate student—I had to make it over some hurdles of grungy work he wanted finished, I guess to test my resolve. However, although my Penn State career started off very well, it suddenly went off the tracks when I sat down to a radio to listen to a former grammar-school chum, Eugene List, play a Beethoven piano concerto with the New York Philharmonic on December 7, 1941, just at the time the attack on Pearl Harbor was announced.

As a raw new graduate student, it was unclear what I would or could do in those circumstances. Fortunately, Young and Winstein were attending the National Organic Chemistry Symposium at Ann Arbor, MI, and I scraped together enough money to take the train and meet them at the Symposium for advice and counsel. They were then in the process of setting up a National Defense Research Council (NDRC) war research project. They invited me back to UCLA to work on it, and I was pleased to accept. The highlight of the Symposium for me was to hear Moses Gomberg, who discovered the stable triphenylmethyl free radical, as the after-dinner speaker talk about his life and enduring the criticism heaped on him from those who were sure free radicals would be far too reactive to exist for an extended time in solution.

Of course, going back to UCLA meant leaving Penn State, where I had made many friends, among them, Harry Mosher, later to Stanford, Leo Sommer, later to the University of California, Davis and Harold Hart, later to Michigan State. Giving up on Frank Whitmore as a thesis advisor was sad, but in subsequent years, we had an excellent relationship that lasted until he passed away rather young in 1947. Penn State made two long-lasting impressions on me. One was to be exposed to Whitmore's research—its style, breadth, ingenuity, and the kind of chemical questions in which he was interested. The other was fractional distillation and how, with my glass-working experience, I could make substantial fractional distillation columns complete down to manufacturing the glass helices favored then as column packing.

War Research at UCLA

Theodore A. Geissman (Figure 11S), a tough-minded natural products professor from the Roger Adams Laboratory at the University of Illinois, supervised the UCLA war project. The goal was to develop procedures for extracting oxygen from the air at low pressure to eliminate pressurized oxygen tanks in bombers at high altitudes, susceptible to missiles from attacking defensive aircraft. The chemistry was based on that of "Salcomine".



Salcomine was a cobalt salicylaldehyde ethylenediamine complex which absorbed oxygen from the air at room temperature and turned black and then on heating to 100 °C released the absorbed oxygen and turned light brown. The reaction cycle could be repeated 50−85 times before degradation was so severe as to render the process inefficient. The degradative process could well have involved singlet oxygen, but that kind of reaction was not known at the time. The operating temperature range was excellent for the purpose of extracting oxygen from the air, but besides some degradation in each cycle, the O_2 absorption rate was regarded as not fast enough. My job on the project was to synthesize other aldehydes to try, under the direction of our extraordinarily talented "foreman", Maurice J. Schlatter, a Caltech Ph.D. with Edwin R. Buchman. As the program progressed to a pilot plant stage in Philadelphia, I was assigned to analyzing degraded Salcomine samples to find which of the components used in their preparation were the most vulnerable to attack by the emitted oxygen.

At this point, a very short detour came about, because a year after returning from Penn State, there was this highly intelligent and lovely female, Edith Johnson (Figure 12S), who went to the same high school as I did, starting seven years earlier, and it seemed like a good time to get married. Thereby, over the years another proof of the old maxim "behind every successful chemist there is a good wife" was supplied. The marriage has lasted 67 years and produced four talented children and nine comparably talented grandchildren.

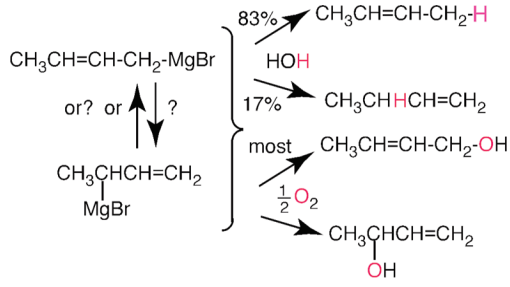
The Salcomine project was finally abandoned when Samuel C. Collins of MIT invented a portable, efficient air liquefier that could be used to provide liquid oxygen for military use. But before this, Geissman inhaled a toxic dose of Salcomine in an explosion in a pilot plant and never really recovered fully from the exposure. As a result, his subsequent chemical research program was necessarily much lower key than expected from his earlier brilliance. We did, however, publish some of the chemistry developed related to Salcomine.[10]

The war period was hectic in the sense of recognized need to get whatever was requested done, and pursuant to this, an ancillary and interesting task was our unknowing participation in assembling small incendiary bombs for the highly secret "bat-bomb" project. The plusses in participating in the NDRC research for me were several; perhaps foremost was the intense training in organic synthesis provided by Maury Schlatter, a thorough literature search mandated by Geissman of the potential value of aromatic metalation for synthesis of salicylaldehyde derivatives (to be discussed later), and the opportunity to sit down with Saul Winstein every week or so to talk about his expanding interests in physical organic chemistry as a bit of relief from his contribution to the war effort working on antimalarial drugs.

Graduate Work at UCLA

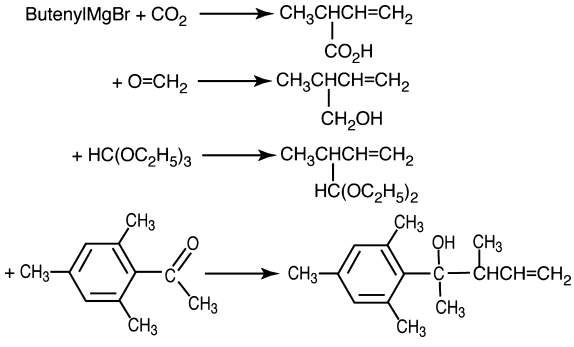
So with the wartime experience, it was on to graduate school, having a well-equipped lab left over from the war project all ready to go and with Bill Young still wanting to have someone

solve the structural problem posed by butenylmagnesium bromide. This turned out to be a great thesis problem. However, all that was really known at my starting time was that preparation of butenylmagnesium bromide gave mixtures of products with water[7] and oxygen. It was also known that the Grignard reagent prepared from the pure primary, the pure secondary, or the equilibrium mixture of butenyl bromides (87% primary, 13% secondary) gave the same mix of butenes when hydrolyzed.



With my thesis research based on determining what products are formed from the addition of butenylmagnesium bromide to carbonyl compounds, a key experimental issue was how to analyze the product mixtures.

In the preceding few years before the mid-1940s, sparked by growing interest in products derived from petroleum, substantial progress had been achieved in fractional distillation methodology, allowing for quite precise analysis of many distillable liquid mixtures. Podbielniak was the gold standard of fractionating columns at the time. Borrowing on my Penn State experience, I designed and put together an automatic fractional distillation setup featuring a "Pod" column in anticipation of analysis problems (Figure 13S). It was automated in the sense that it ran unattended and did that with different choices of input parameters. This distillation system, which took most of a summer to build, ended up being very helpful but was actually not essential because, in contrast to its reactions with oxygen and water, the butenyl Grignard reagent gave only single products containing secondary butenyl groups in reactions with a variety of electrophilic carbon addends.[11−14]



That one product should be observed with each addend, instead of a mixture, coupled with addition forming only the secondary and not the primary butenyl group was a surprise, especially with acetomesitylene, which gave an excellent yield. Indeed, all the other organometallic compounds that had been allowed to react with the acetomesitylene, following hydrolysis, led only to recovery of starting material, enolization of the acetyl group being the sole reaction pathway.

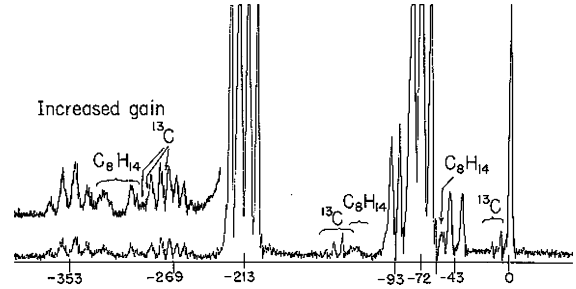
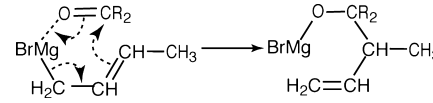


FIGURE 1. NMR spectrum of butenylmagnesium bromide in ether at 60 MHz and 25 °C. The Grignard resonances were assigned: −43 Hz, α-CH_2 doublet; −93 Hz, δ-CH_3 doublet; −269 Hz, γ-CH quintet; and −353 Hz, β-CH quartet. Other resonances are of octadienes formed by halide−Grignard couplings. The scale here is negative from TMS to correspond properly to the signs of the shielding constants.

In my Ph.D. thesis, I suggested that the primary isomer of butenyl Grignard was most likely to be the favored form. My arguments for this conjecture were that the primary isomer should be more stable by having the more C-substituted double bond and that an excellent cyclic mechanism could be envisioned for addition to carbonyl groups in nonpolar solvents.



When published,[15] our conclusions were disputed in 1954 by Kharasch and Reinmuth,[16] who were well-known for their extensive work and mighty tome on Grignard reagents. They claimed that only a physical method could really deliver the goods on the structure. That statement was indeed true, but physical methods useful for Grignard structures were just not available in 1944−1946.

However, 15 years later, NMR spectroscopy could and did solve the problem, as shown by the proton spectrum shown in Figure 1. The shifts and couplings mandate primary (≥95%), with apparently rapid rotation about the C2−C3 bond and therefore rapidly equilibrating between the primary and secondary forms.[17] Of course, according to Curtin−Hammett kinetics, in principle, even the minor component of a rapidly equilibrating mixture could lead to the major product. However, as stated above, we hypothesized that the predominant primary form of the Grignard reacts faster by way of the cyclic mechanism.

Postdoctoral Period at UCLA

After finishing my Ph.D. in 1944, I was hired by UCLA as an instructor to teach analytical chemistry to interested U.S. Navy students in residence at the time and could retain my laboratory to do independent research. I had been reading the first edition of my earlier mentor, Frank Whitmore's *Organic Chemistry*, a most unusual book full of mentions of bizarre compounds and reactions, that he characterized himself as a "one volume Beilstein for practicing organic chemists."[18] (This edition should not be confused with a later one compiled by his students more in the format of a standard organic text.[19]) I was intrigued by Whitmore's conclusion that "cyclopropanol apparently cannot exist." Such statements are always a challenge, and one has to decide what the conditions should, if any, be chosen for determining "existence." I am sure Whitmore meant it would not be stable at room temperature, perhaps

isomerizing, reacting with oxygen or water, possibly not distillable. So, I resolved to see if it could be made and isolated, in accord to what I thought were Whitmore's criteria for its "existence". Oxidation of cyclopropyl Grignard reagent looked like a reasonable approach but required a cyclopropyl halide, which one could not then buy, although cyclopropane (widely used as an inhalation anesthetic at the time) was quite available. At this point, I decided to test out the idea of initiating a major program on small-ring compounds and begin by making a lot of cyclopropyl chloride as an entry to a variety of compounds. Gustavson[20−22] had chlorinated cyclopropane and shown that the 1,1-dichloro compound was the major product. This meant that the monochloride reacted faster than cyclopropane itself and that excess cyclopropane was needed in the chlorination process. To achieve this, I built an apparatus (Figure 14S) which had a high ratio of cyclopropane to chlorine in the chlorination zone and recycled the cyclopropane. Distillation separated the mono- from the dichloride and some chloropropenes, leading finally to about a hundred grams of cyclopropyl chloride.[23] An unexpected windfall arrived when another useful starting material for synthesis of cyclopropyl derivatives, methyl cyclopropyl ketone, appeared on the market in quantity as a byproduct of synthesis of an antimalarial drug.

Conversion of cyclopropyl chloride to the corresponding Grignard reagent was not easy (later Whitmore told me that one of his graduate students had tried unsuccessfully), but after using almost every trick I could think of, it did form and with oxygen gave reasonably stable cyclopropanol. When I bragged about this to Tom Jacobs, I was much deflated when he pointed out that a preparation had been reported few years before from an ethyl Grignard transmetalation of 3-chloropropylene oxide, followed by ring closure.[24,25]

One of my objectives in the small-ring arena was to add to the physical and reaction evidence that indicated, or not, the resemblance of cyclopropane rings to C=C double bonds. One way to do that was to see if the cyclopropane ring would appear to accept an electron-pair from an electron-pair donating substituent by resonance and thereby reduce the compound's dipole moment, in the same way as postulated for similarly substituted double bonds and aromatic rings by Linus Pauling and others. This situation was investigated in a fun collaboration with Max T. Rogers, later of Michigan State, but at this point in time appointed as an instructor at UCLA as a temporary replacement for Charles Coryell, who had gone off to later substantial fame for his work at Oak Ridge National Laboratory. Our collaboration was successful in that the expected effects on the dipole moments were observed for the cyclopropyl compounds used in our study, although they were understandably smaller than for corresponding vinyl compounds.[26]

NRC Fellow and Instructor at Harvard, 1945−46

With helpful encouragement from Paul D. Bartlett (Figure 15S), I applied for and received a National Research Council (NRC) Fellowship for a year to go to Harvard and continue independent research with Bartlett as sponsor in the fall of 1945. The city of Cambridge was initially a bit hard to get used to, particularly because there were was great difficulty in getting acceptable housing. However, Edith solved that problem and soon winter came, and in the late 1940s, quite a few years before global warming began to be felt, the winters were rather severe. On the chemistry side, Harvard was a fantastic place to round out one's education, especially coming from UCLA where there was relatively little academic synthetic chemistry and with few seminars from eastern U.S. or European speakers able to provide a world view of where chemistry might be going in the years ahead. Along with these advantages, there was wonderful mentoring and experience provided by Paul Bartlett and his broad approach to physical organic chemistry, which went far beyond what most of us took to be current knowledge of organic chemistry.

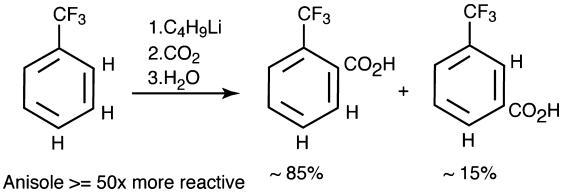
Besides Bartlett, there were two other outstanding and influential organic chemists at Harvard. One was Louis F. Fieser (Figure 16S), and the other, Robert B. Woodward (Figure 17S). These worthies were very different kinds of professors. Fieser (with his wife, Mary) turned out excellent organic textbooks, which drew some but not much from the then current knowledge of physical organic chemistry, even though Howard J. Lucas (Figure 18S) of Caltech published his *Organic Chemistry* in 1935, which broke new ground in bringing in physical principles at least five years earlier.[27] Fieser was a renowned experimentalist, the inventor of Napalm, heavily involved in the "bat-bomb" project mentioned earlier, and was a wonderful role model for any organic chemist with a yen for doing a lifetime of personal laboratory work.

Woodward did some laboratory work for his MIT thesis, but I never heard of any later on. But he was an omnivorous reader and was an excellent planner of syntheses to which he applied the best mechanistic and physical theory he could. He was a treasure for the postdoctoral fellows during my time at Harvard in that he loved to pontificate and match chemical wits with any group that assembled in his office until very late at night. His many idiosyncrasies have been well-documented by others, but many of us liked to say, "He never got drunk, he never got tired and he never perspired." However, over the years that I knew him, at one time one or other, this statement of his "virtues" became incorrect. While I never worked for, or with him, I felt he did mentor me with regard to never accepting simple explanations for phenomena that did not ring true in all respects, but instead looked for the unusual. He also validated my determination not to choose research problems where one could foresee what the results would be. If I can find an interesting reaction or a compound for which, after a lot of thinking and reading, I have no idea as to what the mechanism or structure would be, that is my ideal of a problem to work on. To be sure, such problems may well have trivial solutions, which I missed in my initial analysis, but over the years very few of them turned out that way.

I did not do much laboratory work at Harvard. A lot of my fellowship time was spent in discussions with the extraordinary students, postdoctoral fellows, and staff residents in 1945−46. These included George Hammond, Gardner Swain, Harry Wasserman, Sidney Ross, Charles Heidelberger, and Bernt Witkop. Indeed, nothing cut more into my experimental time than hours of heated discussion with my laboratory partner, Elliot Alexander, a Bell Postdoctoral Fellow from the University of Illinois. Elliot was a very ambitious, chemically conservative in the best Illinois tradition of the time. There was practically no subject one could mention in our lab that did not lead to discussion, except possibly "It is hot outside". Our wives, who became very good friends, fortunately ameliorated the impact of our disagreements. After a later brilliant start as a faculty member at Illinois, Elliot and his wife were killed when a plane

he was piloting crashed in Pennsylvania, after he ignored bad weather warnings for his projected destination.

When I did do laboratory work, it was mainly on solvolysis reactions[28,29] and stockpiling small-ring intermediates for my projected future research. One morsel of research carried out in collaboration with fellow postdoctoral, David Y. Curtin, that turned out to be very helpful later on with benzyne chemistry was metalation of benzotrifluoride with butyllithium. This was a type of reaction that I had previously researched the literature to find possible routes to new salicylaldehyde derivatives.



Shortly after the manuscript[30] was sent out by the ACS for review, Professor A. A. Morton of MIT visited at Harvard and identified himself as a quite dissatisfied Reviewer, who in his own research had reached the conclusion that metalation was basically an initial electrophilic attack of a metal cation on the aromatic ring. This notion had suggested to us exploration of the result of formation of a *meta*-substitution product when a *meta*-directing group, like trifluoromethyl, was involved. Morton was not happy about our comments as to how our experimental results compared to expectations of the result of *meta*-electrophilic attack of a metal ion on benzotrifluoride, as well as our invasion of his research area.

My career as a Harvard Instructor was brief. Louis Fieser had undergraduate academic advisees who needed a one-semester course in physical chemistry to get into medical school, so he arranged for me to give a course for them. Whether this did the students any long-term good or not, besides getting into medical school, is unclear. However, it was very helpful for me to tighten my knowledge of basic physical chemistry. An example of self-mentoring that most often occurs for me is when preparing lectures for a new course to teach.

Up the Academic Ladder at MIT, 1946−53

In the spring of 1946, I had a visit from Arthur C. Cope (Figure 19S), Head of the Department of Chemistry at MIT, who asked if I would be interested in an instructorship at MIT starting in the fall. I told him I was interested but suggested that he could well have difficulties with Professor Morton over appointing me. However, he said he did not care about that. I was myself conflicted, because I had hoped to return to the west coast and had visited and talked to faculty at Stanford and Berkeley about a position. Berkeley seemed like a great opportunity, because I had dreams of taking up after Sam Rubin and Martin Kamen on the fixation of carbon dioxide in photosynthesis. These hopes were dashed when the Dean, Wendell Latimer, told me that Melvin Calvin had already moved into the vacancy left by Rubin's untimely death from an unfortunate accident with phosgene. However, Paul Bartlett, Bill Young, and others counseled that I accept the MIT position, so I did. This despite some misgivings by Woodward (a MIT Ph.D.) as to whether MIT organic chemistry was going to really recover from a slump over the previous decade. Stanford made an offer some months later, but I was already committed then to MIT.

Cope had ambitious plans for revitalization of MIT organic chemistry and made appointments of John C. Sheehan (Figure 20S), at Merck, C. Gardner Swain (Figure 21S), who then had a fellowship to Caltech, and me to assist in the process. These appointments did not sit too well with the existing organic faculty, especially Avery Morton, but Cope kept a firm hand on the tiller and, with his wife Bea, provided a warm social environment.

Swain and I both were interested in physical organic research, except that I tended to follow the Bartlett approach of synthesizing compounds that I thought would be of physical organic interest, while Swain mostly followed the example of Louis P. Hammett using a more physical chemical approach. We enjoyed a lively joint common weekly evening seminar and also participated vigorously in Bartlett's Friday afternoon seminars at Harvard that often featured distinguished visitors, one of the best remembered being the indomitable Michael J. S. Dewar (Figure 22S), then of Queen Mary College in London. Dewar arrived shortly after publication of his *The Electronic Theory of Organic Chemistry*,[31] which he touted as showing that MO calculations can explain "all" of the facts of organic chemistry, and it was also at the height of controversy over his formulation of π-complexes.[32] Needless to say, the discussions were lively.

It was a watershed for me because it led my desire to find out what MO calculations were all about, although in his book, Dewar left several critical issues untouched, such as why trimethylenemethane is not just as stable as butadiene or why the charge of the allyl cation is mainly centered on the CH_2 groups. No problems are encountered with resonance with these simple tests of the theory. I agree with Jerry Berson,[32] that if Dewar had made organic chemists aware of what and how easily simple MO calculations could do for them earlier on, they would not have had to wait for my little book on the subject published in 1961,[33] as will be discussed later.

My wife and I were very close to the Sheehans during our years in Cambridge. After the first two of those years, our offices were changed to be several doors apart and I followed his work on the synthesis of penicillin and other β-lactams with great interest. Knowing about the synthesis of cyclobutanone from ketene and diazomethane, I suggested that he try phenyl isocyanate with diazomethane, and it worked, but only for that one compound.[34]

Getting started in research at MIT was greatly facilitated by a senior thesis requirement for undergraduates. Although the requirement was abandoned in later years, for me to have someone more or less eager to fulfill the requirement was wonderful, especially at a time when graduate students were primarily interested in doing their thesis work with better known faculty and not the very lowest one on the totem pole, who in addition was assigned office and research space rather far away from the center of activity in organic chemistry. However, Cope was well aware that I needed to get going, and fortunately, a MIT Laboratory for Nuclear Science and Engineering was being set up to which I could apply for funds to demonstrate the utility of radioactive ^{14}C as a tracer in studies of organic reaction mechanisms. The leaders of the laboratory were veterans of the highly successful Radiation Laboratory at MIT (radar research) and big thinkers, so at the start of my second year, they awarded me $40,000 for my research, which in current dollars would be about $400,000, a sum I had no idea how to spend effectively. I naturally was awarded rather smaller but adequate amounts in subsequent years. With undergraduates, not always the best

of the crop in the early going, I had an opportunity to reverse being a recipient of mentoring and become a mentor to my thesis students, in a way that I hoped to be comparable to what I had profited from in earlier years.

It was slow for me to get started in the relatively new field of ^{14}C as tracer for structures and reactions and complicated by the fact that ^{14}C emits fairly soft betas and has a several-thousand year half-life. So with little else to go on, we modified a Lauritsen electroscope to measure the beta particles from CO_2 samples precipitated as barium carbonate; not highly sophisticated, but it worked reasonably well.[35] Once that barrier was surmounted we could start our tracer work.

I was on the faculty of MIT for seven years, and during that period I started some 10 different lines of research. Several involved ^{14}C tracing but were in unrelated or distantly related research areas. Art Cope was aghast at the variety of efforts underway and cautioned me that I would do better to concentrate on far fewer research themes. However, while I recognized the value of his concerns, up to my arrival at MIT, I had the advantage, rare at the time, of having worked on five different undergraduate research projects, syntheses for the NDRC, Grignard reactions for my thesis, small-ring compounds, and solvolysis rates at UCLA and Harvard. These were all taken on before extending my toe into tracer studies, and I preferred to keep on dabbling in a multitude of things I found interesting enough to study, especially if each satisfied my desire to confine my research to problems in which I could see no easy solution or involved measurements for which I could not predict the results. Of course, there are limits. As someone said "Attention is like butter, if you spread it too thinly, you can't taste it any longer."

In contrast to what confronts the younger chemists of today, taking on a variety of things was not very hard in the early postwar years. The reason was that so little was then known about structures of large and even quite small molecules, and along with that almost nothing at all about physical organic chemistry of even very common compounds. The result was that there were almost an embarrassing numbers of places to start new research in contrast to the enormity of wading through what has been accumulated in the last 65 years. Furthermore, getting a paper published 65 years ago, if it had at least a modicum of new material succinctly presented, was usually found acceptable for publication in short order. So, I had it rather easy to publish short papers on topics at least appearing to break new ground. Another factor leading to brevity of explanations of the mechanistic aspects of new reactions up to about 1960 was that synthetic organic chemists of the time generally disdained any expression of interest in such secondary matters to preparing new compounds. As one example, the Chemistry Department of the University of Illinois discouraged their faculty from teaching physical organic until Elliot Alexander bootlegged it in under the guise of a course in stereochemistry. Of course today, when physical organic has essentially been subsumed into synthetic chemistry as a basis for understanding and planning existing and new reactions, relatively few courses in physical organic are taught compared to those covering synthesis. It is somewhat unfortunate that the synthetic organic chemists are naturally mostly interested in those important subsets of physical organic, that impinge on synthetic reactions, but this is changing as syntheses of extremely complicated natural product are tackled and many synthetically oriented graduate students and postdoctoral fellows have become interested in quantum calculations and hands-on taking of NMR and mass spectra, as well as X-ray crystal structures.

Through the end of my involvement as a faculty member at MIT (1953), I had published some 85 papers; from 1953 to the present, there have been about 450 more, and very few of these can be reviewed in the limited space available for this article. I have no regrets about that because a more primary purpose is to illustrate the importance and efficacy of faculty mentoring in helping me get me started in a broadly based research career, even without the advantage of solid academic-course credentials. I remember that the dean of UCLA's newly initiated Ph.D. program called me into his office to complain that, although I submitted a Ph.D. thesis, I had not taken even one graduate course. This was an omission he feared would reflect poorly on the rigor of their graduate program. However, he did let me pass and I do not believe UCLA suffered much from my example.

The Rise of Chemical Instrumentation

As a prelude to how the research I initiated at MIT, further evolved and augmented at Caltech, it is well to say something about the concurrent evolution of chemical instrumentation, which more than anything transformed the way research in organic chemistry is carried out.

Before my time, organic research was essentially being done in the same way as it had been done in the previous 50 years. It may seem unbelievable, but in 1938, our best instrument for characterization was the thermometer. With it we could test if two crystalline compounds having similar melting points were the same compound by taking a mixed melting point (mp). No mp depression meant the samples could be regarded as the same (with some exceptions), and different boiling points (bp) could do that for liquids. Identical or close bp liquids could be compared using a Zeiss Abbé refractometer to measure refractive indexes. Structure determinations of any complexity required degradations to smaller compounds of known structure. Thus, many of my purified butenylmagnesium bromide addition products to carbonyl compounds had to be degraded with ozone, and formation of formaldehyde could then be taken as proof of a terminal double bond rather than acetaldehyde, as would be expected from ozonization of addition products introducing the primary butenyl group.[12,14]

During this period, the only really commercially available electronic instrument was the Beckman pH instrument, which used a glass electrode and filled an important need by allowing measurement of pH over a broad range with good accuracy. By the time I went to MIT, the Beckman DU vis−UV spectrometer had become important in many connections and was the first major instrument I was able to purchase for the use of our research group in the "hands-on" mode.

We were able to make excellent use of this spectrometer in studying the mechanisms of the reaction of diphenyldiazomethane[36,37] and ethyl diazoacetate[38] with acids in ethanol, as well as using the rates of reaction of various acids having different substituent groups for analysis[39] or to determine relative substituent electronic effects.[40−43]

Here again, I emphasize "hands-on" use because I feel this has done more for chemical research than may seem now important, because it is so ubiquitous and taken for granted. However, this certainly was not the case 60 years ago. Quite a few "home-built" spectrometers were available for use, but they were hardly suitable for "hands-on" use by all-comers, and

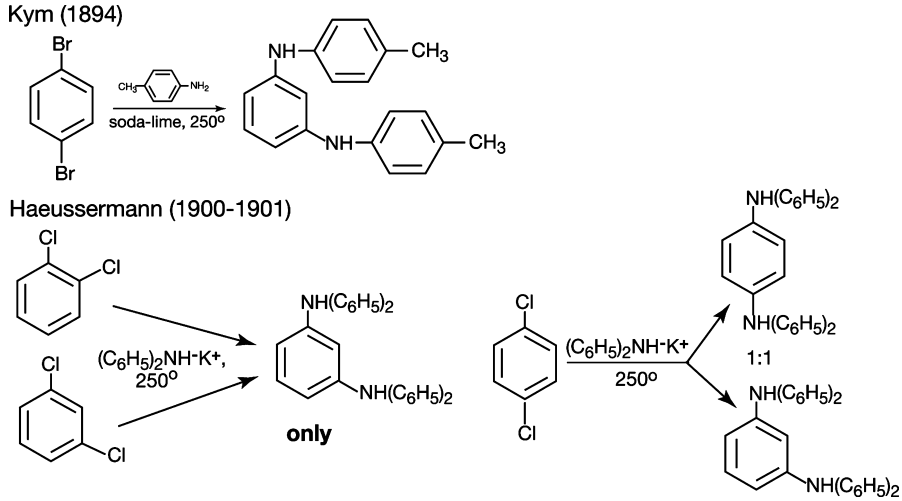


FIGURE 2. Early examples of rearrangements occurring in what could be characterized as nucleophilic reactions of aryl halides.

getting a spectrum usually required that it be done by the instrument's builder or one of his/her staff, often with a substantial wait for service time to become available. The growth of standardized, reliable instrumentation able to be used at any time of day or night greatly facilitated organic research, especially for synthesis where a desired reaction product can usually be identified and its yield measured without intensive purification.

The DU spectrometer, while very useful, was not great for determining structural details, and the advent of routine infrared (IR) spectrometers by Baird, Perkin-Elmer, and Beckman around 1950 added a new dimension for both quantitative and structural analysis. The IR spectrometer was developed for the WWII effort, in part, to analyze butadiene for synthetic rubber. It was also used by Shell Oil laboratories in 1944 to determine that among three alternative structures, penicillin was actually the one that showed by IR to have a fused β-lactam−thiazolidine ring system. IR instrumentation was a wonderful addition for organic research by providing hands-on access, substantial structural detail, excellent discrimination between closely related compounds, and calibrated composition analysis. For several years, IR was ubiquitous, even though its inability to assign specific structures at the level organic chemists used it left a degree of dissatisfaction and hope for something better. Of course, that hope was realized with the advent of nuclear magnetic resonance spectroscopy (NMR), but because of the need to understand a whole new kind of scientific instrumentation and initial operating limitations of the then commercially available spectrometers, NMR did not really catch on in universities until 1954−1955, with Caltech and Harvard being the first. For both universities, the impetus to move ahead was supplied by William D. Phillips, a Ph.D. from MIT, who led the NMR enterprise at DuPont's Central Research Department (CRD). Although excellent NMR work, within the limits of then-available instruments, was also carried on in the laboratories of Exxon, Humble, and Shell. Phillips was working very broadly with proton and fluorine NMR on a wide variety of interesting compounds. I was the conduit on the organic side to Caltech, when I met with Phillips in 1954 while acting as a DuPont consultant. I already knew Phillips by serving on his Ph.D. committee at MIT. Phillips showed me how and what NMR was doing for CRD, and even though I had no understanding of the physics of NMR, it was easy to see from the spectral peaks and Phillips' explanations the wealth of structural and quantitative information that it provided. So I started a campaign with my colleagues to get Linus Pauling (Figure 23S) to help us buy a Varian NMR spectrometer. It was not easy, because Linus knew about NMR and had little faith in its hands-on use by organic chemists who might not even know how the instrument worked. Indeed, he suggested that we hire a physical chemistry faculty member who had experience in the field. This would surely take a long while, and I wanted to get going ASAP. Linus finally seemed to succumb to the lure of using NMR to study resonance vs tautomerism, but perhaps he actually wanted to get rid of my harassing him about our needs; in any case, we were able to acquire the instrumentation in early 1955. This was in many ways a career change for me, because the Varian spectrometer of that era (Figure 24S, 25S) was not very stable, not very rugged, and came with little more information than turning it on and adjusting the field for satisfactory resolution. This meant it was an instrument you had to live with for quite a time to understand how it worked and how to dig into its various capabilities and then be able to use the wealth of different kinds of structural and analytical information it could give you. With this introduction to how I got into NMR, I will return to some of the themes we started at MIT and continued, or did not continue at Caltech. Of course, NMR did not enter into any of those that were terminated before 1955.

The Benzyne Mechanism in the Formation of Aromatic Amines from Aromatic Halides

Probably of all the research in which I have been involved, most organic chemists are likely to be cognizant of nucleophilic aromatic substitution leading to rearrangement products via elimination−addition, the "benzyne mechanism", a reaction mentioned in more or less detail in most elementary organic textbooks. There are many publications demonstrating its utility in organic synthesis; recent spectacular examples have been supplied by Stoltz.[44,45] There is a long historical background for this particular type of rearrangement reaction with examples reported more than 110 years ago, as shown by Figure 2.

These transformations, of course, are high-temperature processes, but the products seem to be stable. To be sure, Kym's experiment[46] is an isolated example. In contrast, the experiments by Haeussermann[47−49] uncovered quite accurately the totality of the basic pattern of these rearrangements, as it is known today, although giving yields of only about 5% of the listed products.

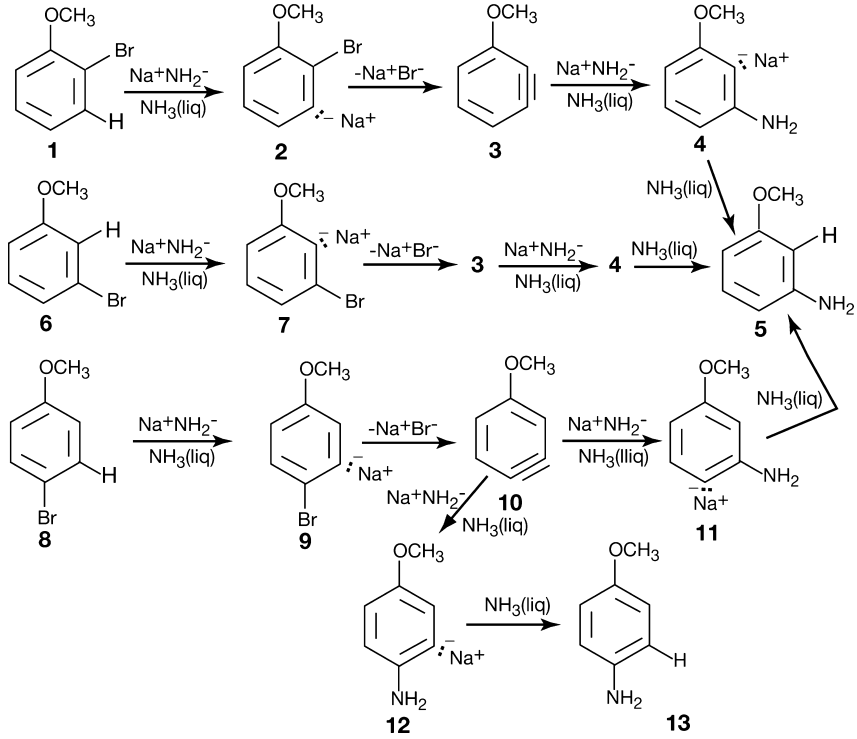


FIGURE 3. Elimination−addition (benzyne) reactions of the bromoanisole isomers with sodium amide in liquid ammonia.

My interest in these rearrangements was whetted by the literature research prompted by Geissman's suggestion that we might (but did not) investigate possible syntheses of salicylaldehyde derivatives by metalating anisole with alkyllithiums in the ortho position and running aldehyde-producing additions reactions. This led to an extensive search of very relevant related papers of Henry Gilman and the already mentioned metalation and carboxylation of anisole and benzotrifluoride.[30]

The real impetus for the benzyne work was supplied by the report by Gilman[50−52] that treatment of 2-bromoanisole with sodium amide resulted in exclusive formation of 3-aminoanisole that was wholly congruent with the results of Kym and Haeussermann[47−49]

My first MIT student to do undergraduate thesis work on the mechanisms on rearrangements of this kind was Edward M. Kosower. At that time, Kosower was a very amiable, intelligent, but rather feckless, C-average student who subsequently went from MIT to a Ph.D. with Saul Winstein at UCLA and later to a very excellent academic career in physical organic chemistry, starting at Wisconsin then to Stony Brook and finally at Tel Aviv. Kosower investigated reactions of aromatic halides, such as *o*-chlorotoluene with lithium diethylamide in diethyl ether. The reaction mixtures were very complex. Surprisingly, substituted biphenyls appeared to be formed along with (diethylamino)aromatics. What looked to be simple when formulated turned out to be quite difficult and, without IR and NMR, was too much of a project for an undergraduate thesis, although Kosower tried very hard to make sense of what he could surmise was present in the reaction mixtures.

My second undergraduate thesis student on the problem was a couple of years later and now it seemed best to try to solve the rearrangements occurring for compounds like 2- and 4-haloanisoles, but not 3-haloanisoles. This was undertaken by C. Wheaton Vaughan, a completely different personality than Ed Kosower, a strong grade record, a patrician aura, and an almost insufferable supply of self-assurance. In discussing possible mechanisms with Wheaton, I talked about metalation of aromatic groups and its propensity to take place on positions *ortho* to electron-attracting groups, such as methoxy groups. Obviously, if methoxy could promote metalation so should the halogens **1** to **2** (see Figure 3). As I looked at the metalation products **2** and **7**, I had to ask myself, "How can the NaBr hang onto the benzene ring? Why doesn't it just fall off and form a triple bond?" And, if so, there was 3-methoxybenzyne **3**! Once you had that, you could see how addition of NH_3 to **3** should first form a transient (3-amino-6-methoxyphenyl)sodium **4**, which with the metal adjacent to the methoxyl group corresponds to favored *ortho*-metalation, and on protonation should proceed to 3-aminoanisole **5**.

The guiding principle for prediction of formation of a particular or a mixture of amine products can best be seen by inspection of the expected most favorable direction of addition of sodium amide to the benzyne triple bond to give a 1-(2-amino)arylsodium where the sodium is most favorable next to a strongly electronegative substitutent, as OCH_3 in **4**.

Clearly, if this mechanism is correct, there must be a hydrogen to be removed, that is located next to the halogen being replaced, to have elimination to occur. Our first experiment to test that supposition was done by Wheaton on 2,4,6-trimethyl-1-bromobenzene (bromomesitylene), and it was indeed exciting to find that the amination reaction did not occur. Then, if you digest this putative mechanism given in Figure 3 for even a few seconds, you see clearly why 3-bromoanisole **6** is also most likely to only lead to 3-aminoanisole **5** with sodium amide. Thus, with the proximate strongly inductive 1-methoxy and 3-bromo substituents, the 2-hydrogen would surely be the favored point of metalation of **6** to **7**, which with loss of NaBr would then lead via **3** and **4** to **5**. After this simple mechanistic triumph, figuring out what occurs with 4-bromoanisole **8** is straightforward. In the first place, only the 4-methoxybenzyne **10** can be

formed from **9** by loss of NaBr. Then **10** could add amide ion to give either/or both the (2-amino-4-methoxyphenyl)sodium **11** or (2-amino-5-methoxyphenyl)sodium **12**. With either **11** or **12**, the methoxy group is either one or two carbons removed from metalation products formed by addition of sodium amide to **10**, and the inductive effects of the methoxy group would have to be very strong to favor formation of **12** over **11**. One might guess this would be sufficiently so that formation of **13** would be at least slightly favored over **5**, but even going back to the work of Haeussermann[47−49] more than 100 years ago, the reported product ratios are quite close to 50:50 (Figure 2).

All of this makes clear the general pattern of rearrangement products with sodium amide and 2-, 3-, and 4-chlorotoluenes, where the 1-methyl substituent has at most a minor inductive effect, meaning that if we replace methoxy with methyl and the bromo with chloro in Figure 3, we should expect little preference for formation of methyl-, chloro-substituted metalation products **2**, **7**, or **9**. So we can expect that the analogue of **3** formed from analogues of **1** or **6** would yield a mixture of 2- and 3-toluidines and the analogue of **10** formed from analogues of **6** or **8** would give 3- and 4-toluidines analogous to **5** and **13**. These expectations have been verified by experiment.[53]

The now well-known formation of benzyne itself as a symmetrical intermediate was demonstrated as part of his doctoral thesis by Howard E. Simmons, Jr. (Figure 26S) through his seminal work on the amination of chlorobenzene-1-^{14}C with sodium amide in liquid ammonia and the showing that aniline-1-^{14}C and aniline-2-^{14}C were formed in closely equal amounts.[54] Simmons, who finished his Ph.D. with Arthur C. Cope, was a brilliant chemist and research leader at DuPont. Finally, he became Senior Vice President in charge of DuPont's Central Research Department. Howard and his wife Liz were long-term family friends.

Wonderful research on the actual mechanistic steps in the formation of benzyne was carried on at Caltech by Dorothy A. Semenow (Figure 27S), who transferred as a graduate student from MIT to Caltech and became Caltech's first female Ph.D. recipient. Not long before, Frank H. Westheimer[55] (Figure 28S) used the hydrogen−deuterium isotope effect to show that the rate-determining step, in the oxidation of isopropyl alcohol to acetone, involved attack on the central C−H bond. Dorothy employed this strategy with chloro- and bromobenzenes by labeling only one of the hydrogens next to the halogen substituent with deuterium. Then by carrying the reaction to about half completion and analyzing the ratio of hydrogen to deuterium in the unreacted halide one can measure isotope effects. It turned out that the hydrogen−deuterium isotope effect with 2-deuteriochlorobenzene was rather small, 2.4, while that with 2-deuteriobromobenzene was quite larger, 5.8, and quite comparable with what would be expected for bond breaking in an elimination reaction. Dorothy found out why. With 2-deuteriochlorobenzene, the compound metalated partially at the 2-position and then some of that intermediate shed chloride ion and went forward to benzyne, while the rest picked up a proton from the solvent and formed ordinary chlorobenzene. She showed that the rate of the back reaction was 0.6 times as fast as the forward reaction. In contrast, 2-deuteriobromobenzene showed no exchange and proceeded smoothly by what Ingold would call an E2 reaction mechanism to benzyne. Christopher Ingold's E1 reaction mechanism involves forming a carbocationic rather than an anionic intermediate.[56] Where there is a rapid and reversible formation of an anion by a base, followed by a slow elimination of a suitable leaving group the overall mechanism is called $(E1cB)_r$. An excellent case for that mechanism of benzyne formation would be fluorobenzene with a rather acidic ortho-hydrogen and not very easy-to-eliminate fluoride ion.

It has always been amazing to me that the correct mechanisms for the rearrangements occurring in aminations of aromatic halides were not suggested much earlier. The pattern of rearrangements is at first glance so bizarre that one would expect someone to note right away that the rearranged products are never more than one carbon away from the halogen being displaced, and that, by itself, should trigger expectation of an elimination−addition mechanism. These reactions were called "cine substitutions" by Joseph Bunnett,[57] and a plausible mechanism evolved that did not lead to benzyne formation. In hindsight, my stumbling onto the benzyne mechanism, to take a parallel to Newton, was like having a very over-ripe apple fall on my head. The ACS Division of the History of Chemistry recognized the benzyne mechanism by a 2008 Chemical Breakthrough Award (Figure 29S).

After its postulation as a reaction intermediate, there were many physical studies of benzyne in the gas and condensed phases. As an organic chemist with specialization in NMR, I am generally inclined to put my trust in that particular modality. Here, I was amazed and pleased by the research published over 30 years later by Ralf Warmuth[58] on the ^{13}C NMR spectra of benzyne at −75 °C when sequestered in a molecular cage and formed by photochemical didecarbonylation of benzocyclobutadienoquinone. Warmuth's analysis of the couplings observed in the ^{13}C spectra suggest to him that a cumulene-like structure gives better agreement than a benzyne-like structure. Simple molecular-orbital models of benzyne Kekulé-type resonance structures are primarily benzenoid, except for the in-plane 1,2 p orbitals, orthogonal to the $p-\pi$ benzenoid orbitals on C2−C6, which provide the extra in-plane bond for each resonance structure. If the cumulene-like resonance structure is the more important, the in-plane bond may contribute less to the hybrid structure and perhaps the benzene π overlaps could move to distances more congruent with a normal benzene hybrid.

Carbocation Reactions and Rearrangements

My early work on small-ring compounds was driven by the desire to study solvolytic reactions and molecular rearrangements primarily via carbocationic processes. I did not want to study allylic rearrangements, I had done enough on those, but I was intrigued by the possibility of a cyclopropane ring behaving like a double bond in cyclopropyl chloride and of cyclopropylmethyl chloride giving reactions like those of allyl chloride. This all seemed reasonable because I had already found that cyclopropyl chloride was extremely inert like vinyl chloride and chlorobenzene in typical cationic reactions of halides such as with aqueous ethanol, silver nitrate solution, and so on. A further and likely much weaker analogy would involve cyclobutyl chloride and cyclobutylmethyl chloride, for which I knew of no supporting evidence at the time. To work on these projects required synthesis of the desired compounds for study, starting frequently from cyclopropyl methyl ketone. We synthesized the following compounds in moderate quantities over the next few years: cyclopropanecarboxylic acid, cyclopropylamine, cyclopropanol and cyclopropyl chloride (both described earlier), cyclopropyl bromide, cyclobutanone, cyclobutane,

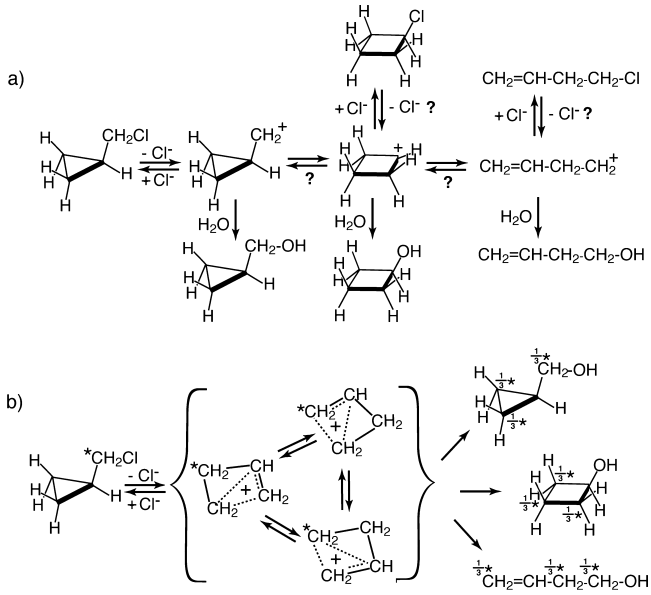


FIGURE 4. Solvolysis of cyclopropylmethyl chloride in aqueous ethanol, with the solvolysis products assumed to be only alcohols, not ethyl ethers: (a) assuming classical carbocation ions as intermediates; (b) assuming nonclassical carbocationic intermediates.

cyclobutyl chloride, cyclobutylamine, cyclobutanecarboxylic acid, and cyclopropylmethyl chloride. Over the next 30 some years, we studied these compounds in detail for their reactivities, rearrangement reactions, carbocationic, radical, and anionic, as well as electrical effects, and NMR spectra. There is far too much to review here, and I will only cover briefly the most interesting feature of this arena; the emergence of what came to be called "nonclassical cations", of which there is no better example than the $C_4H_7^+$cation. This rather simple formula allows for a number of straightforward-looking isomeric cations for which a structural dilemma arises, because whatever $C_4H_7^+$ is, depending on the circumstances, it gives mixtures with various ratios of cyclopropyl, cyclobutyl, and allylcarbinyl (3-buten-1-yl) products. Although unusual properties were ascribed to $C_4H_7^+$ as early as 1951 as the result of research by a most talented graduate student at MIT, Robert H. Mazur (Figure 29S).[59] It took a paper published by George Olah 57 years later, describing very substantial quantum calculations, to be confident that the structure had finally been settled.[60] The gist of this story is that cyclopropylmethyl and cyclobutyl chlorides are very much more reactive than one might expect relative to allyl and cyclopentyl chlorides in S_N1-type solvolytic reactions in aqueous ethanol. These solvolyses were featured by substantial "internal return", a phenomenon investigated extensively by Saul Winstein[61] and illustrated in Figure 4, where a relatively stable carbocation R^+ reacts with an anion X^- to form R−X, the starting halide or, in our case, some of less reactive rearranged products, cyclobutyl or allylcarbinyl chlorides, thus slowing the rate of solvolysis. The mechanisms by which these rearrangements occur could be the result of simple "classical" cationic rearrangements or involve a "non-classical" cation or cations, which could yield rearranged products as seen in Figure 4.

This is a complex problem, and there are too many fine details to discuss here. Instead, look at an oversimplification of the most important points. Figure 4a shows a schematic outline of the products to be expected by way of classical cations, assuming internal return in the first step. It will be seen that, in principle, the cyclopropylcarbinyl cation can react without rearrangement to give cyclopropylmethanol. However, if it rearranges by a familiar Wagner−Meerwein 1,2-shift, it will form the cyclobutyl cation, which then could also participate in internal return, react with water to form cyclobutanol, or undergo ring-opening to the allylcarbinyl cation that with water will form allylcarbinol. Many solvolytic reactions of cyclopropylmethyl X compounds can generally form these products, but the extent of each will depend on kinetic or thermodynamic control. The most stable product is allylcarbinol, and that or allylcarbinyl chloride (a quite unreactive chloride for S_N1 reactions) will be the products of pure thermodynamic control. Kinetic control almost invariably yields about 2:1 mixtures of cyclopropylmethyl and cyclobutyl products with perhaps 5% or so of allylcarbinyl products. Interestingly, this pattern of rearrangements only occurs in carbocationic reactions. With radical or anionic intermediates, rearrangements occur but do not result in formation of the corresponding cyclobutyl products.

The problem with trying to reconcile the results of these carbocationic reactions with the sole intervention of classical cations as in Figure 4a is the relative ease of formation of cations by cyclopropylmethyl and cyclobutyl compounds in solvolysis and related reactions. Literature designations of similar rate-enhanced S_N1 reactions were "anchimeric" (Winstein) and "synartetic" (Ingold), neither of which term is now used much. That does not mean such phenomena are rare, many simply say there is an "extra driving force", if solvolysis is faster than expected from surveys of compounds analogous to the formal structure of the reactant and may lead directly to rearrangement in the transition state.

Skipping over to a somewhat idealized picture of what we think we know today as to the nonclassical intermediates in solvolysis of cyclopropylmethyl chloride, we see in Figure 4b formulation of the expected $C_4H_7^+$ cation as a dynamic mixture of isomers. To be sure, the isomers are only nonequivalent, if one starts with a specifically labeled $*CH_2$ (with the label * being ^{13}C, ^{14}C, ^2H, or ^3H), then 1/3 of the total label will be on each individual CH_2 of equilibrating $C_4H_7^+$, with the particular structure shown christened as the "bicyclobutonium" cation. In our work in this arena, we found nearly statistical product mixtures with ^{14}C and ^2H as labels to determine how fast and complete equilibration is under kinetic and thermodynamic control.[62] The really beautiful NMR work on $C_4H_7^+$under Olah's super acid conditions, where it is quite stable and rapidly equilibrating, is very informative of its nonclassical character.[63,64] Further work along this line was done by Myhre[65] where solutions of ^{13}C-labeled $C_4H_7^+$ were cooled to nearly 0 K. It was astounding that rapid equilibration continued to 60 K, below which point the spectrum changed dramatically. It is quite clear now that $C_4H_7^+$ does not have a single structure, because as the temperature is changed in the Olah experiments, there are significant changes in chemical shifts. Theoretical calculations indicate that the differences in energy between the possible isomeric structures are quite small as are the barriers to their interconversion.

This line of research on classical vs nonclassical cations involved a one-sided bitter wrangle among its protagonists and lasted for many years. The Horatio at the bridge for classical ions was Herbert C. Brown, a brilliant physical organic chemist, who seemed to wear blinders when confronted with the growing evidence for the intervention of nonclassical cations. The evidence that finally appeared to settle the question for the general chemical community involved elegant physical organic

research using reaction kinetics, NMR, and crystal structures. Nonetheless, many synthetic organic chemists sniffed at the seriousness of the warring parties in their efforts to settle the issues involved and also at the concomitant expenditures of grant funds, which may have been diverted from what many thought were more important aspects of organic research. My own view as a relatively secondary participant has always been that it is very important to know what we mean when we draw chemical structures. This was a long-standing and aggravating problem with keto−enol tautomerism as well as aromatic structures. Nonclassical ions present difficulties in somewhat the same way. Modern formulations of benzene and its derivatives differ greatly from Kekulé's 1,3,5-cyclotriene structures and do not correspond to the typical unsaturated compounds, and nonclassical ions do not behave like typical classical cations. Other examples of nonclassical ions we studied at MIT included the norbornyl and dehydronorbornyl cations.

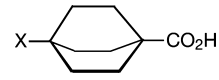
In a different area of carbocations was Paul Bartlett's wonderful experiment showing that a tertiary carbocation could accept a hydride transfer from another hydrocarbon in times as short as a few thousandths of a second.[66] The prime example was of the *tert*-butyl carbocation abstracting a hydride ion from isopentane to give isobutane and the *tert*-amyl carbocation. Our interest in these reactions was to see if by using ^{14}C-labeled isopentane, whether skeletal rearrangements of the *tert*-amyl cation also occurred in these very short reactions. Indeed, they did[67] and were harbingers of the beautiful studies by Martin Saunders of related processes.[68]

Electrical Effects of Substituent Groups

When I first started at MIT, I had a strong interest in substituent effects, particularly the σ,ρ relations of Hammett[69] and their power for correlating reaction rates and equilibria of *meta*,*p*ara-substituted benzene derivatives. Hammett seemed relatively uninterested in how to explain the magnitudes of the σ-values of common substituents, but generally speaking, it was not hard to rationalize them. What I got interested in was seeing what the σ-constants for less common and more interesting looking substituents might turn out, and this seemed to be just what I wanted for senior thesis research projects at MIT. We studied several different substituents to obtain σ-values at both *meta* and *para* positions on benzoic acids and aniline derivatives. Among the first groups, one turned out to be an interesting choice, because just like the nitro group, it had quite different *para*-σ-constants when substituted tested against the acidity of the carboxylic acid group in 4-trifluoromethylbenzoic acid and the basicity of 4-trifluoromethyl-*N*,*N*-dimethylaniline. With the nitro group, the differences in *para*-σ-constants is ascribed to resonance structures involving transfer of electron density from the amino group to the nitro group of *p*-nitroaniline, which does not occur with the corresponding carboxylic acid. What we discovered was that a similar situation appeared to arise with the trifluoromethyl group through fluoride hyperconjugation, $^{-}F CF_2{=}C_6H_4{=}N^{+}(CH_3)_2$.[41] Some physical organic chemists thought this was a bad formulation, but others argued for it and now I believe it is at least grudgingly accepted. Still further σ-constant determinations were carried out on the *m*- and *p*-trimethylsilyl and trimethylammonium groups. The trimethylsilyl group was a weak actor as far as σ-constants were concerned, and nothing exciting was gleaned from it.[43]

The *m*- and *p*-trimethylammonium groups were much more interesting. These are primarily electrostatic groups with positive charges on nitrogen. Ingold posited that such groups could polarize benzene rings in ways, which could lead to larger electron-attracting influences at the carbons *para* to them. Presumably, this would have a larger positive σ-constant at the 4- rather than at the 3-position and, in addition, possibly elicit special resonance effects when tested with acid or amine groups. In our research, no evidence was found for such influences and the trimethylammonium groups appeared to behave as purely electrostatic substituents.[70]

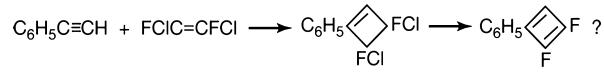
Probably the most important work we did in the electrical effects arena was to synthesize bicyclo[2.2.2]octane-1-carboxylic acid with 4-X groups possessing different electrical effects. These substances were designed to be able to determine σ-type constants by the same procedures used for 3- and 4-substituted benzoic acids. The goal was to separate out the benzene resonance contributions to the σ-constants by using a saturated scaffolding with very nearly the same geometry. The project went very well as carried through by graduate student, Walter Moreland.[71] The expected inductive σ-constants were obtained and were large enough to show that inductive effects were quite efficiently transmitted across the bicyclo[2.2.2]octane ring system.[72] The results of this research were later cited by the American Chemical Society for the 1954 Pure Chemistry Award.



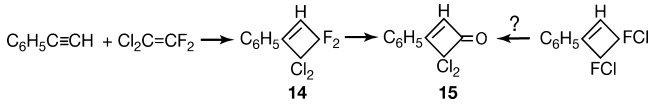
4-X-bicyclo[2.2.2]octane-1-carboxylic acid.

Fluorocyclobutenes and Their Reactions

For many years, inspired by Edwin Buchman, we had ambitions of preparing cyclobutadiene or derivatives thereof, and a simple route seemed to be cycloaddition of 1,2-difluoro-1,2-dichloroethylene to phenylacetylene and removal of Cl_2 with zinc. Unfortunately, although addition occurred very well, the

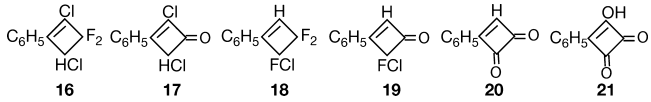


reaction with zinc was poor and nothing like a cyclobutadiene or a dimer thereof appeared to be formed. The graduate student working on the project, Bruce Kline, was discouraged, and that discouragement increased as his further envisioned routes to substituted cyclobutadienes did not pan out either. He wanted something positive for his thesis. I had been reading about sulfuric acid-induced hydrolysis of halogen compounds and suggested he try this with his successful adduct. I felt that, even if he could not make a cyclobutadiene from it, it might yield something interesting. Acidolysis worked well using sulfuric acid. Copious emissions of hydrogen−halide acid fumes were observed, and when the reaction mixture was poured into ice−water it yielded a light-yellow solid. After purification, this did not give the expected analysis for hydrolysis and loss of two chlorines. More discouragement, but on a whim, I guessed that perhaps the fluorines underwent overall hydrolysis, which was correct and the product was found to be a *gem*-dichlorocyclobutenone **15**. That this compound could be formed from the expected structure of the cycloadduct seemed implausible. However, it would be expected to be formed from the cycloadduct from the addition of 1,1-difluoro-2,2-dichloroethylene to phenylacetylene, **14**.[73]



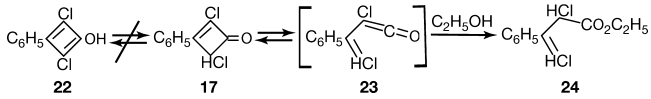
14 15

The supplier of the difluorodichloroethylene was DuPont's Kinetic Chemicals. "Yes, we did send you 1,1-difluoro-2, 2-dichloroethylene instead of what you ordered, but we thought it would not matter, because we expected you to use it as a solvent." Such is serendipity! So when we finally made the desired 1,2-difluoro-1,2-dichloroethylene, it added very poorly to phenylacetylene and the resulting adduct did not give a cyclobutadiene with zinc. Nonetheless, the adducts with 1,1-difluoro-2,2-dichloroethylene and 1,1,2-trifluoro-2-chloroethylene gave a host of interesting compounds. One led to a real fun project involving ketone **17**[73] which might be expected to be able to enolize to a hydroxycyclobutadiene **22**.



16 17 18 19 20 21

To test this possibility, we made optically active **17**, knowing that an equilibrium enolization should cause racemization. Optically active **17** does racemize when warmed to less than 100 °C, but we were able to show that this was not the result of breaking the C4−H bond or the C4−C1 bond. Then the only alternatives are to break the C1−C4 or the C3−C4 bond, and the culprit was C1−C4, which resulted in a reversible formation of the vinylketene **23**, which *could* be trapped when the racemization was carried out in ethanol to give ester **24**.[74]



22 17 23 24

Compound **18** is the adduct of $ClFC{=}CF_2$ with phenylacetylene. It can be hydrolyzed with acid to **19** and **20**. The latter is fairly characterized as a *cyclobutadienoquinone*. In character with the Hückel calculations of aromaticity, it should be "aromatic" and more stable than *o*-benzoquinones, which it is. With chlorine or bromine, **20** reacts readily to give the 4-chloro and 4-bromo derivatives. These substances are like acyl halides and react readily with water or ammonia to give the 4-hydroxy (**21**) and the 4-amino compounds. Compound **21** is an extraordinarily strong acid for a neutral compound of C, H, and O. Its pK_a in water is ~1.0; the corresponding amine is a very weak base, insoluble in aqueous acid.[75,76]

As for cyclobutadienes, the best we have done is in the reaction of **16** with excess phenyllithium, which gave a dimer of fluorotriphenylcyclobutadiene. The original work on the structure and reactions of the dimer were published in 1962.[77] However, there were many gaps in the story[78,79] that were finally filled in by X-ray crystal structures of the existing 1962 samples in 2007.[80]

Hückel Molecular Orbital (HMO) Theory

In some sense, getting involved with HMO was one of my sillier ventures in chemistry. I knew virtually nothing about quantum mechanics; it was not mentioned in any undergraduate course I had at UCLA. Perhaps it was available as a graduate course, but I was not aware of any that included it. I was, of course, familiar with Pauling's qualitative resonance theory and how it provided excellent understanding of simple ideas like acidity of carboxylic acids, low basicities of aniline and amides, the reactivity of ally halides, the stability and substitution orientation of aromatic compounds and so on. However, the manifest failure of resonance to account for the stability of cyclobutadiene for which two reasonable-looking Kekulé type structures could be written was a continual nagging background concern for me. So I followed with interest the rise of the use of orbital models for molecular structures, which seemed then to be, in general, quite compatible with resonance. When M. J. S. Dewar's book, *The Electronic Theory of Organic Chemistry*,[31] was published, I was captivated by what I read and decided this was the way to teach physical organic chemistry. I was so cocky about it; I told my 1950 MIT physical organic class that I was going to explain things that year by MOs, not by resonance. All well and good, and as I prepared to do this, butadiene looked quite nice and so did the allyl cation with two electrons placed in a molecular orbital concocted from three overlapping *p*-π orbitals with one on each carbon. However, the need for explaining to the students how the electrons were distributed seemed vital. Was there an average of +1/2 charge on each of the terminal carbons as predicted by resonance ($^{+}CH_2{-}CH{=}CH_2 \leftrightarrow CH_2{=}CH{-}CH_2^{+}$) or an average of 1/3 of a positive charge per *p*-π orbital or what? A rapid perusal of Dewar's book showed that while allyl intermediates were discussed, nothing was said about how you divined from the orbital arrangements and the number of electrons in each where the charges were. Then looking again at my butadiene orbital model, the image of isomeric trimethylenemethane jumped at me, and here, the resonance method predicted diradical resonance structures. However, treated like butadiene, a molecular orbital system is easily set up with four electrons in three *p*-π orbitals overlapping a single *p*-π orbital on the center carbon. This model looked to my innocent eyes to be just as good as butadiene. While cursing Dewar for withholding the secrets of how to solve such very simple problems, I had to do something to stick to my promise to the students. So, I frantically looked at quantum mechanics textbooks for help. It seemed clear that my questions were so obviously simple that none of the books deemed them worthy of discussion. My former lab partner in undergraduate physical chemistry, William G. McMillan, was at the time a visiting professor at Harvard. I was sure he would know how to dig me out of the hole in which I found myself. When I called him he laughed and told me to read Eyring, Walter, and Kimble's book on quantum chemistry; it is all explained in Chapter 19.[81] I said I cannot even read Chapter 1 and I need help NOW! Then, when I got him to meet with me, not only did he explain how you made and interpreted simple Hückel MO calculations, but showed how the computational labor could be reduced by use of group theory. And all of this could be done by simple straightforward algebra, not density matrix functions! So for quite awhile I threw myself whole heartedly into MO calculations in collaboration with Andrew Streitwieser, Jr. (Figure 31S) who was an independent postdoctoral at MIT after getting his Ph.D. with William E. Doering at Columbia. It was great fun, although solving large algebraic matrices was tedious. Now, such calculations are extremely easy to do on small computers. Andy and I published a sizable collection of calculations on what we thought were interesting molecules and reaction intermediates, down to as simple as the cyclopropenyl cation.[82] Subsequently, we both published books on MO calculations. Andy's is wonderfully scholarly.[83] Mine given the title, *Notes on Molecular Orbital Calculations,* could have been just as well

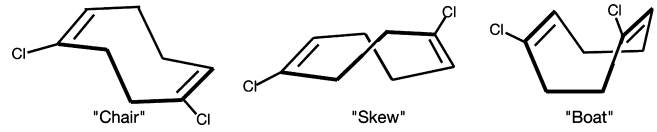
titled as, *MO Calculations for Dummies*, but nonetheless, it went through 16 printings before going out of print.[33]

Conformational Analysis

Conformational analysis can be very simple as with 1,2-disubstituted ethanes or of great complexity as for the usual large proteins, where we can see the locations of the atoms by X-ray or NMR analysis. But figuring out just how the peptide chains of the protein get folded up in a particular way or ways has been an extraordinarily complicated problem. Steady progress has been made on this problem in recent years. Liking simple projects, particularly ones where understanding is not always clear, I have always favored research on conformational analysis of small molecules in solution. Back in earlier days, the tools for investigating the three possible conformations of a symmetrical- or unsymmetrical-substituted 1,2-ethane were rather limited. It had been recognized early on that interconversions of the conformations of such systems are likely to be quite fast. The need was for analytical methods, which can glean something from a weighted average of the conformational preferences unless one of them strongly predominates.

My initial conformational project at MIT was suggested by Cope, who had access to a chloroprene dimer with the structure of *cis*-1,6-dichloro-1,5-cyclooctadiene and hoped we could find out more about its structure. Inspection of models suggests that the dimer can exist in three plausible conformations, but it was not certain at the time as to their relative free energies or how rapidly these would be interconverted. Westheimer and Mayer published in 1946−47 the first papers of what is now know as "molecular mechanics". These beautiful papers showed how to calculate the activation energy of racemization of optically active 2,2′-dibromo-4,4′-biphenyl by taking account of the energies of bond bending, bond stretchings, and nonbonding spatial interactions.[84,85] Using cruder methods, I was able to conclude that the three dichlorocyclooctadiene conformations shown above were likely to be rather easily interconverted and that left finding if one of them predominated. For this, dipole-moment measurements were the method of choice and the compound had a dipole moment of 2.60 D in benzene. The respective dipole moments calculated for the three conformations were chair = 1.5 D, skew = 1.4 D, and boat = 2.8 D. So the boat seemed substantially favored, despite having nearly eclipsed hydrogens along the 3−4 and 7−8 C−C bonds, as well as with the C−Cl dipoles in what might be regarded as the least favorable juxtaposition. Derek H. R. Barton (Figure 30S) was in Harvard for part of this time working further on his examination of the conformations of steroids and was very helpful with suggestions on how improve my calculations of the various interactions for my paper.[86]

The effect with regard to the expected disfavor of having two C−Cl dipoles with their charges fairly close and in an expected repulsive arrangement was also noted by Wilson Baker of Bristol who found the *cis*-dithymotide has a dipole moment of 6.8 D.[87] This corresponds to a conformation with C═O groups in the same kind of alignment. With a dipole-moment apparatus set up at Caltech, another example came from bis(4-chlorophenylcyclopentadienyl)iron **25**, kindly provided by V. Weinmayr[88] of DuPont's Jackson Laboratory. As shown, **25** has a 36° rotational angle about the iron atom. This angle is best understood as the one you see made when you look down along the vertical axis of the ferrocene ring system and observe the relationship between the C−C bond which attaches C1 of the phenyl group on the upper ring and the corresponding C−C bond to the lower ring, **25a**.

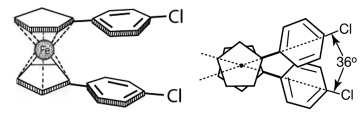


The experimental dipole moment of **25** in benzene was 3.12 D. Calculated values for the dipole moment of **25** with rotational angles of 36° and other rotational angles were based on the moment of chlorobenzene as 1.56 D. For 36°, the calculated moment is 2.97 D, for 0° ("eclipsed"), it should be 3.12 D and for 180°, 0 D. If rotation about the iron atom is "free", all angles equally probable, the dipole moment should be 2.20 D. Clearly something very close to "eclipsed" is in best agreement with the experimental value. So again, C−Cl bonds tend to be most favorable in what looks like a repulsive arrangement.[89] Another possibility is that this orientation of the chlorophenyl groups could be an early example of aromatic-ring stacking.

More on NMR at Caltech

Getting into NMR represented a real change in lifestyle for me. I was young enough in 1955, without too many local responsibilities, to spend a lot of time in the lab finding out how our spectrometer worked and what its capabilities might be. Further, I was close enough to James Shoolery, the head of Varian's applications laboratory, to follow the new developments on the spectrometer. I also encouraged a change that I thought was badly needed—a good temperature-controlled probe for both low and reasonably high temperatures. I designed it and supplied the glassware, while Varian put in the coils and connections to the spectrometer and its description was published in the *Rev. Sci. Instrs.*[90] Subsequently, Shoolery sent me a letter saying that Varian was applying for a patent, but company policy did not allow nonemployees to be named as inventors, so there went my only opportunity to ever make money from a patent. Another possibility was with phenylcyclobutadienoquinone, which very quickly earned a composition of matter patent,[91] but nothing of commercial value ever came along for it.

Our early NMR covered many small projects. Two of the most interesting included the first demonstration of slowing of rotation about a C−C bond with 1,2-dibromo-1,1-dichloro-2,2-difluoroethane. At 0 °C, rotation about the C−C bond is so fast that the separate chemical-shifted resonances of the gauche and trans conformers are averaged to a single line. At −80 °C, the spectra of the separate conformers are clearly evident with a gauche:trans ratio of 1.4:1.[92,93] That the trans is slightly more stable may be the result of its lack of the close Br--Br interactions seen for models of the gauche conformers. On occasion, what may be expected to give quite simple changes of spectra with temperature turn out to be quite complex; a wonderful example is provided by $CF_3-CCl_2-CCl_2-CF_3$.[94]



25 **25a**

Interesting result number two was the demonstration of what was later dubbed the "diastereotopic effect", which is well

illustrated by methyl 2,3-dibromo-2-methylpropanoate. Here, the CH_2 protons of the ester constitute an AB-shift-coupling system because of the three different groups attached to C2. The H−H coupling in this case is 10 Hz, and the chemical shift is 0.43 ppm.[92,93] With diethyl sulfite, the sulfite group makes the ethyl CH_2 protons diastereotopic. Analysis of the complex spectrum shows that the J value of the CH_2 coupling is opposite in sign to the coupling of these protons to the normal positive value of the vicinal coupling of the CH_2 protons to those of the CH_3 group.[95]

Another fun project was developed in his Ph.D. thesis work by George M. Whitesides (Figure 31S),[96] wherein he was able to measure the rate of inversion of the MgCl group at C1 of $(CH_3)_3C-CH_2-CH_2-MgCl$, which presents an AA′BB′ spin system when inversion is slow. It becomes A_2B_2 when inversion is fast. This was very educational for me because George dragged me kicking and screaming into trying to deal with the density matrix formulation of his reaction rates. My later attempt, with missionary spirit, to arouse interest in what I had learned about this subject at a Reaction Mechanism Conference could best be described as a lead balloon.

As our program developed, we studied many different aspects of NMR in physical organic, organic, natural products, and biochemistry. Clearly the most important of all of these for organic chemistry generally was the development of ^{13}C and ^{15}N spectroscopies at natural-abundance levels.[97] These allowed assignments of ^{13}C chemical shifts and couplings in a wide variety of substances as well as natural products such as steroids[98] and terpenes.[99] This work was spearheaded by Frank J. Weigert (Figure 32S), an exceptional graduate student who completed his Ph.D. work in less than three years with 16 publications! Similar broad-gauge studies of the NMR characteristics of ^{15}N were made of natural products, including enzymes, nucleotides, alkaloids, and the like, as well as exacting tracer studies of nitrogen metabolism of molds carried on by Kieko Kanamori.[100] Spectrometers, useful for taking ^{15}N NMR spectra at natural-abundance levels, do it best with very much larger samples than needed for ^{13}C. Such quantities are often just not practically available for biochemical ^{15}N, so that recourse has to be made to ^{15}N labeling. Hopefully with further improvements in NMR sensitivities of detection, ^{15}N spectra will become as easy to use as ^{13}C is today.

An Administrative Interlude

Starting in late 1979 until 1983, I served as provost, vice president, and dean of the faculty at Caltech. It was interesting in many ways and greatly facilitated by a staff led by Mrs. Lea Sterrett, a woman of extraordinary acumen and sensitivity. The position of provost, however, was frustrating in that solutions to only a few of the faculty problems that I worked to solve turned out to be more than temporary. People problems are wholly unlike scientific problems in that they cannot be written up, sent to a journal, and then allow one to go on to other activities. I did keep some research going in this interregnum, but later, on going back to the real world of full-time science, I realized that I had lost several possibly productive years. I briefly tried a career change involving an abortive attempt to make better science out of MRI, for which I was technically poorly equipped. This unfortunately further delayed a return to doing more chemistry with the aid of NMR with which I had more experience.

The Caltech Summer Undergraduate Research (SURF) Program

By the Caltech rules of the time, when under the then existing Federal law, I reached compulsory retirement age in 1988. The Institute's policy did not encourage emeritus faculty to have research groups and continue more or less as before, while freed of teaching and administrative responsibilities. The rule then was for emeriti to work, if and where space was available under a dictum of allowing only personal hands-on work. However, I put in a plea for being allowed to do research with undergraduates and for that, perhaps surprisingly, permission was granted, including permission to raise funds for the purpose. After several diverse undergraduate projects, our modus changed to working with the SURF Program, an Institute and Jet Propulsion Laboratory (JPL)-wide program now more than 30 years old.[101] Over that period, I have had well over 100 participants.

SURF is a marvelous program for mentoring undergraduates. Although financially biased toward Caltech undergraduates, it is possible to take applicants nationally and indeed worldwide. Besides students from many U.S. universities, I have had undergraduates from several European countries and Egypt and cities separated as far as Moscow, Warsaw, and Singapore. The SURF administrative team is a marvel for its efficient aid to SURFers. This is especially true with respect to disseminating general information on the program, suggestions for students in preparation of written and oral reports, providing a top-notch weekly seminar program in wide areas of science, taking care of housing and stipend payments, as well as with assistance for personal emergencies as needed.

Our goal for SURF projects is to provide each of our undergraduates with an individual project with the objective of attaining publishable results in ten weeks of summer research. Because our projects have the common theme of using nuclear magnetic resonance (NMR) to study conformational analysis, there are many opportunities for our SURFers to share mutual interests and laboratory experiences. Research and education are tightly integrated, with each participant having sole responsibility for his/her individual research problem. So in a sense, all participants (including our postdoctoral fellows) are treated as equals among equals. We believe that it will be hard to find a better approach for training beginners to do research, because we bring in almost all of the elements of serious research from beginning to end of a project, except for the ordeals of having to raise the needed funds in competition with many worthy and important projects.

First, there is the task of preparing a proposal in a field congruent with the proposed mentor's interests and/or budgetary constraints. The proposal is then reviewed and approved by an independent faculty committee. After that, successful applicants need to set up a work area and learn how to use the necessary equipment and NMR spectrometers in the "hands-on" mode. The duties of the SURFers, besides planning and carrying out the experimental work, performing analyses of the results, reporting progress (or not) in each weekly group meeting, and writing intermediate progress reports. All of this is accomplished with an overall aim of becoming acquainted with, understanding what it means, what it takes to see the research get done and to understand the lifetime enthusiasm that can be generated, along with critical thinking required in the process. Each of the SURFers is expected to prepare a final report and also make either a 20-min oral or a poster presentation on his/her project.

Many of our group complete their projects to the degree that, by end of the research period, they will have put together at least a first draft of a paper covering their results complete with graphics, tables and literature references. After review and reworking the manuscript as needed (usually not much), the paper is submitted. The next step is for the student authors to suggest changes in the manuscript in consideration of critical comments, if any, by the journal reviewers, and later check proof to complete the publication process.

Obviously, not all projects will get to the same degree of finality, but if not, their researchers (and also those who finish successfully) are expected to store properly labeled samples and index their notebooks, in case further analysis or experimental work is desired. The whole process is a 10-week microcosm of a four-year Ph.D. project and the students benefit greatly from it. Besides SURF, we have had several undergraduates and high-school students do important research during the school year.

Our current research projects are all centered on conformational analysis, most often on simple 1,2-disubstituted ethanes, $X-CH_2-CH_2-X$ or $X-CH_2-CH_2-Y$, for which we can expect three conformations, one trans (anti or antiperiplanar) and two gauche. Unraveling the conformational preferences of such systems will surely appear to many organic chemists as plowing over a well-known, well-understood field of organic chemistry, with little new to be gleaned beyond what is already well-explained in elementary textbooks. Further, many feel that if new information should be desired on some system of the type described above, it should be obtainable with sufficient accuracy by readily available, canned quantum-calculation programs. To adequately refute assertions of this kind would take more space than is available with the limitation on length of this article. However, some idea of the surprises and the problems which have been encountered with as simple a compound as succinic acid when its conformational preferences were studied as a function of degree of ionization, in aqueous and other protic solvents and compared with the corresponding results in aprotic solvents are detailed in a 2006 review article[102] as well as other papers, which are conveniently referenced in SciFinder.

Chemical Consulting

Beyond our own research, I have enjoyed a wonderful 58 years of consulting for the DuPont Company in a wide range of departments, including among other things such products as Dacron, explosives, Orlon, dyes, Neoprene, antiknock agents, fluoro compounds, Nylon, polyethylene formed with Ziegler-type catalysts, fire retardants, antistatic agents, elastomers, photo products, pigments, electronic materials, and NMR services. This lengthy period has been featured by enormous changes in the DuPont Company and in industrial research worldwide. When I started with them, there was a wonderful emphasis in the DuPont Central Research Department on basic research in chemistry, physics, and biology. As years went by, this changed dramatically to much narrower projects, centered on specific businesses and subject to timelines for progress, accompanied by a tendency to hire for the needs of specific projects rather than the best overall researchers for the Department. Along with DuPont, I was also engaged in shorter, more focused, consulting periods with the Oak Ridge National Laboratory, starting while still at MIT, and with the Dart Industries on pharmaceuticals around 1970. A number of legal consulting cases were also extremely interesting, including topics like isotactic polypropylene by ^{13}C NMR, weed killers, Vioxx, and end-group analysis of polyisobutylene among others.

The National Science Foundation (NSF)

A highly interesting period in my scientific life began in 1957 when I was invited by Walter R. Kirner, then director of the NSF Chemistry program, to be a member of his Chemistry Advisory Committee. The first meeting was held shortly after the launch of the Soviet Union's launch of their Sputnik satellite on October 5, 1957. The launch led to great anxiety being expressed as to the apparent failure of the United States to be able to lead in the space race, with strident calls for more support of scientific and engineering research and for future enhancement of the disciplines involved by enhancement of education particularly in universities and colleges. These were all themes, which were echoed by the NSF Director Alan Waterman in our first post-Sputnik meeting. In 1957, the NSF was housed in the historical Dolly Madison House across Pennsylvania Avenue from the White House. NSF had quite a meager annual budget to finance research in chemistry. The small budget reflected the ten or so troubled formative years of the Foundation, but Sputnik spurred many changes for the better, particularly for more fiscal support, which then led to more political and popular support.

The Chemistry Advisory Committee, which was supervised by Kirner, had a very important role in the awarding of research funds for chemistry. Kirner was an organic Ph.D. student with James Bryant Conant, who later became President of Harvard. Kirner was a real gentleman, an astute judge of people who recognized that, by 1957, he was not up to dealing with the details of the exploding contemporary postwar organic chemistry. In consequence, he deferred largely to the Committee's judgment as to which proposals to support and to what extent in dollars. The Committee was definitely blue ribbon, and Kirner was great at resolving differences of opinion.

After my chemistry committee term was up, I was appointed to the Physical Sciences Advisory Committee of the NSF, which had oversight of the areas of Chemistry, Physics, Geology, Astronomy, and Mathematics. This group had no direct fiscal responsibility but was involved in many presentations and discussions of policy regarding large and sometimes multidisciplinary projects with the NSF Division Director. A much-discussed project was the "Mohole," a plan to drill through the earth's crust and see what was to be seen below. Because the earth's crust is thinnest in the depths of the ocean, the idea was to do the drilling from a ship in the deepest practical water depth. The financial costs of doing all of this were quite enough to attract the close attention of Congress. It was my first exposure to the complex national politics of science when real money is involved. Although the expected time of my participation with these committees would normally have been four years, various reorganizations and the like kept me involved for seven years in all. The NSF was amusing in one way, because we kept hearing incessant rumors of undesirable directives that Congress was planning to implement to change the way the Foundation worked or was funded. In observing the results of these barrages, it seemed to me that the organization was like a big bowl of Jello. It quivered and shook when prodded, but seldom moved very much at all. It was very generous to me in support of my research for almost all of my career at Caltech. Significant other support came from the National Institutes of Health, particularly for ^{15}N NMR development and research.

The National Academy of Sciences

I was elected to The National Academy in 1956, rather earlier than would normally be expected, but I had the advantage of being well-known to a number of members at UCLA, Harvard, MIT, and Caltech. The Academy in 1956 had about one-fifth or so of the number of members it has now, and it was easy to get to know members in other disciplines as compared to the crush of present members. Then as now, a small fraction of the members were involved in the National Research Council, which actually carries on the investigations in large part sponsored and paid for by the Federal government, usually at the direction of Congress. The NAS members are not much engaged with the NRC, except in reviews of NRC reports, although the fraction working with that enterprise is not large as it could be or should be.

Very occasionally at business meetings, the members in general have been involved in an important way with decisions made by the NRC. A notable example was a speech made by John Edsall, a biologist at Harvard, decrying a decision made by a NRC committee of aviation specialists to foster a production program of commercial supersonic jets. Edsall was opposed on the grounds of upper atmosphere pollution and sonic booms. A motion against fostering the program was voted favorably by the members present, and the Chairman of the NRC Committee, Jerome C. Hunsaker, a well-known aerodynamicist at MIT, was clearly not pleased.

Another rather sticky question was about whether the Academy should undertake classified work with which the members at large were not well informed as to the objectives or the results. A decision was made to give somewhat more, but not really significant information, which caused one principled member to resign in protest. In recent years, discussions of such matters usually take place in the Council and do not involve the members directly, unless changes are proposed in the Academy's Bylaws or Constitution, both of which require approval by the members.

My part in the Academy governance included a term on the Council and being involved as an officer of the Chemistry Section and of Class 1 of Physical Sciences, as well as on the Committee on Science and Public Policy. In the past decade or so, I have argued strongly against the election of so many more members on the basis of much less interdisciplinary collegiality, less general involvement in the Academy's affairs, and a continual problem of providing space for the Academy's activities, especially at Annual Meetings. The members do not agree, the majority want more of their scientific and institutional colleagues to be elected and will almost always vote for electing more members per year, whenever the opportunity arises and regardless of whether it is good for the Academy or not.

Book Writing

Part of my professional life has been devoted to writing books. It has always seemed like an extension of personal mentoring of students. One of my first books was of tested recipes for preparation of organic compounds or the reagents needed for general synthetic work. This book was written as an Editor of a volume (*41*) for Organic Syntheses, which is a wonderful and magnanimous organization aiming to be of service to organic chemistry in many ways, initially through publication of books. This organization later supports the syntheses community through its Web site. As a member of the Board of Directors of Organic Syntheses for almost 30 years, it has been a great pleasure to see the acumen, efforts, and care so many individuals provided to keep the organization supported financially while providing fellowships and lectureships, along with the Roger Adams Award.

My first book on NMR spectroscopy,[93] published by McGraw-Hill, was carried out under the aegis of William A. Benjamin (Figure 33S), then a chemistry editor, who got it published as possibly the first advanced chemistry text with color graphics. Motivation for writing that book and others requires me to have "mission spirit". If no spirit, no book. However, spirited writing, especially if done in the heat of enthusiasm of discovering a new interesting field of research to write about, can lead to "*A Subject for Dummies*"-type books, which I can only try to justify by their being desired by many who want to learn about the subject. So far as I know, the readers were not necessarily harmed permanently thereby.

Not long after the success of the NMR book, Benjamin decided to start his own publishing company and asked if I would participate. It looked like it could be a fun project so I pitched in and spent a fair amount of time trying to temper his high-spirited approach to running the company and trying to convince my friends to buy stock. What Bill really wanted from me was an organic text, but that would take two to three years to put together. But as the company was to get going, he wanted a book to publish "right now" to show that the company was underway and that it was going to be different. I had been delving into the world of spin−spin splitting in NMR spectra with an initial boost from my colleague, Harden McConnell (Figure 34S, Supporting Information), and became sufficiently confident (or overconfident) enough and possessed of enough of the necessary missionary spirit to try to write about the quantum mechanics involved. Attending a two-week NSF meeting for college teachers in Durango, with Paul Bartlett and George Hammond as codiscussion leaders, provided just enough time and environment I needed to get a book written. Afternoons were free to do as one pleased, so I sat and wrote by a large window with a beautiful mountain view, and by the end of the two weeks I had a first draft of a short book with a very long title: *An Introduction to the Analysis of Spin−Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra.*[103] Benjamin devoted great care to the design of the spin−spin book, insisting on beautiful printing and graphics as well as a splashy dust cover with my portrait on the back. The readership was limited, but the book was elegant and even apparently liked by some experts. One researcher, David Grant of the University of Utah, thought it might be worth redoing as an introduction to quantum mechanics for chemists. With NMR, quantum mechanics is more easily taught than the quantum mechanics of electron binding in molecules, at least until one reaches multiple quantum coherences and density matrix theory. The genesis of my book, *Notes on Molecular Orbital Theory*,[33] also published with Benjamin, was discussed earlier.

The organic text that Benjamin wanted to publish started to come to life again, but as expected, it was a big job. The impetus for producing a text was originally generated by Cope, and I think he envisioned a jointly authored text by Cope, Sheehan, and Roberts (Roberts being the lowest man on the totem pole). At this point in time, I was teaching the first semester of organic and Sheehan the second, so the ball was in my court to get the project going. So I turned out a first chapter, but there seemed some lethargy on the part of the upper end of the triumvirate to

modify it or to produce additional chapters and the project rather quickly sank beneath the waves.

I made rather complete lecture notes when I started teaching the whole year of beginning Organic Chemistry at Caltech, and my colleague, Edwin Buchman (Figure 35S), suggested I get together a syllabus for student use. Buchman, who I first met in 1941, was an excellent chemist with a Ph.D. with von Braun in Germany. He had a self-effacing knack for mentoring both students as well as more advanced persons like Charles Coryell and me. He had apparently been made at least semiwealthy by his contributions to the Williams synthesis of vitamin B and stayed at Caltech for many years as a Research Associate doing independent research on synthesis of cyclobutadiene. I did do some work on a syllabus, but the time seemed to be ripe to get a text out. Fortunately, Marjorie Caserio (Figure 36S), from Bryn Mawr, had been a postdoctoral fellow with me for a couple of years and then became a Senior Postdoctoral Fellow before going to the Chemistry faculty at Irvine. Marjorie was a wonderful addition to our research group with great ideas and a quiet air of authority and was an outstanding writer of papers and reports. It was a natural to try to draw her in as coauthor of the projected text. We quickly worked out a system in which we each selected chapters to write and as they were drafted, sent to the other for suggestions, criticisms and rewriting as necessary. The finished text came out in a wonderfully uniform style. There were many new features in the text, especially the first significant incorporation of spectroscopy for organic structural analysis, problem sets integrated into the text, bond energies and calculations of heats of reaction, new or different explanations of organic structural theory and reaction intermediates, and tables of useful synthetic steps. Therefore, it seemed desirable to produce a syllabus to try out on the students at Caltech, other schools and for reviews by other faculty. The formula graphics were a special problem, because we wanted them to be as good as possible for the final compositor to copy faithfully for the actual text. The syllabus became ready in three sections in 1961−62, a period when typesetting of molecular structures for papers and books was still very crude. Fortunately, we had a secretary, Allene Luke, who was a master of using an IBM typewriter to prepare even quite complicated organic structures. When actual typesetting began, following a final edit of the syllabus text, it was at once clear that the selected compositor was simply incapable, with the then current techniques, to duplicate our desired structures. The only possible solution was to use Allene's formulas in the first edition. It was not as pretty as it could be, but the formulas had the atoms in the right places and the diagrams were certainly serviceable.

The book, *Basic Principles of Organic Chemistry* (1964),[104] even though amounting to 1315 pages, was successful in the sense that it was adopted by many of the best research universities and colleges. It was not a smash seller, because the next level down in rigor desired by many schools was the organic text authored by Morrison and Boyd,[105] a popular favorite for many years. However, my book with Marjorie was successful enough to get one of our four children through UCLA and the other three through Stanford.

As those who write popular textbooks know, the publisher puts on heavy pressure to produce new editions, workbooks, problem sets, and solutions. Benjamin also wanted a shorter, simpler edition to try to compete with Morrison and Boyd. Thus, Marjorie and I put together a shorter version, *Modern Organic Chemistry*,[106] that did pretty well but did not meet the publisher's expectations. A second try was achieved with the participation of Ross Stewart of the University of British Columbia. However, I cannot claim that this edition, *Organic Chemistry—Methane to Macromolecules*,[107] deprived Morrison and Boyd of any sizable fraction of their sales. A few years later, Marjorie and I put together another edition of *Basic Principles*,[108] again a heavyweight, that seemed to be more popular for professors to use to prepare their lectures than for them to adopt and then have to face up to student questioning as to what the authors were trying to teach them. I am convinced that it was the best organic text published up to its time and some beyond. Anyone wanting to test this assertion can download some or all of the text for free from the Caltech Library Web site, http://resolver.caltech.edu/CaltechBOOK:1977.001.

Two later Roberts books were *The Right Place at the Right Time*,[109] a member of the wonderful Jeffrey Seeman (Figure 37S) edited series of biographies of 25 organic chemists in his *Profiles, Pathways, and Dreams* series, and *ABC's of FT-NMR*.[110] The former is my detailed autobiography, at least up to 1989. Much of the material contained in my volume of the Seeman series is presented here in a different way and also represents a 20-year abbreviated update. With completion of correction of several errors in the text, the original volume will also be placed on the Caltech Web site mentioned above. The latter book was written to explain some of the fundamentals of NMR, particularly those which can be critical to getting good spectra in situations where standard spectrometer parameters are not likely to be the best choice. I am sure many rightly feel that this NMR book is unacceptably low level in that it glosses over too many of the common powerful multipulse spectral programs such as COSY, INADEQUAT, TOCSY, and so on of which there are now a very large number to deal with and few, if any, that are easy to explain.

Conclusion

As mentioned at the outset, I feel the important message of this Perspective is about mentoring and how it is so important to be exposed to, not just to improve one's science, but to impart understanding of ethical matters, also to provide an example how and where to speak one's mind, when situations arrive where people are believed to be going in the wrong direction(s) and need is felt to at least get them to think about what they are doing and why. No one individual can teach you all of that because it usually will take events in different contexts involving different people to point up the importance of any particular principle strongly enough to get it firmly to be part of your code for the right thing to do. Quite a few well-known scientists have set examples for me on how to think about what we are trying to do in research and, as a result, to do better science. However, I am still impressed with appreciation and admiration for those less well-known like William R. Crowell, G. Ross Robertson, Charles D. Coryell, and William G. Young, who provided a wonderful springboard very early on to get me into meaningful research in chemistry. I sometimes wonder why those worthies were willing to take so much time to help out. However, perhaps it is more rewarding to make visible progress in trying to convert a sow's ear to a silken purse than to add extra shine to an already brilliant Phi Beta Kappa.

Looking back over my life, there seem to be many who feel they have never had a chance to do really meaningful things. My take on this is that everyone has at least some of those

kinds of chances, but are too often unwilling to step into a rather less than certain situation. However, I have had chances like that and took them, but as I look backward, in fairness, I should note again that most of my chances involved far less risk in the time leading up to, and shortly after, World War II, than in the much more complex science and society of today's world, particularly when that world is now faced with the possible return of another Great Depression.

When people ask me how I am doing (meaning at 90), I find a quote from the 80-year-old renowned architect, Frank Gehry, expresses it well. "I do not feel like eighty. I guess you never think you are the age you are, and, as long as you do not look in a mirror, you are not."[111]

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Supporting Information Available: Photographs of key mentors and various pieces of equipment. This material is available free of charge via the Internet at http://pubs.acs.org.

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