

## THE BEGINNINGS OF PHYSICAL ORGANIC CHEMISTRY IN THE UNITED STATES (1)

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What is this physical organic chemistry that we emphasize in celebrating the centennial of the birth of C. K. Ingold? Some will say it is the study of organic reaction rates and mechanisms, others will include structural organic chemistry, and still others will bring theoretical chemistry under the tent. Whatever it covers, the general recognition of physical organic chemistry as a discipline in its own right is hardly more than sixty years old. However, there have been a great many workers studying reaction rates and mechanisms, structural and theoretical organic chemistry for more than one hundred years.

Another question is who are the real practitioners of physical organic chemistry. I chose to distinguish between what I call *organophysical* and *physical organic* chemists. I look at the first group as physical chemists, who, for one reason or the other, decided that the study of organic compounds needed their physical or theoretical tools to solve structures and/or to interpret reaction rates and reaction mechanisms. Some of the early key players on this side of the fence included G. N. Lewis, Linus Pauling, Henry Eyring, L. P. Hammett, K.S. Pitzer, and Richard Ogg.

The second group I take to be those who started with a more solid organic chemistry background and borrowed what they needed from the physical side to investigate mostly reaction rates and mechanisms. Included here are such worthies as J. B. Conant, F. C. Whitmore, Howard Lucas, M. S. Kharasch, Frank Mayo, W. G. Young, G. W. Wheland, Paul Bartlett, Frank Westheimer, and Saul Winstein.

The difference between these two groups of players is in the way they use organic compounds. The physical side almost invariably works with compounds off the shelf, or donated to them by their organic colleagues. The organic side, trained in the classical mode with a wealth of synthetic experience, has in their hands the

power to synthesize compounds that they can use to test particular predictions, or otherwise be critical to understanding structural elements relevant to the reactions they are studying.

I justify my definition of physical *organic chemistry* on the basis of the immense vitality that the organic chemists have brought to the field, and I choose in what follows to trace the course of the development of the field primarily and chauvinistically from the organic side. This approach greatly cuts down the task of covering the subject and leaves what I regard as the most interesting part of it.

The first person that I am aware to define physical organic chemistry, by that name, was Louis P. Hammett of Columbia, who made an indelible impression on studies of reactivity by organic chemists. Hammett's book of the title *Physical Organic Chemistry*(2), published in 1940, gave validity to the idea that here was an important new discipline and many organic chemists happily clambered aboard the ship. I think some liked the name, because it looked like they were a higher calling of organic chemists, just as some of my physical chemistry colleagues really like to be known as chemical physicists.

Great and influential books often have great prefaces. The one written by G. N. Lewis for his monumental book *Thermodynamics*(3) is classic in which he likened the development of chemistry to the building of a cathedral. The preface to Louis Hammett's book begins(2):

It is one of the commonest occurrences in the development of science that necessary subdivision of the field leads to a temporary neglect of phenomena lying on the borders between specialized fields. Sooner or later the deficiency becomes too patent to overlook, and a new specialty makes its appearance. Something of this sort has been happening in the last

two decades on the borderline between physical and organic chemistry. For a time it was almost a point of honor with both physical and organic chemists to profess ignorance of the other's field, and it remains a useful defense mechanism, if any is needed, to excuse the fact that specialization entails limitation as well as intensification of knowledge. Meanwhile there has grown up a body of fact, generalization, and theory that may properly be called *physical organic chemistry*. The name implies the investigation of the phenomena of organic chemistry by quantitative and mathematical methods.

He later goes on to say in a lovely paragraph, as pertinent today as fifty years ago:

A physicist colleague once mockingly referred to this kind of investigation as the study of soapmaking, whereas any respectable chemist must today busy himself with the chemistry of the nucleus. The remark underestimates both the theoretical and practical significance of soapmaking. Soap is by no means a negligible factor in human civilization; I am not sure that we know more about the fundamentals of soapmaking, which is to say ester hydrolysis, than we do about the nucleus; I think the theoretical problems involved are quite as interesting; and I am convinced that an understanding of the mechanism by which complex naturally occurring substances, the enzymes, accelerate hydrolysis would lead to a great advance toward the interpretation of the phenomena of life.

Louis Hammett might be affronted by my suggesting that he was really an organophysical chemist, but he and his coworkers certainly didn't synthesize many compounds. In the logical extreme, I suppose Sir Christopher Ingold might belong over the fence in the organophysical group, because he didn't do much synthesis either, despite the fact that he received his DSc with J. F. Thorpe. Perhaps he indeed he could, but the mechanisms of the reactions of methyl, ethyl, isopropyl and *tert*-butyl compounds were so poorly explored in his time that there was not much need to go a lot farther than the nearest shelf.

Having defined the field to my own taste, I turn to the question of how and when did physical organic chemistry get started in the United States. In what follows, I will ignore what it was called and focus on organic chemists who were doing what resembled physical organic chemistry as we think of it today.

In Melvin Calvin's recent autobiography, *Following the Trail of Light, A Scientific Odyssey*, you will find the following statements about his book with Branch (5), here somewhat abridged(4).

Actually, Hammett's book was published a year earlier and he had published a substantial review (6) of his ideas on reactivity of organic compounds six years before that.

Calvin goes on to say:

The publication of *The Theory of Organic Chemistry* in 1941 by Branch and me was the *beginning of theoretical organic chemistry in the United States* (emphasis supplied). Our book in effect organized all of organic chemistry in terms of electronic theory. Physical organic chemistry at Berkeley and the United States depends on Gilbert Lewis's electron-pair bond and Branch's evolution and development of that concept and stimulus not only for structure but for reactivity as well. The publication of the book made Berkeley one of the foremost centers in the United States for theoretical organic chemistry.

These statements ignore a lot of history. To be sure, Berkeley did become a center of physical organic chemistry, but less from the Branch and Calvin connection, than from the efforts of Streitwieser, Jensen, Dauben, Noyce, and so on who had very different roots. Indeed, the Branch and Calvin book, while excellent, in as far as it went, was substantially less influential than Hammett's book. Even more important with respect to the beginning of the field, Hammett himself recognized in his preface that what he recognized as physical organic chemistry had been going on at least two decades earlier.

What about before that? Stanley and Ann Tarbell, in their very useful book, *Essays on the History of Organic Chemistry in the United States, 1875-1955* (7) divide organic chemistry in the United States into three different periods. They take physical organic chemistry *per se* as starting in 1914, but they also define a period of studies on reaction rates and mechanisms from 1876-1913. Actually, the first reference they give is to R. B. Warder of the University of Cincinnati in 1881, the pioneer in the quantitative study of alkaline hydrolysis of esters. Warder showed the rate to be proportional to the product of the concentrations of ester and hydroxide ion (8). He also measured the changes of rate with temperature (9).

The Tarbells also comment on E. Emmett Reid of Johns Hopkins University. Reid lived to be 101 and was active to the end, writing a book, *My First Hundred Years* (10). His early research was on acid-catalyzed amide reactions (11-13), but he was particularly well known for his work on divalent sulfur compounds (14).

Arthur Michael (15) (Tufts and Harvard Universities) was another in this period who did what we could

call physical organic research. Michael was a firm believer in the application of thermodynamics to organic chemistry (16), but his efforts in this direction were couched in terms not easy to understand today and, at times, there seems to be confusion of enthalpy and free energy, as well as hand-waving. Among other things, Michael showed that the order of esterification of alcohols with trichloroacetic acid followed the order: methyl > ethyl > n-propyl > isobutyl and found that tertiary alcohols were slow(17).

Julius Stieglitz(18) (University of Chicago) made several contributions to organic mechanisms. In an 1899 paper(19) on imido compounds, he shifts gears and espouses the probability of carbonium ions as reaction intermediates; a concept he said Ostwald rejected out of hand. Another worker on organic reactivities was James F. Norris(20) (MIT), whose name endures in the Norris Awards of the Northeastern Section of the ACS. Norris apparently was the first to isolate triphenylmethyl carbonium salt, but he failed to recognize that carbonium ions might be involved in the formation and hydrolysis of *tert*-butyl chloride(21). Much of the early Norris work on reactivities was rather qualitative, but he did develop some useful ways of studying relative rates, such as of carboxylic acids with diaryldiazomethanes (22), although these rates were measured by gasometric rather than spectroscopic means.

Another pioneer that most of us know little about was Solomon F. Acree (Johns Hopkins University). The Tarbells(7) compare his work between 1904 and 1914 on kinetics and reaction mechanisms favorably with that of England's Arthur Lapworth, whom many regard as the father of physical organic chemistry. If you read some of Acree's very substantial output of papers, you will see that he was a person far ahead of his time with intelligence, style, and clarity. Among other things, he studied the mechanism of oxime formation, and suggested steric crowding to account for the difference in rate between acetone and diethyl ketone(23). His mechanism for oxime formation is quite modern, except that he had hydroxylammonium ion attacking the carbonyl compound in the rate-determining step. More than twenty years later, J. B. Conant(24) made a similar mistake for diazo coupling with phenols even though he had the benefit of, and used, the electronic theories of G.N. Lewis.

Acree(25) also studied the metathesis reactions of halides with alkoxides and other nucleophilic reagents. In this work, he examined a number of mechanistic possibilities involving ionic intermediates and clearly defined a number of intelligent questions as to what needed

to be found out. Acree also considered the importance of association and dissociation in the reactivity of metallic alkoxides(26, 27). Furthermore, he had some rather forward-looking ideas on enzyme mechanisms and recognized the possibility of an enzyme-substrate complex(28). Acree had a monumental polemic with Julius Stieglitz that matched, if not surpassed, the invective of the Ingold-Robinson battles some twenty years later(28). Acree clearly was a person who deserves a much better place in our consciousness as a really great, very early, physical organic chemist.

In their chapter about early studies of rates and mechanisms, the Tarbells omit three individuals whom they cover in other chapters and were enormously influential. One is J. U. Nef(29) (University of Chicago), who both introduced the idea of carbene intermediates and then oversold it by believing that carbenes were more common intermediates than they actually are(30). There also was Moses Gomberg(31) (University of Michigan) and his renowned work on the triphenylmethyl radical(32) which, it turned out was vigorously opposed by James F. Norris(33) of MIT. Last of the three was E. P. Kohler(34) (Harvard University), a person not heard so much about today as thirty years ago. Kohler discovered 1,4-addition of Grignard reagents to  $\alpha, \beta$  unsaturated carbonyl compounds as the result of adding phenylmagnesium bromide to benzalacetophenone(35). Kohler was an extraordinary teacher and spawned a number of brilliant doctoral students. His greatest contribution to physical organic chemistry was James B. Conant of whom more will be said shortly. The unusual reasons for Kohler's success as a teacher are movingly described in a short biography written by Conant(34).

I think it is fair to say that US physical organic chemistry got off to a very good start even prior to 1920, at which point Hammett suggests it began to emerge as a recognized discipline. The Tarbells divide their essays on US physical organic chemistry after 1913 into the periods of 1914-1939 and 1940-1955. The latter of these two periods is clearly the start of the relatively familiar modern physical organic era of Bartlett, Westheimer, Winstein, and so on that will not be covered here.

The great figures in the field between 1920 and 1940 seem to me to be Louis Hammett, Howard Lucas, Frank C. Whitmore, Morris Kharasch, and James B. Conant.

Hammett did wonderful work on the physical chemistry of acids and bases, particularly acidity functions(36-38) and relationships connecting structure with reactivity (6). Both of these were absolutely vital to the success of the emerging discipline, but he did not himself beget a lineage of students to carry on behind him, even though many others used and extended his ideas.

Howard Lucas(39) was a very perceptive and kindly man who only had a master's degree (Ohio State). Legend has it that he was hired by A. A. Noyes to teach organic chemistry at Caltech, but not bother the other chemists by doing odorous organic research. In the then, and still, yeasty Caltech environment, Lucas thrived and went on to start a substantial line of distinguished workers in physical organic chemistry. Lucas had two particularly outstanding students. One was W. G. Young, who is best known for his work on allylic rearrangements. The other was Saul Winstein, who had an enormous impact on the study of carbonium ions and neighboring group effects. Lucas started Winstein down the path on the stereochemistry of neighboring group effects in the course of his own studies of bromonium, chloronium, and iodonium intermediates(40-42). He was one of the very few chemists elected to the National Academy of Sciences without a PhD.

Lucas wrote a pathbreaking elementary organic textbook (43) published in 1936, which was probably the first to introduce, at that level, modern ideas of valence and thermodynamics to organic chemistry. An early chapter of this book details how the free energy changes in the reactions of hydrogen with halogens might be relevant to understanding the corresponding reactions of methane with halogens. Lucas also illustrated the use of bond energies to calculate the enthalpies of halogenation of methane. The treatment predates those of Morrison and Boyd(44) and of Roberts and Caserio(45) by more than twenty-five years. I remember my own professor of beginning organic chemistry telling our class that he did not understand the first chapter of the Lucas book, that we would not understand it either, and so he was going to skip over it.

Frank C. Whitmore(46) was an extraordinarily dynamic individual who brought Penn State to the forefront of organic chemistry. His specialty was hydrocarbons and particularly rearrangement reactions. He published a famous paper in 1932 correlating much of what was known about organic rearrangements(47). He told me that the referees were badly split on the merits of the paper. One thought it was unintelligible; one thought it was just right; and the third thought it was what everyone already knew!

Whitmore deserves enormous credit for his research on organosilicon compounds. He started this work because he was interested in seeing whether trimethylsilylmethyl chloride would behave in the same way as neopentyl chloride in  $S_N1$  and  $S_N2$  reactions(48). This line of work was carried on later by his able student, Leo Sommer. Whitmore published a very unusual

advanced chemistry book, that he said could be characterized as a one-volume *Beilstein* for practicing chemists(49). It is full of strange reactions and compounds that apparently just struck Whitmore's fancy.

Morris Kharasch(50) was another dynamic individual who, like Whitmore, was rather more devoted to exploratory organic chemistry than to the applications of physical theory. He is best known for his development of much free-radical chemistry. With his student, Frank Mayo, Kharasch tackled the existing mass of conflicting information as to the direction of addition of hydrobromic acid to alkenes. Kharasch and Mayo were the first to show that there is competition between normal and the anti-Markovnikoff additions, with the anti-Markovnikoff addition occurring by a free radical chain mechanism(51).

I think the evidence is very good that James Bryant Conant was by far the most influential of the early physical organic types. Conant had so many different careers that it is hard to believe that he could be great shakes as a researcher. However, between 1918 and 1933, in just fifteen years, he not only did some very important studies, but he launched the careers of Louis F. Fieser, Lyndon Small, Robert E. Lutz, W. R. Kirner, and A. H. Blatt, as well as three truly great physical organic chemists: Paul D. Bartlett, George Willard Wheland, and Frank H. Westheimer; each, in his own way, a master of the discipline.

Bartlett in his biography of Conant says(52):

I came to think of Conant as the most truly intelligent man I ever knew. For him, objectivity seemed to be a natural state of mind, rather than something for which one must strive. The habit of viewing the world as it revealed itself, rather than as he might wish it to be, was fundamental to Conant's professional, political and administrative life.

As I mentioned earlier, Conant did his Ph.D. work with E. P. Kohler at Harvard. This came about in an unusual way. When Conant was a student at Roxbury Latin School, he came under the influence of a superb science teacher, Newton Henry Black, who gave Conant very special attention and, in fact, arranged a life plan for Conant which included, not only undergraduate work at Harvard, but also graduate work with the great atomic weight chemist at Harvard, Theodore William Richards. However, before Conant graduated, he did some undergraduate research with Kohler, then newly arrived from Bryn Mawr College, that siphoned him off into organic chemistry. Conant said that Black never forgave him for departing from the plan, although later he and Black wrote a book together called *Practical Chemistry* (53).

It is not stated whether part of Black's plan was for Conant to marry T.W. Richard's daughter, but he did.

At the time Conant started his graduate work on cyclopropane compounds, Kohler had not previously worked in this area and Conant, in his thesis(54) which I read many years ago at Harvard, made a quite good survey of the chemistry of cyclopropane and also commented at length on its resemblance to double-bond chemistry. This survey is not much reflected in his two papers with Kohler published in 1917(55, 56). The research described there is not on simple cyclopropanes, but rather on highly substituted cyclopropane derivatives related to Kohler's beloved and much-studied benzalacetophenone. In these compounds, the three bonds of the cyclopropane ring were nonequivalent and Conant found conditions by which each could be opened selectively. Judging from his thesis and his papers with Kohler, it is clear that Conant had extensive and superior training as an organic chemist.

Many years later, when Conant was President of Harvard, he became quite disturbed about the way the Soviets were excoriating Pauling about resonance, and he offered to give his views on the dangers of mixing political ideology and science at a seminar at MIT. He started his seminar by saying that "Some years ago, I did my thesis work on cyclopropanes and it appears as though nothing has been done in the field since." This caused my colleagues and students much merriment, which Conant clearly did not understand. Later, I sent him some reprints and had a subsequent note from him conceding that indeed some progress had been made.

There was nothing in the Kohler and Conant papers about electrons or mechanisms, but Conant clearly had his ear to the ground because, in 1921, he published a paper(57) drawing on the, as yet unpublished, electronic theories of G.N. Lewis(58) to account for nucleophilic additions to carbonyl groups on the basis of the dipolar character of carbon-oxygen double bonds. Conant's first paper specifically on reaction mechanisms had to do with the formation of mustard gas from ethylene and sulfur dichloride(59). It is interesting that his student, Paul Bartlett, had an important research project on the mechanism of the hydrolysis of mustards during World War II(60, 61).

Conant developed a strong interest in the relationship between thermodynamic and rate properties and, in his work with Fieser and later others, investigated the reduction potentials of quinones as a function of structure(62-64). Conant was very versatile and broad ranging. Of particular importance, to physical organic chemistry, besides the reduction potential determinations, were his studies of:

1. Superacid solutions, in which he specifically uses that terminology, although the work involved acetic acid as the solvent(65).
2. Reactivity of organic chlorides to displacement by iodide ion in acetone, which turned out to be a useful procedure in qualitative organic analysis(66-68).
3. Kinetics and mechanism of coupling of diazonium salts with phenols (24), although as pointed out earlier, Conant postulated incorrectly from the kinetics that the diazotic acid and unionized phenol reacted in the rate-determining step. The currently accepted mechanism was established later by Wistar and Bartlett(69).
4. Kinetics of semicarbazone formation and the demonstration that, with a mixture of carbonyl compounds, one product could be the result of kinetic control, but another product could predominate at equilibrium(70).
5. Relative acidities of a wide range of weakly acidic hydrocarbons by determining whether or not a particular hydrocarbon salt would react with another acidic hydrocarbon(71).
6. The steric effects of strategically placed alkyl groups that substituted for aromatic groups in stabilizing free radicals(72).
7. The effects of high pressure in influencing the rates of polymerization(73).
8. Attempts to synthesize highly hindered alcohols, such as triisopropylcarbinol, by Grignard addition to carbonyl groups and, in consequence, the discovery that reduction by Grignard reagents could be strongly competitive with addition, when addition would lead to extensive steric crowding(74). F. C. Whitmore, who had been a student at Harvard at the same time as Conant, liked to say, "Conant was made President of Harvard because he tried to attach four isopropyl groups to a single carbon." Triisopropylcarbinol was not made until fifteen years later(75). Paul Bartlett carried on Conant's work and successfully prepared tri-tert-butylcarbinol as well as a number of other highly branched alcohols(76, 77).
9. Hemoglobin and chlorophyll; where, over the years, Conant applied the skills and knowledge he had honed as a physical organic chemist(78-88). Thus, he became perhaps the first of the now prevalent breed of physical bioorganic chemists.

This recital of Conant's research interests should leave no doubt that he was indeed a physical organic chemist with a skillful blend of organic and physical talents as well as a keen eye for important problems. Yet along with these achievements, Conant started a formidable dynasty of scholars through his students, Paul Bartlett, G. W. Wheland, and Frank Westheimer. Each went different ways.

Wheland was a postdoctoral fellow with Linus Pauling at Caltech and, although he published some experimental papers from the University of Chicago, he is best known through his wonderfully scholarly books.

The first covers the theory of resonance(89); the second goes over the same subject in greater detail(90); and the third, a detailed and thoughtful advanced organic chemistry book(91), deals with stereochemistry and reaction mechanisms.

Frank Westheimer has been enormously influential through his work with Kirkwood(92) on modification of the Bjerrum electrostatic analysis of the relative strengths of carboxylic acids by taking into account the structure of the solvent; with Mayer on the first true molecular mechanics calculations(93), the mechanism of the chromic acid oxidation of alcohols and the H/D kinetic isotope effect(94), and, perhaps even more, for his exemplary and pathbreaking applications of physical organic chemistry to the mechanisms of enzyme-catalyzed reactions(95).

Compared to Wheland and Westheimer, Bartlett has been the most deeply rooted in organic chemistry. Bartlett's paper(96) on the synthesis of apocamphanlyl chloride for the purpose of determining whether inversion is required for nucleophilic substitution and whether or not carbocations are energetically most favorable in the planar state is one of the most important papers ever published relating to physical organic chemistry. The reason is because this paper illustrates vividly the power of combining imagination with talent for organic syntheses and a sound knowledge of physical principles. Bartlett has been very broad ranging in his interests in physical organic chemistry. Among other things, he has been concerned with free radicals(97, 98), carbocation chemistry(77, 99-101), reactions of singlet oxygen(102), sulfur chemistry(103), cycloaddition reactions (104) and other bridgehead compounds(105, 106).

A wonderful example of the warmth and humor of Bartlett style is contained in his early-on analysis of papers in the carbocation field, *Non-Classical Carbonium Ions* (107). In his comments on H. C. Brown's famous polemic entitled *Strained Transition States* (108), Bartlett concludes by offering a multipart exam for the reader that deftly skewers many of Brown's arguments.

It should be clear from the above that general recognition of physical organic chemistry as a distinct discipline of chemistry in the United States came rather slowly. This was particularly true in the Midwest universities, except for the University of Chicago. I believe that it reached its pinnacle in the '60s to '80s and now seems on a rather steep decline as its experimental practitioners fade away, either through age, or by moving into subdisciplines such as bioorganic and organometallic chemistry, as well as materials science and photo-

chemistry. One enormous effect that the discipline has had has been to revitalize organic synthesis by both providing interesting compounds to make and also by providing deeper understanding of how synthetic reactions work. Another very important effect has been on inorganic chemistry, on the one hand, by example through its successful use of a combination of kinetics and structural theory and, on the other hand, by greatly broadening the study of organometallic compounds.

Much of what is left of physical organic chemistry, as judged by what is currently accepted for publication in the *Journal of the American Chemical Society*, is concerned with theoretical calculations at various levels of sophistication aimed at demonstrating the power of quantum mechanics and molecular mechanics to predict chemical phenomena. Such calculations are impressive in their fantastic use of number crunching with the aid of Cray or massively parallel computers. However, in my view, the results often seem sterile because, while lots of numbers are obtained, little or no qualitative understanding is provided of what those numbers mean.

Another problem is increasing specialization. Fifty years ago, there were many problems that just could not be tackled by any means whatsoever. The instrumentation revolution has made many changes in what we can study. As one example take conformational analysis of 1,2-disubstituted ethanes. There was not much an organic chemist could find out about conformational equilibria in aqueous solution fifty years ago. With NMR, an enormous amount of useful data can be obtained and one can easily become a specialist in data collection, analysis, and interpretation of such conformations. The result is formation of still another subspecialty of physical organic chemistry. The problem for each of us is how much we have to know about the various subspecialties to keep reasonably abreast of the field, much less worry about how much we need to appreciate the early work of Solomon F. Acree.

History shows that, like other sciences, chemistry progresses in cycles. New techniques, new classes of compounds, new instruments and new theories restore vitality to fields that seem to have leveled off. My prediction is that continuing application of physical organic principles laid down over the last seventy-five years or so to biochemistry will keep physical organic chemistry alive for a long time, even though it may well become better known as *biophysical organic chemistry*.

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Hargittai, Editor. We acknowledge with gratitude permission granted from Springer-Verlag to reprint it in somewhat modified form in this issue.

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