Physical organic chemistry after 50 years: It has changed, but is it still there?

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In 1940 a small volume by Louis P. Hammett entitled *Physical Organic Chemistry; Reaction Rates, Equilibria and Mechanisms* was published. The title neatly capsulizes the branch of chemical research which would become recognized as "Physical Organic." The kinetics of organic reactions had been studied by various workers since the fundamentals of kinetic theory were elucidated by van't Hoff in the 1880's and lively discussion of mechanisms and reactivity appeared in the 1930's. These included an acrimonious exchange in the literature between Robert Robinson and Christopher Ingold, British chemists who would both become knights of the realm. However, Hammett's clear and scholarly exposition provided a solid base from which an important chemical subdiscipline could be built.

The two types of reactions most studied in the late 40's and early 50's were electrophilic aromatic substitution and nucleophilic substitution, along with associated elimination reactions, at saturated carbon centers. Ingold and Hughes had distinguished between first order, S_N1, and second order, S_N2, reactions and the concepts had become generally accepted. The first order reactions were postulated to involve ionic dissociation of the substrate to produce carbocations, then called carbonium ions, which then reacted with nucleophiles to produce substitution products or shed protons forming products of elimination.

A tremendous amount of research was devoted to study of reactions attributed to the carbocations. These involved not only substitution and elimination reaction but a huge family of molecular rearrangements. The first to invoke cationic intermediates in rearrangement reactions was probably Frank Whitmore in 1932 although his contribution tended to be ignored, perhaps because he worked with reactions related to petroleum refining rather than with less complicated substrates such as alkyl halides, toluenesulfonate esters and quaternary ammonium salts.

Two other modes of study of mechanisms, stereochemistry and isotopic substitution, were used to probe mechanistic details not revealed by kinetics alone. Stereochemistry had earlier provided evidence that S_N2 reactions normally involve inversion of configuration at chiral reaction centers. However, the stereochemical course of S_N1 reactions was used with great elegance, especially by Donald Cram, to infer intimately detailed knowledge of the structures and behavior of the cationic intermediates. Coupled with results from the laboratory of Saul Winstein on the dramatic influence of stereochemical variation on the rates of some S_N1 reactions, Cram's results gave rise to the notion that some carbocations have "nonclassical" structures. The idea was consistent with results obtained by others, most notably John D. Roberts, using ^{14}C tracers to document shuffling of carbon atoms in ways not revealed by the unlabeled structures of the final reaction products. The results gave rise to another unseemly controversy primarily between Winstein and Herbert Brown, to which George Olah made important contribution by reports of nmr spectra of long-lived carbocations in super acid solutions. The question was really that of whose *model* better fitted experimental results. However, the protagonists spoke and wrote as though they were debating questions of absolute microphysical reality. Unfortunately, a large number of chemists around the world were diverted from more productive activity to contribute to what was little more than a semantic quarrel.

Other transient intermediates were also of great interest and importance. Free radicals had been postulated by Paneth as intermediates in vapor phase reactions many years earlier. However, in the 1930's William Waters suggested in his monograph, *Physical Aspects of Organic Chemistry*, that they could be involved in a number of reactions in solution with a notable example being the anti-Markovnikov addition of HBr to alkenes, a process discovered by Morris Kharasch and coworkers. The results were attributed to free radical chain reactions initiated by thermolysis of peroxides. Extensive study of radical reactions was

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stimulated by the realization that they are involved in polymerization of many vinyl monomers. Kharasch was responsible for much of the early work and two of his coworkers, Frank Mayo and Cheves Walling, became leaders in development of vinyl polymerization. Those two, Paul Bartlett and Herman Melville built the field of radical polymerization in the 1940's and early 1950's. The basic understanding from that work was exploited by dozens of research groups led by people considered to be prototypical, physical organic chemists.

Another class of intermediates, containing divalent carbon atoms, were suggested by John Nef early in this century but his ideas were generally rejected. However, the concept was revived with vigor when Philip Skell showed that: CCl_2, dichlorocarbone, was formed as a reaction intermediate. Carbene chemistry almost immediately became the subject of extensive physical organic research.

Results of a monumental study of nitration, a typical aromatic substitution reaction, were published from the Ingold/Hughes laboratory shortly after the end of World War. They amassed data from kinetics, spectroscopy, and measurement of the colligative properties of strong acid solutions which established unequivocal evidence that the nitronium ion, NO_2^+, was in most cases the attacking agent. They also determined variations in the timing of the reactions with various substrates and under varying conditions. Frank Westheimer also contributed an elegant study which was complementary to that of the University College group. The fact that the work was done and the timing of its release reflected the intensive research devoted to nitration during the war because of the importance of TNT and other nitro compounds as explosives. The work and its interpretation provided a conceptual base for nearly all subsequent discussions of electrophilic aromatic substitution.

Carbanions are a natural fourth group of organic transients to complement cations, free radicals and carbenes. Development of carbanion chemistry followed a somewhat different course, however, in that kinetic studies were not extensively used. The reasons are now fairly well-understood. Most of the species to which "anionic character" is attributed exist in solution tightly bound to cations in ion pairs and more complex aggregates. The role of cations in moderating the reactivity of highly reactive organometallic compounds was recognized in the 1940's by Avery Morton in reports which were largely ignored. Heroic efforts to carry out definitive kinetic study of solutions of Grignard reagents and organolithium compounds usually led to intolerably messy results. However, during the 1950's Cram brought considerable understanding to the field by use of his favored stereochemical methodology. Interestingly, an important extension of his work was demonstration that reactions of chiral compounds could lead to extensive asymmetric induction. The work was an intellectual forebear of what has now become the important field of chiral synthesis.

Elucidation of reaction mechanism was a dominant subject of physical organic research in the period 35-50 years ago. Another topic which was highlighted in Hammett's book, was quantitative study of relative reactivities. His classic empirical correlation of the effects of meta and para substituents on the reactivity of functional side chains in derivatives of benzene inspired extensive research using hisand parameters and the development of a host of other useful linear free energy relationships. Another seminal aspect of Hammett's treatment of reactivity was a concise and clear formulation of the Eyring–Polanyi theory of rate processes, i.e. the transition state model. Prior to 1950 most discussions of the electronic effects of remote substitutions, especially in aromatic compounds, was cast in a language created by Robinson. It involved "inductive" and "mesomeric" effects which were conceptually useful but showed little promise of generating quantitative models. In the 50's it became fashionable, and more enlightening, to speak of transition states which were mental constructs but which could be discussed in the same language as that used to analyze energetic relationships among stable molecules. The resonance method was usually employed in speculation concerning the energetic of the imagined transition states. The results were satisfying but still qualitative since the resonance method does not lend itself to simple quantitative treatment.

A small item in Hammett's book demonstrated his remarkable prescience. He gave a brief discussion of Erich Huckel's molecular orbital theory. Although the theory was initially ignored by most organic chemists it became popular when it was realized that it did indeed offer a wonderfully simple procedure for calculation of approximate energy relationships among similarly constituted molecules. Roberts led that surge of physical organic research but it owed a great deal to Robert Mulliken who laid out the theoretical basis for MO theory and to Charles Caulson and Christopher Longuet-Higgins who developed the approximate methods which made the mathematics doable.

Another group of reactive transients, electronically excited states of molecules, became a focus of attention in the 1960's when physical organikers discovered, and invaded, the field of photochemistry. One member of the Advisory Committee to the Chemistry Section of the National Science Foundation remarked that there was a quantitative relationship between the rate of decrease in the number of papers dealing with solvolysis and the increasing number involving photolysis.

The interaction between physical organic and both other branches of chemistry and biology has been a notable phenomenon. In fact it has been so strong that it is now virtually impossible to say who is a physical organiker and who is not. One early and dramatic example is the fact that Robert Woodward built his school of organic synthesis from a foundation based upon consideration of reaction mechanisms. The importance of free radicals in polymerization has been mentioned but other aspects of polymer chemistry have also been strongly impacted by physical organic concepts and methods. Polymerization of vinyl monomers initiated by anions and by organometallics were not first developed by organic chemists but they have taken an active role in developing the chemistries. Dye-sensitized photoinitiation of polymerization was first reported by Gerald Oster but has been largely developed by organic photochemists, such as David Eaton and Douglas Neckers, whom many would label as physical organic. Cationic polymerization of epoxides and vinyl ethers by photogenerated powerful acids was first demonstrated by Peter Pappas, an organic chemist, and extensively developed by Joseph Crivello whom most would call a polymer chemist. Organometallic chemistry has been a very active field for at least 30 years and the practitioners include both those whose original credentials were inorganic, e.g. Harry Gray, and a number who began in organic, e.g. Robert Bergman and Charles Casey.

Biochemistry and molecular biology as they are now practiced bear some marks of physical organic chemists who ventured into those fields. For example, Carl Nieman and Myron Bender studied the mechanisms of enzymatic hydrolysis of esters for years and contributed to the evolution of modern chemical enzymology. Unique contributions to chemical manipulation of nucleic acids is being done by Peter Dervan and others whose background is solidly physical organic.

Fifty years ago physical organic research was concerned mainly reactions in solution. The extent of fruitful cross cutting of classical disciplines is illustrated by more recent work with reactions in other phases of matter. Study of cations in the gas phase has been reported by John Brauman (icr) and Charles Depuy (ion draft mass spectrometry) who at least began their scientific lives as organic chemists. Research with structure, reactivity, and preparation of engineered surfaces is done by many chemists and physicists but important contributors have been physical organiker such as George Whitesides. There is now much emphasis on study, and control, of reactions carried on in more or less highly organized media ranging from liquid crystals, e.g. Richard Weiss, to zeolites (Eaton and V. Ramamurithy) who are physical organic chemists, at least by heritage. Such work is also done by a host of others with scientific pedigrees in other branches of chemistry or physics. The foregoing paragraphs are not intended in any way to "claim" for physical organic advances in the cited fields; it is an attempt to answer in part the question, "Where is physical organic chemistry today?" Are some polymer chemists and photochemists really physical organikers? Or has the discipline disappeared by assimilation into a number of other sciences? And does it matter how we answer the question? Science has progressed in marvelous ways during recent decades; nothing like it has ever before occurred. What was recognized as physical organic chemistry fifty years ago has contributed significantly to that progress. Of that we can be proud and it matters little what labels we choose to put on people and their work as long as it contributes to the ever forward thrust of science as a whole.

Reflection on the history of the field and importance of Louis Hammett in setting its direction bring to mind an interesting seed that he planted which has not yet come to fruition. The use of transition state theory in understanding structure-reactivity relationships was stimulated by his book. However, an important aspect of his presentation has been largely forgotten. He formulated rate constants *in the language of statistical mechanics.* An implication of that approach is that there are many states of the reacting system having energy equal to, or even higher than, the state in which the chemical transformation is accomplished. This is certainly the implication of Henry Eyring's postulate that "quasi equilibrium" is established between the transition state and other states of the reacting system. Hammett included the partition functions of the various states in his description. They are included in formulation of both the entropy and enthalpy of activation. Since the vibration modes of any of the systems are not known, and hard to guess, most discussion has been based on the presumption that the vibrational partition functions of

ground and transition states are essentially identical. If this were precisely true measured enthalpies of activation, H, would be the same as the internal energies of activation, E. This assumption has virtually always been made implicitly. Consequently reactions are discussed exclusively as excursions over potential surfaces. The powerful methods of modern theoretical chemistry used extensively to "calculate reaction paths" are all based upon the approximation. It is not my intent to denigrate such calculations, but the underlying assumption should not be forgotten. The point is not entirely trivial. Substantial activation entropies are often reported and they are usually regarded as changes in transitional entropy, not an unreasonable first assumption. However, in the reactions of polyatomic molecules other contributions to the changes in statistical entropy may be quite significant. Obvious examples are probably to be found in reactions in which steric effects are important since compression or release are likely to result in significant changes in vibrational partition functions. It is entirely possible that the statistical mechanical contributions may actually be dominant factors for reactions in solution which have low measured values of H. The prospect for explicit inclusion of such effects in theoretical calculations are vastly greater than was the case when Hammett's book was published. The methods of molecular mechanics are obviously applicable giving reasonable calculated approximation changes in the vibrational partition functions in reacting system. I have little double that such excursions will be made with great success in the near future. I don't know how the researchers will be classified, nor do I care. I do hope that some memory of the presentation of the problem by Louis Hammett will be recorded as part of the history.