

Physical Organic Chemistry in the 21st Century, Will it be Recognizable?

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Biography: Edward M. Arnett was born and raised in Philadelphia. He received his A. B., M. S., and Ph. D. (1947) from the University of Pennsylvania. After spending six years in industry and liberal arts teaching, he worked as a postdoctoral fellow with P. D. Bartlett's group at Harvard. In 1957 he moved to the University of Pittsburgh and from there to Duke University in 1980 where he held the R. J. Reynolds Chair of Chemistry until his retirement in 1992. Most of his work has lain in the detailed thermodynamic study of bond-making/breaking processes with particular reference to the stabilities of reactive intermediate carbocations, carbanions, and radicals. His group has made special use of reaction calorimetry and electrochemistry in solution to measure directly the heats of formation of these trivalent forms of carbon from neutral precursors. Other work has probed intermolecular forces by a variety of means including the use of chiral Langmuir-Blodgett monolayers to evaluate packing forces at interfaces. His work in physical organic chemistry has been recognized by a number of awards including the James Flack Norris Award, the ACS Award for Petroleum Chemistry, an Arthur C. Cope Scholar Award, and election to the U. S. National Academy of Sciences.

Futurology is a risky field. As a minor hobby, I have saved a variety of forecasts over the past forty years and have been impressed both with their successes and failures. Although it is dangerous to "steer by looking in the rearview mirror", our only reasonably objective guide into the future is by extrapolating perceived trends from the past. This is an especially risky time for predicting the futures of particular fields of science. The end of the Cold War has marked the end of one relationship between science and the public and it is by no means clear what new paradigm for research support will evolve or how long it will take to do so. Surely, the way priorities are set and the way funding is administered will play as determining a role for future chemistry as it has during the fifty years of the post- World War II era with which we are all familiar. More on this later.

Although one may point to important precedents, I will consider that physical organic chemistry as a coherent intellectual discipline was established in 1940 by the publication of Louis Hammett's ground-breaking volume which named the field. It would be hard for a graduate student in 1996 to imagine the parochialism of the faculties of physical and organic chemistry at that time. Across the intellectual gulf that separated them, the proud title *Physical Organic Chemistry* seemed to some a preposterous oxymoron. We can see now that Hammett's book was one of the first to identify, name, and develop an interdisciplinary field. More importantly, it introduced quantitative structure-energy relationships between thermodynamics and kinetics as a powerful general tool for analysing reactivity. *Physical Organic Chemistry* was so thoughtfully written and so fundamentally sound that it is virtually free of errors or overstatements even with the hindsight of 56 years of intense research.

Operationally and socially, the modern era of physical organic chemistry really began immediately after World War II, when many of the best and brightest young organic chemists returned to academe charged with energy to apply the burgeoning "electronic theory of reaction mechanisms" to the huge amorphous mass of organic chemistry. One may date physical organic chemists in the United States as a self-identified community conveniently from September 3, 1946, when the first *Conference on Organic Reaction Mechanisms* was held at Notre Dame University with Charles C. Price and Paul D. Bartlett as organizers.

The field as defined intellectually and operationally (physical organic chemistry is what physical organic chemists do) has evolved steadily and vigorously since then. Its methodology has become a permanent component of any rational approach to analysing the reactivity of any chemical system from the behavior of isolated small molecules in the gas phase to the extraordinary mechanisms that regulate the human body.

Sooner or later the term *physical organic chemistry* may fade away as the special designation *structure elucidation* did about 35 years ago, when new instrumental methods made the determination of structures a routine part of every study rather than a separate discipline. If so, the loss of a distinctive title for physical organic chemistry, although an occasion for nostalgia by some of its practitioners, would probably be a result of its general acceptance as the routine *modus operandi* for attacking chemical reactivity problems no longer needing a special name. Many trends by which one might hope to divine the future activities of physical organic chemists in the 21st Century are plotted easily by looking back at programs* for Conferences on Reaction Mechanisms, IUPAC, or Gordon Research Conferences on Physical Organic Chemistry through the five decades since 1946. *Ipsa facto*, a recurrent theme is the study of reactive intermediates and their proximal transition states.

Although stable free radicals, carbocations, and carbanions were well characterised by 1905, the role of highly reactive trivalent carbon intermediates was inferred in 1946 primarily from ingenious kinetic studies in solution. Every decade since has shown major advances in characterising species of higher and higher energy with shorter and shorter lifetimes until the latest conference programs advertise the direct study of transition states thanks to femtosecond spectroscopy! Some of the clearest evidence of the power of physical organic protocols is demonstrated by the final isolation and characterisation, under special conditions of media (*e.g.*, gas phase, superacids, superbases) or decreasing time scales, of transient species whose existence was predicted originally from classical kinetics in solution at ambient temperatures.

As a further check on reading the future, I turned to a report* of the *Workshop on Fundamental Research in Physical Organic* sponsored by the U. S. National Science Foundation in June, 1976; two-thirds of the way from 1946 to the present. Twenty-six active workers in the field, including this writer, spent three days evaluating the status and projected future for physical organic chemistry. During the three decades after 1946 a population explosion of physical organic chemists had staffed virtually all chemistry faculties around the world with the students of the students of the original leaders. Competition for more students to continue this process of reproduction was stretching the funds to support them to the limit and it was time to evaluate progress and

set priorities. Inevitably many of the hot areas of the three previous decades had been pretty well mined out. If one were planning a career, the probability of contributing anything really exciting to the solvolysis of bicyclic halides was too low by 1976 to justify any but the most imaginative research. Hundreds of the brightest students of the first generation of physical organic chemists had by now answered most of the original questions and had expanded the frontiers in dozens of new directions.

Although some topics which were important in the 1946 conference still received attention (*e.g.*, free radicals), others such as neighboring group participation, displacement reactions, resonance, and non-classical steric effects had taken a back seat to extensive sections entitled Reaction Intermediates and Transition States, Theory, New Methods of Characterization by Physical Means, Medium Effects, Excited States, Reactivity in Structured Environments, and three chapters on the interfaces to organometallic chemistry, biochemistry, and industry.

Of particular relevance to the present exercise in forecasting is the general success of the 1976 Workshop in predicting the near future. Although a few unexpected breakthroughs (*e.g.*, fullerenes) have burst onto the scene during the past two decades, most of the predicted areas which looked like good horses to back have run very well and may still deserve carefully placed bets into the next century.

Instrumentation: Much of the remarkable progress of the past fifty years is a direct result of the close and steady interaction between the instrument industry supplying powerful new tools for research, creative physical organic chemists applying them to important problems, and peer-reviewed granting agencies supplying the funds to capitalize laboratories and thus provide the market for developing new instruments. Until the mid 1950's the only commercial off-the-shelf instruments in common use were the Beckman pH meter and the DU spectrophotometer. The synergistic relationship between researchers, instrument makers, and federal grant support has generated a trend which can be extrapolated safely into the future as the invention of increasingly sophisticated, available, and user-friendly instrumentation both drives and responds to the advancing research frontier.

Computers: Any prognostication of science must give computer applications a central place. In 1946 the world's first (and therefore most advanced) electronic computer had scarcely the computing power of a modern give-away hand calculator and could run for only two or three minutes between needed replacement of one or more of its 18,000 vacuum tubes. From our present perspective, the discovery/invention of the semiconductor and subsequently the transistor must rank at the top of the technical advances of the 20th century, with practical computers as the most important of its applications. The spectacular application of the computer to chemistry provides one of the steepest and safest trends to project into the next century. Clearly, as computers get faster, more versatile, and cheaper, they will continue to be integrated into smarter, cheaper instruments that are increasingly powerful, adaptable, and user-friendly.

Computers have also provided the necessary tool for applying theoretical chemistry to computation. Like everything else related to computers, this field has become progressively more accessible and useful. It is probably true that some users of computational programs "do not really understand what they are doing" in the fundamental terms of a true theoretician. However, the same may be said of users of many other kinds of sophisticated equipment, and subtle errors can always catch the neophyte off guard. As computation enjoys wider and wider use, it will become more and more dependable as the data base of successes grows and its role for the average user is increasingly clarified.

A word must be added here for the enormous contribution that theoreticians have made to the understanding of organic reactivity through *qualitative theories*. Of these the illuminating principles of resonance, transition state theory, Hückel's rules, the Woodward-Hoffmann rules, and hard-soft acid-base generalizations carry the marks of simplicity and generality that betoken great elegance. They are teachable to first year organic chemistry students, yet they provide fundamental insight and predictive power that would amaze and delight the greatest chemists of a century ago. Although such contributions are rare they are of enormous intellectual power and one may hope that new advances of this type will continue to come during the next century.

Manipulation of Supermolecular Architecture through Intermolecular Forces: In the development of organic chemistry as a science, the 20th century has been the *era of the molecule*. Thanks to its mastery over the covalent bond, synthetic chemistry has been carried to the point where almost any molecule whose structure can be drawn according to the rules of valence can be synthesized and produced in large quantity if sufficiently profitable. Almost all of the thousand-odd pages of present day undergraduate organic textbooks are devoted to developing the basic skills for manipulating reactions of the functional groups and understanding them through the electronic theory of organic chemistry so that exquisite control of molecular construction in three dimensions is a straightforward rational process.

What is missing, or delegated to a chapter or two at the end of the book, is any discussion of the supermolecular systems constructed of intermolecular bonds that make up the non-liquid, non-crystalline organic world that surrounds the student everywhere he/she looks. A chapter or two on biochemistry usually provides some introduction to the forces that organize living systems with discussion of molecular recognition *par excellence* in replication through DNA or enzymes as catalysts. Brief reference to the properties of polymers may also be given. However, any real discussion of the relationships of gross physical properties such as hardness, flexibility, or flow of these wonderful systems of molecules, that are as close to you as your skin, is inevitably deferred in favor of simple molecular systems whose three-dimensional structures we know so well.

I predict unhesitatingly that some of the biggest advances and most active physical organic research in the early 21st century will be in developing the rational empirical background for control of supermolecular architecture of assemblies held together by intermolecular forces. Whether this is done under the rubric of physical organic chemistry, biophysics, material science, or polymer science it will be done and it will probably be done best by people who have a thorough grounding in the intimate details of three dimensional molecular structure and are

eager to relate it to physical interactions. The problems of characterising the structures of such systems are a major challenge, but the first ingenious studies of molecular recognition and engineered aggregation are appearing and should expand rapidly.

How About a New Textbook? The modern sophomore organic chemistry textbook may be regarded as an unqualified triumph of physical organic chemistry! A few moments for comparison with even the best of the classical textbooks of the 1940's will confirm completely the intellectual power and sophistication that is the payoff from fifty years investment in the serious investigation of electronic mechanisms of organic reactions. Instead of facing a seemingly endless jungle of unrelated reactions, organized only by functional groups and named arbitrarily for their discoverers, the student knows by Christmas the fundamental electrostatic driving forces for making and breaking two-electron bonds. By Easter he/she can understand **and predict** reactions which would have stymied more than one Nobel Laureate of even the late 1940's. All of this is built on simple, rational generalizations firmly established on basic physical principles by the efforts of three generations of physical organic chemists. What a magnificent tribute to those who had the foresight in the 1930's and 40's to believe, despite stern warnings to the contrary, that organic reactions really could be understood and controlled.

However, it now is clear that understanding and manipulating covalent bonds is not enough. It follows from the above discussion that it will soon be time for someone to write a new kind of textbook which provides a more balanced treatment of intermolecular forces and the properties of materials, probably at the cost of displacing some of the present elaborations of synthetic chemistry. It is worth recalling that a key moment in the revelation of DNA structure was when Watson and Crick were introduced to the hydrogen bond.

Students who have been trained from the first to think of the relationships between organization at the molecular level and the properties of observable macroscopic materials will be better prepared to move into a wide range of academic, medical, and industrial areas than those whose introductory education is limited by the present type of textbook. The next major step forward in learning the language of molecular science is well under way in bioorganic chemistry and the structure-energy relations of the physical organic chemistry of aggregated systems is the key.

How Research Will be Done: I have indicated that there is good precedent for believing that most of the really exciting areas of contemporary physical organic chemistry will continue their present trends into the future for at least a decade although their priorities for attention and funding may change as the principal questions are answered and new advances, many growing at the interfaces with other fields, reveal new opportunities. What is not clear yet is how the social demands of the post cold war period will affect the mix of completely untargeted research of very broad significance; basic, but goal-oriented work; and important, but routine, development. Physical organic chemists are well-positioned to continue through all of these approaches to scientific and technical problems.

The past 50 years have provided what may be a unique period of public support for single investigator academic research on an enormous range of basic questions. Now 1996 finds the U. S. heavily burdened with legacies of the Cold War: a colossal national debt, and some horrendously expensive environmental problems, on top of a wide range of other urgent social and technical problems. How well support for chemistry will fare against these other demands with a public whose respect for science has been characterised as "a mile wide and an inch deep" remains to be seen. Anti-intellectual anti-science forces on the extreme fringes of the religious right and academic left are challenging the position of unquestioned prestige that science has enjoyed for the past half century. Clearly, much of the future of physical organic chemistry in the 21st Century will depend on how the public will perceive the returned value on its investment of tax dollars in science. At one end of the scale, technologies on which the national economy and jobs depend are easy to understand. At the other end one must also recognize true public appreciation for the deep questions "who are we?" and "where did we come from?" by the significant support and interest given to astronomy, archeology, and paleontology, for example. Which of these sciences can answer the crude question "what have you done for me lately?" in purely utilitarian terms?

Barring major national disasters, there is every reason to believe that chemical research will continue as a major contributor to our future well-being. However, there is no guarantee that it will follow a linear extrapolation from the near past through the present. A serious public relations problem for chemistry actually lies in its much-touted role as "the central science". On the one hand it is so ubiquitous that it is taken too easily for granted, on the other the widespread use of chemicals can occasionally lead to serious accidents and many risks, both real and perceived, that engender *chemophobia* in the public mind.

It is likely that the mode of single investigator academic research to which most of us are accustomed will be replaced to a greater extent by interdisciplinary partnerships and team studies. Much of industrial research has moved in this direction and insofar as it is an effective way to solve specific problems and meet specific goals it will become increasingly established in academic and government laboratories. What sort of balance this may make with the present paradigm for doing chemistry remains to be seen. Undoubtedly adjustments will have to be made; for example how do you assign appropriate credit for team research toward a tenure decision for an assistant professor?

What can be said is that new ways of doing things usually cause anxiety but people adjust to them. Many possible flaws in the present system were pointed out during its early years as it was being proposed and established. Some predicted problems have turned out to be real (*i.e.*, too much time spent on writing and reviewing proposals); however, basically the system of peer-reviewed grants has been an outstanding success though there is no reason to think that it cannot be improved on or be adapted to future realities.

One way or the other, whatever it may be called in the future, the methodologies and protocols of physical organic chemistry are here to stay as part of the basic approach to molecular science.

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