

## Physical organic chemistry in the 21st century: Evanescent or transcendent?

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*Biography:* K. N. Houk is Professor of Chemistry at UCLA. Born in Tennessee, he received his Ph. D. with R. B. Woodward at Harvard in the orbital symmetry era. He has been on the faculty at LSU, Pittsburgh, and UCLA, where he has served as Chair of the Department of Chemistry and Biochemistry. He was Director of the Chemistry Division of the National Science Foundation and has served on the Photochemistry and Physical Organic Commissions of the IUPAC. He was awarded the James Flack Norris Award in Physical Organic Chemistry of the American Chemical Society in 1989.

Jeehiun K. Lee is an NIH postdoctoral fellow at UCLA. Born in New York, she was an undergraduate at Cornell, where she explored the mechanism of glycosidases with Bruce Ganem. She was a Department of Defense graduate student at Harvard with Joseph Grabowski, where she examined gas-phase organic reactivity. She is currently an NIH Fellow studying enzymatic and antibody catalysis using theoretical methods.

Physical organic chemistry was defined originally as “the investigation of the phenomena of organic chemistry by quantitative and mathematical methods” (1). Conceived as a new scientific specialty on the borderline between organic and physical chemistry, physical organic chemistry traditionally involves the exploration of organic structures and mechanisms using the techniques of physical chemistry. In 1996, has this field matured and faded away, or is it still a powerful sub-discipline of chemistry?

Our thesis, supported by a bit of history, a few anecdotes, and viewpoints of different generations, is that physical organic chemistry has transcended its original definitions and has spawned many different cutting-edge areas of organic chemistry. At the same time, the term “physical organic chemistry” is fading from usage as the problems of the past are replaced by a variety of new challenges that give their names to these sub-disciplines.

Physical organic chemistry was born in the 1930's during the heyday of organic mechanistic elucidation and led to broad understanding of the relationships between organic structures and the reactions they undergo. The detailed investigation of reactions in solution led to the deduction of properties not directly observable: the structures of reactive intermediates and transition states (2). The accomplishments of this era are most impressive and demonstrate the productive synergy from the union of two areas of science.

A notable example of such a perfect union is the famous nonclassical ion controversy. By kinetics, substituent effects, and product analyses - all “indirect” techniques from physical chemistry - it was possible to deduce the nature of this cation, and to differentiate very subtle differences in geometry and electronic structure for bridged cations (3). Saul Winstein and a host of other organic chemists involved in this area - Bartlett, Roberts, Brown, Olah, Schleyer, to name some of the most celebrated - left their indelible stamp of intellectual vigor and penetrating search for truth on the field. Because of the concentration of intellect and the heat of the arguments, the non-classical cation field was, for a time, synonymous with physical organic chemistry. Although some said that the contentious debates, especially between Winstein and Brown, damaged the field, the extraordinary detailing of mechanisms and structure was a major achievement of the human intellect.

Another fine example involves the understanding of the mechanisms and transition states of cycloadditions, both concerted as in the Diels-Alder reaction and stepwise as in [2+2] cycloadditions. Rolf Huisgen and Paul

Bartlett were among the leaders who used classic kinetic and stereochemical methods, early IR and NMR instrumentation, and theory to develop a detailed understanding of transition states and factors controlling rates. Not surprisingly, this field generated controversy also. The Huisgen-Firestone debates about experiments in the 1960's and 1970's and debates among many of us and Michael Dewar in the 1970's and 1980's about theoretical results carried on the tradition of public controversy associated with physical organic chemistry.

The heyday of physical organic chemistry was an era in which the search for detailed descriptions of mechanism yielded surprising new reactive intermediates, such as non-classical cations, biradicals, radical ions, and divalent carbon species, named "carbenes" by Doering, Winstein, and Woodward during a legendary "nocturnal taxi" ride.

After 40 years of extraordinary development in the elucidation and understanding of mechanisms, the 1970's brought an infusion of new physical methods and new types of physical organic chemistry. The Woodward-Hoffmann Rules are perhaps the most prominent example, which brought the predictive power of theory to organic reactivity. The discovery of a guiding principle of modern organic chemistry by premier synthetic chemist R. B. Woodward and a young physical chemist, Roald Hoffmann, is a paradigm for the achievements of physical organic chemistry. Before that time, Roberts' *Notes on MO Calculations* and Streitwieser's *MO Theory of Organic Chemistry* (4) defined organic theory on the basis of Hückel and perturbation theory. Computational methods were developed at about the same time as the Woodward-Hoffmann rules. This development was driven by Pople (CNDO/2, GAUSSIAN70 and successors) and Dewar (MINDO, MNDO, AM-1). These theoretical and computational advances created the field of theoretical organic chemistry from what was previously the very separate fields of physical organic chemistry and theoretical physical chemistry.

John Brauman also ushered in a new era in the 1970's by using traditionally analytical instrumentation to probe the mechanism and reactivity of organic species in the gas-phase. Such mechanistic studies were in the tradition of the famous solution studies done in decades past, only the environment had changed from a solvent to the gas phase.

From experimental and theoretical studies of half a century spanning from the 1930's to the 1980's, we now know the mechanisms of most types of organic reactions in solution. We can write a reasonable approximation of the structure of any intermediate or any transition state. Physical organic chemistry as *mechanistic* organic chemistry has been extraordinarily successful! Have we learned all there is to learn in this branch of science? "If one believes in science, one must accept the possibility - even the probability - that the great era of scientific discovery is over" (5). Is this true of physical organic chemistry?

The study of mechanism has become an adjunct to other questions, not the principle focus of a large number of organic chemists. Louis Hammett once quoted Katchalsky as saying: "the ultimate goal of every science is to become trivial, to become a well-controlled apparatus for the solution of schoolbook exercises for practical application in the construction of engines" (1). Has physical organic chemistry reached this goal, thus becoming a trivial endeavor?

### *Decidedly not!*

There has been a profound transformation of physical organic chemistry as the problems have changed and as physical organic chemistry has coalesced with other disciplines to produce new areas of chemistry.

In the 1990's, physical organic chemistry, like all previously extant sciences, has undergone a widening of definition. The use of physical methods to solve problems of interest to organic chemists has intensified. Physical organic now means everything from the use of physical methods to explore problems like femtosecond dynamics pioneered by Zewail (6), now applied to organic chemistry for biradical intermediates and the inversion of cyclooctatetraene (7), to complex biological problems, such as protein folding and the mechanism of signaling in cells (8). In some cases cutting-edge instrumentation gives the answer (COT), while in other cases traditional physical organic instrumentation such as UV-VIS, MS, NMR, and ESR yields the desired information. Only rarely are such studies called "physical organic chemistry," but they are known by newer, more glamorous names: femtochemistry, biophysics, immunochemistry.

Physical organic chemistry has disappeared as a specific field and has emerged as an overarching way of thinking, a way of doing science and approaching problems. Whether physical organic techniques are being

used to explore molecular structure, molecular recognition, or biological mechanisms, the approach is in the tradition of physical organic chemistry. Arthur Kornberg, noted molecular biologist, remarked that "Much of life can be understood in rational terms if expressed in the language of *chemistry*" (9). We would argue that much of organic and biological chemistry can be understood in the language of *physical organic chemistry*.

Several fields are the result of the expansion and combination of physical organic chemistry; they thrive today, and will expand and further sub-divide in the future. Such specialties include molecular recognition, self-assembly of surfaces, and bio-organic chemistry, including structures of DNA, RNA, proteins, antibodies, and sugars. Also important is the field of materials science, including the synthesis of fullerenes, dendrimers, conducting polymers, and nanostructures.

The ever-expanding power and pervasiveness of physical organic chemistry is clear. Paradoxically, the name is used less as it is replaced by newer names of smaller sub-disciplines. This particular trend has parallels in chemistry itself, as reflected in another passage from Arthur Kornberg: "The coalescence of the biological and medical sciences ... is based largely on their expression in a common language, chemistry. Understanding all of life ... as chemistry links the biological sciences with all the physical sciences ... yet the importance of chemistry as the foundation of all medical science is readily submerged and obscured by attention to specific and urgent problems" (9).

Physical organic chemistry brings a body of experience, a style of inquiry, and the most sophisticated modern techniques of physical chemistry to bear upon problems of contemporary interest. The year 2000 is only about 3.5 years away! We are confident that the strong influence of physical organic chemistry will continue into the twenty-first century. In answer to the question posed in our title, the label of a limited subfield of chemistry as "physical organic chemistry" is evanescent, but the influence of physical organic chemistry on the progress of science is transcendent.

## REFERENCES

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