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Whither Physical Organic Chemistry? Wither? Or Wider?

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Abstract

A personal view of the field of physical organic chemistry (broadly construed), its history, its current status, and what it may become in the future.

Keywords

molecular structure, chemical reactivity, transition state, methodology, definition of terms, applications

History of Physical Organic Chemistry

What is physical organic chemistry? One (circular) definition of physical organic chemistry is that it is the area of research that physical organic chemists work in. My definition is broader, including many aspects that might be excluded from organic chemistry. Physical organic chemistry is the study of whatever is interesting about the relationship between molecular structure and chemical reactions. In my opinion physical organic chemistry represents the intellectual basis of organic chemistry. It asks (and answers!) fundamental questions about how chemical substances behave, and it rationalizes that behavior.

Louis Hammett had supposed that it was possible to make quantitative the general principle of organic chemistry that like changes in structure produce like changes in reactivity.¹

He acknowledged that an inspiration for the Hammett equation (eq 1), relating rate constants to acidity constants of benzoic acids, was Brønsted's linear free-energy relationship (eq 2) between rate constants of proton transfer and equilibrium acidity constants. Hammett's equation established organic chemistry as a science with regularities, rather than only a collection of observations and preparations. His 1940 monograph, *Physical Organic Chemistry*,² was instrumental in giving a name to this field and establishing its credibility. It presented an early example of interdisciplinarity, which has become so popular today.

$$\log_{10}(k_X/k_H) = \rho \log(K_a^X/K_a^H) = \rho \sigma \quad (1)$$

$$\log_{10}(k_{HA}/k_{HA0}) = \rho \log(K_a^{HA}/K_a^{HA0}) \quad (2)$$

It is disgraceful that Hammett never won a Nobel Prize for his work. One explanation is that it would have been appropriate for him to share it with C. K. Ingold, who also wrote an influential book,³ but who had made enemies through his adoption of the "invective effect".⁴ Another, more depressing explanation is that the judges were misinformed, as I inferred from a dinner many years ago with a member of the Nobel Committee for Chemistry, who thought that Bob Taft deserved the prize more than Hammett did.

A concept key to the study of chemical reactions and to the field of physical-organic chemistry is the transition state. Treating the transition state as though it is in equilibrium with reactants converts a kinetic problem into a thermodynamic one, whereby reactivity can be described in terms of energetics and molecular structure. Although the theory is often attributed to Eyring, the idea of a transition state was used by Brønsted and by Bjerrum in accounting for the dependence on ionic strength of the rates of reactions between ions.⁵ Eyring's contribution was to use statistical mechanics to derive the pre-exponential factor, $k_B T/h$. Thus the rate constant of the Arrhenius equation (eq 1) was transformed into the "absolute" reaction rate constant (eq 2). However, that pre-exponential factor can be obtained simply by dimensional

analysis. All that is necessary is to seek a quantity with dimensions s^{-1} in terms of physical quantities that might conceivably be relevant to reactivity, such as Boltzmann's constant, Planck's constant, the speed of light, and the absolute temperature. The problem is expressed in eq 3, to be solved for the exponents w , x , y , and z . The solution is indeed $k_B T/h$, arbitrary to a multiplicative constant that can be identified with the transmission coefficient.

$$k = A e^{-E_A/RT} \quad (1)$$

$$k = e^{-\Delta G^\ddagger/RT} \quad (2)$$

$$s^{-1} = (\text{erg/K})^w (\text{erg}\cdot\text{s})^x (\text{cm/s})^y K^z \quad (3)$$

Historically the emphasis in physical organic chemistry was on solvolysis because conductometric measurements are convenient and give accurate values for rates of formation of ions. Unfortunately the long controversy over nonclassical carbocations gave a bad name to physical organic chemistry and reduced funding across the field. Nevertheless it did lead to Olah's development of superacid chemistry.⁶ It also led to the development of the Method of Isotopic Perturbation by Martin Saunders, who used it to demonstrate that the norbornyl cation is a single, symmetric structure and not a rapidly equilibrating mixture of two classical carbocations.⁷ This result documents the remarkable example of a transition state for a 1,2-alkyl shift that has been stabilized so much that it is lower in energy than the original carbocations, as illustrated in Fig. 1. Thus it becomes possible to extrapolate from this stable minimum to the structure of the elusive transition-state maximum. We subsequently adapted Saunders' method to test whether hydrogen bonds that were thought to be single symmetric structures are instead a mixture of solvatomers,⁸ where solvatomers are defined as isomers (or, as in this case, tautomers) that differ in their solvation.⁹

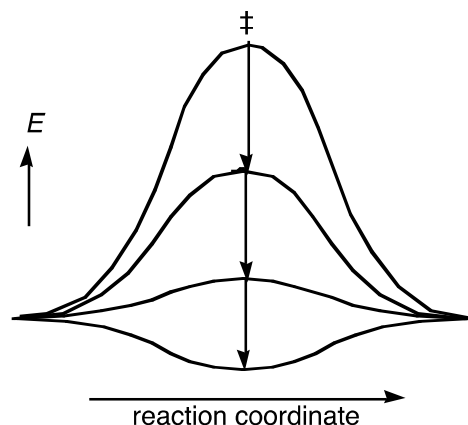


Figure 1. Energy diagram for 1,2-alkyl shift, with increasing stabilization of the transition state.

One stimulating feature of research in physical-organic chemistry was the access to popular organic seminars. As presided over by Woodward at Harvard and by Winstein at UCLA those seminars addressed current topics of research, sometimes presented by visiting researchers and sometimes dedicated to topics of interest to the organizer. The discussion was free, allowing in-depth consideration. A key feature was that they were open-ended, with no fixed closing time, sometimes lasting until 1 AM, when the subject was finally exhausted, along with some of the participants.

In my view organic chemistry can be considered as an example of an abstract algebra. An abstract algebra consists of a collection of elements, along with an operation that converts one or more of those elements into another element. To chemists the most familiar example of an abstract algebra is group theory, where the elements are symmetry operations and the product of two elements is another symmetry operation. Thus in the abstract algebra that is organic chemistry the elements are all possible substances, which can be combined into other substances according to specified rules. Our task is to determine what those rules are.

When I took introductory organic chemistry from Louis Fieser, it was largely descriptive, based on classification by functional groups and with little mechanistic

understanding. That same year I was also taking calculus, which was a sharp contrast. In math classes the axioms and postulates were stated and we next used those axioms and postulates to prove the theorems, which we needed to solve the problems. In organic chemistry we were given the theorems, in the form of examples of chemical reactions that are known to occur, but to solve the problems we needed to intuit what the axioms and postulates must be. Now those axioms and postulates are codified as the principles of organic chemistry.

In those early days theories of reactivity focused on the structure of the reactant rather than on the energetics of the transition state. For example, a methoxy substituent was understood to be activating and ortho/para directing in electrophilic aromatic substitution because of the additional resonance forms in Fig. 2a available to methoxybenzene (**1**). Similarly, a nitro substituent was understood to be deactivating and meta directing in electrophilic aromatic substitution and activating and ortho/para directing in nucleophilic aromatic substitution because of the additional resonance forms in Fig. 2b available to nitrobenzene (**2**). An example that shows the fallacy of that approach is the directive effect of a nitroso group. Either it is activating and ortho/para directing in electrophilic aromatic substitution, owing to the additional resonance forms **3abc** of nitrosobenzene in Fig. 3a, or it is deactivating and meta directing in electrophilic aromatic substitution and activating and ortho/para directing in nucleophilic aromatic substitution, owing to the additional resonance forms **3def** in Fig. 3b. It cannot be both, because one or the other of those sets of resonance forms must dominate. In fact a nitroso group is activating for both electrophilic aromatic substitution and nucleophilic aromatic substitution, because the intermediates (**4,5** in Fig. 4) and transition states in both substitution reactions are stabilized by the nitroso group.

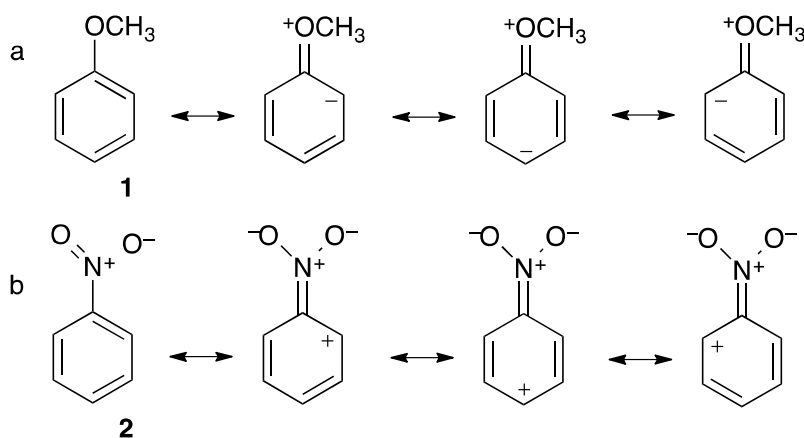


Figure 2. Resonance forms of (a) anisole (1) and (b) nitrobenzene (2), which accounted for the activating and deactivating effects of methoxy and nitro substituents.

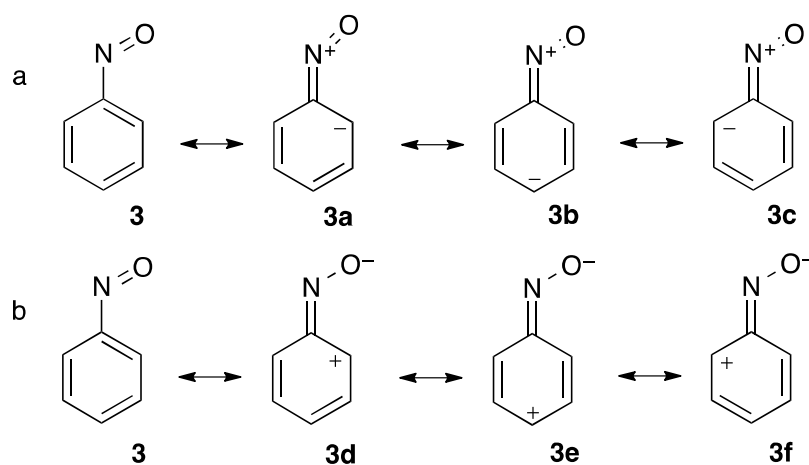


Figure 3. Resonance forms of nitrosobenzene (3), which would account for either an activating (a) or a deactivating (b) effect of a nitroso substituent.

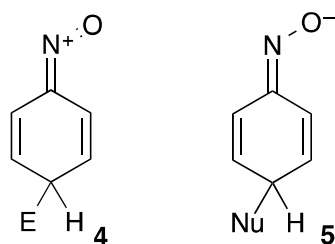


Figure 4. Intermediates in electrophilic (4) and nucleophilic (5) aromatic substitution on nitrosobenzene, accounting for the activating effect of a nitroso substituent on *both* reactions.

One of the intellectual triumphs of organic chemistry is the Woodward-Hoffmann Rules for pericyclic reactions.¹⁰ Hoffmann developed his theory initially by calculating the molecular

orbitals of the reactant rather than the energetics of the transition state. Fortunately Woodward and Hoffmann abandoned this old-fashioned approach and expanded their theory by following the energy along the reaction coordinate, leading to the Principle of Conservation of Orbital Symmetry. I regret that during the Thursday night seminars that I attended Woodward never disclosed his puzzlements regarding pericyclic reactions. I had read Streitwieser's book on MO theory,¹¹ so I would have recognized the relevance of aromatic transition states,¹² as subsequently presented by Dewar and Zimmerman.¹³

Physical organic chemists have always been willing to adopt new methodology and instrumentation. J. D. Roberts brought nuclear magnetic resonance to organic chemistry, and NMR has revolutionized structure determination. It has made organic chemistry a deductive science. Frank Westheimer and Bill Jencks applied the methodology of physical organic chemistry to biochemistry. Their research was a fitting counterpart to Hammett's, in that it established biochemistry as another science with regularities of reactivity that could be addressed quantitatively. One of the heroes of structural and mechanistic chemistry was Linus Pauling. Many chemists have told me that his book, *The Nature of the Chemical Bond*,¹⁴ was especially influential in their careers. It engendered a confidence that everything is knowable and understandable. Pauling had a very strong visual sense, which unfortunately limited him to localized pictures, and he never embraced the delocalized picture of molecular orbital theory that has been so powerful. I regret that I cannot give credit to all who have advanced the field, but I recommend two excellent reviews on the history of physical organic chemistry in Britain and in the US.¹⁵

Physical Organic Chemistry Today

Physical organic chemistry has become a victim of its own success. Even if few are

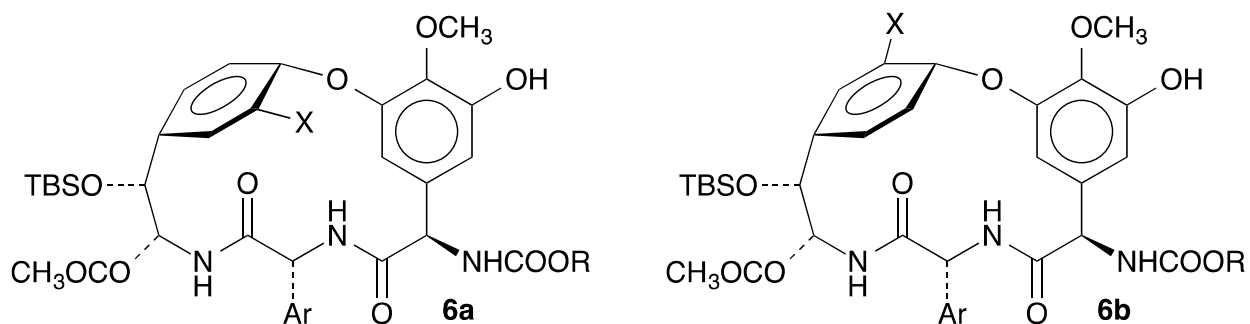
engaged directly in research whose methodology would be distinctively physical organic chemistry, its conclusions have been thoroughly adopted by synthetic organic and inorganic chemists and by mechanistic biochemists.

A strength of physical organic chemists is their fearlessness in adopting new instrumental techniques. Structure determination has been revolutionized by X-ray, mass spectrometry, and multinuclear NMR. Measurement of rate processes is now extended to faster reactions, to picosecond and femtosecond scale. Matrix isolation permits the study of reactive species. Photochemistry opens the possibility of novel synthetic methods and the new realm of excited-state structures, where the restriction of Lewis structures to ground states requires the application of molecular-orbital theory. Much insight is provided by computations, which can address questions about structures that are too unstable to be studied experimentally.

Modern synthetic chemistry owes a great debt to physical organic chemistry, which informs the development of reagents and of new reactions and the control of reaction conditions and of solvent.

One elegant example of the application of principles of physical organic chemistry to organic synthesis appears in Boger's total synthesis of vancomycin aglycon.¹⁶ The synthetic intermediate **6a** (R, Ar, and TBS immaterial) was obtained, along with diastereomer **6b**, differing in the orientation of the two perpendicular aromatic rings. At elevated temperatures in *o*-dichlorobenzene these could be converted to a 1:1 equilibrium mixture of the two, from which the desired **6a** could be separated and the other recycled. For X = Cl the activation energy for the equilibration is 30.4 kcal/mol, whereas for X = NO₂ it is considerably lower, 26.6 kcal/mol, because delocalization of an oxygen lone pair to the nitro group stabilizes the transition state, in which the two aromatic rings are coplanar. This difference made it possible to equilibrate the diastereomers when X = NO₂ and then preserve the stereochemistry by

converting NO₂ to Cl.



A course in physical organic chemistry is currently still offered in most US colleges and universities, although often by someone whose research is not dedicated to physical organic chemistry *per se*. Many excellent textbooks are available, including the old but instructive one by Lowry and Richardson,¹⁷ a readable one by Carroll,¹⁸ and a more advanced but idiosyncratic one by Anslyn and Dougherty.¹⁹ There is also the comprehensive textbook of advanced organic chemistry with a strong foundation in physical organic chemistry by Carey & Sundberg,²⁰ and also the compendium of organic chemistry originally by March and frequently updated.²¹ My own teaching has encompassed part of our introductory sequence in organic chemistry, for majors in chemistry, biochemistry, pharmacological chemistry, and biology, plus more advanced courses in Structure & Properties of Organic Molecules, Kinetics & Mechanism, and Applied Spectroscopy, all aimed at the average organic chemist. I also created a course on mathematics for chemists, for which I wrote a textbook.²²

Physical organic chemistry relies heavily on logic, a skill that is often underdeveloped in students. We must remember that it is not possible to prove a mechanism. We can, however, follow the implications of a possible mechanism to experimental tests. If the results of those experiments are what the mechanism predicted, the mechanism has withstood the test. If the results of those experiments do not match what the mechanism predicted, the mechanism must

be rejected, or at least modified.

One of the goals of physical organic chemistry is the precise definition of terms. This is often not possible, because those terms arose historically and new techniques arise to probe them. Examples include aromaticity, hydrogen bonding, electronegativity, and atomic charge. Besides, scientists are always seeking to transcend boundaries and explore the limits of those definitions. Nevertheless a group of us, working under the auspices of the International Union of Pure & Applied Chemistry, succeeded in assembling a Glossary of Terms Used in Physical Organic Chemistry,²³ available also in Finnish, Polish, and Russian translations.

The international chemical community has become more unified since the time when graduate students were required to have a reading knowledge of German and either French or Russian. When I arrived at UCSD, that was still the requirement. Joe Mayer had been a post-doc in Göttingen and believed that an educated scientist ought to know a foreign language. Although that is a worthy goal, there is too much else to learn on the way to a Ph.D. Therefore I argued against the requirement and maintained that for many students, especially the biochemists, the relevant literature was exclusively in English. For some years I proposed to permit Fortran, or any other computer language, as an acceptable option. At one time I urged my colleagues to accept Italian as satisfying the requirement for a student who grew up in a bilingual family. They relented, with the proviso that I find a suitable paper to assign and then administer the exam. Unfortunately the chemical terminology in the paper was not part of the vocabulary he learned at his mother's lap, and I could not honestly pass him. Eventually he found an Italian speaker in the Department of Romance Languages who would pass him. Nevertheless, it took many more years to abolish our Departmental requirement.

Now English has become the universal language of science, used at nearly every conference. As a native English speaker I feel obligated to participate, even to asking stupid

questions. I sympathize with speakers whose native language is not English, but I strongly encourage all students to attempt to speak English in order to promote their futures in science.

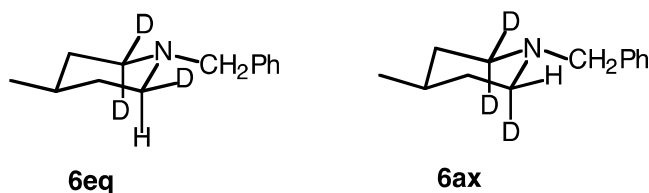
It should be noted that quite a few organic chemists have succeeded as high-level academic administrators: Among them are Robert Caret (President, Towson University, San Jose State, and University of Massachusetts), James B. Conant (President, Harvard), Marye Anne Fox (Chancellor, North Carolina State and Univ Calif San Diego), Greg Geoffroy (President, Iowa State), Ira Remsen (President, Johns Hopkins), John P. Schaefer (President, University of Arizona), Helmut Schwarz (President, Alexander von Humboldt Foundation), Chih-Huey Wong (President, Academia Sinica), and Mark Wrighton (President, Washington University in St. Louis). These were not all physical organic chemists, but they were equipped to deal with administrative challenges by their broad training which fostered the ability to analyze quantitatively and to deal with uncertainties and incomplete information.

When people ask what my research involves, I answer that we are trying to learn how molecular structure determines chemical reactivity. I served as Chair of the IUPAC Subcommittee on Physical Organic Chemistry and changed its name to the Subcommittee on Structure and Mechanism.

One of the strengths of physical organic chemistry has been the ability to design and synthesize molecules. The inside covers of the 1964 edition of *Organic Chemistry* by Cram & Hammond showed a gallery of 29 unusual molecules that were presented as challenges to synthesis. By the next edition, in 1970, half the molecules had been synthesized. Many such structures are intriguing, often of pleasing symmetry, or were designed to test a hypothesis regarding bonding or reactivity. Often the challenge was to design the precise molecule that isolates the feature being assessed.

I am proud of one such molecule, 1-benzyl-4-methylpiperidine-2,2,6- d_3 , which we

synthesized as a mixture of two isotopomers (isomers that differ in the position of an isotope), **6eq** and **6ax**.²⁴ The goal was to measure their relative basicity. Such a measurement, on substances that are so very similar, was made possible by an exceptionally accurate NMR titration method.²⁵ We found that the isotopomer **6ax** with deuterium axial is more basic, with $K_a^{\text{eq}}/K_a^{\text{ax}} = 1.060 \pm 0.006$.²⁶ This result supported our hypothesis that secondary deuterium isotope effects on basicity are of stereoelectronic origin. It ruled out an alternative hypothesis that the effect is of inductive origin, arising from interaction of the N^+ in the conjugate acid with the C-H or C-D dipole moment, an interaction that would be independent of dihedral angle.



The breadth of modern physical organic chemistry is quite remarkable: At the ACS symposium for the most recent (2015) James Flack Norris Award in Physical Organic Chemistry, the awardee's talk was on classical but somewhat atypical physical organic chemistry, addressing isotope effects, stereochemical aspects of reactivity, and structure of hydrogen bonds.²⁷ However, the other talks, by researchers who had been associated with the awardee, were on substituent effects on the stability of aryl trifluoroborates,²⁸ dynamic combinatorial chemistry to select receptors for peptides containing methylated lysines and arginines,²⁹ stereoselectivity in addition of ethylzinc to carbonyl groups,³⁰ and a critical assessment of cation- π interactions.³¹

This breadth is in marked contrast to early physical-organic chemistry, which had dealt with a narrow area of kinetics and mechanisms of reactions in solution. A strength of physical-

organic chemistry is its ability to connect with other fields, including solid-state and supramolecular chemistry, gas-phase reactions, computation, biochemistry, and materials. Indeed, a large proportion of recent Nobel Prizes in Chemistry have been awarded for advances in various areas of structure and mechanism, as listed in Table 1.

Table 1. Recent Nobel Prizes in Chemistry for advances in structure and mechanism, broadly construed.

Year	Awardees	Prize-winning Research
1987	Donald J. Cram, Jean-Marie Lehn, Charles J. Pedersen	host-guest chemistry
1989	Sidney Altman, Thomas R. Cech	catalytic RNA
1990	E. J. Corey	methodology of organic synthesis
1992	Rudolph A. Marcus	theory of electron transfer reactions
1994	George A. Olah	carbocation chemistry
1995	Paul J. Crutzen, Mario J. Molina, F. Sherwood Rowland	formation and decomposition of ozone
1996	Robert F. Curl Jr., Harold W. Kroto, Richard E. Smalley	fullerenes
1998	Walter Kohn, John A. Pople	computational quantum chemistry
1999	Ahmed H. Zewail	spectroscopy of transition states
2000	Alan J. Heeger, Alan G. MacDiarmid, Hideki Shirakawa	conductive polymers
2001	William S. Knowles, Ryoji Noyori, K. Barry Sharpless	chiral hydrogenations and oxidations
2005	Yves Chauvin, Robert H. Grubbs, Richard R. Schrock	olefin metathesis
2007	Gerhard Ertl	heterogeneous catalysis
2010	Richard F. Heck, Ei-ichi Negishi, Akira Suzuki	palladium-catalyzed cross coupling
2013	Martin Karplus, Michael Levitt, Arieh Warshel	multiscale models for complex systems

The Future of Physical Organic Chemistry

In 1997, as a guide to future prospects for research, IUPAC Commission III.2 organized a Symposium in Print, "Physical Organic Chemistry in the 21st Century".³² The authors were

Edward M. Arnett, Ron Breslow, Fulvio Cacace, Jan Engberts, Marye Anne Fox, Ken Houk, Keith Ingold, Alan Katritzky, Ed Kosower, Meir Lahav, Teruaki Mukaiyama, Oleg Nefedov, George Olah, John D. Roberts, Jean-Michel Savéant, Detlef Schröder, Christoph Heineman, Helmut Schwarz, Andrew Streitwieser, Daniel Bellus, Frank Westheimer, and Akio Yamamoto. I will not try to second-guess these illustrious thinkers, but I will speculate on where physical organic chemistry may progress further.

We face many challenges to find improvements in existing technology. One of the strengths of physical organic chemistry is the ability to explore and predict the effects of small variations. Admittedly this is a pedestrian approach that lacks a bold new vision, but it will provide incremental improvements that represent true but limited success. Among the areas where this approach offers promise is in the development of new synthetic methods and new catalysts, with improved control over yield and stereoselectivity. In the chemical industry the task of scaling up a synthetic procedure lies with process chemists, who must contend with the mechanics of mixing, control of temperature, and the fate of byproducts and solvents, but that is no different from applied physical organic chemistry. Moreover, there is considerable opportunity beyond the confines of organic chemistry, such as in the areas of organometallics, bioorganic chemistry, molecular recognition of polysaccharides, and catalysis by proteins and nucleic acids.

Other challenges for the future will require a concerted effort that draws upon all those areas. We must find an alternative source for all the raw materials that we now obtain from petroleum. To conserve that limited resource, we cannot continue to burn it simply for its energy content. Instead we must develop a renewable energy source. Conversion of the sun's energy requires high-efficiency solar cells and high-capacity storage batteries. Large-scale production of electricity from wind farms or from hydroelectric power requires materials with

strength and stability for long-term use. All of these are projects where the methodology of physical organic chemistry can provide insight into finding solutions.

However, I doubt that physical organic chemists will continue to design and synthesize molecules to test a hypothesis regarding bonding or reactivity. Instead molecules and materials will be designed and synthesized to exhibit desired properties, such as conductivity, optical conversion, and sequestration, that make them useful in devices. Physical organic chemistry has lost much of its intellectual style and has become much more applied. One currently fashionable area that I expect will atrophy is the synthesis of molecules that can only be described as cute. They are molecules with evocative shapes or molecules that perform a nanoscale operation. However, they provide no new understanding and demonstrate only that an elaborate synthetic procedure succeeded as planned. Unless those substances can perform useful operations, their synthesis will not justify the expense.

Certainly computational organic chemistry has a strong future, led by the early proponents Streitwieser, Dewar, and Hoffmann and continued by Schleyer. I am continually amazed by the increasing power of computers. In college I took a course on computer programming where the final exam was to program in machine language a table-size computer to calculate the sine of an arbitrary angle! As a graduate student I was the lab's expert on linear least-squares analysis because I knew how to operate efficiently the table-top computer with four memory registers. As a post-doc I wrote a massive Fortran program to analyze multicomponent kinetics. Now Excel spreadsheets greatly facilitate analysis of our kinetic data. And my students and I do DFT calculations of structure and energy on a desktop Mac, because the Gaussian program has made such calculations accessible to nontheoreticians. The cost of computation has diminished relative to the costs of laboratory instrumentation, supplies, and safety, so that a large number of chemists worldwide are able to participate in the research

enterprise. Moreover, computational chemistry makes it possible to adequately address weaker interactions, including hydrogen-bonding, halogen-bonding, cation- π interactions, and π stacking, and to model intermolecular forces, including a reasonable model for the influence of the solvent.

Among the open questions of fundamental importance where a mechanistic approach may be fruitful are the origin of life, the origin of homochirality, and the molecular basis of consciousness. Along these lines is the challenge of creating a living cell. Questions of a more applied nature involve the development of cures for cancer and other diseases, as well as improvements in photocells, sensors (especially a glucose sensor for control of diabetes), batteries, and responsive materials, including the kinetic control of drug release by new drug-delivery systems. Many of these projects will involve what has become to be known as supramolecular chemistry, going beyond the properties of single molecules to the development of assemblies of molecular subunits. Success in this area requires the understanding of noncovalent interactions, which are weaker and less directional than the well-understood covalent forces that hold molecules together. Other efforts will be directed toward environmental issues, such as pollution control (in air, water, and land), the storage of CO₂ and of H₂, and improving energy efficiency. A related issue is the need for biodegradable polymers, to avoid the accumulation of packaging and structural materials in the environment. These areas can also be called molecular engineering, the design of molecular structures to carry out a useful task.

Many of these projects will require teamwork because of the large number of techniques and constraints involved. Who can be expert across such diverse topics as molecular structure, modes of action, binding kinetics, biodegradation, and biocompatibility? These projects will thus require a high level of managerial skill and the ability to communicate with coworkers

with different expertise. Research universities are responding to these needs by dissolving departmental boundaries and encouraging interdepartmental appointments.

The future of physical organic chemistry, like that of all scientific research, will be strongly dependent on the funding situation. For almost 40 years I have been fortunate to maintain grants continually from the US National Science Foundation, which has long felt an obligation to support basic research. The emphasis has shifted toward applied research, and the responsibility for its support rests with both government and industry.

In summary, my answer to the question posed in the title, "Whither physical organic chemistry? Wither? Or Wider?" is that the historic physical organic chemistry has indeed withered, but the promise of physical organic chemistry is that its methodology is being applied to an ever wider set of problems.

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