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Rethinking physical organic chemistry

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Biography: Edward M. Kosower was born in Brooklyn, N.Y., in 1929 and attended Stuyvesant High School in New York City. After MIT (Senior thesis: John D. Roberts) and UCLA (Ph. D., Saul Winstein), he spent two postdoctoral years (1952-1954) at Basel, Switzerland (Cyril A. Grob), and Harvard University (Frank Westheimer). At Harvard and at Wisconsin he developed solvent polarity parameters (Z-values), and at SUNY (Stony Brook), he discovered the stable and distillable pyridinyl radicals, and the thiol-oxidizing agent "diamide". After moving to Tel-Aviv University in 1972, he worked on "membrane mobility agents", fluorescence labeling agents (bimanes), on electron-transfer reactions, and fiber optic FTIR spectroscopy on silver halide fibers. He has written four books, *Molecular Biochemistry, Introduction to Physical Organic Chemistry, Molecular Mechanisms for Sensory Signals*, and the 4th edition of *Introduction to Organic Chemistry* (Streitwieser, Heathcock and Kosower, 1992). Together with his wife he received the Weizmann Prize in 1977. In 1984 he received the Kolthoff award from the Technion, and in 1996 the Rothschild Prize in Chemistry. In 1992, he became the incumbent of the Josef Kryss Chair in Biophysical Organic Chemistry.

INTRODUCTION

Physical organic chemistry was born from the need to understand the structure and reactions of organic molecules. The number of molecules was exploding, the variety of reactions was increasing, and the classical logic which had served organic chemistry so well was no longer adequate to organize the enormous increase in information.

In my 1969 book, *An Introduction to Physical Organic Chemistry* (1), I pointed out that there were two ways to deal with the subject. Either the physical approach is emphasized, with theoretical concepts at the center, or the "organic" approach is used, in which the phenomena of organic chemistry are analyzed at whatever level seems suitable or accessible. Several authors have tried to systematize the subject, either through a summary of the concepts (2) or through posing and solving problems organized according to an outline of the subject (3). These attempts to codify physical organic chemistry have not been entirely successful, as witnessed by a widely used book in which a chapter entitled, "Some fundamentals of physical organic chemistry" opens with the sentence, "In this chapter we review several aspects of the physical chemistry of organic compounds..."(4). Another popular book is called *Advanced Organic Chemistry, Reactions, Mechanisms and Structures* (5), and includes much material which would nominally be within the purview of physical organic chemistry. A book which first applied physical organic ideas to biochemistry (6) would not now be necessary, because modern biochemistry books (the reaction of thiamin with pyruvate, for example (7)) display an adequate knowledge of mechanism and other aspects of physical organic chemistry. More recently, an attempt has been made to relate some of the empirical concepts of physical organic chemistry to molecular orbital theory and valence bond theory (8).

Success has attended many of the forays of physical organic chemistry into organic chemistry, beginning with the reaction of bromine with ethyl acetoacetate or acetone, continuing with the development of linear free energy relationships, especially those leading to the substituent and reaction constants of Hammett (9), the mechanistic dichotomy of S_N1 (ionization) and S_N2 reactions by Hughes and Ingold , solvent polarity parameters (Y, Z, and E_T (30)), the Woodward-Hoffmann rules and pericyclic reactions, the application of molecular orbital theory to organic chemistry, the detection and identification of all manner of stable and unstable intermediates (11), and ending with the direct observation of transition states in simple reactions by femtosecond techniques. Some of these advances were made by chemists whose primary affinity was not to the field of physical organic chemistry. This all-too-short summary indicates that developments in physical organic chemistry "belong" to all of chemistry. While we can be pleased by this rapid permeation of the pool of knowledge by our theories and results, the lack of a clear distinction between physical organic chemistry and the rest of chemistry and biochemistry presents us with a problem in organization, with regard to both recruitment and financing.

CONTEXT OF PHYSICAL ORGANIC CHEMISTRY: ECONOMICS AND CULTURE

There are two kinds of questions we must address. First, we must consider the cultural climate within which we want to continue our efforts. By cultural climate I mean how we are perceived by the world, a vague term which summarizes the feelings of the public, the consumers of the products of science and of information, literature, art and music, television, plays, and movies. From the public comes the atmosphere which motivates the financiers and users of the results of our scientific work to provide support. There is neither time nor space to discuss the whole of the cultural climate, which includes both logical and emotional elements. We will focus on the economic aspect; the perception of our economic role has a direct bearing on how we are supported in our work. I will present an analysis of economic policy (Table I) which may help both the givers and the receivers to understand our roles. The ideas have a bearing on the organization of scientific policy and funding, both in the university and industry.

Analyses of large-scale economic activity in countries are generally subsumed under the name of *macroeconomics*. If one invests in new railroads, for example, the effects ripple through the economy, affecting movements of goods and services, requiring different investments in roads, new types of trains, new terminals, different evaluation of property along the railroad, different demands for electricity, *etc*. Analyses of specific local economic activities (markets for food, plumbing repairs and other service industries, health care) are generally considered under the rubric of *microeconomics*. Local economic welfare can depend on whether or not these small or medium-sized industries function well, and investment in such activities is considered an important stimulus to the overall success of communities. In both microeconomic and macroeconomic planning, outcomes are generally considered in terms of inputs. We can immediately recognize that the difference between the two scales is one of timing. Macroeconomic time scales are clearly much longer than microeconomic time scales. Put in these terms, we can see that there must exist intermediate time scales for various investments and we now introduce the word *mesoeconomic* to cover this gap. Scientific research is a prime example of a mesoeconomic activity, and the failure to recognize this can result in serious mistakes, with consequences that can be considerable. In this connection we can cite the discussion of middlemen by Sowell (12); a failure to appreciate their role (both microeconomic and mesoeconomic) has had catastrophic consequences for economic activity in a number of countries.

An example of a macroeconomic problem is a need for more electric power in the service area of a large utility company. Just to build the plant requires up to 10 years, because a site must be located and purchased, the connecting infrastructure must be put into place, along with all the problems attendant upon acquiring rights-of-way, civil permissions, licenses, *etc*. However, many questions have to be settled before the ten-year clock starts ticking. What kind of fuel for the power plant (oil, gas or coal, with nuclear power now put aside)? The complicated process of making a choice has been discussed with relation to solar power by Awerbuch in trying to make the choice between expense-intensive sources (coal, oil) and capital-intensive sources (solar power) (13). A deep understanding of the technical capacity of the supplier industries is required and today, an evaluation of the environmental impact of each choice. What size should the power plant be, with the answer necessitating substantial knowledge of the mix between conservation (more efficient light bulbs or motors, for example) and consumption. What type of distribution system (above-ground or below ground)? How fast will the economic activity in the service area increase? These questions are so complex and so difficult to answer even on a long time scale that spreading the risk is becoming more common in the electric power industry, with a mix of small producers competing in certain areas with large-scale producers. Those who remember the catastrophic economic results of the "brown-outs" that occurred in the United States several decades ago will appreciate the need for reserve capacity. Very few scientific activities take place on this time scale, although large physics projects, and construction of new university buildings approach this level. Assuming that no new large-scale facilities are needed, most scientific research takes place on a 5- to 10-year time scale, and the time scale is generally shorter in the area of physical organic chemistry. The design of the problem often takes into account the fact that the association of a student or postdoctoral associate with the effort is limited, between 1-5 years. On the other hand, scientific research is not based on daily or weekly transactions such as is the case for most microeconomic activity. In terms of financing and execution, *scientific research is a mesoeconomic activity.*

The business administration approach to the activities of corporations has resulted in their treatment in microeconomic terms, with both mesoeconomic and macroeconomic factors ignored in looking at the quarterly balance sheet. Research is a mesoeconomic activity, and has been downgraded or discarded by many of the largest corporations because it does not contribute to the quarterly balance sheet. Since the need for certain types of research still exists, many corporations push these mesoeconomic activities into public institutions, by decreasing the amount of public finance for "free" (*i.e.*, basic) research and by increasing the amount of private finance allocated to specific projects. For their part, politicians in the USA are allocating by law a small but significant fraction (more than 2% of the NSF budget) to Small Business Innovation Research. They have begun to promote participation of university researchers in collaboration with business (14), an activity that conflicts with the free exchange of ideas within the university because of the need to protect property rights in the results of the research. Similar efforts are being pursued in other countries (15). In some contrast to these efforts to direct research towards "useful" targets, Japan has decided to promote university science, particularly basic research (16).

Table I. Time Scales in Economic Planning

Economic Scale	Time Scale	Finance	Income	Project
Macroeconomic	>10 years	private	private	Electric power
	>10 years	public	public	Highways*
	30 years	private	private	Food additive#
Mesoeconomic	3-5 years	private	private	"Weak" glues$
	3-10 years	public	public	Basic research
Microeconomic	1-2 years	private	private	House repair
	1-2 years	public	public	Teaching laboratory

*A limited number of toll roads and toll bridges are financed privately (government corporation or other quasi-public body) and collect income.
#About $200M has been spent on a fat substitute, Olestra (Procter & Gamble, USA) [*Chemical & Engineering News*, May 13, 1966, p. 25]. Widespread use of such an additive would affect many industries and services.
$ A chemist at the 3M company realized that a "weak" glue could be useful and developed Post-It notes. Eventually a substantial business developed from this simple idea. A physical organic chemist might develop the scientific basis for such weak binding.

BASIC RESEARCH IN CHEMISTRY

Wong has pointed out that basic research not only provides the technical basis for industrial development but also creates the people and the environment within which the basic research may be reduced to practice. Further, it is difficult to achieve a direct return on investment in basic research even though the aggregate return to society is enormous. Thus, public rather than private investment is appropriate (17). In terms of the present discussion, an investment without a direct return should be public rather than private, on micro-, meso-, and macroeconomic levels.

We stated above that scientific research is a mesoeconomic activity. To put this idea into the context of chemistry, it is convenient to take the list given by Miller in connection with formulating research proposals (18).

1. Choose a molecule and synthesize it or study its structure.
2. Choose a reaction and study its mechanism or improve its utility.
3. Choose an interaction and study it.
4. Choose a physical method and develop or understand it.
5. Choose a theory and develop or understand it.
6. Choose a physical property and study or develop it.

How does one make the choice? We have to locate the scientific target for our choice, a target *which has moved out of the areas of our historical focus*. In the case of the synthesis of a molecule, the target may be a natural product with known biological properties (usually therapeutic). The economic outcome of research towards such a goal is unclear because the synthetic drug may be too expensive, and other approaches (for example, through biotechnology) may be possible. Nevertheless, there is a strong argument for the research, because we wish to establish that the molecule as a drug has the optimal structure and that synthetic variants are less effective. We might also want to label it in specific ways to study its biodegradation, bioavailability, *etc*. A synthesis research program for a drug (assuming that a clever organic chemist is attracted to the target) will take 4-8 years, and is thus a mesoeconomic project. There may be multiple designs for the synthesis (as in the case of taxol) and it would be impossible to decide a priori which approach would be best. Thus, multiple mesoeconomic projects might be needed. The time scale for financing should be 4-5 years, with one renewal for a similar period. The historical aim of synthesis research, to climb the mountain because it is there, has been replaced by a much more comprehensive aim which takes into account what the "public" expects from the synthesis of the molecule (better drugs, better drug management, cheaper syntheses, variety of derivatives, *etc*.).

Interestingly a single 5-year period was chosen for frontier research in "hot areas" at the new CAESAR, Centre of Advanced European Studies and Research, now being built in Bonn, Germany (19). At least one or two of the probable subject areas (nanotechnology, bioelectronics) lie within the province of physical organic chemistry.

PHYSICAL ORGANIC CHEMISTRY

What about physical organic chemistry? This can be defined as a somewhat organized collection of conceptual and experimental techniques for solving problems in the chemistry of materials. This immediately means that the problems are often those identified by individuals in fields other than physical organic chemistry, those fields including not only chemistry and its manifold branches, but also physics, biology, biochemistry, medicine and engineering. If we review the history of physical organic chemistry, we find that this is true for a good part of the vast effort which revealed the intermediates in reactions, defined their properties, and allowed statements by which one may write the mechanisms through which reactions proceed. The fruits of that development are in the past and are accessible to anyone with a reasonable background in organic and physical chemistry. The dendritic efflorescence of knowledge that began with the Lapworth mechanism for addition of cyanide to carbonyl groups and the Meyer addition of bromine to the enol of ethyl acetoacetate has filled much of the territory of microscopic chemistry. In essence the course of physical organic chemistry has been enmeshed in the development of organic chemistry. Under these conditions, how can we select an appropriate set of fields for the next century of physical organic chemistry?

We can divide our answer into two parts, one addressing the economic constraints facing those who carry out research without a direct economic target, and the second, a general approach to the types of problems that might be addressed by a physical organic chemist.

To open the discussion, I would like to recall an exhibit of animal behavior displayed at the American Museum of Natural History in New York a long time ago. A chicken, a dog, and a monkey were separated from their food by a short fence. The chicken came to the fence and remained staring at the food that was so close but not within reach. The dog kept his eyes on the food while he moved around the fence to the side from which the food was in easy reach. The monkey looked at the food, turned his back on it, walked around the fence, and reached the food very quickly. To extend the idea, we quote an old proverb, "The long way is the short way". The investment in basic research can have an economic outcome that is often immeasurable. Einstein's relation between mass and energy is the most spectacular example, but on lower levels of sophistication, the distinction between ionization and displacement reactions has had an huge economic outcome affecting the syntheses of many compounds.

The support of science is decided on the grounds of macroeconomics: it is thought that a certain percentage of gross national product should be devoted to research and development. *In the private sector*, resources are channeled according to the particular activities of the corporations carrying out the research, with the depth and sophistication determined by the demands of the subject and the wisdom of the corporation's managers. As examples, we can cite two IBM developments that led to Nobel Prizes: scanning tunneling microscopy (STM) and high-temperature superconductivity. These achievements have had no direct economic outcome for the company, although STM and its associated microscopies have been used to probe the surfaces of electronic components used in computers. Still, the promise of both subjects for the world can be stated only in superlatives.

In the public sector, we expect that developments will strengthen science generally, without being certain that the outcome will have an economic effect. We utilize a global sum determined by macroeconomics to make a selection of mesoeconomic projects. The selection process is an art in which we recognize the capacity of individuals or groups to succeed without being certain of the outcome. If we decide, as I think we should, that physical organic chemistry in the broadest sense is an appropriate recipient of support, then we must develop two numbers. First, how much support should be generated on the macroeconomic side? Second, how much will it cost on the mesoeconomic side? If we estimate that we must support 500 physical organic chemists in *all of the world's universities*, we are speaking of an investment of no more than US $50M per year. For this amount, we obtain the forceful and determined effort of dedicated scientists who will provide the intellectual infrastructure for the organic materials scientists of the 21st century. This sum should be raised (1) from public sources (50%), (2) from support by industry for infrastructure development (40%), and (3) from other sources (10%). If monkeys are clever enough to get to their goals by an indirect path, then surely humans are too.

In the second part of this prescription for physical organic chemistry, I introduce the idea that we should focus on *mesoscopic* problems. *Microscopic* problems are those concerned with the structure and behavior of individual molecules. *Macroscopic* problems are directed at large collections of molecules, such as the strength of solids or the flow of liquids or the formation of clouds. *Mesoscopic* problems are those in between, generally involving small collections of molecules, with a length scale between 10 Å and 10000 Å. For example, analysis of crystal structure will yield microscopic information about individual molecular dimensions and mesoscopic information about intermolecular interactions, the latter helping us to understand directions of crystal cleavage, resistance of the crystal to deformation, *etc.* In another example, we can consider the properties of liquids. It is clear that a single molecule is neither solid, liquid or gas, but that its mesoscopic behavior leads to the properties of any state it is found in.

We are now ready to state a prescription for *mesoscopic physical organic chemistry.* Classical physical organic chemistry was concerned with the structures, properties, and reactions of individual organic molecules. The new era of mesoscopic physical organic chemistry has already begun and will be concerned with solving the problems of small collections of molecules, problems for which the behavior cannot be readily understood in terms of individual molecules.

Many practical and theoretical problems must be studied at the mesoscopic level. (Supramolecular chemistry, a current buzz word, is a subfield of mesoscopic chemistry). More complex structures, such as phase mixtures (grain boundaries are extremely important in metallurgy) or block copolymers (molecular mixing on a mesoscopic scale), should be treated. We will note only a few examples here.

Liquid crystals are generally organic compounds which have a variety of uses, such as in displays like those in digital watches. Some varieties contain metal ions (20), while others can be assembled using hydrogen bonds rather than covalent bonds (21). Their mesoscopic organization determines their utility, and is a consequence of the microscopic properties of their components. The liquid crystalline character of some parts of polymers plays a role in polymer properties. The study of mesoscopic organization of molecules is a proper subject for the next century of physical organic chemistry.

We should develop the principles for the design of medium scale and mesoscopic molecular systems, ranging from unusual molecules like buckminsterfullerene to polymers with unusual organizational features. Dendrimers are one type of such polymers. In a well-designed phenylethyne derivative, energy transfer can be so efficient that a new class of light-utilizing systems can be created. Efficient energy transfer can lead to efficient utilization of solar energy and devices for near field spectroscopy. Self-assembling dendrimers have been made and might have uses in nanotechnology (22). There is no reason why the province of "small clusters" (23) should be reserved for physical chemists and chemical physicists. An exciting development in "nanocrystal" technology has been achieved by Bawendi in the reaction of dimethylcadmium and tri-n-octylphosphine selenide in a coordinating solvent, tri-n-octylphosphine oxide. Nanocrystals of cadmium selenide are generated, with a size that can be controlled, and the particles can be aggregated after dispersion in an octane-octanol mixture. The nanocrystals are potential "quantum dots" and might be useful in devices (24).

The solutions to mesoscopic problems can have practical outcomes, but their economic outcome cannot easily be predicted. The famous blue laser diode problem is a good example, with remarkable effects on information storage technology to be expected for a successful solution. First one has to construct a blue laser diode. Then one has to show that the device can actually be used in the anticipated manner. Last, one has to produce the device in an economic way. Blue gallium nitride diodes have been made but have only recently reached the stage of working at room temperature (25). From the point of view of society, a public investment in the basics of blue laser light production might be more effective, until the scientific infrastructure is established well enough to allow individual private institutions to proceed.

Anderson proposes an emphasis on emergent complex phenomena, which do not appear to be logically consequent on the microscopic laws of physics (26). I believe that the same idea can be applied to physical organic chemistry through the study of mesoscopic problems.

It would be presumptuous on my part to try to give a complete discussion of the subjects that I have raised here. The ideals of physical organic chemistry can be turned to good purpose if we leave behind some past tendencies to belabor points that are not central to the progress of chemistry. Let us go where no scientist has gone before!

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