40 Years of Supramolecular Chemistry

*François Diederich**

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François Diederich, Chairman of the Editorial Board of *Angewandte Chemie*.

The year 2007 commemorates the 40th anniversary of supramolecular chemistry and the 20th anniversary of the awarding of the Nobel Prize to the pioneers of the field, Charles J. Pedersen, Jean-Marie Lehn, and Donald J. Cram. What began with the discovery of the crown ethers, cryptands, and spherands as macrocyclic ligands for alkali metal cations expanded in the 1970s into broader host–guest or molecular-recognition chemistry, and studies were aimed at a quantitative understanding of the various noncovalent intermolecular interactions in chemical and biological systems. In 1978, Jean-Marie Lehn introduced the term "supramolecular chemistry" to generalize the early developments and, at the same time, lay out future concepts and visions that resulted from an enhanced understanding and application of the noncovalent bond. He defined supramolecular chemistry as the "chemistry beyond the molecule", bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. Today, a large fraction of papers (20–30%) published in the leading general chemistry journals such as *Angew. Chem.*, *Chem. Commun.*, *Chem. Eur. J.*, or *J. Am. Chem. Soc.* report on the practical realization of the concepts and visions in supramolecular chemistry which span from the core of chemistry to the interfaces of biology, physics, advanced materials, and nanosciences. The impact on journals in the areas of advanced materials and nanomaterials is indeed even larger. Supramolecular chemistry has been popularized by a large variety of monographs and has advanced to an essential component of modern classroom teaching.

Some Thoughts about the Early Days

Looking back to the initial phase some forty years ago, one notices that seminal developments started in industrial corporate research laboratories, which today have nearly completely vanished from the basic research landscape. Not only did Pedersen discover the crown ethers and their cation-binding properties at the Experimental Station of DuPont in Wilmington, but Park and Simmons from the same laboratories reported one year later, in 1968, the first synthetic receptors for anion complexation. Without the newly arising objectives of molecular-recognition studies, that is, the quantification of individual intermolecular interactions and the deciphering of the highly complex solvent effects, physical organic chemistry would have declined dramatically after the National Institutes of Health (NIH) in the United States basically discontinued funding of this field around 1970. As a result of this decision, which also impacted developments outside the United States, physical organic chemists increasingly entered molecular-recognition studies, thereby fertilizing the field with quantitative experimental study and theoretical concepts.

Today, the enhanced insight into molecular-recognition principles that was generated in synthetic host–guest complexation studies with a plethora of diverse, mostly macrocyclic or cleft-type receptors capable of complexing nearly any desired ligand—cationic, anionic, or neutral—provides invaluable assistance in deciphering biomolecular recognition and greatly facilitates structure-based lead optimization towards the development of new drugs. In fact, the influence of supramolecular chemistry on biology has been a profound one from the beginning on. Although naturally occurring ionophores such as the antibiotics nigericin and lasalocid were known since the early 1950s, their modes of action as alkali metal ion-complexing and membrane transport agents were only recognized after the Pedersen discovery. The value of the crystallographic insight into cation binding by valinomycin and monensin that was gained by structural chemists in the late 1960s was later acknowledged by Roderick MacKinnon in his masterful reports on the structure and function of the potassium ion channel. Some other major contributions of synthetic host–guest chemistry to biological recognition include the demonstration of the importance of preorganization of binding partners for complexation affinity and selectivity, the detection of strong enthalpic driving forces for tight apolar complexation in aqueous solution, the establishment of rules governing the energetics of multiple hydrogen-bonding arrays ("secondary electrostatic interactions"), and, in particular, the discovery of cation–π interactions by Dougherty, which are ubiquitous in nature and provide one of the strongest driving forces for biological complexation. The development of chiral stationary phases in separation sciences has particularly benefited from the results of host–guest chemistry, which today continue to address in sophisticated study very weak forces such as those involved in dipolar and quadrupolar interactions.

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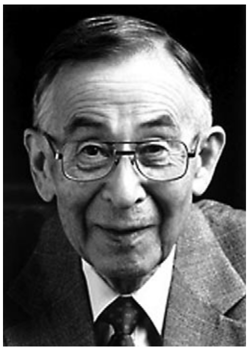
[*] F. Diederich
Organic Chemistry Laboratory
ETH-Zürich
ETH-Hönggerberg
Wolfgang-Pauli-Strasse 10
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1109
E-mail: diederich@org.chem.ethz.ch



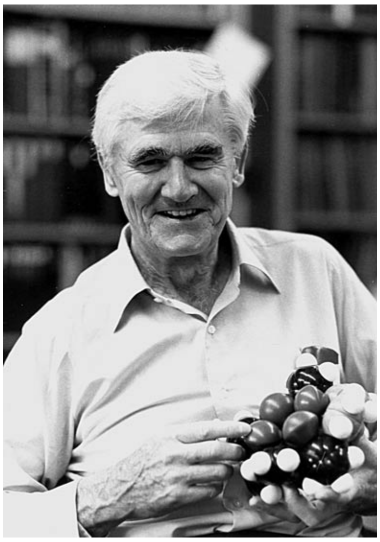
Charles J. Pedersen. Copyright The Nobel Foundation.

The Continuing Challenge of Enzyme-Like Catalysis

While crown ethers rapidly became important agents in phase-transfer catalysis and supramolecularly assembled ligands have more recently been successfully introduced into asymmetric catalysis, efforts targeting the transformation of various classes of synthetic receptors into efficient enzyme-like catalysis have been less successful. A great variety of elaborate, active supramolecular catalysts have been prepared, but similar to the catalytic antibodies, they never reached the activity of the natural enzymes, whose function has evolved over millions of years. Also, the model character of supramolecular systems for elucidating individual factors contributing to enzymatic catalysis has been rather limited. Here, major challenges remain.

Supramolecular Synthesis

Supramolecular synthesis, that is, the construction of chemical structures through or mediated by noncovalent bonding, complements covalent synthesis perfectly and provides access to structures and arrays with nanometer dimensions which would not be available by the use of the covalent bond only. Template effects, pioneered by Daryle H. Busch in the preparation of macrocycles, enabled the synthesis of carcerands, which entrap their guests in a unique inner phase, in the Cram laboratories. This finding provided the grounds for spectacular new physical organic chemistry, with capsules replacing low-temperature argon matrices to study for the first time the spectroscopy and reactivity of cyclobutadiene, benzyne, and other highly reactive entrapped species at room temperature. The synthesis of rotaxanes and catenanes was greatly shortened and the yield improved by the use of metal ion templates, or templates acting as a "mold" through hydrogen-bonding or charge-transfer interactions. Fascinating molecular architecture produced by self-assembly includes double and triple helices, molecular knots, capsules, molecular grids and pillars, supramolecular polymers, dendrimers, and recently the Borromean rings, prepared by Stoddart and co-workers in a remarkable templated, eighteen-component reaction. Self-assembly in solution, on surfaces, at interfaces, and in the solid state follows the principles used by nature to construct complex functional structures, such as nucleic acid duplexes and triplexes, telomers, protein complexes, viruses, or cellular membranes. Basically, preorganized molecular entities are intelligently programmed with the information for modular self-assembly, which relies on noncovalent interactions and occurs under thermodynamic control, thereby allowing error checking and high product fidelity. Many of these processes are efficiently template-assisted. Dynamic combinatorial approaches represent the next milestone in the formation of functional supramolecular systems. Recognition and self-assembly at biological interfaces hold great promise for the development of new biomaterials. Functional nanoarrays and nanopatterned surfaces and interfaces will enable further miniaturization of sensors and other analytical devices.



Donald J. Cram. Copyright 2002, Hargittai, www.roadtostockholm.com.

Dynamics and Controlled Motions

A new level of sophistication and promise, both in terms of basic science and technology, has been reached by establishing controlled motions, such as translation and rotation, as well as switching under various stimuli between different stable states of distinct geometries and properties in supramolecular systems. Molecular motors and, ultimately, molecular electronic circuitry are no longer science fiction, as the review by Kay, Leigh, and Zerbetto in this issue of *Angewandte Chemie* illustrates in an impressive way, but rather hold promise to create immense technological advances in future energy development and storage as well as in molecular electronics. The mimicry of natural motors and muscle motion is actively pursued. It is clear that there is hardly any area in chemistry that today is not affected by the principles of supramolecular chemistry. Many of the visions that Jean-Marie Lehn implicated/associated with the introduction of the term "supramolecular chemistry" are rapidly becoming reality.

Jean-Marie Lehn.