Chemistry in the Image of Biology

The constant theme of organic chemists, which is to imitate the tricks of biology, is being neared by learning how molecules recognize each other

THIS year's Nobel Prize in chemistry is being awarded to Donald Cram of the University of California, Los Angeles, Jean-Marie Lehn of the Louis Pasteur University, Strasbourg, France, and Charles Pedersen, formerly with E. I. du Pont de Nemours and Company, Inc., for their pioneering work in elucidating mechanisms of molecular recognition, which are fundamental to enzymic catalysis, regulation, and transport. Mimicking the tricks of nature has long been the goal of organic chemistry, with molecular recognition as its focus. "Through their work, Cram, Lehn, and Pedersen have shown the way," observes the Royal Swedish Academy of Sciences in its Nobel citation.

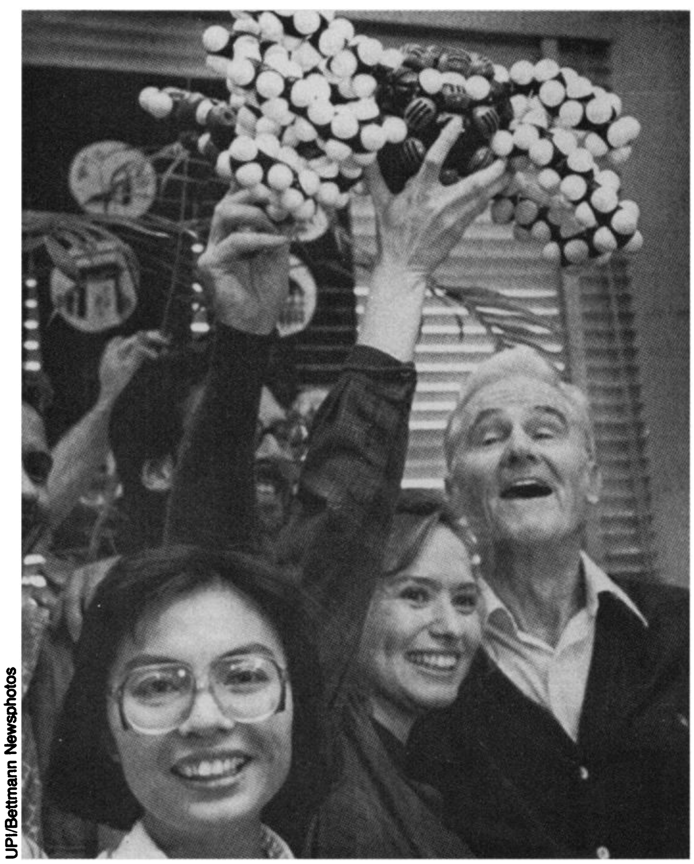
Pedersen, 83, kicked off the initiative in 1967 when he published several papers that described the binding of alkali metal ions—lithium, sodium, potassium, rubidium, and cesium—by compounds called crown ethers, which effectively are made up of a large circle of carbon atoms interrupted at regular intervals by oxygen atoms. In the absence of metal ions, the crown ether ring is "floppy." Introduce a metal ion, however, and it may be bound at the center of the circle, which now assumes a more organized, plate-like shape.

Soon afterward, in 1969, Lehn, 48, took Pedersen's principle into three dimensions, by adding more layers (like stacking plates), creating polycyclic compounds which he called cryptands because they contained molecular clefts or crypts. The effect of the additional layers was to make the structure more rigid and to expand the range of substrates that could be bound. Nevertheless, whenever the cryptand bound something in its crypt, its overall structure was reorganized to some degree. Lehn called this supramolecular chemistry, because what was of interest was the specific but transient interaction between the two entities, not the formation of strong, semipermanent covalent bonds, which is the basis of molecular chemistry.

Cram, 68, meanwhile, was also following Pedersen's inspiration, but by creating cyclic compounds that would remain rigid whether or not they were binding a substrate. This principle of "preorganization" has therefore been built into the more than 500 binding molecules, or cavitands, so far synthesized by Cram and his colleagues. Looking for some Anglo-Saxon terms with which to describe the system, Cram called it host-guest chemistry, the host being the receptor molecule, the guest being the substrate received.

So, although Lehn and Cram employed different approaches, they were united in using synthetic organic chemistry to attempt to build compounds that were sufficiently rigid and contain cavities of a size and shape that would accomodate a desired substrate. The challenge was that, not only is the average sized organic molecule tremendously flexible, but it typically does not have suitable cavities. "Because chemical bonds radiate outwards from nuclei, most organic compounds have convex surfaces composed of hydrogen bonds bound to carbon, oxygen, or nitrogen," explains Cram. "In order to create concave surfaces—cavities—you need many more atoms."

Nature gets around this by having very large molecules, principally proteins and nucleic acids, with molecular weights of 20,000 daltons and more. However, organic chemists much prefer to handle compounds of about one-tenth that size. But when Cram and his colleagues embarked on their venture, only about a dozen of the existing 7 million synthetic organic compounds had significant concave surfaces. They could have chosen to work with cyclodextrins, torus-shaped carbohydrates manufactured by bacteria, but decided instead to ply the synthetic organic chemistry route "because ultimately your options are limitless." Some researchers, incidentally, have brilliantly exploited the framework of cyclodextrins in creating "synthetic enzymes," most notably Ronald Breslow and his colleagues at Columbia University, New York.



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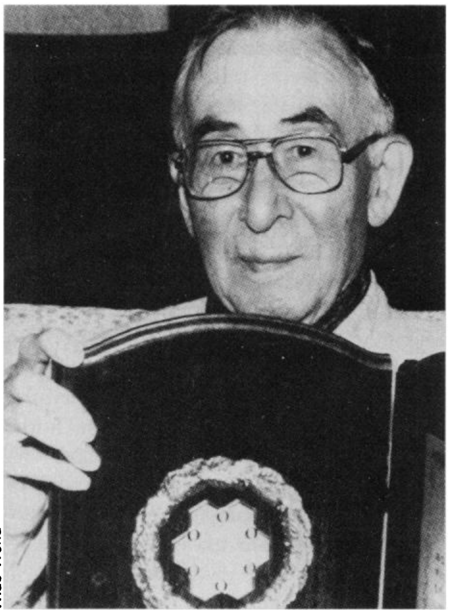
Donald Cram

Celebrates with his graduate students, who hold aloft a CPK molecular model of a cavitand.

In modifying and scrutinizing the efficacy of synthetic hosts, organic chemists have been able to dissect key components in molecular recognition processes, and in so doing have converged with biological chemists who study the natural systems. "As a result, we are now able to tailor host molecules so as to determine the rates at which the guest enters and leaves," says Cram. "We have a very long way to go before we can match natural systems, but we are on the road."



Wide World

Charles Pedersen *initiated molecular recognition work with crown ethers.*

Because host-guest chemistry is essentially the art of understanding the shape and flexibility of large molecules in three dimensions, Cram makes extensive use of Corey-Pauling-Koltun (CPK) molecular models, the colored, interlocking balls that give a very close approximation of bond lengths and angles. "I have never felt I could understand something until I could visualize it," says Cram. "I have spent hundreds of hours making CPK models, and then asking myself what such a compound could do, what kind of enzyme might it mimic?"

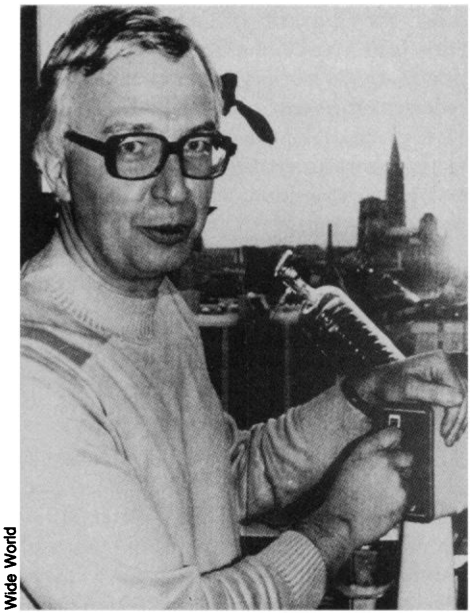
By now Cram and his colleagues have produced crystal structures of some 90 hosts and complexes, and have been able to determine how much the structure reorganized on binding. They then compared the results with the predictions made from the models. "They have mislead us a few times," he admits, "but not much."

Although the field of molecular recognition in organic chemistry was slow to be appreciated by the world at large, it is now booming, in both basic and applied research spheres. Cram reckons that by the turn of the century at least 40% of chemists will be directly employing molecular recognition systems. And one of the most recent developments from his laboratory promises a minirevolution in chemistry.

"We have made molecular cells," says Cram. "We make them by bonding two hemispherical compounds together at their rims, thus forming prisons for whatever is inside." The contents are determined by whatever is in the reaction mixture when the hemispheres are bonded. Cram sees these cells, or carcerands, as potential vehicles for the slow release delivery of drugs or pesticides. "Carcerands can also be little laboratories, where we can watch chemical reactions going on under extraordinary conditions."

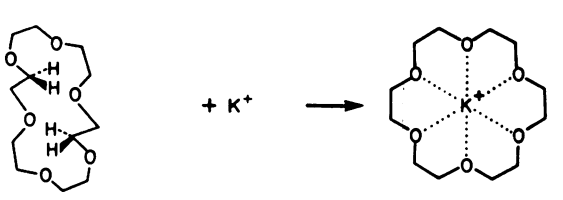
"The potential of the molecular recognition field is enormous," says Breslow. "The full impact of it is not yet clear." ■

ROGER LEWIN



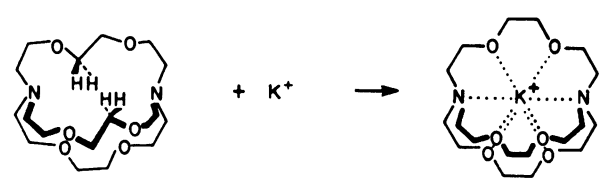
Wide World

Jean-Marie Lehn *extended Pedersen's crown ether concept into three dimensions.*



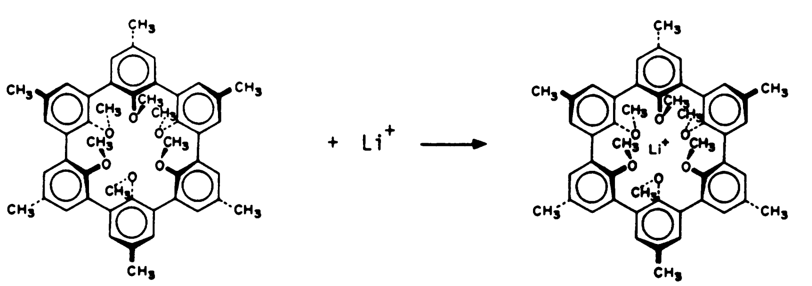
1, 18-crown-6 (no cavity)

2, 18-crown-6-K^+ complex (cavity organized by K^+)



3, [2.2.2]cryptand (no cavity)

4, [2.2.2]cryptand-K^+ complex (cavity organized by K^+)



5, a spherand (enforced cavity)

6, a lithiospherium complex (cavity filled by Li^+)

D. J. Cram

Chemical hosts. *For binding of guests by hosts, a degree of molecular organization is required. Host 1 is a crown ether, which is organized when, for instance, it binds a potassium ion, giving complex 2. Host 3 is a cryptand, which is more rigid than a crown ether, but nevertheless is to some degree organized during binding, giving complex 4. Host 5 is a spherand, which, like all cavitands, is "preorganized," and does not change shape when the complex is formed.*