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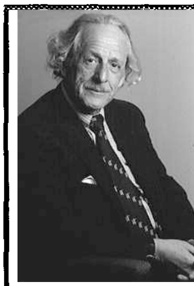

Current Comments®

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Work on Molecules That Mimic Biological Processes Leads to 1987 Nobel Prize in Chemistry for Jean-Marie Lehn, Charles J. Pedersen, and Donald J. Cram

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The 1987 Nobel Prize in chemistry was awarded to Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn for their work in the field of organic synthesis of molecules that mimic biological processes. These scientists have previously appeared in ISI® studies of most-cited papers in the physical and chemical sciences and the most-cited papers from 1961-1982. The history of the discoveries that led to the 1987 award is reviewed, as well as a *Citation Classic*® commentary by Pedersen on his seminal work involving crown ethers.

For over 30 years, one of the goals of synthetic chemistry has been to faithfully imitate biological activity. The 1987 chemistry prize was awarded to three researchers—two American and one French—for their work in elucidating mechanisms of molecular recognition, which are fundamental to enzymic catalysis, regulation, and transport. In the words of the Nobel committee, "The laureates' research has been of great importance for developments within coordination chemistry, organic synthesis, analytical chemistry, and bioorganic and bioinorganic chemistry, and has thus laid the foundation for the active interdisciplinary area of research within chemistry that has now come to be termed host-guest chemistry or supramolecular chemistry."[1]

Crown Ethers: A History

In 1967 Charles J. Pedersen, formerly of E.I. du Pont de Nemours and Company, Wilmington, Delaware, published two papers that described the binding of alkali metal ions (lithium, sodium, potassium, rubidium, and cesium) by compounds he called "crown ethers" (cyclic polyethers).[2,3] These compounds are made up of a large circle of carbon atoms (the "crown" conformation) interrupted at regular intervals by oxygen atoms; in the absence of metal ions, the crown ether ring is "floppy." However, upon introducing a metal ion (where the binding takes place at the center of the crown ether's circle), the ion makes the crown assume a more organized, plate-like shape.[4]

Pedersen's seminal paper, "Cyclic polyethers and their complexes with metal salts,"[2] has been explicitly referenced in nearly 1,400 publications since its appearance in 1967. According to Pedersen, he began his work on crown ethers rather late in his career, in 1961 at the age of 57. In a 1985 *Citation Classic*® commentary on the work, he observed

> the crown ethers might have been stillborn in another environment. They were discovered in the Elastomer Chemicals Department of E.I. du Pont de Nemours and Company, but what had they to do with elastomers? Moreover, the small amount of the byproduct might have been tossed out or disregarded as something other than the desired product.... I worked independently with these compounds for nearly eight years.[5]

Pedersen's discovery was the beginning of a new direction in chemistry research,

Table 1: Charles J. Pedersen's most-cited papers. A=number of citations. B=bibliographic citation. The *SCI®* research fronts to which the paper is core are included in parentheses.

A	B
1,368	**Pedersen C J.** Cyclic polyethers and their complexes with metal salts. *J. Amer. Chem. Soc.* 89:7017-36, 1967. (86-4022, 85-4065, 84-1038, 83-1019, 81-1304, 78-0920, 77-2325, 76-0762, 75-0644, 74-0609, 73-0063)
652	**Pedersen C J & Frensdorff H K.** Macrocyclic polyethers and their complexes. *Angew. Chem. Int. Ed.* 11:16-25 1972. (85-4065, 84-0420, 81-1304, 78-0920, 77-2325, 76-0762, 75-0644, 74-0609, 73-0063)
306	**Pedersen C J.** Crystalline salt complexes of macrocyclic polyethers. *J. Amer. Chem. Soc.* 92:386-91, 1970. (86-4022, 85-4065, 83-1019, 81-1304, 79-1376, 77-2326, 76-0762, 75-0644, 74-0609, 73-0063)
306	**Pedersen C J.** Letter to editor. (Cyclic polyethers and their complexes with metal salts.) *J. Amer. Chem. Soc.* 89:2495-6, 1967. (86-4022, 85-4065, 84-1038, 83-1019, 81-1304, 78-2143, 77-2326)
237	**Pedersen C J.** New macrocyclic polyethers. *J. Amer. Chem. Soc.* 92:391-4, 1970. (85-4065, 83-1019, 78-2143, 77-2326, 75-0644, 74-0609, 73-0063)

with an emphasis on ionic bonding. According to François Diederich, Department of Organic Chemistry, University of California, Los Angeles (UCLA), "Chemists in the century before Pedersen's work concentrated on the covalent bond. From now forward, there will be increased focus on the noncovalent bond—on very weak interactions in biological and abiotic systems."[6] Nobel laureate Linus Pauling (chemistry, 1954; peace, 1962) initiated work on weak interactions in the 1940s, especially focusing on the partial ionic character of chemical bonds, using the concept of negativity.[7] Table 1 lists Pedersen's most-cited papers.

In 1969, via the paper "Diaza-polyoxamacrocyclic and macrobicyclic compounds,"[8] Jean-Marie Lehn and coauthors B. Dietrich and J.P. Sauvage, Institute of Chemistry, Strasbourg, France, took Pedersen's principle into three dimensions—by adding more bridges of these crowns, creating polycyclic compounds that Lehn called "cryptands." These three-dimensional molecules contain molecular clefts, or crypts. The effect of the additional bridges was to make the structure less floppy and to expand the range of substrates that could be made to fit.

This achievement had its roots back in 1966, when Lehn's curiosity about the processes occurring in the human nervous system led him to wonder how a chemist might contribute to the study of these biological functions.[9] Then Lehn read about Pedersen's work the following year, and recalls that

> for me the crown ether results were an important indication about the category of chemical functions that may bind alkali cations. However, the start was really my interest for neurochemistry...ionophoretic antibiotics...[and] about the structure and synthesis of these substances.... I wish to stress these points because the natural antibiotics acting as ionophores have been neglected in presentations of the field, and, for me at least, they gave the first clues that alkali ion transport and binding was achievable with macrocyclic chemical substances of suitable structure. This then led to the cryptates [complexes in which the cation is contained inside the molecular cavity—the crypt], which incorporated the demonstration by Pedersen that ether functions were suitable binding sites.[10]

Lehn termed the complexes of bridged crown ethers supramolecular chemistry—"chemistry beyond the molecule"[9]—because of the specific but weaker intermolecular interaction between the two entities (the molecule and the substrate), instead of the formation of strong, intramolecular covalent bonds (which is the basis of molecular chemistry). Table 2 lists Lehn's most-cited papers.

Table 2: Jean-Marie Lehn's most-cited papers. A = number of citations. B = bibliographic citation. The *SCI®* research fronts to which the paper is core are included in parentheses.

A	B
569	**Lehn J-M.** Design of organic complexing agents. Strategies towards properties. *Struct. Bond.* 16:1-69, 1973. (86-4436, 85-4065, 84-4861, 83-1019, 82-2755, 81-1304, 78-0920, 76-0759, 75-0721, 74-0609)
350	**Lehn J-M.** Cryptates: the chemistry of macropolycyclic inclusion complexes. *Account. Chem. Res.* 11:49-57, 1978. (86-4436, 85-0920, 84-0420, 83-1019, 81-1304, 80-1084)
298	**Lehn J-M.** Nitrogen inversion. Experiment and theory. *Fortschr. Chem. Forsch.* 15:311-77, 1970. (84-8029, 83-8092, 82-2723, 77-2043, 76-1519, 75-1263, 74-1230)
271	**Dietrich B, Lehn J-M & Sauvage J P.** Diaza-polyoxa-macrocycles et macrobicycles (Diaza-polyoxa-macrocyclic and macrobicyclic compounds). *Tetrahedron Lett.* 34:2885-8, 1969.
259	**Lehn J-M & Sauvage J P.** (2)-cryptates: stability and selectivity of alkali and alkaline-earth macrobicyclic complexes. *J. Amer. Chem. Soc.* 97:6700-7, 1975. (86-4436, 85-4065, 84-4861, 83-1019, 81-1304, 77-2066)

In 1978 Donald J. Cram, Department of Chemistry, UCLA, coauthored a paper with his wife, Jane M. Cram (also of UCLA), entitled "Design of complexes between synthetic hosts and organic guests,"[11] which was inspired by Pedersen's original work. But Cram's efforts were towards creating cyclic compounds that would remain rigid—whether or not they were binding a substrate. This principle of "preorganization" has been designed into the more than 500 binding molecules, or cavitands, synthesized so far by Cram and colleagues. Cram calls this phenomenon "host-guest" chemistry, with the "host" containing binding sites that converge and "guests" binding sites that diverge to meet one another.[12] Cram's most-cited works are listed in Table 3.

Although Lehn and Cram employed different approaches, they both used synthetic organic chemistry in their attempts to build compounds containing cavities shaped to accommodate a desired substrate.

The historiograph in Figure 1 shows the growth of the specialized area of chemistry that deals with crown ethers and the subsequent advances in supramolecular and host-guest chemistry from 1978 to 1986.

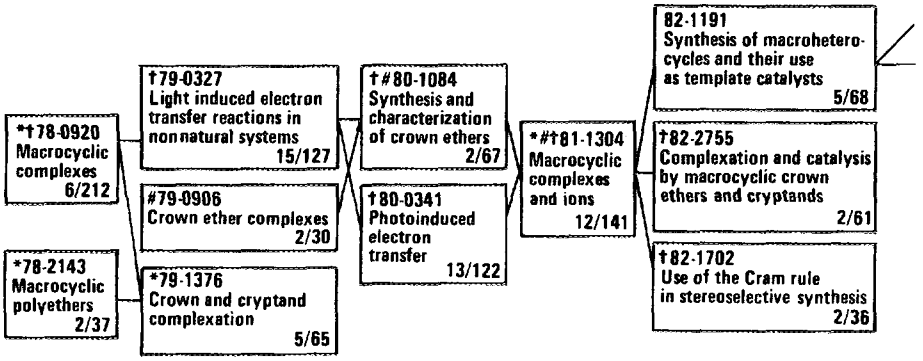
Citation Analysis of the Laureates

It is hardly surprising that the three chemistry laureates have turned up in several "most-cited" studies that have appeared in *Current Contents®* since 1980. Lehn, who first appeared in a study in November 1980,[13] has appeared in a total of five studies.[13-17] Cram and Pedersen have each

Table 3: Donald J. Cram's most-cited papers. A = number of citations. B = bibliographic citation. The *SCI®* research fronts to which the paper is core are included in parentheses.

A	B
571	**Cram D J & Elhafez F A A.** Studies in stereochemistry. X. The rule of "steric control of asymmetric induction" in the synthesis of acyclic systems. *J. Amer. Chem. Soc.* 74:5828-35, 1952. (86-0989, 85-0967, 84-1969, 83-4315, 82-1702, 73-0657)
351	**Cram D J & Kopecky K R.** Studies in stereochemistry. XXX. Models for steric control of asymmetric induction. *J. Amer. Chem. Soc.* 81:2748-55, 1959. (85-0967, 84-1969, 82-1702, 73-0657)
219	**Cram D J, Allinger N L & Steinberg H.** Macro rings. VII. The spectral consequences of bringing two benzene rings face to face. *J. Amer. Chem. Soc.* 76:6132-41, 1954. (83-1156)
214	**Gokel G W, Cram D J, Liotta C L, Harris H P & Cook F L.** Preparation and purification of 18-crown-6. *J. Org. Chem.* 39:2445-6, 1974. (82-1904)
212	**Cram D J & Cram J M.** Design of complexes between synthetic hosts and organic guests. *Account. Chem. Res.* 11:8-14, 1978. (86-4022, 85-0920, 83-1019, 81-1304, 80-1084)
212	**Cram D J.** Studies in stereochemistry. I. The stereospecific Wagner-Meerwein rearrangement of the isomers of 3-phenyl-2-butanol. *J. Amer. Chem. Soc.* 71:3863-70, 1949.

Figure 1: SYNTHESES OF MOLECULES THAT MIMIC BIOLOGICAL PROCESSES. Historiograph showing developments in this research. Numbers of core/citing papers are indicated at the bottom of each box. Asterisks (*) indicate research fronts in which C.J. Pedersen is a core author; daggers (†) indicate research fronts in which J.-M. Lehn is a core author; and number signs (#) indicate research fronts in which D.J. Cram is a core author.



appeared in one—Cram in March 1982[14] and Pedersen in October 1984.[18]

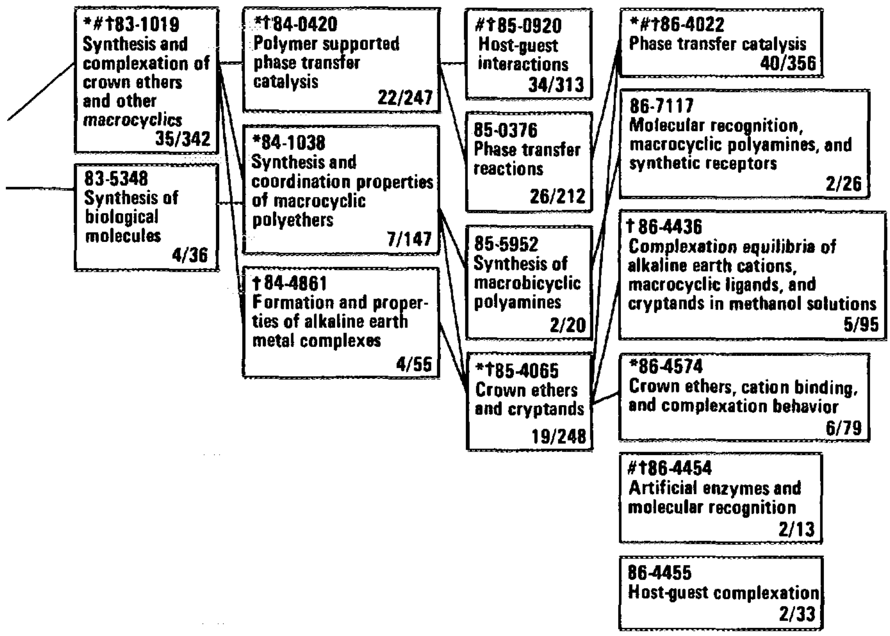
A multidimensional scaling map for C2-level research front #86-0466 on host-guest chemistry and molecular recognition is depicted in Figure 2. The map shows the interrelatedness of cryptands, organic synthesis, and crown ethers research.

The laureates' work has implications for the better understanding of how biological mechanisms function, especially those of the human body. Their work provides insights into how enzymes recognize substrates and the way hormones communicate with cells. The results of the prizewinning research also illuminate how neurotransmitters propagate signals, how cells read genetic code, as well as how antibodies and immune cells recognize antigens.[6] This research may also have applications in the design of extremely sensitive chemicals for use in removing poisonous substances from contaminated soil or water,[19] and already experiments have shown that rats have been partially detoxified of lead and radioactive strontium by using crown ethers.[20] "We have a very long way to go before we can match natural systems, but we are on the road," asserted Cram during a *Science* interview.[4]

Biographical Sketches of the Laureates

Charles J. Pedersen was born in 1904 in Pusan, Korea, of Norwegian and Japanese parents. He earned his BS degree in chemical engineering at the University of Dayton, Ohio, and an MS degree in organic chemistry at the Massachusetts Institute of Technology, Cambridge. It is indeed unusual for a non-PhD to be awarded the Nobel Prize in chemistry.

In 1927 he began to work at du Pont, where he remained for 42 years, retiring in 1969. While at du Pont he was the author of 65 patents. In 1968 he received the Delaware Section Award of the American Chemical Society (ACS).[21]



Donald J. Cram was born in 1919 in Chester, Vermont. He received his BS degree in chemistry from Rollins College, Winter Park, Florida, and his MS degree in the same field from the University of Nebraska, Lincoln. He then worked at Merck and Company for three years. Cram graduated from Harvard University, Cambridge, in 1947 with a PhD in chemistry; in that same year he became a professor at the UCLA Department of Chemistry, where he has remained. Cram has had much influence throughout the international chemistry community.[21] He was elected to the US National Academy of Sciences (NAS) in 1961, at the age of 42; in 1965 he received the ACS Award for Creative Work in Synthetic Organic Chemistry, as well as further ACS awards—in 1974, the Arthur C. Cope Award, and in 1985, both the Roger Adams Award and the Willard Gibbs Medal.[22]

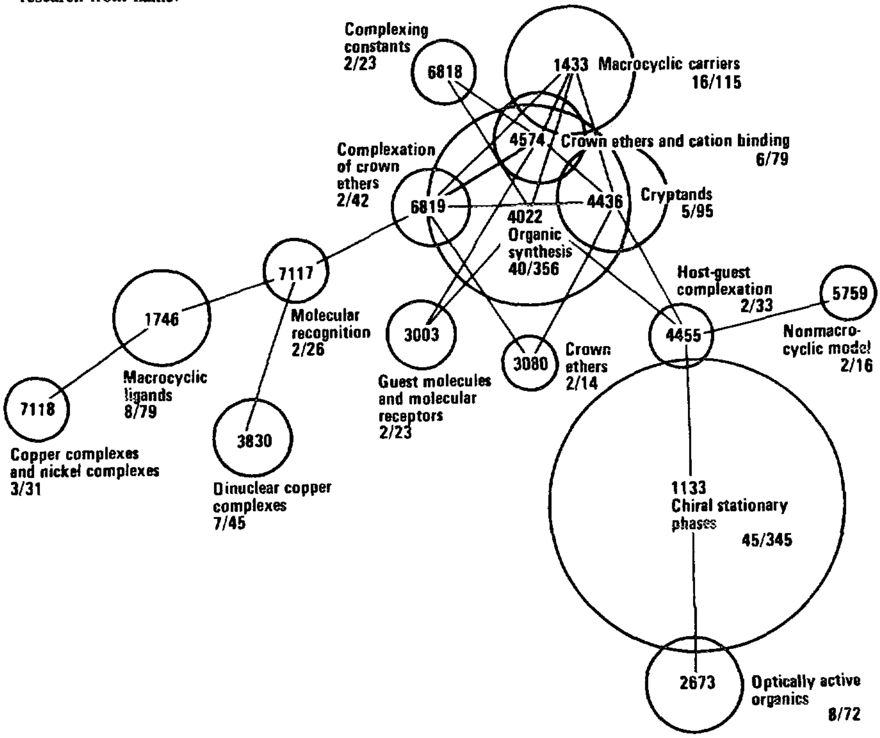
Jean-Marie Lehn was born in 1939 in Rosheim, France. He received his BS, MS, and PhD (1963) in the field of chemistry from the University of Strasbourg. Since 1970 he has been a professor of chemistry at Louis Pasteur University, Strasbourg, and since 1979, also a professor at the College of France, Paris. Lehn has been called the foremost chemist in France,[21] and the National Center for Scientific Research (CNRS) has conferred upon him their bronze, silver, and gold medals for his work in chemistry. He was also the recipient of a gold medal from the Pontifical Academy of Sciences in Rome in 1981 and the 1982 Paracelsus Prize of the Swiss Chemical Society. Lehn is a foreign associate member of the NAS.[23]

Crowning Conclusion

According to the Nobel committee, the work of these three chemists is part of the

> goal...to produce synthetic host molecules that recognize biologically active molecules.... The explosive development of the art of organic synthesis has enabled Cram and Lehn to produce hosts which to some extent mimic enzymes such as proteases,

Figure 2: HOST GUEST CHEMISTRY AND MOLECULAR RECOGNITION. Multidimensional scaling map for C2-level research front #86-0466. The size of the circles is determined by the total number of cites received by the core papers in the research front. Numbers of core/citing papers in each C1 front are indicated after the research-front name.



ATP-ases and transacylases. Supercomplexes which bind organic substrates and metal ions have recently been produced by Lehn. It will thus be possible to produce supermolecules which do not suffer from the present limitations on substrate structure and reaction type in, for example, enzymes. Through their work, Cram, Lehn and Pedersen have shown the way.[1]

Outside of the laboratory, poetry is a favorite means of self-expression for some scientists. There are a number of eminent scientists, including chemists, who have published their poetry; we have discussed the works of Carl Djerassi and Nobel laureate Roald Hoffmann.[24] Some, like Pedersen, draw upon their research activities as a source of inspiration. In his *Citation Classic* commentary,[5] Pedersen includes his poem, reprinted below, on crown ethers.

THE CROWNING

The alkaline earth cations
And the alkali too,
Used to act like freeborn lions,
Scorning some things to do.

Organic ligands they disdained
Till crown ethers were found,
Now with these compounds science ordained
They can be meekly crowned.

* * * * *

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