Charles J. Pedersen: Innovator in macrocyclic chemistry and co-recipient of the 1987 Nobel Prize in chemistry

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Charles J. Pedersen began life in Korea where his father was employed as an engineer at a gold mine in a remote region of that country. He received his primary and secondary school education in Japan and university training in the United States. He was employed as an organic research chemist at DuPont for 42 years. The signal accomplishment of this unusual individual was his serendipitous discovery of macrocyclic polyethers and of their selective complexation of alkali metal cations. This discovery sparked the development of a new field of chemistry and led to his sharing the Nobel Prize in Chemistry in 1987. An attempt is made to understand Pedersen as a person in this article.

The Nobel Prize in Chemistry was awarded on December 9, 1987, to Charles J. Pedersen, Jean-Marie Lehn, and Donald J. Cram for their development and use of molecules with structure-specific interaction of high selectivity.[1] The present paper is aimed at elucidating the contributions of Pedersen to the early development of the field of macrocyclic chemistry which led to this Prize. He published few papers in this field, but these, especially the first two on cyclic polyether preparation and characterization,[2,3] were the catalyst for its explosive growth. The significance of Pedersen's work is described by Cram, a co-recipient of the Nobel Prize, in a personal communication to Herman E. Schroeder,[4] a co-worker of Pedersen.

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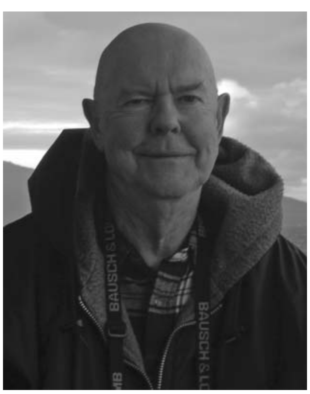
"Pedersen's discoveries illustrate organic synthesis and the organic chemist at their best. Using a simple Williamson ether synthetic procedure and simple starting materials, he synthesized in good yields a new family of cyclic polyethers. He noted that these "crown compounds" complex and lipophilize metal guest cations whose diameters are similar to the diameters of the host crown compounds. He attributed the good yields of the crown compounds in part to templating effects during the ring closures. He varied the ring sizes over a wide range by appropriate selection of starting materials and the orders in which the molecular parts are assembled. The anions of salts lipophilized by the crown compounds had in many cases never been brought into non-polar organic media before, and show greatly enhanced reactivity over what they have shown in polar media.

"Charles Pedersen's discovery of the crown compounds has had a major impact in a variety of investigative fields: inorganic chemistry (the crowns are ligand assemblies); organic chemistry (the crowns are commercial synthetic aids); physical organic chemistry (crown compounds greatly affect ion pair organization); biological chemistry (crowns are important ion transport agents); and analytical chemistry (analytic reagents and ion selective electrodes are based on crown compounds). Pedersen's discoveries were not the usual result of the efforts of a group of competitors that he led or beat into print. Nor are they those of a large group of scientists under a director; they were his alone.

"He had no competition—he was alone—he was original—he did something important—he knew it was important—and he knew what to do with his discovery… It is my belief that Pedersen's demonstration of the feasibility for synthesizing multiheteromacrocycles is leading to the development of a whole new synthetic field of organic host–guest chemistry."[4]

Details of Pedersen's early life, his professional career, and his serendipitous



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Reed M. Izatt received his PhD degree in inorganic chemistry from The Pennsylvania State University in 1954. Following two years at Mellon Institute of Industrial Research (now Carnegie Mellon University), he accepted a faculty position at Brigham Young University. He is presently the Charles E. Maw Professor of Chemistry, Emeritus, having retired from BYU in 1993. His research interests include the thermodynamics of host–guest interactions and of chemical reactions in high temperature aqueous solutions.

discovery of crown ethers have been presented in his first-hand accounts,[1,5,6] and by Schroeder.[4] About ten years after his initial papers appeared, Pedersen published a detailed and extensive historical account of the compounds he had prepared, including their synthesis, their physical and metal complexation properties, and projected applications that he thought they might have.[6] He recognized that the use of cyclic polyethers for the solubilization of inorganic salts in organic solvents had significant potential applications. His description of the solubilization of solid $KMnO_4$ in benzene is classic:

"When a pinch of powdered potassium permanganate crystals is lightly sprinkled on the surface of benzene in a tall vessel, the particles settle rapidly to the bottom and leave no sign whatever of their passage through the colorless liquid. If this procedure is repeated with a benzene solution of dicyclohexyl-18-crown-6 [dicyclohexano-18-crown-6], the particles descend like a flock of tiny peacocks, each trailing a tail of flashing purple. Eventually a solution is obtained exceeding 0.02 M in permanganate."[6]

Pedersen recognized that he had received significant assistance and encouragement from many individuals in DuPont and in the scientific community. He paid tribute to these people in one of his accounts.[6] One of these tributes showing a bit of humor was to "the many investigators who requested samples for use in their studies, for adding support to the belief that all this was not just a flash in the flask."

Pedersen was born in Fusan, Korea on October 3, 1904 and died October 26, 1989 in Salem, New Jersey.[4] His father, Brede Pedersen, was a Norwegian engineer who worked at gold mines in northwestern Korea near the Yalu river and his mother Takino Yasui was a Japanese citizen who had accompanied her family to Korea where they entered into a large scale trade in soybeans and silkworms. At the age of four, he spent his first and last winter at the mines where his father worked. He describes his early life in this remote area in his Nobel Prize address, "Large Siberian tigers still roamed the countryside and were frightened away with bells on the pony harnesses. Wolves killed children during the cold winter nights, and foxes slept on roofs against the chimneys to keep warm."[1] Pedersen believed that his early environment had an effect on his later life. For example, he felt that having to take care of oneself in such an environment taught a "certain independent approach to problem solving." He believed that his interest in chemistry may have begun by watching the process of recovering gold at the mines. He remembered the beautiful sight of "pouring molten gold." In addition, he loved to play with a "collection of colorful Siberian minerals." He also learned and spoke English because this was the common language in use at the mine.

His parents were interested and involved in his education.[4] Because foreign language schools did not exist in Korea at that time, he was sent at the age of eight to a convent school in Nagasaki, Japan. He completed secondary school in Japan in 1922, and came to the United States where he received a BS degree in chemical engineering at the University of Dayton in 1926 (Fig. 1) and an MS degree in organic chemistry from Massachusetts Institute of Technology in 1927. For financial reasons, he opted not to pursue a PhD degree, but to accept a position with DuPont where he remained for 42 years until his retirement on April 3, 1969.[6]

Pedersen's career in industrial research at DuPont was a productive one and resulted in many notable practical and scientific achievements including numerous patents.[4] His account of the serendipitous discovery of dibenzo-18-crown-6[1,5,6] and the recognition of its structure on July 5, 1962[6] is fascinating to read. He had found the first synthetic compound that formed stable complexes with sodium and potassium ions. Further studies resulted in the synthesis and characterization of about sixty macrocyclic polyethers.[1,5,6]

Fig. 1 Charles Pedersen on campus at the University of Dayton in the mid-1920s (Reproduced by permission).

Daryle Busch remembers visiting DuPont as a consultant in late 1965 or early 1966.[7] As part of that visit, he talked with Pedersen. Busch was a pioneer in the synthesis of nitrogen and sulfur-containing macrocycles and in the characterization of their reactions with transition metal ions.[8] Recognizing the significance of Pedersen's work, Busch suggested that he present his results at the Nikko, Japan International Coordination Chemistry Conference that was to be held in September 1967. This presentation together with the publication in the same year of his papers in the *Journal of the American Chemical Society*[2,3] brought a fast and enthusiastic response from the worldwide scientific community.

This was the point at which the late Professor James J. Christensen and I met Pedersen.[9] In February 1968, Jim and I were traveling to Philadelphia and had stopped to visit George Eisenman at the University of Chicago because of our common interest in alkali cation transport in biological membranes. Eisenman mentioned Pedersen's recently published papers.[2,3] Jim and I contacted Pedersen and arranged to visit him a few days later at his DuPont laboratory (Fig. 2). He received us graciously and we left with a sample of dicyclohexano-18-crown-6 (mixed isomers) which became the basis for our initial study of log K, ΔH, and ΔS values for cyclic polyether-alkali metal ion binding.[10,11]

Jerald Bradshaw and I edited a special issue of the *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry* in 1992[12] which contained contributed papers dedicated to the memory of Pedersen as well as papers by Pedersen[5] and Schroeder[4] reprinted from *Current Topics in Macrocyclic Chemistry in Japan*, ed. E. Kimura, Hiroshima University School of

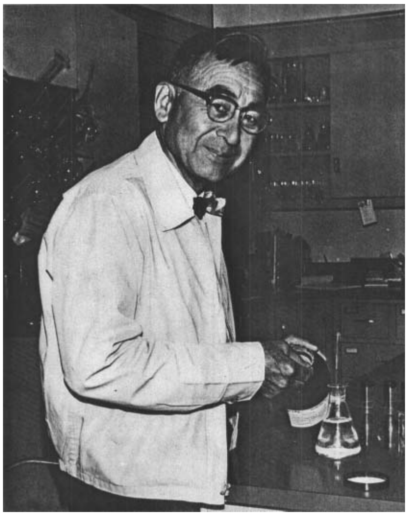

Fig. 2 Pedersen in his laboratory at the DuPont Experimental Station in 1968 (Reproduced by permission).

Medicine, Hiroshima, 1987. This special issue contains comments by several macrocyclic chemists about the influence Pedersen had on their early research. Considerable insight is provided in these accounts about the importance of Pedersen's work and about some of his personal characteristics. Several of these reflections are now summarized.

Eisenman realized that the new cyclic polyethers provided a promising system to study selective permeation in lipid bilayer membranes,[13] and introduced Pedersen and his work to that community. Pedersen had earlier recognized the similarities between the crown ethers and the naturally occurring macrocyclic antibiotics.[6] An excerpt from Eisenman's paper[13] follows.

"The importance of these molecules [crown ethers] as model compounds for ion carriers in membranes, and their fundamental similarity to the neutral antibiotic ion carriers like valinomycin and monactin was immediately recognized.[14] Indeed, the first author [Eisenman] had the pleasure in 1968 of inviting Pedersen to present his work to the American Physiological Society Symposium on 'Biological and Artificial Membranes'.[15] Pedersen's pioneering work provided a crucial system in which to confront classical chemical concepts and measurements with those of the newly opened field of ion permeation in lipid bilayer membranes. It played a central role in establishing a rigorous understanding of the chemistry underlying the effects of macrocyclic carrier molecules on bilayer membranes[16–18] and ultimately proved to be central in clarifying a number of fundamental assumptions regarding the stoichiometry of membrane carriers.[19] Understanding how ions selectively interact with his [Pedersen's] molecules is still fundamental to understanding ion binding to the peptide backbone, a central feature of ion binding sites in protein enzymes and channels.[13]"

The important and productive work of Fraser Stoddart in macrocyclic and supramolecular chemistry originated in large part by the encouragement he [Stoddart] received from Pedersen's work to incorporate carbohydrates into chiral crown ethers.[20] George Gokel met Pedersen in the late 1970s and remembers Pedersen's comment that he felt like a father forced to give up a child for adoption.[21] Gokel interpreted this comment to mean that Pedersen had many ideas he could not try because of his retirement. Gokel then wondered "what direction crown chemistry might have taken had Pedersen been involved longer in its development." Richard Bartsch observed[22] that "Without his [Pedersen's] discovery of synthetic routes to crown ethers and the initial exploration of metal salt interactions with such molecules, it is unlikely that our program, which uses crown ethers with pendant acidic groups to perform metal ion separations in solvent extraction, liquid membrane, and ion exchange resin systems, would have developed." James Dye traces the preparation of the first sodide, $[Na^+(C222)Na^-]$[23] to Pedersen's observation that alkali metal salts were solubilized by coordination of the metal ion with crown ethers.[1,3,5,6]

Fyles and Gandour[24] observe that Pedersen was always careful to point out that "some of the molecules [crown ethers] might resemble the drawings, [but] they are not intended to represent their actual conformation." Subsequent X-ray structures confirmed the presence of well-developed cavities and well-defined structures for alkali metal complexes.[6] Furthermore, a correlation was found between the ratio of cavity and metal ion radii and the log K value for complex formation. The largest log K values occurred when this ratio was unity.[25] Mary Truter did early X-ray crystallographic studies of crown ether-metal ion systems.[26] Truter and Pedersen became acquainted following his retirement, as an aftermath of Pedersen's paper at Nikko, Japan. Sir Ronald Nyholm heard the paper[26] and invited Pedersen to visit his [Nyholm's] laboratory, the Agricultural Research Council's Unit of Structural Chemistry at University College, London, UK. Pedersen accepted this invitation and, accompanied by his wife Sue, spent three enjoyable months in London following his retirement from DuPont. Mary Truter and David Fenton were at the Unit during this period and had close association with Pedersen. Payne and Truter remembered[26] that Pedersen "ran his own infrared spectra, modestly refusing a suggestion that this was a waste of his talent by saying 'I see things when I do it myself.'" Following Pedersen's death, Truter prepared a detailed obituary of him which was published in *The Guardian*, Manchester, UK, Friday, November 3, 1989 and is reprinted in the Special Issue.[26] In the obituary, Pedersen is characterized as "a most delightful person, very modest and extremely kind and helpful to young people. He liked to work at the bench himself, always wearing his black beret, and chose not to have assistants. He was a keen fisherman and gardener with a happy home life." Fenton[27] recalls the quiet and unassuming American chemist, recently retired from DuPont and author of a seminal paper on the coordination of alkali metal ions by cyclic polyethers, who came to visit the Unit. Fenton's task at this time was to prepare complexes and grow crystals suitable for examination. He acknowledges that Pedersen's wide ranging chemical experience was valuable to him as he [Fenton] synthesized the required polyethers.

Eiichi Kimura had interest in Pedersen both as a scientist and because of his [Pedersen's] Japanese ancestry. In 1987, Kimura organized the 12th International Symposium on Macrocyclic Chemistry at Hiroshima, Japan and dedicated the meeting to Pedersen.[28] This was twenty years after Pedersen had orally presented his crown ether discovery in Nikko, Japan. The dedication letter was placed at the front of the Symposium Abstracts and a copy was sent to Pedersen before the meeting. A letter from Pedersen acknowledging this honor was received by Kimura just prior to the Symposium. The letter is dated 10 July 1987, about three months before the 1987 Nobel Prize was announced. An extract from the letter follows.

"I must confess that tears welled up in my eyes when I saw the beautiful page with your kind and eloquent dedication. I will always treasure it and I thank you and your collaborators with all my heart.

"Most men achieve "Immortality" through their progeny. I have no child of my own. Possibly, the Crown Ethers will serve, in a small way, to mark my footstep on earth.

"I am impressed more than ever by the scope of the intrusion of Crown Ethers into chemistry. I will enjoy reading the abstracts more carefully at my leisure.

"Can you doubt that I greatly regret not being with you on July 20, 1987?"[28]

In 1977, ten years after the publication of Pedersen's seminal papers,[2,3] Professor Christensen and I organized the first Symposium on Macrocyclic Compounds in Provo, Utah.[29] This Symposium was a direct result of the extensive activity in macrocyclic chemistry that originated with Pedersen. This symposium series continues and provides a forum for macrocyclic chemists (young and old) to present results of their research, to exchange ideas, and to develop collaborative efforts. Since 1992, the Symposium has presented the Izatt–Christensen Award sponsored by IBC Advanced Technologies, Inc. to individuals who have made significant contributions to the field of macrocyclic chemistry. A history of the Symposium and listing of Izatt–Christensen Awardees through 2005 has been published.[29] Without Pedersen's discovery, none of this would have happened.

Richard Feynman, recipient of the 1964 Nobel Prize in Physics, made a prescient observation in 1960 about the possible result of being able to rearrange atoms at the molecular level.

"What would the properties of materials be if we could really arrange the atoms the way we want them? They would be very interesting to investigate theoretically. I can't see exactly what would happen, but I can hardly doubt that when we have some control of the arrangement of things on a small scale

Fig. 3 Sign at the entrance to Salem, New Jersey, 1989 (Photographed by Reed M. Izatt).

we will get an enormously greater range of possible properties that substances can have, and of different things that we can do."[30]

An important outcome of Pedersen's pioneering work is our increasing ability to synthesize macrocyclic hosts that have predetermined selective interactions with guest species (anions, cations, and neutral molecules). As we increase our knowledge of the factors that determine host–guest selectivity, we come closer to realizing Feynman's dream of arranging atoms the way we want them in order to obtain desired results.

The photographs of Pedersen in Fig. 1, 2, 4 and 5 show him at various stages in his life. In Fig. 3, a sign erected by his hometown of Salem, NJ following his receipt of the Nobel Prize is shown. During a conversation with him at his home in 1989, we talked about the sign depicted in Fig. 3. He was amused at the series of events triggered by the announcement of the 1987 Nobel Prize awardees two years earlier. It took a while for the City Fathers to identify the Nobel Prize recipient living quietly among them (Fig. 4). Once they found him, there was a great deal more activity

Fig. 4 Pedersen in his home in Salem, New Jersey, 1989 (Photographed by Reed M. Izatt).

than Pedersen normally experienced. The sign was an outward expression of their interest in him and of the honor this recognition brought to the city of Salem.

Despite his declining health, Pedersen was able to attend the Nobel Ceremony in 1987 (Fig. 5) because DuPont provided a corporate jet. All of us in the macrocyclic chemistry field owe a debt of gratitude to Charles Pedersen. In a sense, we who practice macrocyclic chemistry in all of its myriad aspects are the "progeny" spoken of by Pedersen.[28] We have had the opportunity for nearly four decades to witness and participate in the spectacular growth of a new field of chemistry from its beginnings to being one of the most active areas of chemical research today. Many of us would echo

Fig. 5 Pedersen receiving the Nobel Prize in Stockholm (Reproduced by permission).

the remark made in appreciation by Richard Bartsch, "Thanks to you Charlie for allowing me to have so much fun with my chemistry."[22]

References

1 *Nobel Lectures, Chemistry 1981–1990*, ed. B. G. Malmstrom, World Scientific, London, UK, 1992, pp. 411–511.
2 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 2495–2496.
3 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017–7036.
4 H. E. Schroeder, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 11–21.
5 C. J. Pedersen, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 3–10.
6 C. J. Pedersen, in *Synthetic Multidentate Macrocyclic Compounds*, ed. R. M. Izatt and J. J. Christensen, Academic Press, New York, 1978, pp. 1–51.
7 D. H. Busch, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 389–395.
8 D. H. Busch and C. Cairns, in *Synthesis of Macrocycles: The Design of Selective Complexing Agents*, ed. R. M. Izatt and J. J. Christensen, Wiley Interscience, New York, 1987, pp. 1–51.
9 C. Y. Zhu, J. S. Bradshaw, J. L. Oscarson and R. M. Izatt, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 275–289.
10 R. M. Izatt, J. H. Rytting, D. P. Nelson, B. L. Haymore and J. J. Christensen, *Science*, 1969, **164**, 443–444.
11 R. M. Izatt, D. P. Nelson, J. H. Rytting, B. L. Haymore and J. J. Christensen, *J. Am. Chem. Soc.*, 1971, **93**, 1619–1623.
12 *J. Inclusion Phenom. Mol. Recognit. Chem.*, guest editors R. M. Izatt and J. S. Bradshaw, 1992, **12**(1–4), 401 pp.
13 G. Eisenman, O. Alvarez and J. Aqvist, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 23–53.
14 G. Eisenman, S. Ciani and G. Szabo, *Fed. Proc.*, 1968, **27**, 1289–1304.
15 C. J. Pedersen, *Fed. Proc.*, 1968, **27**, 1305.
16 G. Eisenman, S. Ciani and G. Szabo, *J. Membr. Biol.*, 1969, **1**, 294–345.
17 G. Eisenman, G. Czabo, S. G. A. McLaughlin and S. Ciani, in *Symposium on Molecular Mechanics of Antiobiotic Action on Protein Biosynthesis and Membranes*, ed. E. Munoz, F. G. Ferrandiz, and D. Vasque, Elsevier, New York, 1972, pp. 545–602.
18 G. Eisenman, G. Szabo, S. Ciani, S. McLaughlin and S. Krasne, in *Progress in Surface and Membrane Science*, Academic Press, New York, 1973, vol. 6, pp. 139–241.
19 S. McLaughlin, G. Szabo, S. Ciani and G. Eisenman, *J. Membr. Biol.*, 1972, **9**, 3–36.
20 P. Ellwood, C. M. Spencer, N. Spencer, J. F. Stoddart and R. Zarzycki, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 121–150.
21 M. Tsesarskaja, T. P. Cleary, S. R. Miller, J. E. Trafton, S. Bott, J. L. Atwood and G. W. Gokel, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 187–197.
22 W. Walkowiak, E.-G. Jeon, H. Huh and R. A. Bartsch, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 213–222.
23 J. L. Eglin, E. P. Jackson, K. J. Moeggenborg, J. L. Dye, A. Bencini and M. Micheloni, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 263–274.
24 T. M. Fyles and R. D. Gandour, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 313–332.
25 J. J. Christensen, J. O. Hill and R. M. Izatt, *Science*, 1971, **174**, 459–467.
26 M. P. Payne and M. R. Truter, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 361–375.
27 A. Atkinson, N. A. Bailey, D. E. Fenton, P. D. Hempstead and G. P. Westwood, *J. Inclusion Phenom. Mol. Recognit. Chem..*, 1992, **12**, 175–186.
28 E. Kimura, H. Kurosaki, T. Koike and K. Toriumi, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 377–387.
29 R. M. Izatt, K. Pawlak and J. S. Bradshaw, in *Macrocyclic Chemistry: Current Trends and Future Perspectives*, ed. K. Gloe, Springer, Dordrecht, 2005, pp. 1–14.
30 R. P. Feynman, *Eng. Sci.*, 1960, **23**, 22–36.