

The productive scientific career of Charles J. Pedersen supplemented by an account of the discovery of 'crown ethers'

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Abstract - Charles Pedersen's career is reviewed from the time of his early life in Korea and Japan and scientific training in the United States to the present. His research with the du Pont Company spanned 42 years and was fruitful in practical and scientific accomplishment. Early in his career he made an important improvement in the yield of the commercial process for the antiknock compound, tetraethyl lead. He then turned toward the stabilization of gasoline and oils and found the first agents for inhibiting the catalytic effects of copper and other metals in promoting oxidation. These metal deactivators are important in preventing degradation of fuels, lubricating oils, and rubber. This led to a study of the interactions of metals with various chelating agents and the effects of coordination compounds on oxidation reactions. His studies extended to the behavior of peroxides and their reaction products with substrates. Later, he quickly recognized the unusual character of ferrocene and discovered its antiknock activity. Then while studying the effects of various ligands on the catalytic activity of vanadium he discovered the crown compounds and their unusual ability to complex alkali metal ions. He immediately recognized their significance and devoted the last years of his career to elaborating their fascinating chemistry.

I. SCIENTIFIC CAREER OF CHARLES PEDERSEN (by H. E. Schroeder)

We have assembled at this symposium to commemorate the 20th anniversary of the announcement by Charles Pedersen of his discovery of the "Crown Ether" compounds here in Japan at the Tenth International Conference on Coordination Chemistry. Mr. Pedersen regrets his inability to come for reasons of health but sends his regards and greetings. I shall take this opportunity to give a historic account of Charlie Pedersen's discoveries supplemented in second part by Mr. Pedersen's own account of the discovery of "Crown Ethers".

After a few years learning how to do research Charlie started to develop his characteristic research style and thus to make surprising discoveries. In 1932 he was assigned to a problem of increasing the yield of tetraethyl lead (TEL). In the plant process the consumption of sodium-lead alloy indicated that the yield was much greater than what could be isolated by steam distillation. On observing that the reaction mass consisted of a sludge of very fine lead particles, he concluded that they adsorbed the TEL so strongly that it could not be recovered efficiently by simple steam distillation. This he proved by taking 10 ml. of TEL, adding 100 grams of the most finely powdered lead he could obtain, and steam distilling. He recovered only 10% of the TEL compared with 99% when TEL was distilled in the presence of coarse lead shot. He then added a non-foaming wetting agent to the experiment with the powder. A 15 minute distillation yielded the rest of the TEL! Thus he enabled a substantial increase in plant yield of a high volume process and made what was probably the most profitable discovery of his career (Ref. 1)!

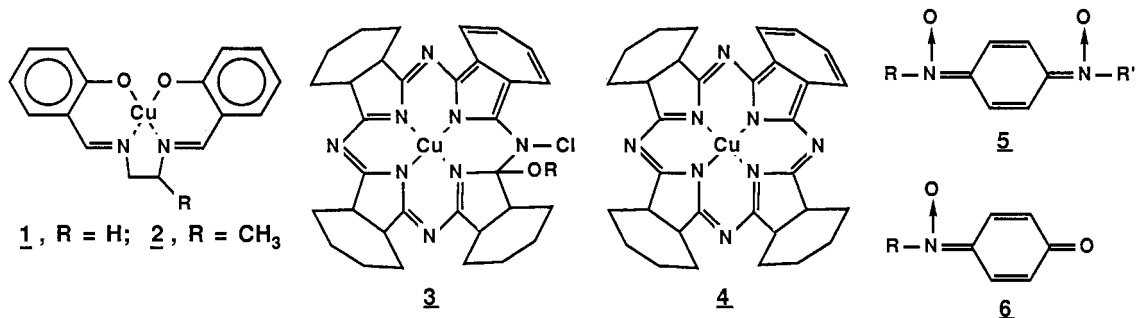
Next came a succession of important industrial patents: corrosion inhibitors and evaporation retarders for ethanol anti-freeze (Ref. 2-4) and a very effective stabilizer, rosin acid, for sodium hydrosulfite which was then very important as a reducing agent for vat dyes (Ref. 5). The plant had such faith in Charlie by then that he actually had to go out to the plant to treat each batch as produced. They knew he would do it right!

In 1935 Charlie struck gold again. This time it was discovery of the first metal deactivators for petroleum products and rubber. Heavy metals, especially copper, were normal contaminants in gasoline, oils, and rubber and were known to catalyze their oxidation. Ethylene diamine was moderately effective in countering this but is insoluble. When Pedersen was asked if he could make an oil soluble derivative by

Charles J. Pedersen became the joint winner of the 1987 Nobel Prize in Chemistry for his discovery of "Crown Ethers" — announced towards the end of 1987.

alkylation, he instead chose to look up reagents which precipitated copper and found the chelating agent, salicylal oxime. Research seeking suitable analogs in turn led him to disalicylal ethylene diimine **1** which was a far better precipitant than the oxime. However, it was high melting and was almost insoluble (<0.01%) in gasoline. So Charlie prepared the 1,2-propylene diamine derivative **2**. With one chiral center this compound had two enantiomorphs and the melting point dropped to 45°C. while the solubility increased 100 fold, more than enough to make it practical. Disalicylal propylene diamine proved very helpful in countering the degradative effects of copper and other heavy metals in gasoline and oils and was also very effective in natural and synthetic elastomers. It became a very important commercial product and is still so today (Ref. 6-9).

The discovery of the metal deactivators reshaped Charlie's career. It turned his attention toward peroxide and radical behavior, oxidation processes, the catalytic effects of metal ions, and the behavior of metals in complexes (Ref.10). In loving detail he varied the structures of the polydentate ligands to determine those particular features which led to the strongest complexes and the most effective removal of the transition metals. Also over the next ten years he and the group he came to lead studied degradative oxidation particularly in petroleum products. He studied the kinetics of oxidation of gasoline and fuel oil with and without inhibitors and deactivators, and also examined the corrosive action of the oils on metals while looking for means of inhibiting those processes. He himself became the inventor or coinventor of about thirty patents covering anti-oxidants, stabilizers and inhibitors, particularly chelating compounds for transition metals. He also sought stable synthetic lubricants which could better resist heat and oxidation.



As a Research Associate, Charlie continued his studies of the pro-oxidant catalytic activity of metal chelates and the mechanism of antioxidant action plus those on the course of the decomposition of peroxides (Ref. 11-13). Then new developments appeared. The first followed discussions of the redox behavior of iron and cobalt phthalocyanines which did not appear to be shared by the copper, nickel or metal free types. When Charlie looked at that situation he soon found that these purportedly stable types readily formed adducts **3** with peroxides which were solvent soluble. Subsequent reduction, chemical or photochemical quickly restored the original pigments **4** (Ref.14). He also showed that these reactions could be employed to produce brilliant fast blue and green colors on textiles or to generate photographic images. Similar conversions could be effected by simple but careful treatment with chlorine in methanol to form the soluble adduct from which the pigment was then easily reconstituted.

Another interesting development arose from Charlie's curiosity as to what happened to the N,N'-disubstituted p-phenylene diamine antioxidants when they were consumed during their protection of a substrate. This led to discovery of a new class of N,N'-disubstituted p-quinonediimine-N,N'-dioxides **5** (Ref. 15). Charlie prepared a wide range of these interesting substances and found they possessed unusual properties. They function as both polymerization inhibitors and antioxidants and in these capacities appear to react with hydrocarbon radicals themselves rather than with the peroxy intermediates. Further, when exposed to light (300-450mμ) they decompose very rapidly and quantitatively into N-substituted p-quinoneimine-N-oxides **6** and azo compounds (Ref. 16). Further irradiation with light of 20mμ shorter wavelength converts these N-oxides to the p-quinone and the appropriate azo compounds. Mixtures of azo compounds are obtained from unsymmetric N,N'-dioxides.

One afternoon in December 1951 Charlie came bustling into my office all excited. He had just read an interesting note in Nature about Kealy and Pauson's discovery of an unusual soluble dicyclopentadienyl iron complex later called ferrocene. He felt that they had not fully grasped the nature of the substance nor the significance of their discovery. He described his own conception of what they had, which later proved to be correct. On the strength of Pedersen's enthusiasm I invited Pauson to visit our Laboratory to discuss his work and there we made arrangements to help Pauson file an appropriate patent case. We also secured a license so that we could use the invention in some of the areas Charlie visualized as of practical interest.

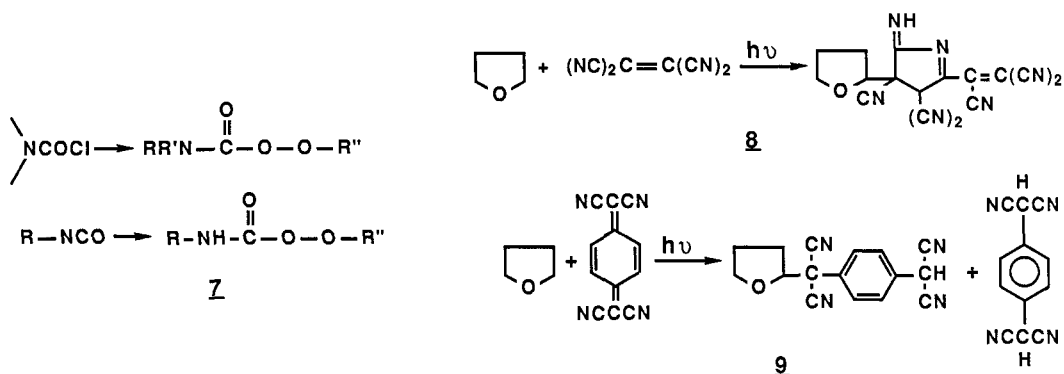
Charlie went right to work on the compounds and quickly made two important discoveries. He found that dicyclopentadienyl iron compounds were excellent combustion control agents specially valuable because they were both hydrocarbon soluble and volatile (Ref. 17). Most importantly ferrocene functioned as an anti-knock when added in very small amounts to gasoline. This was very exciting as these compounds were the first really different highly effective anti-knock agents since the discovery of tetraethyl lead and promised great advantages because they would avoid the toxicity problems encountered with lead derivatives. Charlie quickly filed a patent application on the discovery (March 19, 1952) (Ref. 18). In view of its importance the application was immediately placed under U.S. government secrecy order. This was rescinded in 1960 but by then larger scale practical tests had showed that the ferric oxide formed on combustion of ferrocene-gasoline compositions caused excessive engine wear. Nevertheless the patent proved to be valuable as we were able to trade rights for a patent covering a new method for handling sodium lead alloy which was worth over a million dollars to us.

Charlie's other discovery also related to the extraordinary catalytic effect of ferrocene. Small amounts (0.1%) stop the formation of soot or smoke in a hydrocarbon flame by catalysis of combustion. When a hydrocarbon fuel containing ferrocene was mixed with fuming nitric acid the mixture ignited spontaneously (Ref. 19). Such a hypergolic mixture was of potential value as a rocket fuel so it was of great interest to the U.S. government.

In 1957 our Organic Chemicals Department was divided to form a new Elastomer Chemicals Department with Carter and me as Research Directors. With our strong encouragement Charlie chose to join us. Although we never tried to influence Charlie's program, he somehow seemed to feel he should work on subjects he deemed of interest to us. This included elastomers, elastomer chemicals, and isocyanate and urethane chemistry.

He soon made an important contribution. We were trying to find ways of increasing the use of neoprene in light colored stocks, particularly for tire side walls where its ozone and age resistance are outstanding. Its use was largely restricted to black stocks, however, since white stocks discolored. Charlie showed by the simplest of experiments (exposing neoprene to light in the presence and absence of water and air) that the goal was attainable but with practical difficulties. On photolysis neoprene liberates hydrogen chloride which in turn catalyzes color-forming condensation reactions involving the aldehyde and ketone oxidation products. If water or bases are present to dilute or neutralize the acid, no color is formed. But impractically large amounts of basic oxides would be required to protect the neoprene completely over the life of a tire.

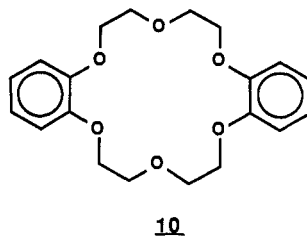
Then Charlie took a look at the chemistry of peroxy-carbamates **7** which he synthesized by reaction of hydroperoxides with isocyanates or carbamoyl chlorides. They were found to decompose smoothly both homolytically and by intramolecular reactions and were of interest as polymerization catalysts (Ref. 20). After a brief excursion into photochemical addition reactions of tetrahydrofuran to tetracyanoethylene and tetracyanoquinodimethan (Ref. 21) **8,9**, he shifted his attention toward elastomeric polymers. He prepared for the first time novel functionally substituted ethylene/propylene copolymers with pendant amino and sulfide groups which had many very interesting properties (Ref. 22-23).



Despite the obvious practical possibilities of these studies, I felt that this simple chemistry was not the best use of Charlie's unusual capabilities, so I encouraged him to return to his beloved coordination chemistry. As a start, I suggested that the chemistry of transition elements like vanadium might interest him. We were then using vanadium in a coordination catalyst system for a very important polymerization wherein microstructure depended on the vanadium ligands. When polymerization was completed, we used an acid extraction to remove the vanadium residues from the elastomer since vanadium catalyzed its oxidative degradation. So I asked him if he would like to study the catalysts and also whether he could think of any substances from his earlier work with metal deactivators which might deactivate the vanadium so that the costly extraction would not be necessary.

Charlie jumped in enthusiastically. He suggested that it would be interesting to study polydentate oxy structures derived from various polyhydric phenols since these had not been examined. A few months later he told me he enjoyed the catalyst ligand chemistry but that the various complexing agents all enhanced the pro-oxidative behavior of vanadium except for tetrasalicylal pentaerythritol tetraamine which was not practical for manufacture. He also planned synthesis of a new pentadentate ligand for possible use as a catalyst (Ref. 24). (It later turned out to be ineffective.)

This is when the lightning struck! From one of his reactions he isolated the first of the **Crown Ethers**, what he later called **dibenzo-18-crown-6**, **10**. Charles Pedersen's own description of his discovery and his reaction thereto, are given on p.450. Charlie first described his research at the Nikko conference and in the beautiful 1967 note and paper in the Journal of the American Chemical Society (Ref. 25) which describes about 50 crown ethers with from 9- to 60-membered oligoether rings. This was an amazing accomplishment for a single chemist assisted by one technician. Charlie's description of events leading to the discovery can be found in Reference 26.



Reaction to Charlie's work was fast and enthusiastic. The Angewandte Chemie noted it in the hot news section of their July 7, 1967 edition and in early 1968 it won the American Chemical Society, Delaware Section's award for best paper of 1967. Now everyone wanted a talk or paper from him! Knowing full well the unusual nature of his discovery Charlie spent the rest of his career with du Pont until he retired in 1969 on the chemistry of the Crown Ethers. After he retired, at the invitation of the late Sir Ronald Nyholm, Charlie spent three months collaborating with Professor Mary Truter (University College, London). Their work was concerned mainly with the crystal structures of Crown Ethers and their metal derivatives (Ref. 27).

His own further studies broadened the scope greatly and included syntheses of new crown ethers plus products with sulfur and nitrogen in the rings, extensions of the preparation and characterization of crystalline salt complexes, ionic complexes, and unusual thiourea complexes with many suggestions for uses of the Crown Ethers which have been proved prophetic. He was fully aware of the potential of these substances for carrying various metal ions into a organic media to effect reactions. They are described in 6 papers and 10 patents listed in references 28-35 and in the publications of some of his colleagues. In the course of this work he also studied reactions of Crown Ethers as organic chemicals and their utility as catalysts and as agents for effecting ionic reactions in organic media.

While complexing of transition-metal cations is a commonplace phenomenon, practically no alkali-metal ion complexes were known before the advent of the crown compounds. Thus the discovery of a large variety of easily synthesized alkali-cation-complexing agents represented a real breakthrough. This complexing property is far more than a laboratory curiosity; in fact, it is the key to the importance of the crown ethers. The complexes are soluble in a variety of organic solvents in which the uncomplexed salts are at best sparingly soluble. Moreover, the inter-ionic forces are considerably reduced by the oligoether ring which surrounds the cation, so that there is far less ion pairing and "naked cations" are available in much higher concentration for reaction.

The major impact of Pedersen's discovery is shown by the frequency of citation of his crown ether papers and even more strikingly by the many new directions of research it has opened up in which many groups have been engaged. These include: cryptates, M.J.Lehn; host-guest chemistry, D.J.Cram; naked-ion chemistry, C.L.Liotta; phase-transfer catalysis, C.J.Liotta; solubilization of alkali metals, J.L.Dye; ion pairing in non-polar solvents, J.Smid; X-ray structure of complexes, M.J.Truter; crown ethers as ionophores, G.Eisenman; and others.

As Professor D.J.Cram described it:

"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 have 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."

Professor D.J.Cram then commented:

"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 multiheteromacrocyclized is leading to the development of a whole new synthetic field of organic host-guest chemistry".

The man who did all this was not after riches, glory, or status. He loved the thrills and problems of research and in his heart he most wanted his work to be worthwhile and so recognized. We could not find so deserving nor a more modest and unassuming person to honor today than my dear friend and associate Charles Pedersen.

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II. THE DISCOVERY OF 'CROWN ETHERS' (by C. J. Pedersen)

I regret that I have nothing new to add to this field in which so many able investigators have obtained interesting results extending the scope of my discovery. So I must resort to old material, perhaps so old that some have forgotten, and some of the younger of you never known of it. Briefly, I will recount how I discovered the crown ethers and the fun I had doing so (Refs. 1 & 2).

In 1961, at Dr. H. E. Schroeder's suggestion, I began research on vanadium compounds. We hoped that an understanding of the effect of various ligands on the catalytic behavior of vanadium might lead to the development of superior catalysts for the polymerisation of olefins. We also hoped to find means for suppressing the pro-oxidant catalytic action of residual vanadium in the resulting polymers. There was then little understanding of the effects of structure on contemporary V catalysts. Most were discovered empirically by reactions of inorganic vanadium compounds, such as vanadium tetrachloride or vanadyl chloride (VOCl_2), with various aluminum alkyls.

I decided to study the effects of uni- and multidentate phenolic ligands on the catalytic properties of VO. To this end, I had synthesized the desired ligands up to and including the quadridentate. Now I was preparing the quinquedentate, bis[2-(*o*-hydroxyphenoxy)ethyl] ether **3** by reacting a catechol derivative with a protected hydroxy group **1** with bis(2-chloroethyl) ether in the presence of sodium hydroxide (Fig. 1). The sample of the partly protected catechol **2** was known to be contaminated with about 10% unreacted catechol, but it was used without further purification.

A brownish goo was the product of the reaction, and in my initial attempt to recover the desired quinquedentate ligand, I obtained a colorless crystalline by-product in 0.4% yield. This fibrous substance had an intriguing combination of properties:

1. elementary analysis fit benzo-9-crown-3, a possible product of the reaction of the contaminant catechol with bis(2-chloroethyl) ether;
2. it was little soluble in methanol but solubilized by sodium hydroxide;
3. its UV spectrum was that of a phenolic compound but without a hydroxyl group which would have explained the solubilization by sodium hydroxide and;
4. its UV spectrum was altered by the base in a way we had never seen before (Fig. 2).

There was no known cause for the solubilization in methanol by sodium hydroxide without an appropriate functional group. To complete the picture the product was submitted for molecular weight determination.

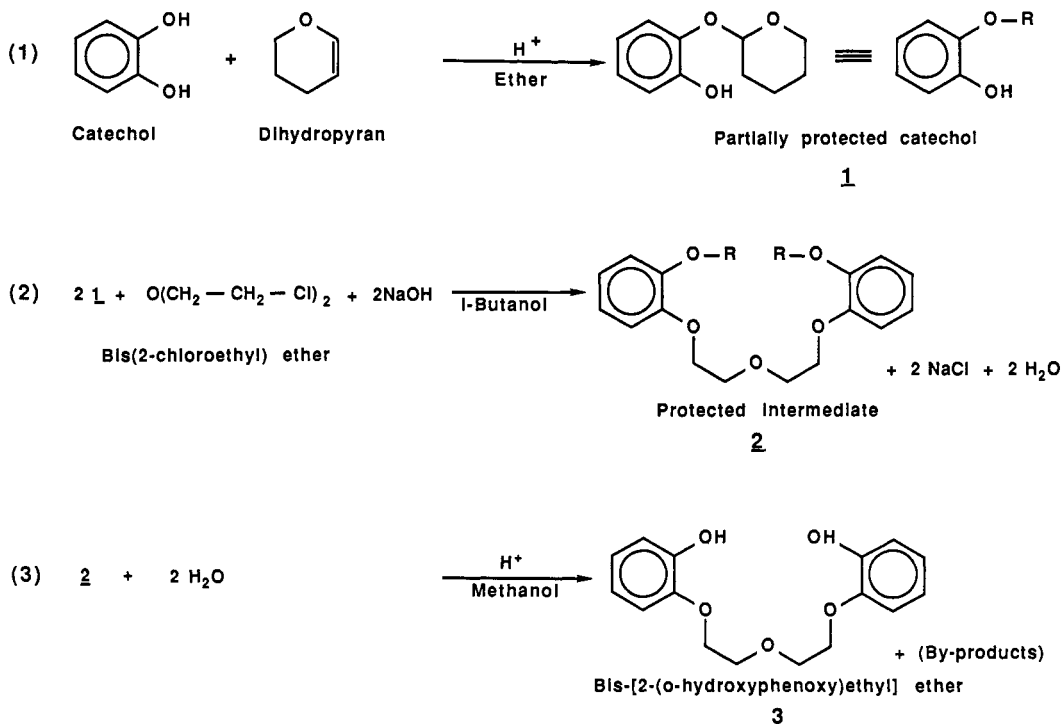


Fig. 1. Synthesis of bis-[2-*o*-hydroxyphenoxy]ethyl ether.

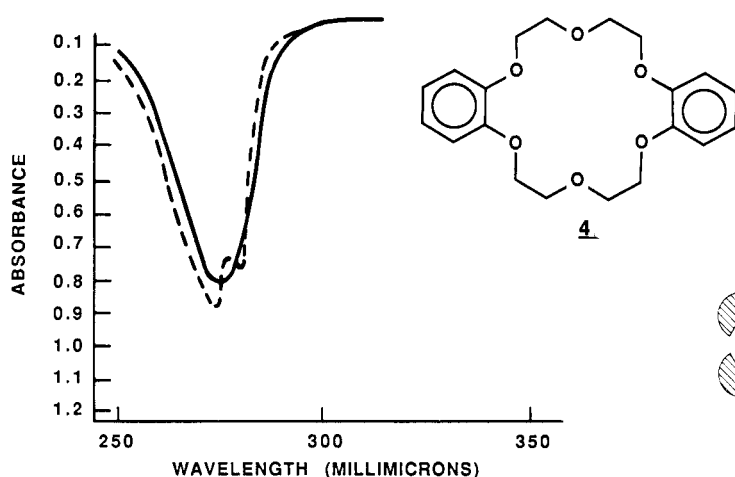


Fig. 2 Effect of NaOH on ultraviolet spectrum of dibenzo-18-crown-6, 4, (----, after addition of NaOH). Soluble sodium salts have the same effect.

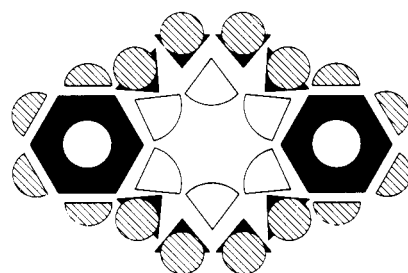


Fig. 3 Courtauld model of dibenzo-18-crown-6, 4.

In the meantime, I was greatly excited to discover that the unknown was solubilized in methanol by any methanol-soluble salt of the alkali metals. Therefore solubilization by sodium hydroxide was due to the sodium cation and not to the base! Its molecular weight was found to be double that of benzo-9-crown-3, namely corresponding to dibenzo-18-crown-6 4 in Fig. 2. The mystery was solved; in my synthesis of the quinquedentate ligand, nature had lent a hand to produce a hexadentate ligand by reacting two molecules of the contaminant catechol with two molecules of bis(2-chloroethyl) ether and thus closing the ring.

Thus did I discover dibenzo-18-crown-6, the first crown ether and the first synthetic compound capable of complexing the alkali metal cations. So now, with the realization that I had something very unusual and with the utmost curiosity and anticipation, I devoted all my energies to the study of this fascinating class of ligands by synthesizing a great variety of macrocyclic polyethers and determining their interaction with inorganic cations. I was specially interested in the stability of the "complexes" and the reason for their behavior. For example, I found that for maximum stability of its salt complex, each cation has an optimum size of the ring of the polyether. A complex can form even if the fit is not the best by forming a sandwich complex consisting of two molecules of polyether per cation. The thermal stability of some salt complexes, e.g. KCNS, is attested to by their having melting points higher than those of the components.

When their unique properties were realized, an exhilarating period of research was inaugurated. Every successful experiment produced a significantly novel result and led to new thoughts on what to synthesize and also as to the many potential uses of these extraordinary substances. I also derived great esthetic pleasure from the structure of the crown ethers as shown in the Courtauld model (Fig.3): so simple, elegant and effective a means for the trapping of hitherto recalcitrant alkali cations. The crown nomenclature was created because the official names of the crown ethers were so complex and hard for me to remember.

It might appear that the work on the crown ethers was mine alone save for the help of an able laboratory technician. True, the concepts and decisions were mine, but there was a host of indispensable collaborators who made all this possible. I would be more than remiss were I not to make the following acknowledgement; to the management of the Elastomer Chemicals Department of the du Pont Company for support in every way for almost a decade; to the Analytical Groups of the Company who made all their resources available; for consultations with the technical staff of the company, and the versatile skill of my laboratory technician.

And now, I place myself again in the kindly hands of my friend and mentor, Herman Schroeder. I cannot adequately express my gratitude to him for all his actions on my behalf.

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