

*Special Paper***CROWN ETHERS**

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Introduction

Recently the chemistry of crown ethers has caught the fancy of a large number of chemists. The subject has its roots in the discovery of dibenzo-18-crown-6 compound as a case of serendipity. It was detected as a minor byproduct in the synthesis of bis [2-(*o*-hydroxyphenoxy) ethyl] ether from bis (2-chloroethyl) ether and the sodium salt of 2-(*o*-hydroxyphenoxy) tetrahydropyran which contained a small amount of catechol as impurity.

The reason behind such a widespread interest is the fact that many of these cyclic polyethers containing 5-10 oxygen atoms form stable complexes with the elements belonging to the following groups of periodic table: all in IA and IB, most in IIA, some in IIB, and a few in IIIA, IIIB and IVB. Depending on the anion, many of these complexes can be isolated in the crystalline form. Some of the polyethers have been found ^{6,14,17} to render inorganic compounds such as KOH and KMnO₄ soluble in a number of organic solvents including aromatic hydrocarbons. The complexes are held together as a result of ion-dipole interaction between the cation and the oxygen atoms of the cyclic polyether, which serves as the negative end of the dipole. The stoichiometry of the complexes is one molecule of the polyether per single ion, regardless of the valence. But 2:1 and 3:2 polyether-salt complexes are also known.^{6,7} The overall stoichiometry is determined by the relative sizes of the cation, and cavity in the polyether ring. It has been confirmed by X-ray crystallographic work⁷ that the metal cation is held in the cavity of the polyether with its valencies directed towards the oxygen atoms. The orientation of the cation in the polyether cavity and thus the structure of the complex is determined by the polyether cavity. If the two sizes, i.e. the cation and the cavity in the polyether are incompatible in such cases, different structures are formed for the complex. An example of this kind is the complex of cobalt dichloride and dicyclohexyl-18-crown-6 ether⁸ V.

The stability of such polyether-salt complexes is controlled by a number of factors which include:

(i) The relative size of the cation, and the cavity in the polyether ring.

(ii) The number of oxygen atoms in the polyether ring — stability goes up as the number of oxygen atoms increases provided the oxygens are coplanar, and symmetrically distributed in the polyether ring.

An arrangement like this, is best achieved when all the oxygen atoms are evenly spread around in the circle, and the apex of the C-O-C angle is centrally directed in the same plane as the oxygen atoms. This arrangement, however, is not feasible when the number of oxygen atoms is more than seven.

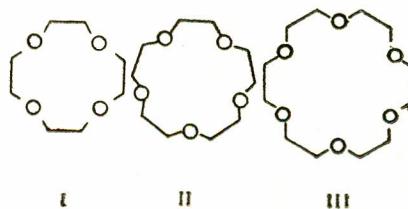
(iii) The stability is directly related to the basicity of the oxygen atoms — the more basic the oxygen atoms, the more stable is the complex.

(iv) Other factors such as the electrical charge density on the ion and steric hindrance in the polyether ring play a significant role in the stability of the complex.

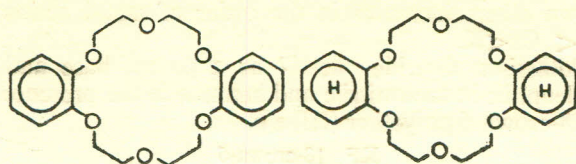
Apart from oxygen, compounds containing oxygen and nitrogen, oxygen and sulphur, sulphur and nitrogen, oxygen, sulphur and nitrogen in the ring are known

Nomenclature

The systematic names of these compounds are very long, difficult to remember and inconvenient to use. For example compounds, I, II and III are 1,4,7,10-tetraoxacyclododecane, 1,4,7,10,13-pentaoxacyclopentadecane and 1,4,7,10,13,16-hexaoxacyclooctadecane respectively. The names become even more complex when cyclohexyl or benzo groups form part of the polyether ring. In order to surmount this difficulty, a set of common names is assigned to these compounds. As a general class they are referred to as crown ethers. This name is derived from their similarity to a crown, and their ability to crown the cation. The common names take into consideration the number and the kind of the hydrocarbon ring, and the total number of atoms in the polyether ring.



Thus compounds I, II and III are named as 12-crown-4, 15-crown-5 and 18-crown-6 respectively. While compounds IV and V are called dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 respectively.



IV (Dibenzo-18-crown-6) V (Dicyclohexyl-18-crown-6)

Synthetic Methods 6,9,11,21

As early as 1937 cyclic polyethers of resorcinol were made by Luttringhaus and his coworkers³ followed in 1941 by the synthesis of hydroquinone polyethers by Adams and his coworkers.⁴ There are also other earlier reports about the cyclic tetramers of ethylene oxide and propylene oxide. The property³ of these open-chain polyethers to dissolve small quantities of potassium and sodium potassium eutectic was known. In such cases unstable blue solutions of solvated electrons and cations were obtained. But sodium, lithium and calcium did not give such blue solutions.

After this early work, and the recent finding about their complexing property, a tremendous industrial potential was foreseen in such compounds. The dissolution of metal salts was rather unusual, since such salts are not ordinarily dissolved by organic solvents. In addition to many new interesting applications, a completely new chapter in the field of multiphase reactions was opened.

After the early work many new synthetic schemes have since been developed. A general scheme of wide applicability used for the synthesis of aromatic crown polyethers employs simple condensation of a viscinal diol with a dihalide in the presence of an alkali or a tertiary amine to trap the HCl evolved. Dimethyl aniline, triethyl amine, quinoline and pyridine are a few reagents employed for this purpose. The reaction is usually carried out at reflux temperatures of 2-butanol and requires about 12-24 hr for completion. A number of variations of this original method employ various kinds of leaving groups, such as tosylates etc to facilitate the condensation process resulting in better yields.

Saturated crown polyethers can be derived from the corresponding aromatic precursors by catalytic hydrogenation⁶ in 2-butanol at 100°C and 7-10 atmospheric pressure over a ruthenium catalyst.

Recently crown polyethers derived from simple open chain diols have been made using a modified Williamson procedure⁹ in good yields. Thus 12-crown-4, and 15-crown-5 polyethers have been synthesized using a lithium perchlorate catalyst. The method uses commercially available starting materials and can be executed without using anhydrous conditions.

A similar procedure has also been used for the synthesis of benzo-crown amino ethers.^{10,11,21}

New polyether ligands containing 4 and 5 donor sites per molecule, and with one or two of the ether linkages replaced by secondary or tertiary amino groups have been synthesized.¹⁰ Some of these new compounds, e.g. 18-crown-6 are known to possess even more en-

hanced activity of effectively complexing and solubilizing metal salts in nonpolar and polar aprotic solvents. Some also form solid complexes with a variety of dipolar molecules such as nitriles.

Properties

Aromatic crown ethers are generally colourless, crystalline compounds, insoluble in water and sparingly soluble in alcohols and many other common solvents at room temperatures. They are soluble in chloroform and methylene chloride. Their melting point rises with the number of benzo groups in the molecule. Their saturated analogs are colourless viscous liquids or low melting solids. They differ from the aromatic compounds in that they are soluble in water as well as petroleum ether, and other solvents of intermediate polarity. They are thermally stable and can be distilled in the absence of oxygen at as high temperature as 380°.

In chemical properties the aromatic compounds are similar to veratrole and they can be halogenated, nitrated or condensed with formaldehyde to give resins.

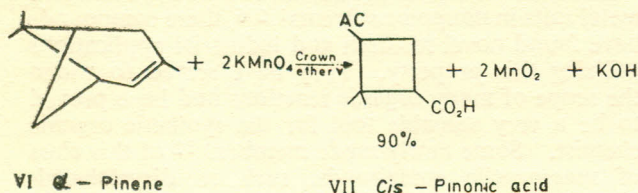
Since their main characteristic is to dissolve alkaline metal salts in nonpolar solvents^{1,2,6}, these compounds have found novel research and industrial applications utilizing this property. They have served to widen the scope of many organic reactions and have proved to be a very valuable tool for the synthetic organic chemist. Some newly made members¹² of this class of macrocyclic compounds, such as dicyclohexyl-18-crown-6 (V) have offered even a greater ability of complexing property. They provide an alternative to dipolar aprotic solvents. While the utility of some of these compounds is limited, since to be effective particularly in nucleophilic substitution reactions equimolar amounts of these compounds have to be used. Nevertheless, some of these polycyclic ethers are effective in very small amounts in two phase organic aqueous systems. Crown ethers such as V serve as phase transfer catalysts.¹³ The catalytic activity increases from dibenzo-18-crown-6 to benzo-15-crown-5 to dicyclohexyl-18-crown-6, following the increase in aliphatic character of the crown compound, and solubility in organic media. The presence of 0.05 molar equivalents of crown ether (V) is enough to induce alkylation of carbanions, oxidations and reductions.¹⁵ This technique is very usefully applied to a large number of organic reactions conducted in organic aqueous multiphase systems in the presence of crown ethers as phase transfer catalysts, and it eliminates the necessity for anhydrous reaction conditions. Apart from crown ethers the other widely used phase-transfer catalysts are quaternary ammonium and phosphonium salts, and experimental data indicate that crown ethers are at least as effective.¹³

The solubilization of inorganic salts by polyethers, which evidently results via complexation of the cation, is not a simple function of the solvent polarity. Many other factors such as the size of the anion, solvation of the anion, and competition between solvent and polyether, have much greater influence than simple polarity effects. The complex formation results in

the change of conductivity of the solution, and as a matter of fact this property can be utilized to detect the formation of the complex and determine its stoichiometry.

In the following paragraphs we will cite a few representative examples to illustrate the effect of crown ethers on the course of a given reaction.

It has been found¹⁴ that KMnO_4 can be solubilized in benzene by complexing with dicyclohexyl-18-crown-6 to provide a potent oxidant for organic compounds under relatively mild conditions. Oxidations of olefins, alcohols, aldehydes and alkyl benzenes have been successfully carried out.¹⁴ In the absence of crown ether, KMnO_4 has no detectable solubility in benzene, and no reaction occurs with the above mentioned organic substrates. The mechanism of oxidation in benzene is not known, but it is assumed that a pathway similar to the case of aqueous systems is followed.¹⁴ These KMnO_4 oxidations in the presence of crown ethers should be extremely useful in cases where mild conditions are dictated by various factors, such as presence of sensitive groups in the same molecule, and where water solubility is a major problem. Thus α -pinene



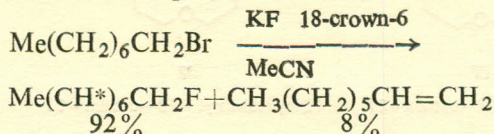
is oxidized to *cis*-pinonic acid in 90% yield in the presence of crown ether (V). While in its absence in aqueous system only 40-60% conversion is obtained.

The effect of dicyclohexyl-18-crown-6 polyether on rates and the stereochemical course of potassium alkoxide catalyzed carbanion generating reactions in alcoholic solvents has been studied.¹⁵ The presence of crown ether increases dramatically both the isotopic exchange and racemization. In the absence of crown ether the reaction occurs with 89-93% net retention of configuration. These results are interpreted in terms of the ability of the crown ether to occupy the coordination sites of potassium ion, and forbid these sites to the leaving and entering groups on the front face of the carbanion intermediates in these electrophilic substitution reactions.

The amount of carbon and *o*-alkylation of metal enolates of acetoacetic ester by ethyl tosylate with and without crown polyethers IV and V were studied.¹¹ The largest effect of crown polyether was observed in weakly polar solvents such as benzene and ether, in which the amount of *o*-alkylation was reduced to 40-50%. It is proposed that solvent effect on the C-*o*-alkylation ratio depended on the selective solvation of the free enolate ion and that electrophilicity of the solvent should parallel the C-*o*-alkylation ratio. Thus the electrophilicity of the solvent should decrease in the order $\text{MeCN} > \text{Me}_2\text{SO} > \text{DMF} > \text{tetramethylene sulfone} > \text{N-methyl-2-pyrrolidone} \approx \text{hexamethylphosphoramide}$. In all the solvents studied¹⁶ the degrees of dissociation of the enolate in the presence of

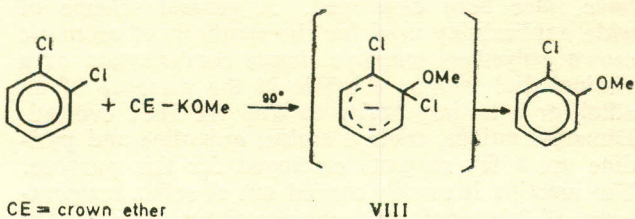
crown ethers increases in the order of metal action $\text{Na} < \text{Cs} < \text{K}$.

Potassium flouride acts¹² as a potent base and nucleophile in acetonitrile and benzene in the presence of 18-crown-6 polyether (III) e.g.



This complex which is termed 'naked' flouride gives the following types of reactions¹²: (a) displacement reactions at sp^3 hybridized carbon with leaving group located at primary (1°), secondary (2°), tertiary (3°) and benzylic positions; (b) competing elimination processes; and (c) displacement reactions at sp^2 -hybridized carbon. The products of the reaction are either fluorides, alkenes or mixture of these.

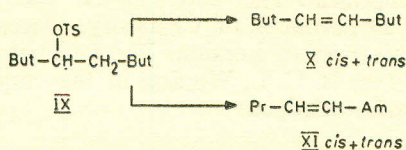
Similarly¹⁷ other potassium halides, hydroxide and methoxide participate in nucleophilic substitution and elimination reactions in the presence of dicyclohexyl-18-crown-6 polyether. Potassium bromide and potassium iodide complexes of the polyether (V) also show enhanced reactivity in acetone in nucleophilic substitution and elimination reactions. The KOMe -complex of this ether shows surprisingly facile nucleophilic aromatic substitution reaction. Thus with *o*-dichlorobenzene it gives *o*-chloroanisole in 40-50% yield as the only product through a nonbenzyne mechanism. No phenols or diphenyl ethers (hydroxide ion products) or *m*-chloroanisole



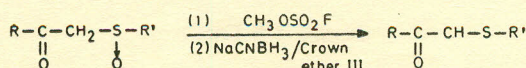
(benzyne product) were detected. The reaction with *m*-dichlorobenzene gave the corresponding product albeit in low yield probably via an intermediate similar to VIII perhaps of reduced stabilization. These are probably the first examples of nucleophilic aromatic substitution reactions of methoxide ion with unactivated aromatic halides.¹⁷

Macrocyclic polyethers effectively fill the coordination sites of alkali metal cations and increase dissociation of ion-pairs causing an increase in the conductance of the solution. This in turn leads to greater anion reactivity. On account of this crown ethers can serve as valuable tools for elucidation of ion-polarity effects. Thus an investigation¹⁸ of the effect of crown ether V on the stereochemical course of elimination reaction of 5-decyl tosylate (IX) with potassium *tert*-butoxide in solvents of varying polarity such as benzene, *tert*-butanol, and dimethylformamide, reveals that the crown ether (V) exerts a very significant effect and alters the course of the reaction completely to produce more *trans*-olefin in the solvents of low polarity such as mentioned above. However, no change in the course of the reaction was

observed in DMF. This indicates that the nature of the participating base is changed in the first two solvents.



The reduction of alkoxy-sulfonium fluoroborate salts to their corresponding sulphides by sodium borohydride is an attractive method for the preparation of the latter compounds. But it suffers from one significant disadvantage, i.e. the drastic conditions of sodium borohydride reduction render it unsuitable for compounds with sensitive groups elsewhere in the molecule. This difficulty, however, has been overcome by the use¹⁹ of sodium cyanohydridoborate in the presence of 18-crown-6 ether (III) in methylene chloride solution. Thus a catalytic amount of III added to the alkoxy-sulfonium salt increases the yield of the reduced product, sulphide from 2.7 to 58.3%. There are no side reactions, and part of the starting material is recovered. Thus the yield of sulphide is quantitative based on the recovered starting material.¹⁹



But, butyl; Pr, propyl; Am, amyl

Thus it offers a useful procedure¹⁹ for high yielding reduction of sulphoxides to sulphides carried out under relatively mild conditions. It may be used in the presence of aldehydes, and ketone functions to give only sulphoxide reduction. Use of crown ethers in this reaction extends the scope of the solvents used for cyanohydridoborate anion reductions. To explain the mechanism of increased reactivity of anions in the crown-ether-substrate complex it may be emphasized that in such a complex the dissociation of ion pairs is increased, while the degree of solvation is negligible. This naturally increases the potency of the given anion as compared with solvated ions in reactions without crown compounds.

Crown ethers also serve in the resolution of α -amino acids,²⁰ and have opened a way for chemists for the preparation of organometallic compounds by catalysing the reaction between metals and carbon-halogen or acidic C—H compounds. They act as phase transfer catalysts, thus enabling organic reactions to be carried out in aqueous-organic two-phase systems.

One can also extract various salts from aqueous solutions into organic solvents with the aid of crown ethers. This type of extraction, however, is practical only if the anion is large, and highly polarisable such as picrate anion, which has an added advantage of having an absorption band at 360 nm in the UV. This absorption band particularly helps to follow the extraction process, and can be utilized to follow the overall analysis. In addition to the size of the anion in the complex, the overall strength of the complex

and the solubility of all species in both the phases also affect the extraction of the salt.

Crown ethers affect cationic transport across bilayer membranes. This property may conceivably be utilized in many biological processes.

Finally in addition to the crown polyethers, a large number of crown compounds have been prepared¹¹⁻²¹ in which sulphur or nitrogen atoms have replaced the oxygen atoms. The method of their preparations are similar condensation procedures as employed for polyethers exclusively containing oxygen atoms. Some bicyclic polyether ring compounds have also been reported.

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