CROWN ETHERS: SYNTHESIS & APPLICATIONS

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ABSTRACT:

Crown ether's discovery remains the remarkable growth in the chemistry. The first crown ether was synthesized by noble prize winner, **Pedersen** nearly half decade ago. This discovery brought progresses in the supramolecular chemistry. Crown ethers are macrocyclic polyether with repeating (-CH_2-CH_2-O-) unit. They have peculiar property to bind the cation hence is known as crowns rather than their systematic names. They envelope the guest cation as if it is crown not that cation and hence the name crown ether. Hetro- atom in the ring provides ability to co-ordinate with wide range of cation in empty cavity of molecule. The interests in crown ethers have increased recently owing to their numerous applications. The important application of crown ether is in PTC as anionic catalysts, ion transport mechanism in biological system, host guest chemistry and in solar cell system.

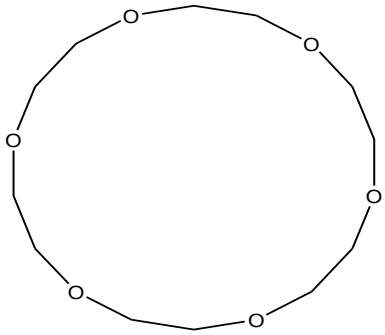
KEY WORDS

Aprotic, catalyst, cyclic, DBC, hydrophilic.

INTRODUCTION

Crown ethers are macrocyclic polyether with several (-CH2-CH2-O-) entity. These are cyclic in nature and consistof a ring containing numerous ether groups known as crown ethers.Other name of crown ether is **macrocyclic polyether.** They are polar aprotic solvent that is they favour SN2 reactions. They trap the cations of the reagent and its anion which is freely available in the solution so that the reaction takes place.

They have peculiar property to bind the cation hence well-known as crowns rather than their systematic names. These cyclic ethers has crown like structures when bound to cation. The first number in Crown ethers resembles the number of atoms in the cycle and the second number resembles of oxygen or the numbers of oxygen present in the cycle. They are designated as **n- crown –m** or **n-C-m (Fig I)**. Where **n** is the ring size, **m** is the number of oxygen atoms in the ring.[1] Crown ethers with more than 3-20 oxygen atoms are now known. The first crown ether is **18-Crown-6** which is synthesized by Pedersen[2,3] in 1967 and for this discovery, he got noble prize.



18 Crown 6

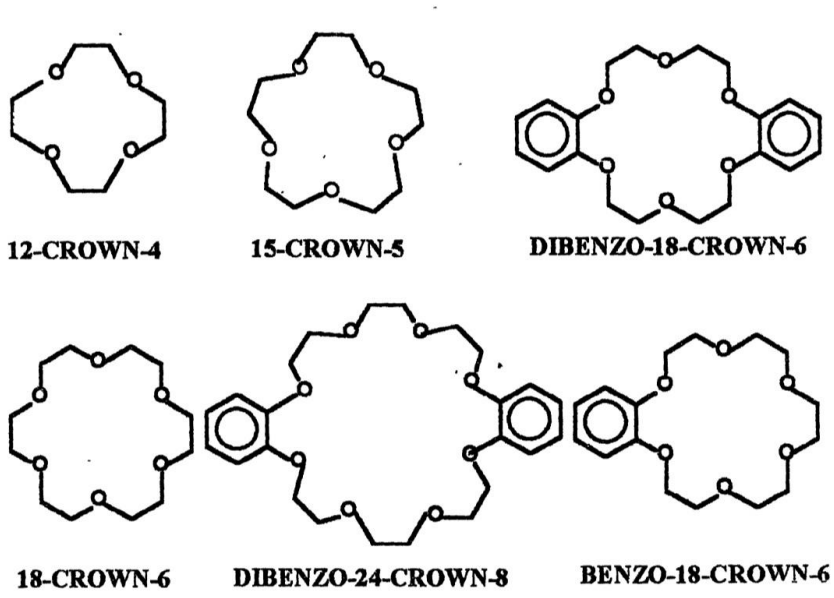


Fig I: Examples of crown ethers

CHEMISTRY OF CROWN ETHERS

The hydrophobic ethylenic group surrounds the oxygen atoms in the hydrophilic (electron rich) cavity in the chemical structure of crown ethers. Thus the presence of hydrophobic ethylenic group makes it feasible for metals to solubilise into organic solvents. The discrimination of various chemical species is the basic purpose of design of various crown ethers. The complexing capability of crown ethers can be changed as per requirement by varying the cavity size, substituents and coordinating atoms in the cavity. The complexing capacity of crown ether mainly depends on:

1. Size of cavity

2. Size of cation

3. Charge density,

4 . Nucleophilicity of counter ion

5. Nature of solvent

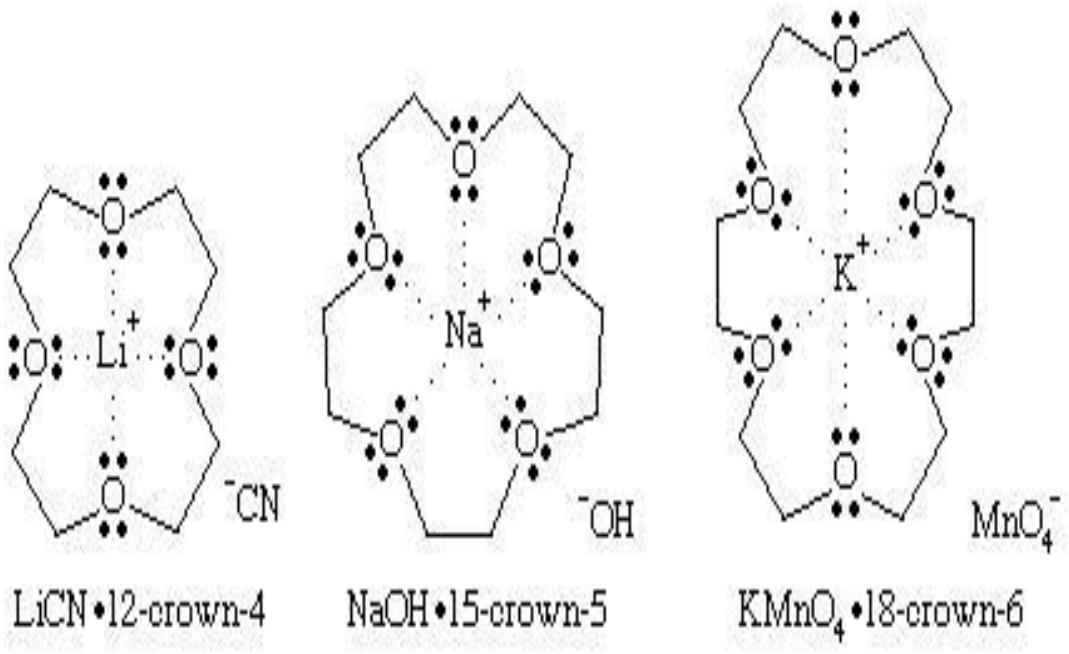


Fig II

Some examples of crown ether complexing with metalion**(Fig II)** are potassium(K+) coordinates well with 18-crown-6 whereas sodium (Na+) ion is the fits in 15-crown-5 cavity. Lithium (Li+) coordinates with 12-crown-4 cavity.[4]These ligands have central cavity which complexes with suitable size of metal ions.[5]

The stability of coordination complexes for the small crown ethers depends on the cation penetration into the cavity and alkali metal form stable complexes with oxygen forming bond with metal ion. These interactions are electrostatic in nature and the organic framework form a crown-like structure and hence**crown ethers**are the name. Charge density is also responsible for complexation apart from the size of cavity and the cation. Since the larger the crown ethers,higher the conformational mobility and can contain the wide variety of cations into the cavity. The formation of sandwich compounds is also possible such that cation made sandwiched between the two crown ether molecules[6] (**Fig III**). The ring size of the crown is the main factor responsible for affinity of an alkali metal ion. If the ratio of radius of cation to cavity size is bigger than or smaller than 1, the complexes formed will be less stable since the size of ring will either be too insignificant to mount or too large to interact with the metal ioneffectually.

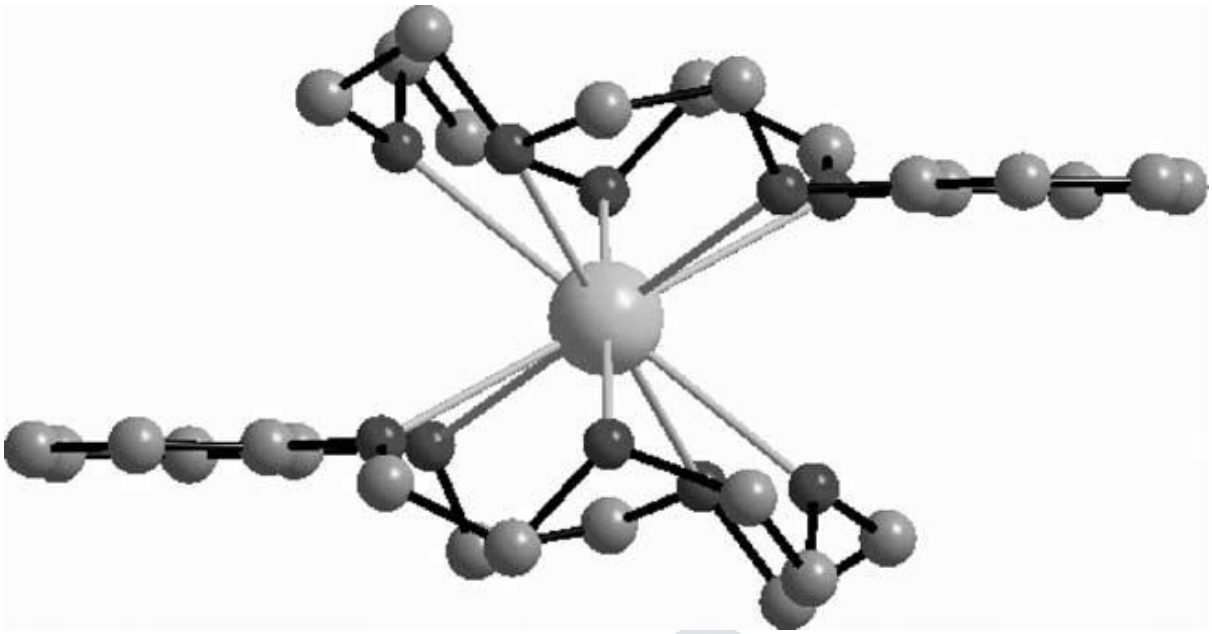


Fig III: Sandwich

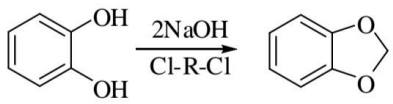
Factors that affect Stability of crown complexes

(i) Number and position of oxygen atoms
(ii) Size and shape of the macrocyclic ring and
(iii) Metal ion's size.

SYNTHESIS PROCESS

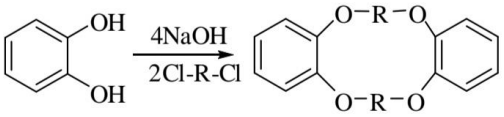
The synthesis of crown ether involves four methods which were given by Pedersen by using techniques called high dilution which undergo cyclization of acyclic molecules.[7] (**Scheme I**)

Method A

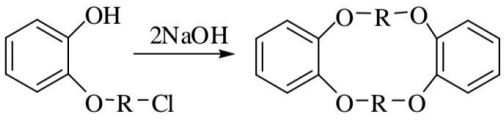


Method B

Method C

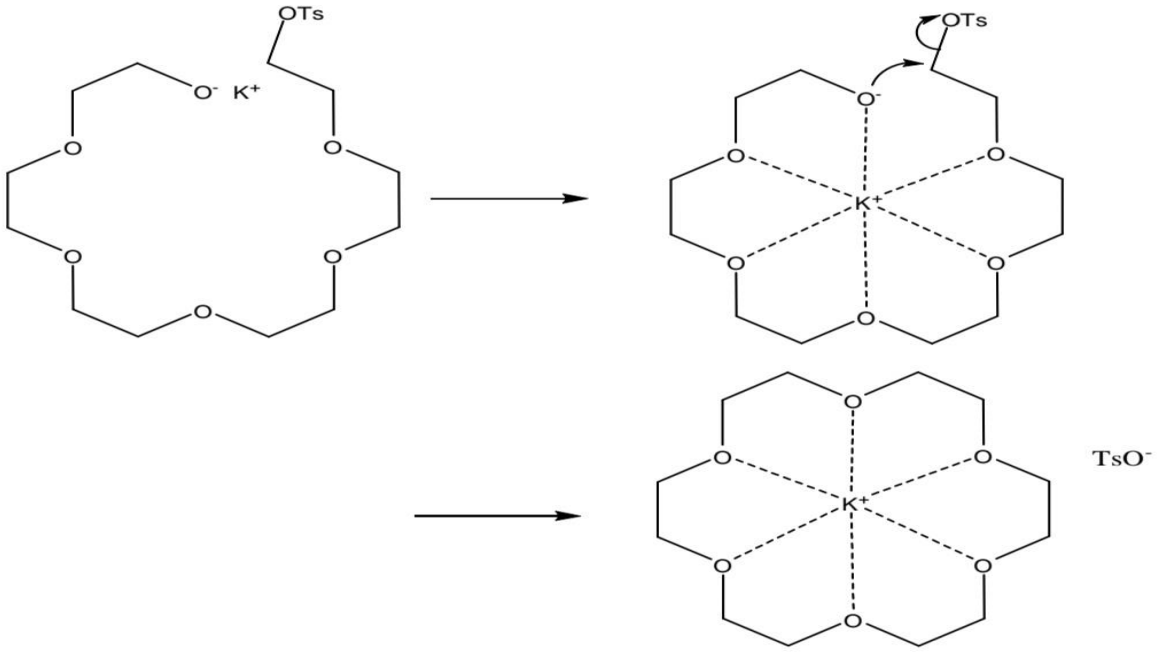


Method D



Scheme I

Besides usualtechniques, an stimulatingprocess of synthesis of these complexes is '**template effect**' given by Dale *et al*[8] in double Williamson synthesis of 18-Crown-6 (**Scheme II**)



Scheme II

The synthesis of crown ether rings is favoured by the presence of a suitable size cation as template, which can help the partially formed ligand in place. This process is called **template effect**. There is binding interaction between the template cation and the acyclic molecule.[9]

The interaction between partially formed ligand and cation template are weak whereas the cation interactions with ethereal oxygen are stronger than the above interaction in crown ether.[10]

Template effect was further studied by Mandoline[11] for cyclization of starting material to synthesize 18-Crown-6 ether by using the various hydroxide bases. It was profound that the most effective templating cations are Na^+ and K^+ due to size-fit relationship.**Fig IV** shows the potassium ion in the cavity of 8-Crown-6, (3D **view**).

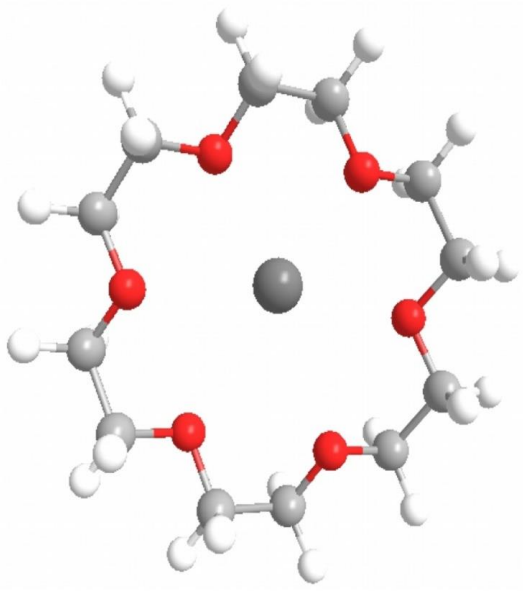


Fig IV

APPLICATION OF CROWN ETHERS

Crown ether has numerous applicationsand uses.They are as follows:

1. SyntheticApplication (phase transfer catalyst)

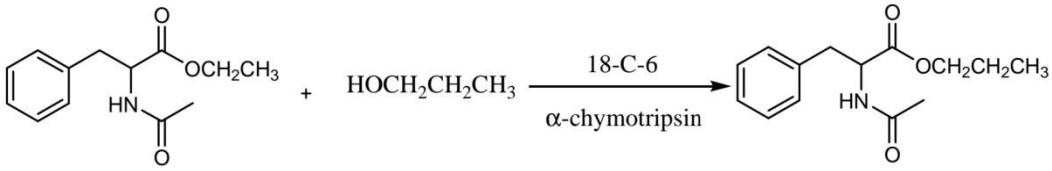
2. AnalyticalApplication (chemical sensor)

3. BiologicalApplication

1. SYNTHETIC APPLICATION:

They are used as phase transfer catalyst (PTC) that promotes the reaction between mutually immiscible reagents as the hydrophobic ring in the crown ethers is used for increasing the solubility of alkali metal salts in polar solvent. There are over 600 industrial organic reaction processes on which PTC is applied[12].The

transesterification of N-acetyl-phenylalanine ethyl ester is increased by 18-Crown-6 with 1-propanol and it is catalysed by alpha chymotrypsin in various organic



solvents.[13]

Macrocyclic polyethers which have important application as PTC[14], named as **crown ethers** and **aza-crown ethers** having the ability of forming the specific complexes with metal ions and anion gets transfer from a solid or an aqueous phase to organic phase (less polar).These are neutral ligands and can complexes with selective cations. Because of electroneutrality, an anion is taken up along with cation.

2.ANALYTICAL APPLICATIONS

The analytical applications of crown ethers are:

1. For potentiometric ion selective electrodes, Crown ethers are used as sensors.Till date, more than 200 such sensors[15,16]have been reported.
2. For resolution of various chiral compounds, chiral crown ethers have been widely used. For the resolution for several types of analytes,[17] stationary phases developed from (18-crown-6)-2,3,11,12-tetracarboxylic acid (18-C-6-TA) were utilized.
3. Crown ethers have high selectivity and affinity towards specific metals. So they are used as potent extracting agents for removing alkali metal salts[18] from mixture.

3. BIOLOGICAL APPLICATION

Recognition, membrane transport, signal transduction, biocatalysis, information storage, processing and reproduction based on supramolecular interaction between molecular components, are some of the biological process. All these functions can be carried out by supramolecular such as crown ethers. Through investigation in between the host and guest species, it is obtained as a great importance in biology in case of hydrogen bonding, ion dipole interaction, dipole-dipole interaction, transferof charge phenomenon and the solvent influence which has a reliable basis that provides the chemical structure designing which function in biological system in the form of complex chemical structure. Since crown ether's discovery, there is recognition of number of natural ionophores. e.g**Valinomycin,** is natural potassium ions ion carrier high selectivity.[19] Crown ethers act as the building blocks which are very essential and that functions as bilayers in the ion transporter form. Crown ethers are the useful template to synthesize the supramolecular devices in biological processes.[20]

Biological activity:

Biological activity in mammals: By the discovery of the crown ethers, higher organisms are affected by crown ethers toxicity which was observed. The study of toxicity of crown ethers was done over multiple species (mice, rats and dogs). 12-crown-4, 15-crown-5,18-crown-6 and 21-crown-7 studies through oral toxicityhave shown effects on behaviour and nervous system[21]and causes irritation on skin and eyes.[22] Some crown ethers lethal concentration in mice is found to be same as for aspirin.[23]

In reticulocytes, there is synthesis of protein inhibited by dicyclohexyl 18-crown-6 and valinomycin.[24]In cell free system, no effect was found over it.The structural and functional properties of ribosomes were normal. As the concentration of valinomycin is high with irreversible inhibition, whereby there were completely inactive isolated ribosomes. There are some of theaza and benzo-aza crown compounds derivatives which has antimutagenic and protective effects over human cells. Garlic extract is similar or quiet comparable to antimutagenic result. Garlic extract has protective effect which is related to some antioxidant properties whereas the non-antioxidant activity is shown by crown compounds.

Antimicrobial activity: Metabolites of microorganisms are the naturally occurring ionophores and are first identified by the stimulating energy effect which is linked transport and present in mitochondria (powerhouse of the cell). This causes disturbance in ions flow in and out of the cell. Hence results in the dissipation of cellular ion gradient which leads to osmotic and physiological stress. The most sensitive are the bacteria due to this effect. The convenient synthetic model compounds serve as in the form because there is a clear discrimination over cyclicpolyether's among different ions for their biological counterparts and functions in the similar form.[25]In prokaryotes and eukaryotes cellular systems, crown ether was found to be toxic and all these lead to further studies over incensement in potential for pharmacological agent. Crown compounds are synthesized with the sizes of ring from 14 to 30 atoms by **Brown and Foubister** which displayed the activity of anticoccidial in vitro against *Eimeria tenella.*[26]

Antitumor activity: In the cells of mammals, the cytotoxic effects were found early. Possibleantitumoractivity of crown ether was not performed.[27]

Huszthy*et al* synthesis fluorescent acridono- and thioacridono- 18-crown-6 ligands, (**Fig VI**) of chemotherapeutic importance.[28]

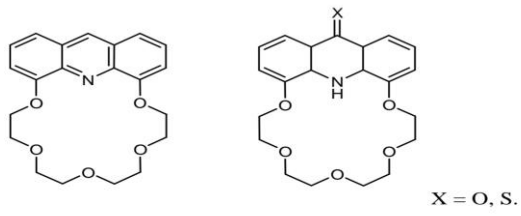


Fig VI

The compounds that contain aziridinyl groups are synthesized by Brandt *et al* which bears crown that are attached to cyclotriphosphazine which results in the improvement of the therapeutic properties of aziridinyl

cyclophosphozenes. Tetraaziridinyl lariat ether are synthesized which are tested for the purpose of in vitro antitumor activity which is similar as in an investigational AIDS-related lymphona screen.[29]All these have a remarkable cytostatic activity which results in the interaction with the DNA by the process of synergistic effect which interacts central metal and (di)alkylating capacity of aziridinyl group. As a result, DNAcause damage halts cell proliferation which makes the compound cyctostatic drug.

CONCLUSION

There are several phases gone over the chemistry of crown ether since its discovery. Various structures are prepared at the first stage of the development of these compounds and further studied the behaviour of these compounds in solution, solid state and its interaction with the ionic species. Crown ethers are emergent class of compounds having enormoususefulnessin chemistry and industry. Also they have innovative applications as potential novel anticancer drugs.Further research in this area should be stimulated.There is deficiency of the complete understanding of these privileged compounds. Therefore, advanceinvestigation in this domain should be continued owing to their numerous applications.

CONFLICT OF INTEREST

Conflict of interest declared none.

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