Chemistry and Applications of Crowns and Cryptates

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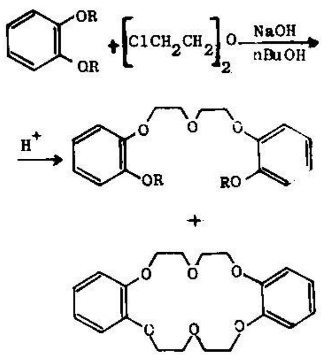
Introduction

Prior to 1967, no one envisioned complexing of alkali and alkaline earth metal ions by neutral molecules and in turn solubilizing salts like KCl, NaOH, and $KMnO_4$ in organic solvents like benzene, toluene and DMSO[1]. Moreover, by making use of organic molecules (crowns and cryptands), Dye and coworkers[2] in 1974 isolated a crystalline salt which contained sodium in its Na^- form. These and other similar observations provided new domains to all divisions of chemistry.

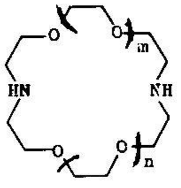
Pedersen's fascinating discovery of a broad range of macrocyclic ethers, now called "crowns" was however accidental. He attempted a synthesis of a bis-phenol by the following route. Alongwith desired product, he also isolated a crystalline compound now known as dibenzo-18-crown-6 in a very small amount. Then a series of related polyethers were synthesized by him. Their potential importance in the development of "host-guest" complexes which simulate the selectivity of enzymes has been emphasized[3].



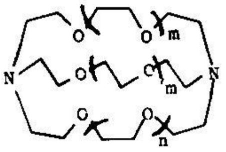
Dibenzo 18-crown-6

Furthermore, preparation of macrobicyclic polyether diamines (known as cryptands) by Lehn and coworkers[4] in 1969 presented multitude of new properties. Cryptand's selective binding of cations results in their use as models of carrier molecules involved in active ion transport across biological membranes. Their antiviral activity against A^2 influenza virus, and inhibition of catechol amine induced free fatty acid mobilization, are some of their other interesting applications[5].

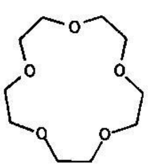
The purpose of this article is to provide background information of these novel macrocycles and about the applications of these fascinating molecules in organic synthesis and in the area of metal complexation. Moreover, the emphasis will be on their characteristic usage rather than discussing the structural variations presented by ever increasing number of these macrocycles since their discovery. There are several dozens of these molecules of various sizes which have been synthesized so far. Following are the structure of some representative macrocycles which are now commercially available. The structures of many other macrocycles are given in reference 6 and other discussion is available as well.



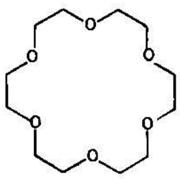
m=o　n=1　21
m=1　n=1　22



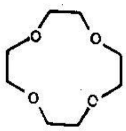
m=0　n=1　211
m=1　n=0　221
m=1　n=1　222



15-Crown-5



18-Crown-6



12-Crown-4

Structural Features:

Topologically, cryptands differ from the crowns in their bicyclic nature. All of the crowns are two dimensional monocycles presenting a circular cavity in the centre of the molecule. The addition of another strand leads to a bicycle which has a three dimensional spherical cavity. A common structural feature is that all oxygen binding sites are separated by a two carbon bridge (–O–CH_2–CH_2–O–). These linkages provide the necessary conformational flexibility needed by these host molecules to shape their cavity, in a way to best wrap around the guest species. Hence they present an exterior framework exhibiting hydrophobic properties and interior cavity of hydrophilic nature.

An additional interesting feature of macrobicyclic cryptands is the potential for pyramidal inversion at nitrogen allowing for "out-in" or "exo-endo" isomerism which changes the internal cavity size of the ligand. The spherical shaped cavity is especially suited for the recognition of the spherical alkali, alkaline-earth and other cations. Appreciably stable complexes with alkali and alkaline-earth cations are known for only about twelve years with natural and synthetic macrocycles, among them all, cryptands form most stable complexes in consonance with their topology.

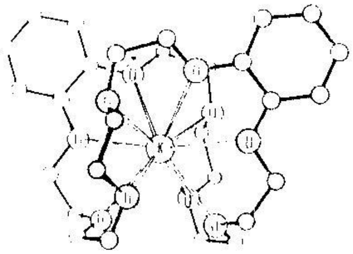
Crown ethers, particularly those containing more than one benzo-group, are nearly insoluble in water and sparsely soluble in alcohols and many other common solvents at room temperature. They are readily soluble, however, in methylene chloride and chloroform. The saturated polyethers are much more soluble in all solvents than their aromatic precursors. Most of them dissolve even in petroleum ether and yet display appreciable water solubility. The cryptands are soluble in almost all solvents ranging from water to hydrocarbons. This wide range of solubility make them comparatively more useful in variety of applications in research.

Metal Complexation Studies:

(i) Alkali and Alkaline Earth Metal Complexes:

Extensive work is being done with these group of metal ions because of the biological implications of these cations. Moreover, it has been only in the last decade that stable coordination complexes of these cations with neutral species have been isolated and fully characterized. The macrobicyclic cryptands form with alkali and alkaline-earth cations (1:1) inclusive complexes of unexpected stability even in aqueous solution.[7] The following table lists some of the macrocycles from an ever increasing number of ligands, which have been established to form 1:1 complexes with alkali and alkaline earth cations.

The structures of some crystalline complexes have been determined by X-ray diffraction studies and was hence confirmed that metal ion resides in the central cavity of the molecule. Some special interest resides in the crown macrocycle with much larger rings. Because of more conformational flexibility, they may envelop the cations completely, like antibiotics in their complexes. X-ray analysis of one such crown complex *KI-dibenzo-30-crown-10,* was found to possess wrap around structure.



(ii) Transition Metal Complexes:

Transition metal complexes of porphyrin or corrin ring systems and phthalocyanine have been investigated for a long time. These macrocycles present in nature, form stable complexes with variety of transition metal cations. It is only very recently that crown and cryptates have been shown to form macrocycle complexes with these metal ions.[8] However, typically macrocycles with nitrogen donor atoms, as compared to oxygen, form more stable complexes with transition metal cations.

The complexation of cobalt (II) with cryptand 2:2:1 indicates that the cobalt is bonded to each of the seven binding sites and is completely encryptated.[9] The unusual pentagonal bipyramid geometry produced can be correlated with number of metallo-enzyme systems where steric hindrance around metal ion results in unusual coordination geometries.

In another extensive study,[10] several mono and bicyclic ligands were complexed with Cu^{2+}, Ni^{2+} and Co^{2+}. Stability measurements were carried out and

Table 1. Stability Constants (Log) of Some Cations with Various Ligands

Compound	Solvent	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
18-crown-6	CH_3OH	–	4.3	6.1	–	4.6	–	–	–	–
dibenzo-18-crown-6	CH_3OH	–	4.4	5.0	–	3.6	–	–	–	–
dicyclohexyl-18-crown-6	H_2O	0.6	1.7	2.2	1.5	1.2	–	–	3.2	3.6
	CH_3OH	–	4.1	6.0	–	4.6	–	–	–	–
benzo-15-crown-5	H_2O	1.0	0.3	0.6	–	–	–	–	–	–
	CH_3OH	–	3.7	3.6	–	2.8	–	–	–	–
2:1:1	H_2O	5.5	3.2	2.0	2.0	2.0	2.5	2.5	2.5	2.0
2:2:1	H_2O	2.5	5.4	3.95	2.55	2.0	2.0	6.95	7.35	6.3
2:2:2	H_2O	2.0	3.9	5.4	4.35	2.0	2.0	4.4	8.0	9.5
	CH_3OH/H_2O	1.8	7.21	9.75	8.40	3.54	2.0	7.6	11.5	12.0

a differing behaviour from alkali and alkaline earth cation complexes was noticed, which is attributed partly due to the more covalent nature of the bonds formed between transition metal cations and macrocylic crown and cryptand type other molecules.

(iii) Heavy and Lanthanide Metal Cation Complexes :

Heavy metal cations like Tl^{+1}, Cd^{2+}, Hg^{2+}, Pb^{2+} are very toxic and the highly selective complexation by those ligands which may remove only these harmful cations and not effecting the levels of biologically important ones (Na^+, K^+, Ca^{2+} etc.) is both of fundamental interest and of potential practical importance from their therapeutical decorporation point of view and to control the pollution of these metal ions in the environment. Remarkable complexation properties of cryptand ligands have been found towards these toxic heavy cations.

By combining two structural parameters i.e. cavity size and nature of binding sites, Lehn and Monta von studied[11] the formation of highly stable cryptates with Cd^{2+}, Hg^{2+} and Pb^{2+}. Stability constants of these complexes are several orders of magnitude greater than alkali and alkaline earth cation complexes. In detoxication studies, cryptands have very high Pb^{2+}/Ca^{2+} and Hg^{2+}/Ca^{2+} selectivities which are much higher than those of EDTA.

Although lanthanoid ions complex strongly with those oxygen containing ligands in which the bonding oxygen atom carries a negative charge, such as RCO_2^-, their affinity for ethers has been minimal. However, an ether oxygen atom in a multidendate ligand will coordinate, and solid complexes of crown ethers and cryptands have been successfully isolated and characterized.[12,13]

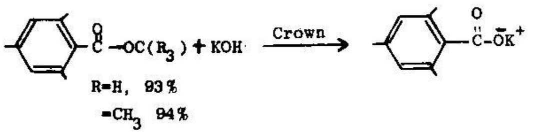
We published[14] few years ago a first preliminary report on the preparation and novel redox, NMR and kinetic properties of some lanthanide cryptates. These complexes are obtained only working with anhydrous solvents. Because of the strong basicity of cryptand ligands, lanthanide salts in presence of water form the protonated ligand with precipitation of metal hydroxide. With crown ethers, several reports have been published about the formation, isolation and characterization of lanthanide complexes, but mostly with 15-crown-5 and 18-crown-6 ether type molecules[12,15-16].

(iv) Alkali Metal Anions:

We are accustomed to only +1 oxidation state of alkali metals but there can no longer be any doubt that −1 oxidation state of the alkali metals exists under a variety of conditions. The crystalline salt of Na^{-1} as a cryptate complex has been isolated[17] and its X-ray crystal structure shows that a solvent is not required for the existence of such anions. The shiny gold-colored crystals of the solid are in a hexa-gonally closest packed arrangement. Moreover gold-colored solids of K^{-1}, Rb^{-1} and Cs^{-1} have also been prepared and fully characterized by the same workers.[18]

Application in Organic Syntheses

The power of crown ethers was first pointed out by Pedersen, who showed that potassium hydroxide could be solubalized in toluene and that the crown complexed potassium hydroxide was a powerful base. Basic hydrolysis of mesitoic acid (2,4,6−trimethyl benzoic acid) esters was carried out in the presence of a crown ether in a quantitative fashion whereas in absence, no reaction was observed at all:



Since the crown ethers and cryptates have the ability to solvate cations in non-polar environment, their utility clearly parallels to that of quaternary ammonium cations which are used as phase transfer catalysts. However the major difference is that crowns and cryptates may catalyze a direct solid/liquid phase transfer of salts into non-polar solvents whereas quaternary ammonium - catalyzed reactions are done from a liquid (aqueous) phase into non-polar solvents.

Utility in Phase Transfer Reactions and Survey of Reactions of Naked Anions.

Crowns and cryptates can be employed as phase-transfer catalysts in anion promoted reactions with results similar to those obtained in the presence of onium salts. Other factors being equal, the catalytic activity increases with increase in organo-philicity of the macrocycles. Since the crown and cryptate macrocycles are able to surround the cation completely, these molecules are powerful anion activators and are highly efficient catalysts in aqueous, organic two-phase reactions.

1. Nucleophilic Substitution.

(i) By Halide ions:

Montanari et al. in a series of papers have reported[19] the reactions of a series of octyl derivatives with a variety of potassium halides under liquid-liquid phase transfer catalytic conditions using an alkyl substituted 2:2:2 cryptand or dicyclohexyl-18-crown-6. The reactions were carried out by stirring a mixture of the organic substrate and a saturated aqueous solution of alkali metal salt at 60-80°C in the presence of 0.05 molar equivalent of crown or cryptate. Some of their results are summarized in Table 2.

$$C_8H_{17}X + Y^- \xrightarrow{\text{Crown},H_2O} C_8H_{17}Y + X^-$$

The remarkable ability of the macrocyclic polyethers to draw salts into non-polar solution has also been utilized in reactions involving fluoride ion. 18-crown-6 assists the solubalization of KF in either acetonitrile or benzene and the poorly solvated fluoride anion exhibits potent nucleophilic properties.[21,21]

$$C_6H_5CH_2Cl + KF \rightarrow \underset{100\%}{C_6H_5CH_2F}$$

$$H_3C\,(CH_2)_6CH_2Br{+}KF \rightarrow \underset{92\%}{H_3C\,(CH_2)_6CH_2F}$$

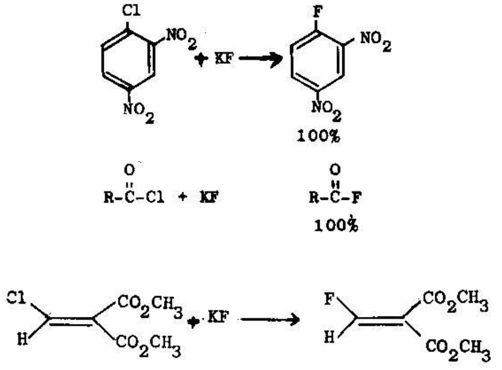
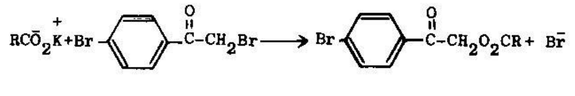


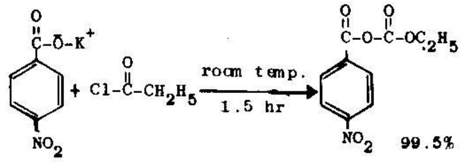
Table 2. Efficiency of Crown-ether Catalysts in Substitution Reactions and Phase-Transfer Conditions.

Substrate	Reagent	T/°C	Time/h	Yield/%	Product
n-$C_8H_{17}Br$	KI	60	0.2	100	n-$C_8H_{17}I$
n-$C_8H_{17}Cl$	KI	80	5.0	77	n-$C_8H_{17}I$
n-$C_8H_{17}Cl$	KCN	80	5.0	93	n-$C_8H_{17}CN$
n-$C_8H_{17}OSO_2Me$	KF	120	4.0	85	n-$C_8H_{17}F$
n-$C_8H_{17}Br$	PhSNa	20	0.1	100	n-$C_8H_{17}SPh$
$PhCH_2COMe$	n-BuBr	20	0.75	94	PhCH(Bu-n)COMe
n-$C_6H_{13}COMe$	$NaBH_4$	20	4.0	97	n-$C_6H_{13}CH(OH)Me$
$PhCH{=}CH_2$	NaOH,$CHCl_3$	20	24.0	60	$PhCHCCl_2CH_2$

(ii) By Carboxylate ion:

The carboxylate ion is not generally considered a good nucleophile due to its negative charge delocalization, however in non-polar media, it is quite nucleophilic. The naked acetate ion reacts readily with n-heptyl bromide in acetonitrile to yield n-heptyl acetate.[22]





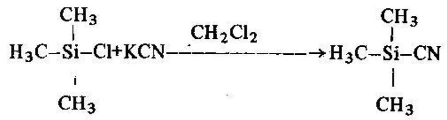
(iii) By Cyanide ions:

The bare cyanide ion exhibits similar behaviour in S_N2 reactions. The nitriles are prepared by simply pouring the substrate solution directly over excess KCN and stirring the two phase system at ambient or reflux temperature. Little or no reaction occurs in the absence of crown ethers.

$$C_6H_5CH_2Br + KCN \rightarrow C_6H_5CH_2CN$$

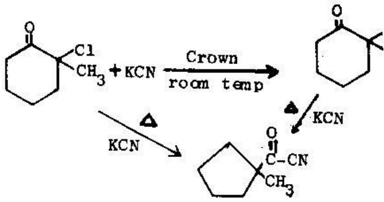
$$Br{-}CH_2{-}CH_2{-}Br{+}KCN \rightarrow NC{-}CH_2CH_2{-}CN$$

A particularly interesting case of nitrile synthesis is reported by Zubrick et al.[23] They reported the following synthesis of trimethyl silyl cyanide from its respective chloride by naked cyanide ion in 45% yield.



$$H_3C{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}Cl{+}KCN \xrightarrow{CH_2Cl_2} H_3C{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}CN$$

A striking effect of temperature is illustrated in the following reaction where at reflux temperatures, the Favorskii product was obtained in high yield.

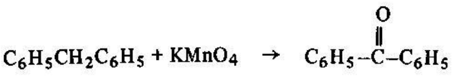


2. Oxidation Reactions

It has been demonstrated by Sam and Simmons[24] that $KMnO_4$ solubalized in benzene in the presence of a crown or cryptate, provided a convenient, mild and efficient oxidant for a wide variety of organic reactions. The reactions are usually carried out at room temperature and the products are isolated in quantitative yield.

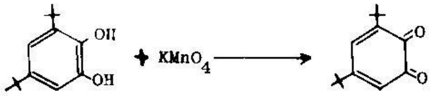
trans $C_6H_5-CH=CH-C_6H_5 + KMnO_4 \rightarrow C_6H_5COOH$

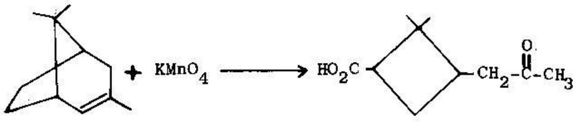
100%



$C_6H_5CH_2C_6H_5 + KMnO_4 \rightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-C_6H_5$

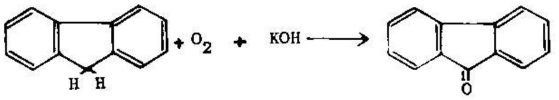
100%





90%

Dietrich and Lehn in 1973 published[25] about the air oxidation of the fluorenyl anion with molecular oxygen to yield the fluorenone in good yield. The reaction of fluorene was carried out with KOH solublized in toluene in the presence of a cryptate 2:2:2.

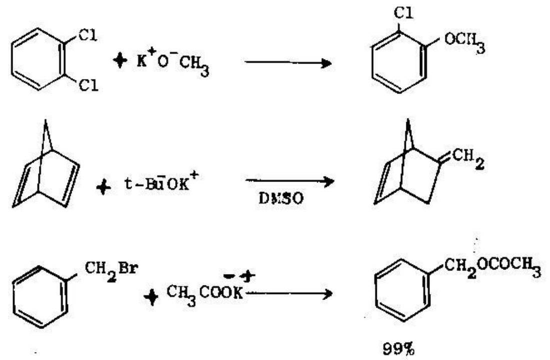


95-100%

Similarly aniline undergoes oxidative condensation to azo-benzene in 35-40% yield.

3. *Activation of Alkali Metal Enolates and Bases*

The strong basic ability of alkali metal enolate cryptand solution has been clearly depicted by the results published in a series of papers by Pierre and co-workers.[26,27] Furthermore, it was Pedersen who for the first time reported that even sterically hindered esters of 2,4,6 trimethyl benzoic acid were saponified with KOH-crown ether complex in aromatic hydrocarbons. The same reaction when carried out in hydrolytic solvents gave essentially no product. The utilization of macrocyclic ligands which selectively complex the metal cation activates the alkali enolate, hydroxide or hydride anions. Following are the few examples cited from the literature:



$H_3C-(CH_2)_6-CH_2Br + CH_3-CH_2\ COO^-K^+$

$\rightarrow H_3C-(CH_2)_6\ CH_2-OCOCH_2CH_3$

90%

An exceptionally strong basicity by alkali metal enolate at room temperature was exhibited in the following reaction. When triphenylmethane ($pKa = 31.5$) was added to any of the lithium, sodium or potassium enolates of cyclohexanone solution in the presence of a cryptand (2:2:2), the red color of the carbanion appeared instantaneously whereas in the absence of cryptand, no reaction occurred. The same behaviour was observed using diphenylmethane ($pKa = 33$) however toluene ($pKa = 37$) is not ionized by the same procedure.

Finally Corey et al. have reported[28] the nucleophilic reactions of naked super-oxide (O_2^-) with a wide variety of organic substrates using KO_2 in DMSO, DMF or diethyl ether in the presence of a crown ether molecule.

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