COMPLEXATION STUDIES OF CROWN ETHERS WITH ALKALI METAL CATIONS IN METHANOL

by

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ABSTRAK

Tindak balas pengalkilan di antara dibenzo-15-mahkota-5 (DB15C5) dengan *t*-butanol dalam asid trifluoroasetik akan memberi 2,3,8,9-(4',4"-di-*tert*-butil)-dibenzo-1,4,7,10,13-pentaoksasiklopentadeka-2,8-diena (t_2-DB15C5). Selain itu, f_2-DB18C6 (campuran 4',4"-di-formil benzo-18-mahkota-6 dan 4',5"-di-formil benzo-18-mahkota-6) telah disintesis daripada dibenzo-18-crown-6 (DB18C6) melalui proses pemformilan menggunakan heksametilenatetramina serta asid trifluoroasetik. Kedua-dua sebatian memberikan hasil yang agak tinggi (~ 80% untuk t_2-DB15C5 dan 55-65% untuk f_2-DB18C6). Struktur mereka ditentukan dengan menggunakan analisa komposisi unsur, spektroskopi IR, spektroskopi jisim, spektroskopi ^{1}H NMR dan juga spektroskopi ^{13}C NMR.

Pengkompleksan DB15C5 dengan kation logam alkali serta Sm^{3+}, Nd^{3+} dan Pr^{3+} dalam metanol diteliti menggunakan spektroskopi ^{1}H NMR dan spektroskopi UV. Kompleks stoikiometri 1:1 didapati dengan Li^+ dan Na^+ serta Sm^{3+}, Nd^{3+} dan Pr^{3+} manakala K^+ memberi kompleks 2:1 (sandwich). Kompleks 1:1 dan 2:1 (sandwich) didapati dengan Cs^+. Jenis kompleks DB15C5-Rb^+ yang didapati bergantung kepada nisbah perumah kepada tetamu yang digunakan. Apabila nisbah perumah kepada tetamu yang digunakan adalah 1:1, kompleks yang didapati adalah campuran kompleks 1:1 dan 2:1 (sandwich). Apabila tetamu berada dalam keadaan berlebihan, kompleks yang diperoleh ialah kompleks 2:1 (sandwich).

Pemgkompleksan t_2-DB15C5 dengan kation logam alkali juga dijalankan dalam methanol. Kompleks dengan stoikiometri 1:1 didapati dengan Li^+ dan Na^+ manakala K^+, Rb^+ dan Cs^+ kesemuanya memberi kompleks 2:1 (sandwich). Untuk kompleks dengan stoikiometri 1:1, kumpulan *t*-butil pada gelang benzena eter mahkota didapati meningkatkan kestabilan kompleks satu kali ganda. Nilai pemalar penyekutuan kompleks stoikiometri 1:1 telah diperoleh dalam turutan $Li^+ > Na^+$ untuk DB15C5 dan t_2-DB15C5.

Pengkompleksan DB18C6 dan f_2-DB18C6 dengan kation logam alkali dijalankan dalam campuran metanol-kloroform (8:2 v/v). DB18C6 akan memberikan kompleks stoikiometri 1:1 dengan Li^+, Na^+ dan K^+ manakala Cs^+ memberikan kedua-dua kompleks stoikiometri 1:1 serta 2:1 (sandwich). Jenis kompleks DB18C6-Rb^+ yang didapati bergantung kepada nisbah perumah kepada tetamu yang digunakan. Apabila nisbah perumah kepada tetamu yang digunakan adalah 1:1, kompleks yang didapati adalah campuran kompleks 1:1 dan 2:1 (sandwich). Apabila tetamu berada dalam keadaan berlebihan, kompleks yang diperoleh ialah kompleks 2:1 (sandwich). Nilai pemalar penyekutuan kompleks stoikiometri 1:1 telah diperoleh dalam turutan $Na^+ > K^+ >$ Li untuk DB18C6. Untuk f_2-DB18C6, selain daripada oksigen eter, oksigen karbonil turut memainkan peranan dalam pengkompleksan dengan kation logam alkali.

COMPLEXATION STUDIES OF CROWN ETHERS WITH ALKALI METAL CATIONS IN METHANOL

ABSTRACT

The alkylation reaction between dibenzo-15-crown-5 (DB15C5) and *t*-butyl alcohol in trifluoroacetic acid yielded 2,3,8,9-(4',4"-di-*tert*-butyl)-dibenzo-1,4,7,10,13-pentaoxacyclopentadeca-2,8-diene (t_2-DB15C5). The f_2-DB18C6 (mixture of 4',4"-di-formyl benzo18-crown-6 and 4',5"-di-formyl benzo18-crown-6) was synthesized from dibenzo-18-crown-6 (DB18C6) via a facile formylation process employing hexamethylenetetramine and trifluoroacetic acid. Both compounds were obtained in good yield (~ 80% for t_2-DB15C5 and 55-65% for f_2-DB18C6). The structures were identified using elemental analysis, IR, MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

The complexation of DB15C5 with alkali metal cations as well as Sm^{3+}, Nd^{3+} and Pr^{3+} in methanol were investigated using ^{1}H NMR spectroscopy and UV spectroscopy. A 1:1 stoichiometry complex was observed with Li^+ and Na^+ as well as Sm^{3+}, Nd^{3+} and Pr^{3+} while K^+ gave 2:1 (sandwich) complex. Both 1:1 and 2:1 (sandwich) complexes were observed Cs^+. The type of complex formed by DB15C5-Rb^+ depends on the ratio of host to guest used. At 1:1 host to guest ratio used, DB15C5-Rb^+ showed a mixture of 1:1 and 2:1 sandwich complexes. Nevertheless, when we have excess of host DB15C5-Rb^+ form 2:1 sandwich complex.

The complexation of t_2-DB15C5 with alkali metal cations was also carried out in methanol. A 1:1 stoichiometry complex was observed with Li^+ and Na^+ while K^+, Rb^+

and Cs^+ all gave 2:1 (sandwich) complex. For 1:1 stoichiometry complexes, the *t*-butyl substituent groups on the benzene ring of t_2-DB15C5 increase the stability of the complex by one fold compared to DB15C5. The association constants for 1:1 stoichiometry complexes were found in the order of $Li^+ > Na^+$ for DB15C5 and t_2-DB15C5.

The complexation of DB18C6 and f_2-DB18C6 with alkali metal cations were carried out in the methanol-chloroform (8:2 v/v). DB18C6 gave 1:1 stoichiometry complexes with Li^+, Na^+ and K^+ while Cs^+ gave both 1:1 and 2:1 (sandwich) complexes. The type of complex formed by DB15C5-Rb^+ depends on the ratio of host to guest used. DB18C6-Rb^+ gave 1:1 complex when we have excess guest. However, when we have excess host, the majority of complex formed was 2:1 sandwich complex. The association constants for 1:1 stoichiometry complexes were found in the order of $Na^+ > K^+ > Li^+$ for DB18C6. For f_2-DB18C6, besides the ether oxygens, the carbonyl oxygens were also involved in the complexation with alkali metal cations.

1. INTRODUCTION

1.1 Background

In 1894, Emil Fischer, a far-sighted chemist, came up with his brilliant "*lock-and-key*" idea. In his famous paper (Fischer, 1894), he proposed that enzyme and substrate would only selectively bind just as lock and key. It was Paul Ehrlich who recognized that molecules do not act if they do not bind, thus, introducing the concept of receptor (Ehrlich, 1906). Finally binding or fixation requires interaction, affinity between partners that may relate to the idea of coordination introduced by Alfred Werner (Werner, 1893).

According to these basic concepts, molecular recognition implies complementary lock-and-key type fit between molecules. The lock is the molecular receptor and the key is the substrate that is recognized and selected to give a defined receptor-substrate complex. Hence molecular recognition is one of the three main pillars, fixation, coordination and recognition; that lay foundation of what is now called supramolecular chemistry (Vogtle, 1993; Lehn, 1995; Weber, 1993 and 1995). Figure 1.1 below shows the principal mechanisms of formation of a receptor-substrate complex.

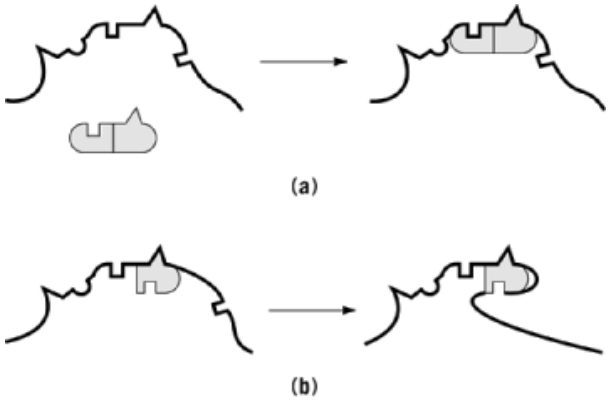


Fig 1.1(a): Fischer's rigid "*lock and key*" model; (b) "*induced fit*" model showing conformational changes of the receptor (solid line) upon substrate (dotted area) binding.

The past three decades have seen an enormous amount of money not to say time and energy channeled into the expansion of research in supramolecular chemistry. The power of this field in exploring significant and interesting questions in chemistry could not be denied anymore. In fact, it has found a strong footing in such diverse fields as biochemistry and genetic engineering (Bradshaw et. al., 1996).

One of the forefront contributions of supramolecular chemistry is in designing and synthesizing macrocycles that can selectively bind a particular guest. This is extremely important especially in our pursuit of knowledge in biological systems. Where it is difficult to study the humongous molecules such as enzyme, it is much easier to simulate the studies in smaller molecules that have the same properties. This is where supramolecules come in useful; where it can mimic the features of biosystems.

Binding of molecules to the active sites of macrocycles may occur through formation of specific non-covalent bonds. These include van der Waals interaction, ionic bonding, ion-dipole interaction (can be seen when crown ether complex with metal ions), hydrogen bonding (partly involve in stabilization of protein molecules), CH-π interaction (complexation between cyclotetrachromotropylene and alcohols/sugars) (Poh & Tan,1993), π-π interaction (Hamilton & Van Engen, 1987) and cation-π interaction (Kebarle et. al., 1981; Gokel et. al., 1999**a**).

A very simple example of showing the principles of π-π interaction is illustrated in Figure 1.2 (Hamilton & Van Engen, 1987). The flat heterocyclic substrate, uracil derivatives, fits in face-to-face mode into the conformationally stepped receptor macro ring containing a naphthalene π-stacking unit and being bound via a system of extra

hydrogen bonds to a diamidopyridine unit. The association constant for the analogous receptor molecule without the π-stacking unit is more than four times lower. The role of the π-π interaction clearly indicates a substantial improvement of recognition behaviour and increment of binding energy.

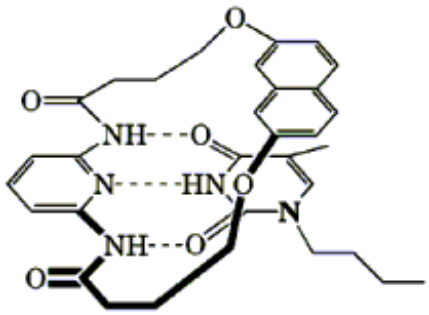


Fig 1.2 : π-π stacking recognition of flat aromatic-heteroaromatic substrates.

Cation-π interaction has received considerable attention since the pioneering studies of Kebarle and co-workers in 1981 (Kebarle et. al., 1981). They showed that the interaction between benzene and K^+ in gas phase was stronger than a similar interaction with a single water molecule (ΔH = -30 vs –29 kcal/mol). Apart from that, Burley and Petsko (Burley & Petsko, 1986) noted a high tendency for amines to be located near aromatic amino acid side chains in a survey of protein structures. They proposed that this *"amino-aromatic"* interaction contributed to protein stability. Theoretical studies by Dougherty and others suggested that the aromatic side chains of Phe, Trp and Tyr should be strong donors for the biologically important Na^+ and K^+ cations (Meccozi et. al., 1996; Dunbar, 1998; Cubero et. al., 1999). However, experimental observations of Na^+ and K^+ cation-π interactions have been hampered by lack of sufficient resolution in protein structures (Kooystra et. al., 1988) and model systems (Gokel et. al., 1999**b**).

1.2 Cyclodextrins

One of the most well known and extensively studied naturally occurring macrocycles is the structurally complex oligosaccharides known as cyclodextrin (Davis & Wareham, 1999). It can range from 6-8 glucopyranose units.

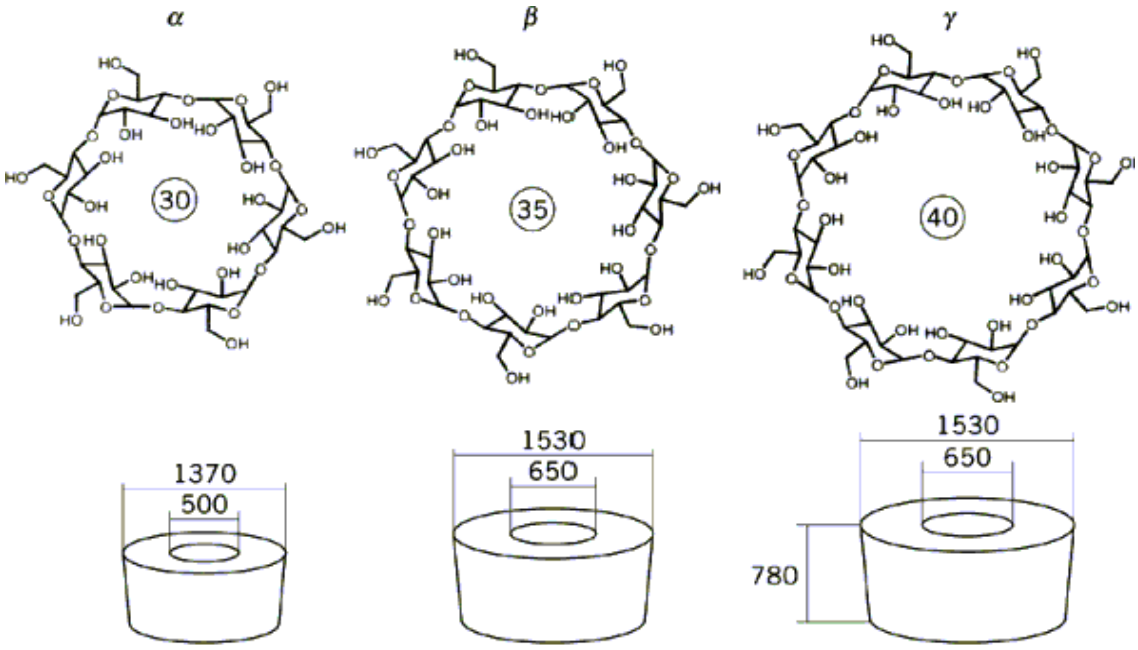


Fig 1.3 : Prototype examples of cyclodextrins with their dimensions.

Cyclodextrins are water soluble hosts and because of this they remain a very important class of macrocycles in complexation studies of hydrophobic guests in aqueous solution.

1.3 Podands

Podands (Figure 1.4) are open-chain crown-type of compounds. They are acyclic collection of binding sites held together by spacer units. During the complexation to form a podate (podaplex), many degrees of conformational freedom must be frozen.

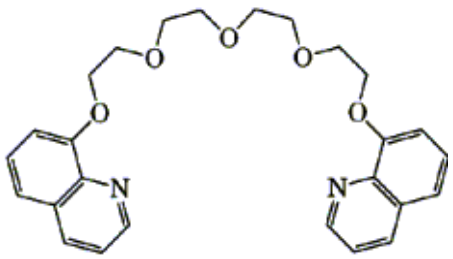
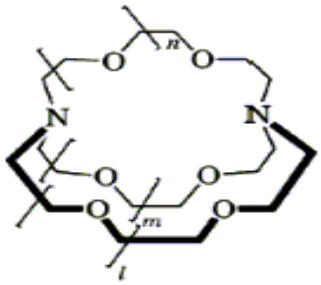


Fig 1.4 : An example of a podand

1.4 Cryptands

Cryptands (Figure 1.5), bridged crown analogues, developed by Lehn and co-workers have three-dimensional cavities. These ligands are usually bicyclic or tricyclic. They produce inclusion complexes, termed *"cryptates"*, with the cations (Poonia, 1979).



(a) $l = m = n = 0$ [1.1.1]
(b) $l = 1, m = n = 0$ [2.1.1]
(c) $l = m = 1, n = 0$ [2.2.1]
(d) $l = m = n = 1$ [2.2.2]

Fig 1.5 : Examples of crytands

1.5 Spherands

Spherands (Figure 1.6) are at the end of the unfolded progression of receptor structures with regard to the parameter of preorganization. Hence they are characterized

as completely preorganized receptor systems possessing an enforced cavity with perfect octahedral arrangement of six donor oxygen atoms.

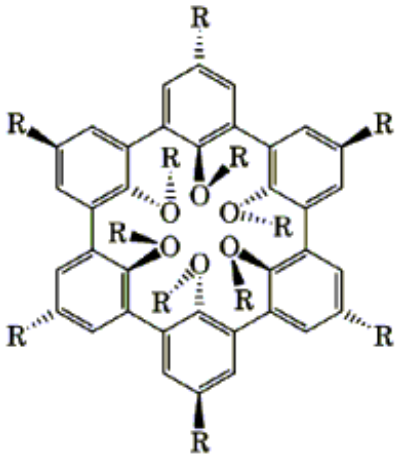


Fig 1.6 : An example of a spherand

1.6 Calixarenes

Calixarenes are cyclic oligomers, which are formed by benzene units bridged with methylene groups. The origin of calixarenes can be traced back to von Baeyer's discovery of phenol-formaldehyde resins in the 1870s although the name *"calixarene"* did not enter the literature until 1978 (Gutsche & Muthukrishnan, 1978). Gutsche was the first to draw attention to the potential of these oligomers as molecular receptors or enzyme mimic and in 1978, together with Muthukrishnan he proposed that they be known collectively as *"calixarenes"*. In the 1990s it is the receptor properties of the calixarenes for ions and neutral molecules that aroused most interest (Shinkai, 1993). The basic structures for calixarenes are shown in Figure 1.7.

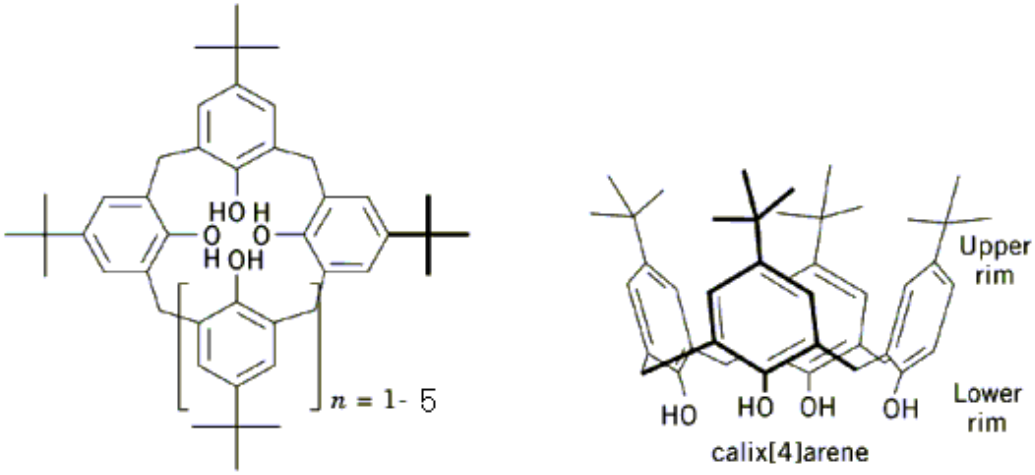


Fig 1.7 : Prototype examples of calixarenes with their conformational structures.

Early work by Ungaro and co-workers (Ungaro et. al., 1982) showed that polyether podands could be attached to the lower rim of *p-tert*-butyl-calix[4]arene, -[6]arene as well as –[8]arene in the presence of a base. Whereas the calix[6]- and calix[8]arene derivatives are conformationally mobile in solution, the analogous calix[4]arenes are fixed in either the cone or the partial cone conformation. Later, several groups demonstrated that halogenated esters (Ungaro et. al., 1984; Chang & Cho, 1986), amides (Ungaro et. al., 1988; Chang et. al., 1987), ketones (Arnaud-Neu et. al., 1989; Ferguson et. al., 1987) and methylpyridines (Bottini et. al., 1989) could be used to attach functionalized podands to the lower rim of calixarenes. In the tetramer series, the majority of ester, amide and ketone derivatives exist in stable cone conformations. However, Iwamoto and Shinkai (Iwamoto & Shinkai, 1997) have managed to isolate the *p-tert*-butyl-calix[4]arene ethyl ester in stable cone, partial cone, 1,2-alternate and 1,3-alternate conformations (Fig 1.8). The availability of such diverse identical series of

derivates is useful for probing the dependence of cation complexation selectivity on receptor conformation.

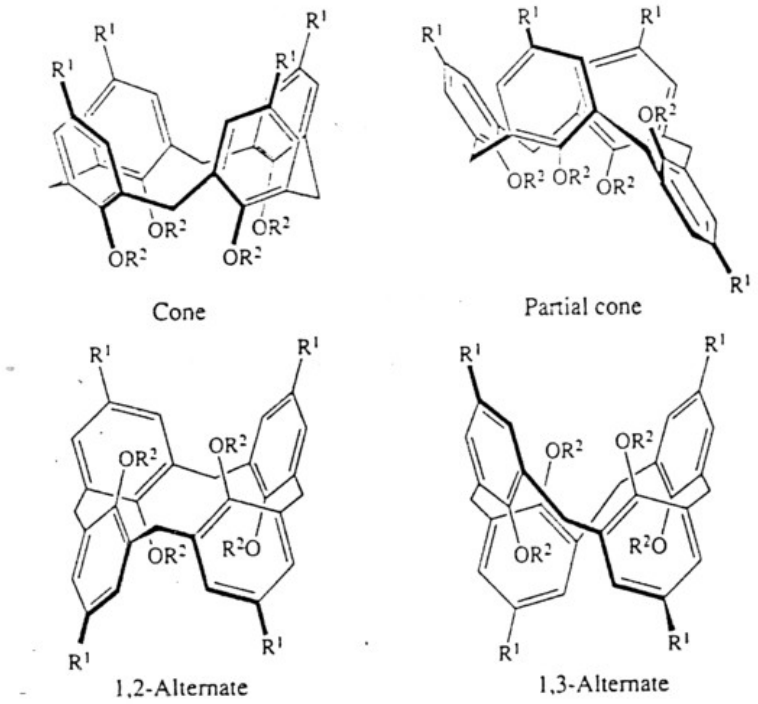


Fig 1.8 : Four principal conformations of calix[4]arenes, designated cone, partial cone, 1,2-alternate and 1,3-alternate

Although a large variety of calixarenes with functional groups on the upper rim are now available, they have not been used for selective cation complexation to the same extent as their lower rim counterparts. The most significant substitutions are those bearing the carboxylate, sulfonate or amino groups (Gutsche & Lavine, 1982; Shinkai et. al., 1987; Verboom et. al., 1992). In some cases the derivates are also water soluble (Shinkai, 1991; Atwood & Bott, 1991).

1.7 Crown Ethers

Since the pioneering studies of Pedersen (Pedersen, 1967), the remarkable ability of macrocyclic ethers to selectively complex metal cations has been a topic of fundamental interest in coordination chemistry. A multitude of crown ethers have been synthesized and modified since Pedersen's landmark paper to enhance the effectiveness of the crown ethers to complex with metal cations.

So what actually are crown ethers and what makes them so special? Crown ethers, as originally defined are those compounds with multiple ether oxygen atoms incorporated in a monocyclic backbone. The term *"crown"* was used because the cavity shape of the macrocycle resembled a crown (Bradshaw et. al., 1996). Figure 1.9 below shows some of the more common crown ethers.

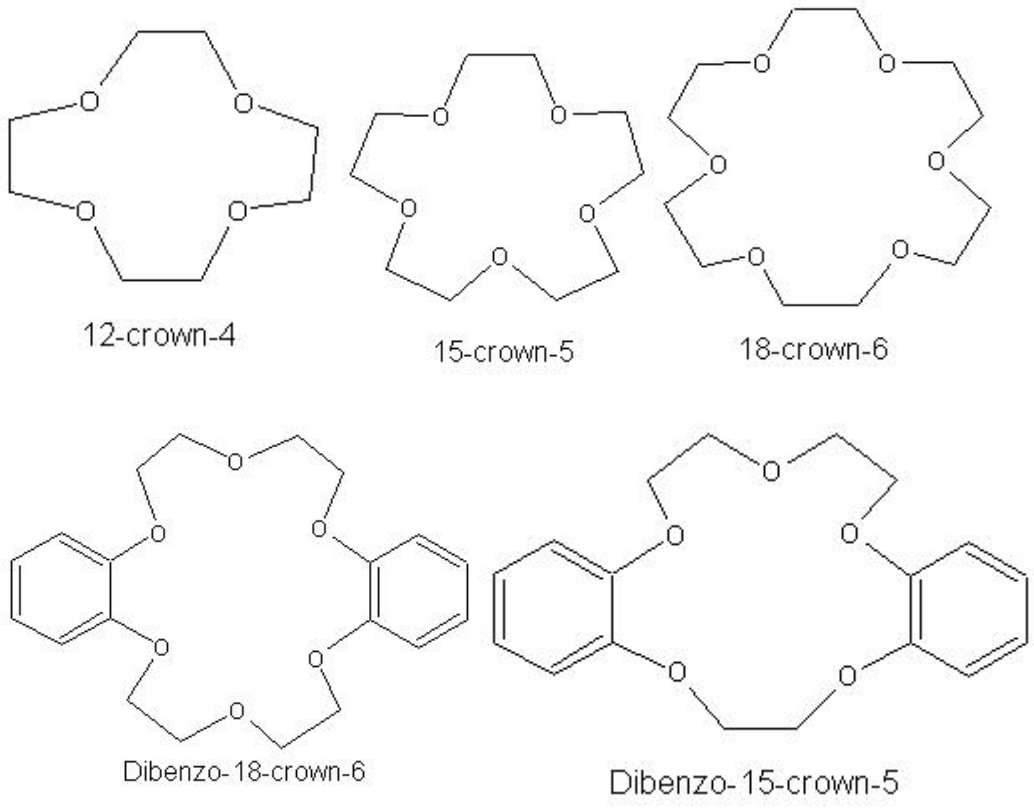
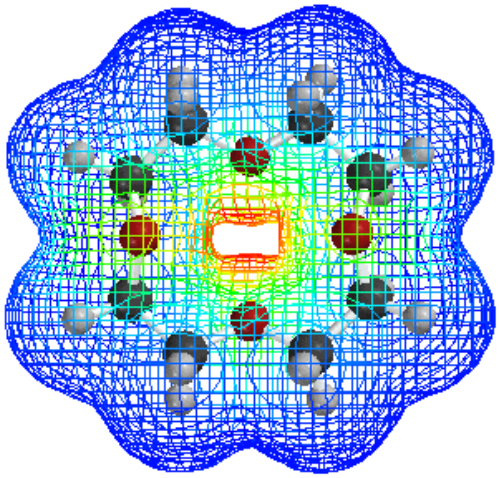


Fig 1.9 : Several examples of crown ethers

A crown ether has a cavity that is electron rich (oxygen lone pairs) where the binding with cation takes place and an exterior that is hydrophobic. Figure 1.10 shows 12-crown-4 in computer-generated model.



12-Crown-4 Electric Potential Surface: The electric potential surface is a measure of charge distribution. Red indicates regions of negative charge, green corresponds to neutral areas, and blue indicates regions of positive charge. From this map we can see that the positive charge is distributed over a very large area, and that the center of the crown ether is negatively charged.

Fig 1.10 : Computer-generated model of 12-crown-4 (Taken from www.webchem.ucla.edu/~harding/crownethers.html)

However, as the study of crown ethers and their derivatives developed, this definition has been greatly extended. There are now macrocyclic compounds that contain nitrogen atoms in the macrocycle which are called azacrown ethers and those containing sulfur atoms which are called thiacrown ethers.

Crown ethers have appreciable binding strengths and selectivities toward alkali and alkaline earth metal cations (Pedersen 1967 and 1970**a**). These special properties make crown ethers the first synthetic compounds that mimic many of the naturally occurring cyclic antibiotics (Ovchihikov et. al., 1974; Pressman, 1976; Hay, 1984). Due to the importance of alkali and alkaline earth metals (sodium, potassium, magnesium, calcium) in biological systems (Ochiai, 1977), in high –power batteries (lithium) (eds. Clark & Halpert, 1992) and in isotope chemistry and radiochemistry (Heumann, 1985), crown ethers are important ligands in the study of the chemistry of these metal ions. Crown

ethers are used in a wide range of areas such as analyses; separations, recovery or removal of specific species, ion selective electrodes, biological mimics and reaction catalysts. In fact, derivatives of crown ethers have now been touted as potential powerful anti tumor agents which is a very important step in fighting fatal diseases such as AIDS (Brandt et. al., 2001; Labarre, 1982; Huizen et. al., 1983).

The studies of crown ethers and their derivatives have led to important advances in the area of molecular recognition and to the emergence of new concepts such as supramolecular chemistry (Cram, 1988; Lehn, 1988). The rapid development and the importance of molecular recognition as applied to macrocyclic compounds can be seen in the awarding of the Nobel Prize in chemistry in 1987 to three of its pioneers, namely Pedersen, Cram and Lehn.

Actually long before Pedersen discovered crown ether by accident, there were others like Luttringhaus (Luttringhaus, 1937) who had preceded Pedersen in synthesizing macrocyclic polyethers. However, those researchers did not understand the unique cation-ligating properties of the cyclic polyethers. So Pedersen is widely regarded as the father of these important compounds.

In most cases, metal cation-crown ether complexation processes can be explained by the multistep Eigen-Winkler (Eigen & Winkler, 1970) mechanism (Equation 1) :

$$M^+ + L \rightleftharpoons M^+\text{---}L \rightleftharpoons M^+L \rightleftharpoons (ML)^+ \quad (1)$$

where M^+ = solvated metal ion, L = free macrocyclic ligand, M^+---L = solvent-separated metal-macrocyclic ligand pair, M^+L = contact pair, $(ML)^+$ = final complex with metal cation embedded in the macrocyclic cavity.

The Eigen-Winkler mechanism consists of a series of steps where for the same metal cation, both solvent and crown ethers may influence the activation energy profile of the process. The first step, after the outer-sphere complex is formed, involves partial rearrangement of the macrocyclic ligand and partial cation desolvation. The second step leads to the encapsulation of the metal ion and more complete desolvation.

In spite of crown ethers acting as remarkable hosts for metal ions, it has been reported that crown ethers itself could become the guest of larger macrocycles. This was reported by Poh (Poh & Tan, 1995) when 15-crown-5, 18-crown-6 and dibenzo-18-crown-6 were found to be included into the cavity of cyclotetrachromotropylene (Fig 1.11).

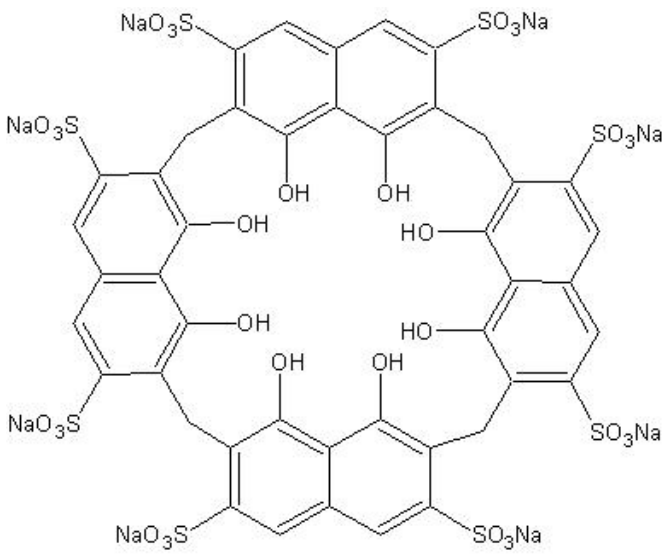


Fig 1.11 : Cyclotetrachromotropylene

1.8 Fundamental factors affecting complexation

In crown ethers where complexation with metal cations has been studied extensively, factors that control metal ion recognition, stability as well as selectivity remain incompletely understood. These include macrocycle cavity dimensions; shape and topology; substituent effect; conformational flexibility; donor atom type as well as type of solvent used (Izatt et. al., 1991). Generally, when the metal ion radius matches the ligand cavity radius, the complex is usually more stable. (Lamb et. al., 1981). The cavity sizes for the crown ethers and the sizes of several metal ions are listed in Table 1.1 and 1.2 respectively.

Table 1.1 : Diameter of crown ether cavity

Crown ethers	**Diameter of cavity, A**
15-crown-5	1.7[a] , 2.2[b]
18-crown-6	2.6 , 3.2
21-crown-7	3.4 , 4.3

[a] According to Corey-Pauling-Koltun atomic models. [b] According to Fisher-Hirschfelder-Taylor models. Both sets of data taken from Pedersen, 1970**a**.

Table 1.2 : Cationic diameter

Cation	**Cationic diameter, A**	
	[a] Pauling	**[b] Electron density**
Li^+	1.36	1.86
Na^+	1.94	2.34
K^+	2.66	2.89
Rb^+	2.96	3.28
Cs^+	3.34	3.66
Sm^{3+}	1.93	-
Pr^{3+}	2.03	-
Nd^{3+}	1.99	-

[a] Weast, 1971 ; [b] D. F. C. Morris, 1968

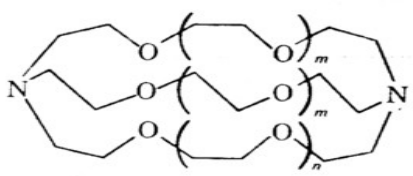
One obvious reason for the size-matching selectivity is that when the size of the ligand cavity and the size of the metal ion match, the metal ion can be positioned in the center of the ligand cavity and in the ligand plane with optimal metal ion-donor atom distances. This environment should allow optimal ligand-metal ion interaction and will result in maximal complex stability (Bradshaw et. al., 1996). However, the size-matching selectivity concept does not always apply. Doubt arose about the validity of this concept (Izatt, et. al., 1974), when it was discovered that silver (Pedersen & Frensdorff, 1972) and thallium (Poonia & Truter, 1972) formed 1:1 complexes with benzo-15-crown-5 (B15C5) as compared with the similar-sized potassium, which formed 1:2 sandwich complexes with the same crown ether (Poonia & Truter, 1972; Pedersen, 1967). Some other results that cannot be explained by this concept include the following:

1. B15C5 produces 2:1 complexes with larger cations, such as K^+, Rb^+ and Cs^+ (Poonia & Truter, 1972; Pedersen, 1967). as well as with smaller Mg^{2+} (Poonia, 1976). However, with Li^+, which is about the same size as Mg^{2+}, this crown ether ordinarily forms a 1:1 complex (Poonia, 1976).

2. DB30C10 forms a 1:1 complex with K^+, as revealed by X-ray analysis of K(DB30C10)I (Bush & Truter, 1972). However, a crown ether of smaller cavity, namely DB24C8, can form a bimetallic product with the same cation as determined by X-ray analysis of $(KNCS)_2$(DB24C8) (Truter et. al., 1972).

3. The ionic size of rubidium and cesium suits the formation of 2:1 host to guest complexes with crowns of the cavity size 18C6. However, the complexes RbNCS(18C6) (Dobler & Phizackerley, 1974) and CsNCS(TEMF) (Mallinson, 1975) have been found to be 1:1 complexes that dimerize in the crystal lattice.

Crown ethers are flexible and conformational changes sometimes occur when they are in different solvents. Interactions of crown ethers with solvents can alter their conformation and affect their complexing ability. Thus, it is expected that a simple donor and acceptor approach to the complexation behaviour may not always apply (Ozutsumi & Ohtsu, 2003). Furthermore the role of the solvent was also seen through the association constant value derived from each cryptate (Fig 1.12) as listed in Table 1.3 below (taken from Lehn & Sauvage, 1975). The solution stability for each cryptate is higher in methanol-water (95:5) than in water.



1, $m = 0$; $n = 1$ [2.1.1]
2, $m = 1$; $n = 0$ [2.2.1]
3, $m = n = 1$ [2.2.2]
4, $m = 1$; $n = 2$ [3.2.2]
5, $m = 2$; $n = 1$ [3.3.2]
6, $m = n = 2$ [3.3.3]
7, $m = 1$, (third bridge = $-(CH_2)_8-$ [2.2.C_8]

Fig 1.12 : Cryptands used for complexation by Lehn & Sauvage, 1975.

Table 1.3 : Stability constants (log K) of 1:1 M^+-cryptands complexes (Taken from Lehn & Sauvage, 1975).

Ligand	Medium	Log K				
		Li^+	Na^+	K^+	Rb^+	Cs^+
[2.1.1]	W	5.5	3.2	<2.0	<2.0	<2.0
	M-W	7.58	6.08	2.26	<2.0	<2.0
[2.2.1]	W	2.5	5.4	3.95	2.55	<2.0
	M-W	4.18	8.84	7.46	5.80	3.9
[2.2.2]	W	<2.0	3.9	5.4	4.35	<2.0
	M-W	1.8	7.2	9.75	8.45	3.54
[3.2.2]	W	<2.0	1.65	2.2	2.05	2.0
	M-W	<2.0	4.57	7.0	7.3	7.3

W : Water ; M-W : Methanol-water (95:5)

Another important aspect is the substitution effect. Table 1.4 summarizes the association constants of the various 4-substituted benzo-15-crown-5 complexes with Na^+ (Ungaro et. al., 1976). Inspection of Table 1.4 reveals that the association constant shows a pronounced dependence on the nature of the 4-substituent in the crown. An electron withdrawing group decreases the binding ability while an electron donating group increases the binding ability.

Table 1.4 : Association constants (log K) of 1:1 complexes of 4-substituted benzo-15-crown-5 and Na^+ (Taken from Ungaro et. al., 1976).

4-substituent	**Log K**
NH_2	3.91
CH_3	3.60
H	3.54
Br	3.31
CO_2H	3.21
CHO	3.05
NO_2	2.56

A single method of measurement was usually employed when studying the complexation of crown ether-cation. Table 1.5 shows that generally electrochemical techniques (potentiometry, conductance and polarography) were used to study the properties of the complexes of cations with crown ethers. However, there are limitations to such techniques where detailed analysis (eg determination of the geometry of complexes) is not possible. We reason that to get a better understanding of the complexation mechanism of crown ether-cation in solution (in this case methanol), we need to apply a multi-pronged approach because different techniques can give different information. Here, we would like to present a more complete picture of crown ether-cation studies through the combination of ^1H NMR and UV spectroscopy. These two techniques were

chosen because they complement one another very well. ^{1}H NMR spectroscopy proved to be very useful in determining the geometry of the complexes while UV spectroscopy was used to calculate the association constants of the complexes because it is more sensitive.

Table 1.5 : Association constants (log K) of 1:1 stoichiometry alkali metal cations-DB15C5/DB18C6 complexes in solution various solutions.

Ligand	**Cation**	**Log K**	**Method**	**Solvent**	**Ref**
DB15C5	Li^+	3.00	Fluorescence	Acetonitrile	Yapar & Erk, 2002
	Na^+	1.74	Fluorescence	Acetonitrile	Yapar & Erk, 2002
	K^+	1.74	Fluorescence	Acetonitrile	Yapar & Erk, 2002
DB18C6	Li^+	1.90	Polarography	MeOH-C_6H_6(8:2/v:v), 0.025M Bu_4NClO_4	Blasius et.al., 1984
		4.06	Conductance	THF-$CHCl_3$ (4:1/v:v)	Sinyavskaya et.al.,1986
	Na^+	2.87	Potentiometry	DMF	Chantooni et.al.,1988
		4.89	Ion selective electrode	MeCN, 0.05M Et_4NClO_4	Buschman, 1988
		4.37	Conductance	MeOH	Parpiev et.al.,1983
		5.60	Conductance	THF-$CHCl_3$ (4:1/v:v)	Sinyavskaya et.al.,1986
DB18C6	K^+	4.03	Solv Extr UV	Acetophenone	Buncel et.al., 1984
		3.63	Solv Extr UV	Acetonitrile	Buncel et.al., 1984
		3.49	Solv Extr UV	Benzyl Alcohol	Buncel et.al., 1984
		5.00	Ion selective electrode	MeOH	Inokuma et.al., 1988
		4.80	Potentiometry	MeOH	Harris et.al., 1977
		2.50	Polarography	DMF, 0.05M Et_4NClO_4	Bogoslovskii et.al.,1987
	Rb^+	4.36	Calorimetry	MeOH	Izatt et.al., 1986
		4.58	Conductance	MeOH	Parpiev et.al.,1983
	Cs^+	3.20	Potentiometry	MeOH	Harris et.al., 1977
		3.30	Conductance	THF-$CHCl_3$ (4:1/v:v)	Sinyavskaya et.al.,1986

The aims of this project are :

(1) To synthesize new derivatives of crown ethers;

(i) di-*tert*-butyl benzo-15-crown-5 (t_2-DB15C5), Fig 1.13

(ii) di-*formyl* benzo-18-crown-6 (f_2-DB18C6),.Fig 1.14

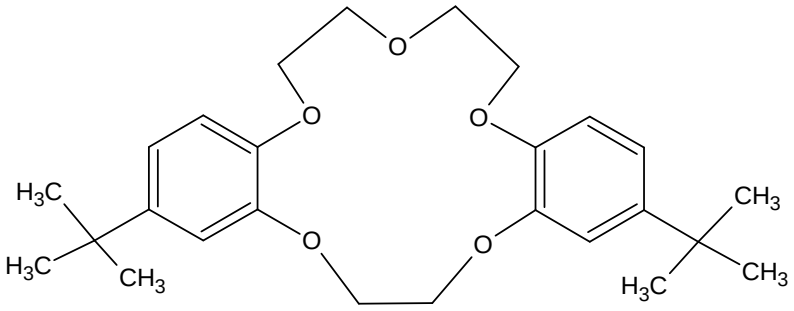


Fig 1.13 : di-*tert*-butyl benzo-15-crown-5 (***t*$_2$-DB15C5**)

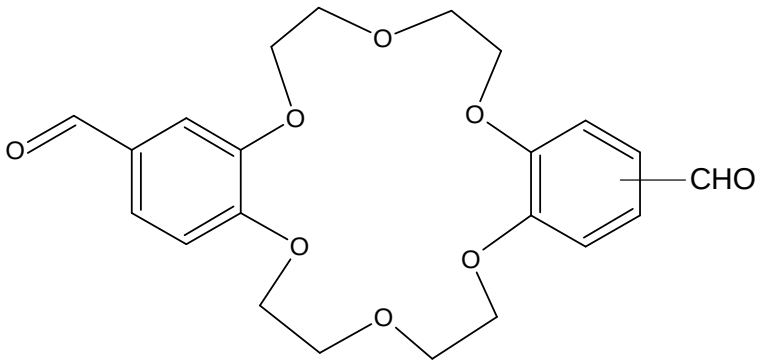


Fig 1.14 : di-*formyl* benzo-18-crown-6 (***f*$_2$-DB18C6**)

(2) To study the complexation of alkali metal ions with DB15C5, DB18C6, t_2-DB15C5 and f_2-DB18C6 in methanol.

We chose the above mentioned four crown ethers in our study for two reasons. First, we would like to find out the size effect of the 15-membered-cycle ring and 18-membered-cycle ring on the association constant. Second, DB15C5 and t_2-DB15C5 as well as DB18C6 and f_2-DB18C6 were used to find out the substituent effect of an electron donating (*t*-butyl) group and an electron withdrawing (CHO) group on the association constant.

2. EXPERIMENTAL

Chemical Reagents and Materials

1. 15-crown-5, Fluka Chemika, Germany, purity 98.0%
2. 18-crown-6, Aldrich Chem. Co, USA, purity 99.5%
3. Acetone, Merck, Germany
4. Benzaldehyde, Riedel-de-Haen, Germany
5. t-Butanol, Ajax Chemicals, Australia
6. Cesium Chloride, BDH Limited, England
7. Chloroform, Carlo Erba, Spain
8. Dibenzo-15-crown-5, Fluka Chemika, Germany, purity ≥ 97.0%
9. Dibenzo-18-crown-6, Fluka Chemika, Germany, purity ≥ 98.0%
10. Deuterated chloroform $CDCl_3$, Merck, Germany, min. deuteration degree 99.8%
11. Deuterated methanol CD_3OD, Merck, Germany, min. deuteration degree 99.8%
12. Dichloromethane, Merck, Germany
13. Ethanol, Systerm, Malaysia
14. Hexamethylenetetramine, Aldrich, USA, purity ≥ 99.0%
15. Hexane, Merck, Germany
16. Anhydrous lithium chloride, Fluka Chemika, Germany, purity ≥ 98.0%
17. Methanol, Systerm, Malaysia
18. Neodymium (III) trinitrate hexahydrate, BDH Limited, England
19. Potassium chloride, BDH Limited, England
20. Praseodymium (III) trinitrate hexahydrate, BDH Limited, England
21. Rubidium chloride, Merck, Germany, purity ≥ 99.0%
22. Samarium (III) trinitrate hexahydrate, BDH Limited, England

23. Sodium chloride, R&M Chemicals, UK
24. Sulfuric acid 95-98%, Systerm, Malaysia
25. Trifluoroacetic acid, Fluka Chemika, Germany, purity ≥ 98.0%

Instrumentation

1. Bruker AC 300MHz NMR Superconductor Spectrometer
2. Bruker AC 400MHz NMR Superconductor Spectrometer
3. Hitachi Spectrophotometer Model U-2000
4. Elemental Analyzer, Model Perkin Elmer PE2400
5. FT-IR, Perkin Elmer System 2000
6. Hewlett Packard 5989 A Mass Spectrometer
7. Hewlett Packard 5890 Series II Gas Chromatograph
8. Gallenkamp melting point apparatus
9. ESI Mass Spectra by the Chemistry Department, National University of Singapore

2.1 Synthesis of t_2-DB15C5 (Modified from Wang et. al., 1982)

(i) Experiment One

DB15C5 (0.10 g, 3.2×10^{-4} mol), *t*-butanol (64 μL, 6.7×10^{-4} mol), trifluoroacetic acid, TFA (10 mL) and 100 μL of 1.0 M sulfuric acid were mixed in a round bottom flask. The solution mixture was stirred at 75 ^{o}C in an oil bath under nitrogen atmosphere for 4 hours. Then the solution mixture was concentrated to about 2 mL. 10 mL of dichloromethane was added and then followed by 10 mL of water to remove any excess acid or alcohol. The organic layer was then removed and concentrated until a gel-like residue was formed. The residue was recrystallized from methanol to give white powderish product. Yield : 80% , mp: 96-98 ^{o}C.

(ii) Experiment Two

All the parameters of the experiment are the same as Experiment One except the temperature was lowered to 60 ^{o}C. The resulting white powder product is a mixture of isomers which we were unable to separate. The overall yield of isomers was approximately 60%.

(iii) Experiment Three

All the parameters of the experiment are the same as Experiment One except the temperature was lowered to 45 ^{o}C. The resulting white powder product is a mixture of isomers which we were unable to separate. The overall yield of isomers was approximately 46%.

*All complexation studies were carried out using product obtained from Experiment One.

2.2 Synthesis of f_2-DB18C6 (Modified from Smith, 1972)

DB18C6 (0.20 g, 5.55×10^{-4} mol), hexamethylenetetramine, HMTA (0.16 g, 1.11×10^{-3} mol) and TFA (10 mL) were mixed in a round bottom flask. The solution mixture was stirred at 90 ^{o}C for 24 hours under nitrogen atmosphere. The resulting brown solution was poured onto 30 g of ice and subsequently extracted with 4 parts (10 mL each part) of dichloromethane. The solution was concentrated to about 5 mL. Then, 10 mL of acetone was added to force out light orangish powder as the crude product. It was filtered and dried. The crude product was then dissolved in dichloromethane. 20 mL of hexane was then added and white precipitate was formed. It was then filtered to get the product (white precipitate). Yield : 55-65% , mp: 180-182 ^{o}C.

2.3 Complexation studies of crown ethers with alkali metal cations using proton NMR Spectroscopy.

Proton NMR spectra in $CDCl_3$ and CD_3OD at 25 ^oC were recorded with a 400 MHz Bruker AC400 Superconducting NMR Spectrometer. Solvent peak at 7.30 ppm (for $CDCl_3$) and 3.32 ppm (for CD_3OD) were used as internal references.

Experimental Procedures

2.3.1 Complexation of 15-crown-5 (15C5) with alkali metal salts

- Alkali metal salts used for complexation were LiCl, NaCl, KCl, RbCl and CsCl
- Preparation of 15C5 + LiCl was presented as an example and the procedure was repeated with other alkali metal salts.
- 0.48 mL of 15C5 was diluted in 2 mL CD_3OD (1.20 M). A LiCl solution of concentration $2.40x10^{-2}$ M was prepared by dissolving the appropriate weight in 1 mL CD_3OD. 10 μL stock solution of 15C5 (1.20 M) was added to 0.5 mL of the salt solution giving a 1:1 15C5:Li^+ ratio. Addition of every 10 μL of the crown ether stock solution increases the host concentration by one fold.

- Table 2.1 : Molar concentration of 15C5 and Li^+ used for ^1H NMR analysis.

Ratio of 15C5:Li^+	**[15C5], M**	**[Li^+], M**
1:1	$2.40x10^{-2}$	$2.40x10^{-2}$
2:1	$4.80x10^{-2}$	$2.40x10^{-2}$
3:1	$7.20x10^{-2}$	$2.40x10^{-2}$
4:1	$9.60x10^{-2}$	$2.40x10^{-2}$

2.3.2 Complexation of DB15C5 and t_2-DB15C5 with alkali metal cations

- Preparation of t_2-DB15C5, DB15C5 with Li^+ was presented as an example and the procedure was repeated with other alkali metal cations.
- A LiCl solution of concentration 2.00×10^{-3} M was prepared by dissolving 0.0034 g LiCl in 1 mL CD_3OD. Then 100 μL was pipetted out and diluted to 1 mL with CD_3OD. 2.00×10^{-3} M of t_2-DB15C5 (molecular weight = 428) and of DB15C5 (molecular weight = 316) were prepared by dissolving the appropriate weight of the crown ether into 0.5 mL of the Li^+ solution.

2.3.3 Complexation of DB15C5 with lanthanide(III) cations

- Lanthanide salts used for complexation were $Nd(NO_3)_3.6H_2O$, $Pr(NO_3)_3.6H_2O$ and $Sm(NO_3)_3.6H_2O$.
- Procedure similar to **2.3.2**

2.3.4 Complexation of 18-crown-6 (18C6) with alkali metal cations

- 0.6340 g of 18C6 was dissolved in 2 mL of CD_3OD (1.20 M). Salt solutions of concentration 2.40×10^{-2} M were prepared by dissolving the appropriate weight in 1 mL CD_3OD. 10 μL stock solution of 18C6 (1.20 M) was added to 0.5 mL of the salt solution giving a 1:1 18C6:M^+ ratio. Addition of every 10 μL of the crown ether stock solution increases the host concentration by one fold.