

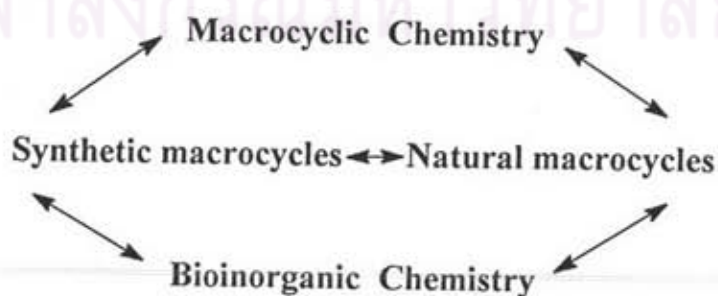
CHAPTER I

INTRODUCTION



Review of Macrocyclic Compounds

The metal ion and host-guest chemistry of macrocyclic ligands has been developed rapidly over recent years and now impinges on wide areas of both chemistry and biochemistry. Macrocyclic ligands are polydentate ligands containing their donor atoms either incorporated in or, less commonly, attached to a cyclic backbone. As usually defined, macrocyclic ligands contain at least three donor atoms and the macrocyclic ring should consist of a minimum of nine atoms. Macrocyclic ligand complexes are involved in a number of fundamental biological systems and have long been recognized. Since 1960, a very large number of synthetic macrocycles have been prepared and this has resulted in a great increase in interest in all aspects of the chemistry of macrocyclic systems. Many 'bioinorganic' studies have involved complexes of both natural and synthetic macrocycles. Thus there has been an element of cross-fertilization between these two developing areas, viz.:



A considerable amount of research involving synthetic macrocycles has been directed towards the preparation of model compounds for the natural macrocycles. The resultant development of new macrocyclic ligand chemistry has provided a valuable background against which the natural systems can often be seen in clearer perspective. Macrocyclic compounds have properties to bind with metal [1] and the stability and specificity of macrocyclic ligands with metal ion or other guests depend on some important properties of the ligand [2] such as:

1. The relative cation and ligand cavity sizes
2. The binding sites within the macrocyclic compound such as nitrogen (-aza compounds), oxygen (-oxa compounds) and sulfur (-thia compounds)
3. The oxidation number and the size of cation or other guests
4. Steric hindrance in the ring
5. Solvent effect

In fact, the large macrocyclic ligands can be more flexible than the small ones because of the ring strain; moreover, the stability constant of complexation relies on the interaction between ion or guest with ligand such as ion-dipole and charge-induced dipole [3]. Each type of macrocyclic compound is different in structure, some types have one ring in the molecule, example is crown ether, some types have a three dimensional ring and also consist of different donor atoms in the molecule, example is cryptand and large complex molecules such as cyclophane, cyclodextrin and calixarene.

Crown Ether

Crown ethers are macrocyclic compounds of two dimensions, having oxygen donors in the ring to complex with ion or other guests (Figure 1.1).

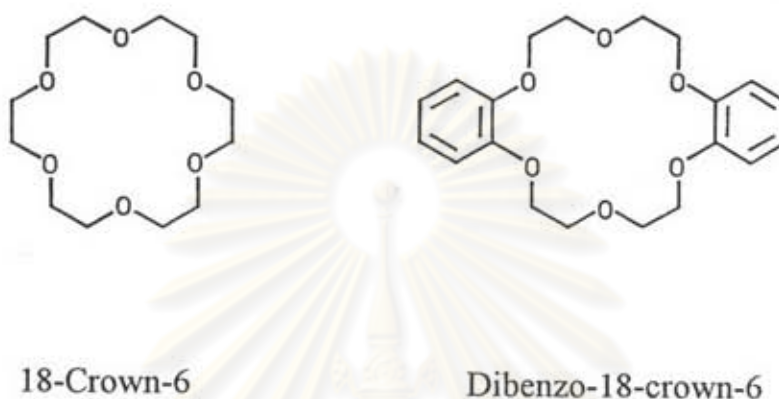


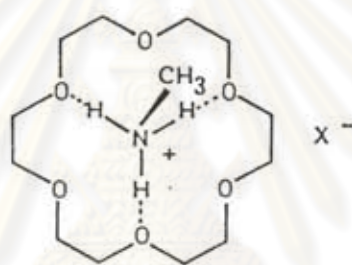
Figure 1.1 Examples of crown ethers

A typical property of this system is the ability to form stable complexes with alkali metals and alkaline earth metals. Prior to the synthesis of the crowns, the coordination chemistry of the above metal ions with organic ligands had received very little attention. Pederson marked the ability of some crown ethers to form complexes with alkali metal ions which, in certain cases, are stable in aqueous solution [4]. Indeed, they also yield stable complexes of a range of non-transition metal ions but tend to bind less strongly to transition metal ions. This study also showed that rings incorporating between five and ten oxygen atoms tended to form the most stable complexes and complexes with some or all of the following metal ions were isolated: Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ , Ag^+ , Ca^{2+} , Sr^{2+} , Ba^{2+} , Cd^{2+} , Hg^{2+} , La^{3+} , Tl^+ , Ce^{3+} and Pb^{2+} . In such compounds, the ether-oxygen interactions with the metal cation were considered to be essentially electrostatic. Complexes with many other ions

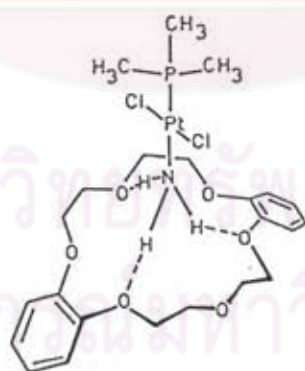
have been characterized. Crystalline 1:1 (metal : ligand), 1:2 and 2:3 complexes as well as species of their stoichiometry have all been isolated and the X-ray structures have been studied as shown in Figure 1.2 and 1.3.



Figure 1.2 X-ray structure of the RbNCS complex of dibenzo-18-crown-6 [5]



Complexation between 18-crown-6 with CH_3NH_3^+ [6]



Complexation between dibenzo-18-crown-6 with $[\text{PtCl}_2\text{P}(\text{CH}_3)_3\text{NH}_3]$ [7]

Figure 1.3 The complexation between other guest molecules with crown ethers

Apart from metal ions, many of these polyether compounds also exhibit complexing ability for a range of other inorganic and organic cations as well as for a variety of neutral molecules. Some examples are shown in Figure 1.3. Complexes such as these, which contain species incorporate in the macrocyclic cavity, are usually known as inclusion complexes; the general area covering the binding of all types of substrates in molecular cavities often being referred to as host-guest chemistry.

Mixed-donor Crown Ether

Mixed-donor crown ethers are crown ethers incorporating other heteroatom types beside ether oxygens. Sulfur is the most common heteroatom (other than oxygen) in mixed crown compounds, they are thia-derivatives. When the nitrogen groups replace some ether groups in the crown polyethers they have been called "aza-crown". Examples of these two derivatives are presented in Figure 1.4.

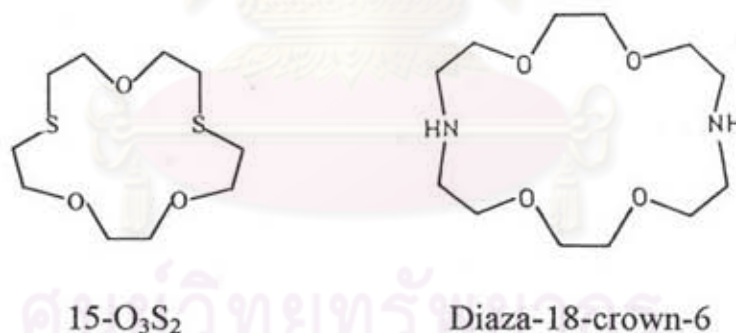


Figure 1.4 Examples of mixed-donor crown ethers

Complexation between aza-crown and guest is interesting due to intermediate complexation properties between all oxygen crowns, which strongly complex alkali and alkaline earth metal ions, and all nitrogen cyclams which strongly bind heavy metal cations. These mixed complexation properties

make the aza-crowns important as synthetic receptors in molecular recognition process [8]. In addition, the aza-crowns are important intermediates for the synthesis of cryptands (for diaza-crown). There are a number of interesting uses of aza-crowns as catalysts in nucleophilic substitution and oxidation reactions [9, 10].

Cryptands

Lehn and coworkers developed a range of three-dimensional, polycyclic ligand systems which they named cryptands[11] (Greek: *cryptos* = cave). The metal complexes of these ligands are called cryptates. The development of such systems was of major significance to the field of polyether metal-ion chemistry and subsequently, an extremely large number of studies involving such species have been carried out. The parent series of cryptands may be represented by Figure 1.5 and Table 1.1.

Table 1.1 Representative parent series of cryptands

m	n	Abbreviation	Estimated cavity diameter (Å)
0	0	1:1:1	1.0
0	1	2:1:1	1.6
1	0	2:2:1	2.2
1	1	2:2:2	2.8
1	2	3:2:2	3.6
2	1	3:3:2	4.2
2	2	3:3:3	4.8

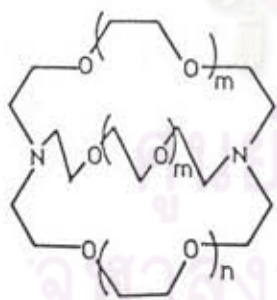


Figure 1.5 The representative parent series of cryptands

The assignment for common names to cryptands is done by counting number of oxygen atoms in each chain [12] as shown above. Not only the simple types above but also macrotricyclic ligands (a) and (b) (Figure 1.6) may be synthesized by multistep high-dilution procedures [13]. They contain spherical cavities which are able to accommodate suitable guests whether they be cationic, neutral or anionic.

Both of these cages form complex with alkali and alkaline earth ions. In particular, the caesium complex of (a) is especially stable, compared to other complexes of this ion.

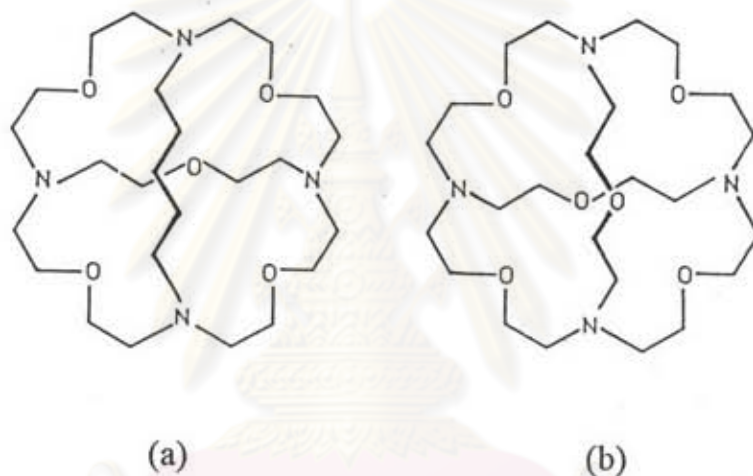


Figure 1.6 Examples of macrotricyclic cryptands

The cryptand readily forms complexes with a range of metal ions, provided the ion involved is not too large to be contained in the macrocyclic cavity. A range of crystal structure determinations confirm that the metal ion normally resides in the central cavity of such ligands. The X-ray structure of the Rb^+ complex of 1:1:1 is shown in Figure 1.7 [14].

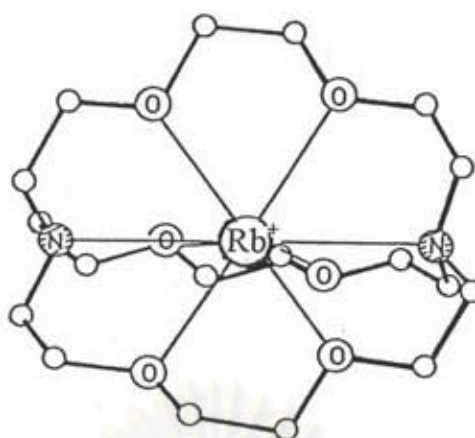


Figure 1.7 Structure of the Rb^+ complex of cryptand 1:1:1

Cryptate complexation involving a range of transition and other heavy metal ions has been investigated [15]. Similarly, the cryptands also form stable complexes with the lanthanide ions [16]. Macrotricyclic ligand (a) in Figure 1.6 also forms a complex with ammonium ion. The latter is arranged in the cavity such that there appears to be a tetrahedral array of hydrogen bonds formed between the ammonium hydrogens and the nitrogen donor sites of the cage. The ether oxygens also appear to interact electrostatically with the central (charge) nitrogen atom. When the ligand (a) was partly protonated to acidic form, it has been shown to include a water molecule in the cavity, Figure 1.8 (c). In other studies, it has been shown that both tetraprotonated macrotricyclic ligands (a) and (b) form inclusion complexes with halide anions [13]. The chloride complexes of both cages are quite stable with the log K values being approximately 10^4 in each case. These systems exhibit selectivity for chloride over bromide. The commodation of a spherical halide anion by the tetrahedral bonding arrangement is illustrated by Figure 1.8 (d). The iodide ion (radius 3.57\AA) is too large for the cavities of these cages. Similarly, the larger polyatomic anions NO_3^- , CF_3^- , ClO_4^- and RCOO^- are not included.

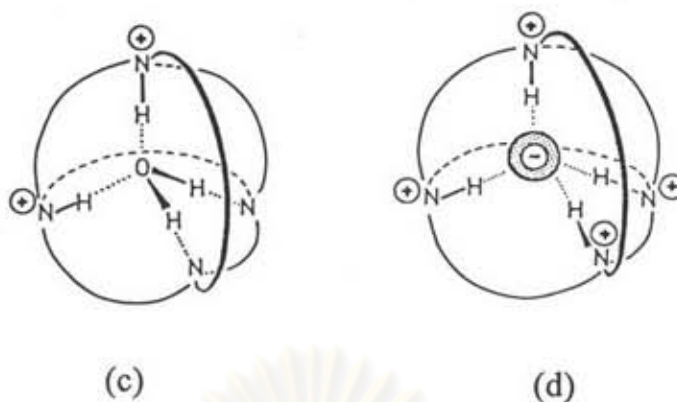


Figure 1.8 The complexation between water molecule and anion with protonated cryptands

For a large cage host, the fully protonated macrotricyclic ligand (d) has a cavity to accommodate azide anion (Figure 1.9) [17]. It is interesting that, the cylindrical triatomic azide ion (N_3^-) better matches the cavity shape. This guest is bound by two pyramidal arrays of three hydrogen bonds and each of which interacts with a terminal nitrogen from the azide ion.

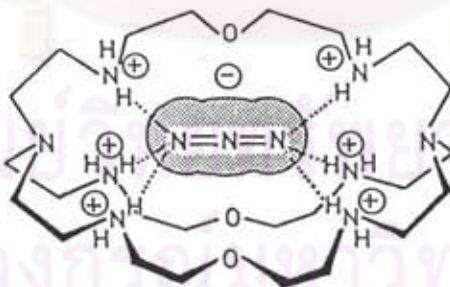


Figure 1.9 The complexation between azide anion with cryptand

Cyclophanes

Cyclophanes are large-ring compounds incorporating benzene nuclei in the rings. In one sense, the cyclophanes may be considered to be a further category of the cavitands since the aromatic rings impart rigidity to the overall cyclic structure. In 1955, cyclophane derivative of type (e) (Figure 1.10); (with $n = 3$ or 4) were described [18]. After recrystallization from benzene or dioxane, these species crystallized as 1:1 adducts of these solvents. Once such adducts are formed, it is difficult to remove the solvent and it was concluded that the solvent molecules are housed inside the cavities of the respective guests. In accord with this, the smaller ring system (e ; $n = 2$) is unable to form similar complexes with these solvents.

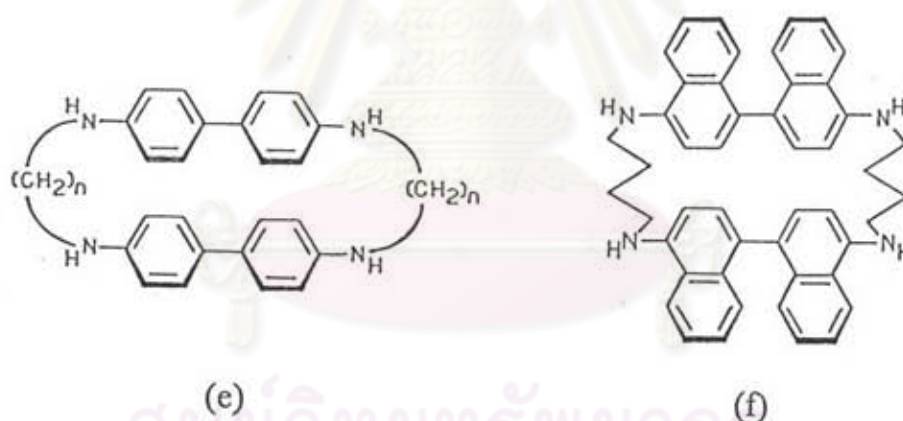


Figure 1.10 The derivative of cyclophane

A large number of related inclusion complexes are now known. Heterocyclophane (f) (Figure 1.10) is also water soluble and presents a rectangular hydrophobic cavity to an incoming guest. This derivative forms 1:1 molecular complexes with CHCl_3 , CH_2Cl_2 , CH_2BrCl or CH_3CN [19].

Cyclodextrins

Cyclodextrins, of which cyclohexaamylose in Figure 1.11 is an example, are natural cyclic oligosaccharides and were first isolated in 1891 [20] from the action of amylase of *Bacillus macerans* on starch and related compounds. The family of cyclodextrins consists of from six to twelve α -1,4-linked D-glucose units and are approximately doughnut shaped. Nevertheless, they are not perfectly cylindrical but are somewhat distorted towards a cone. The three most common cyclodextrins are composed of six, seven and eight glucose units and are referred to as, α -, β -, γ -cyclodextrins, respectively.

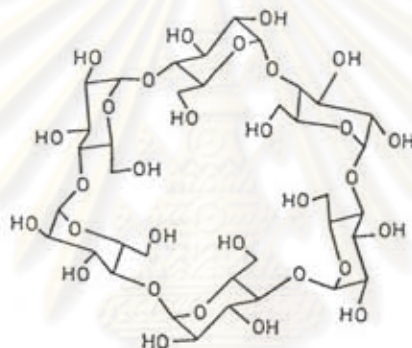


Figure 1.11 An example of the derivatives of cyclodextrins

The interior of each cavity contains C-H groups, none of the hydroxyls point into the cavity. The size of the central cavity increases with the number of glucose units in the ring and, for example, in α -cyclodextrin it is about 4.5Å in diameter and 6.7Å deep. It should be noted that molecular complexes of the cyclodextrins may be isolated as crystalline solid; for example, a crystalline complex is obtained with iodine (which resembles the well known blue complex between iodine and starch), as well as with a large number of other inorganic and organic guests. For strong complexation, the guest molecule should fit the cavity well. The attachment of a metal ion to a

functionalized cyclodextrin was carried out in order to provide a model for substrate binding in metalloenzymes. One system investigated is the adamantan-2-one-1-carboxylate adduct of the zinc-containing β -cyclodextrin derivative contain Zn(II) in Figure 1.12 [21].

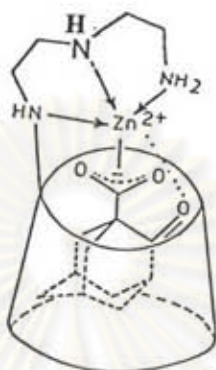


Figure 1.12 The β -cyclodextrin derivative adduct

The hydrolysis of esters by the nickel derivative in Figure 1.13 provided an early example of the use of metal-capped cyclodextrin as a catalyst (show here as its *p*-nitrophenyl acetate inclusion complex) [22].

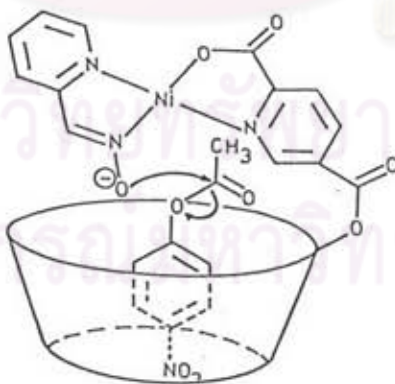


Figure 1.13 The hydrolysis of esters by the nickel derivative

A number of other 'structurally developed' cyclodextrins have been synthesized. For example, hosts containing two hydrophobic binding sites called 'duplex' cyclodextrins, such as that containing either α - or β -cyclodextrins (Figure 1.14) have been prepared for use in catalytic studies [23].

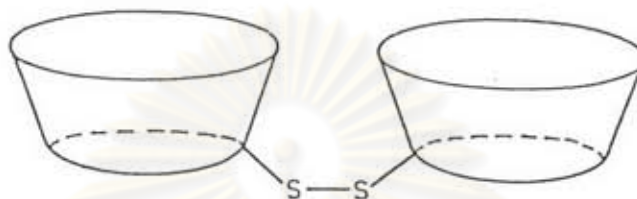


Figure 1.14 Example of duplex cyclodextrin

Nevertheless, the success in this area will depend to a large part on the ability to modify cyclodextrins so that favorable structuring of the guest in the binding sites is engendered.

Calixarene

Recently, chemists have become interested in a new class of macrocyclic molecules, supramolecular molecules and one substance in this class is calixarenes. Calixarenes are macrocycles made up of phenolic units meta-linked by methylene bridge (Figure 1.15) and possessing basket-shape cavities. The name "calixarene" has been given by Gutsche [24] because of the resemblance of the four-membered ring with a chalice (in Greek : calix). The suffix "arene" indicates the represent of aryl rings in the molecular framework.

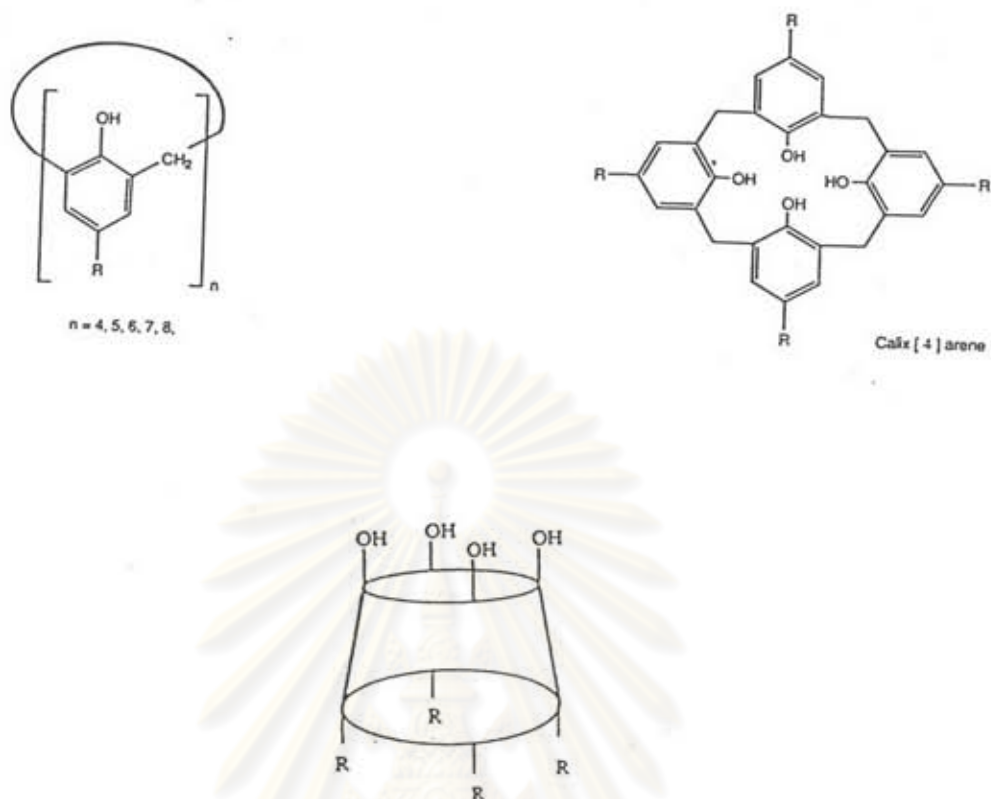


Figure 1.15 General formula of calixarenes

In host-guest chemistry, calixarenes have attracted much interest because of their unique characters: (1) Calixarenes can be prepared from para-substituted phenols and formaldehyde which are commercially available at a reasonable price; the preparation affords calixarenes with the desired ring size selectively according to reaction conditions. (2) Calixarenes have cyclic phenolic hydroxyl groups which are useful for the building-up of the functionalized host molecules. (3) Calixarenes have several-size π -rich cavities for including guest compounds. Table 1.2 shows the comparison of three representative host molecules [25], and calixarene has the advantage of complexation with both ionic and neutral guests compared with other two host molecules. Moreover, as described above, calixarene seems to be easy to

derivatize to the more functionalized host molecules. These facts consistently suggest that host-guest chemistry using calixarene and their derivatives can develop the new area of supramolecular chemistry.

Table 1.2 Comparison of three representative host molecules

	Cyclodextrin	Crown ether	Calixarene
Systematic change in the ring size	O	O	O
Large-scale preparation	O	O	O
Spectroscopic transparency	O	O	X
Neutrality under working conditions	O	O	Δ
Optical-activity	O	Δ	Δ
Synthetic access to derivatives	Δ	O	O
Functions as ionophores	X	O	O
Functions as cavity-shaped host	O	X	O

O denotes that the macrocycle already satisfies requirement; Δ denotes that the requirement can be easily satisfied by simple modification; X denotes that it is especially difficult to satisfy the requirement.

For specifying the size of the macrocycle, one intercalates between brackets a number of phenolic units constituting the calixarene. The most useful way to prepare calix[4]arene, calix[6]arene and calix[8]arene is to condense formaldehyde onto *p*-substituted phenol in the presence of a base. Generally, the selectivity of cyclization follows the order calix[8]arene > calix[6]arene > calix[4]arene. The base-catalyzed condensation of *p*-alkylphenols (alkyl is isopropyl or *tert*-butyl) leads predominantly to the formation of calixarenes with an even number of phenolic units along with oxa-calixarenes (Figure 1.16).

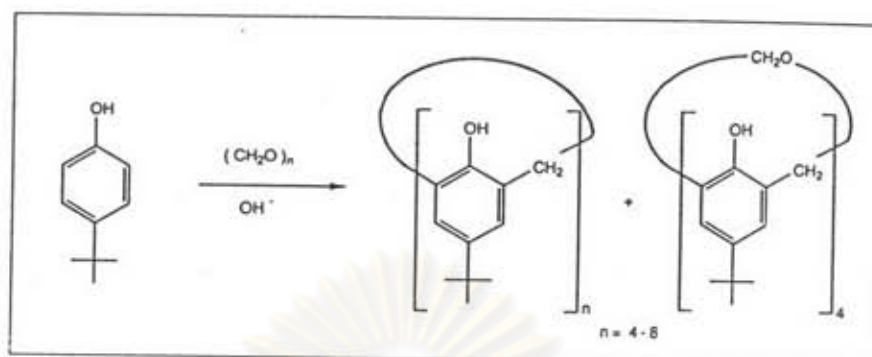


Figure 1.16 Products of basic condensation of *p*-*tert*-butylphenol with formaldehyde

Because of the presence of a cavity in their molecular structure, calixarenes are good candidates for providing chemical systems involved in supramolecular chemistry. Thus, chemical modifications have been investigated to give calixarenes new properties such as solubility in water, improved ability in complexation. They can be chemically transformed on three reacting sites:

- reactions of hydroxyl groups
- reactions of aromatic rings
- reactions of methylene bridges

Because calixarene are made up of phenolic units, the reactions of hydroxyl groups are usually those performed on phenols [26].

Calix[4]arenes

Calix[4]arenes are one type of calixarenes and they are very useful building blocks as receptors for cations [27], anions [28] and neutral molecules [29]. The introduction of bulky substituents at the lower rim of the calixarene prevents the interconversion among the four possible stereoisomers (cone, partial cone, 1,2-alternate and 1,3-alternate) in Figure 1.17 [30].

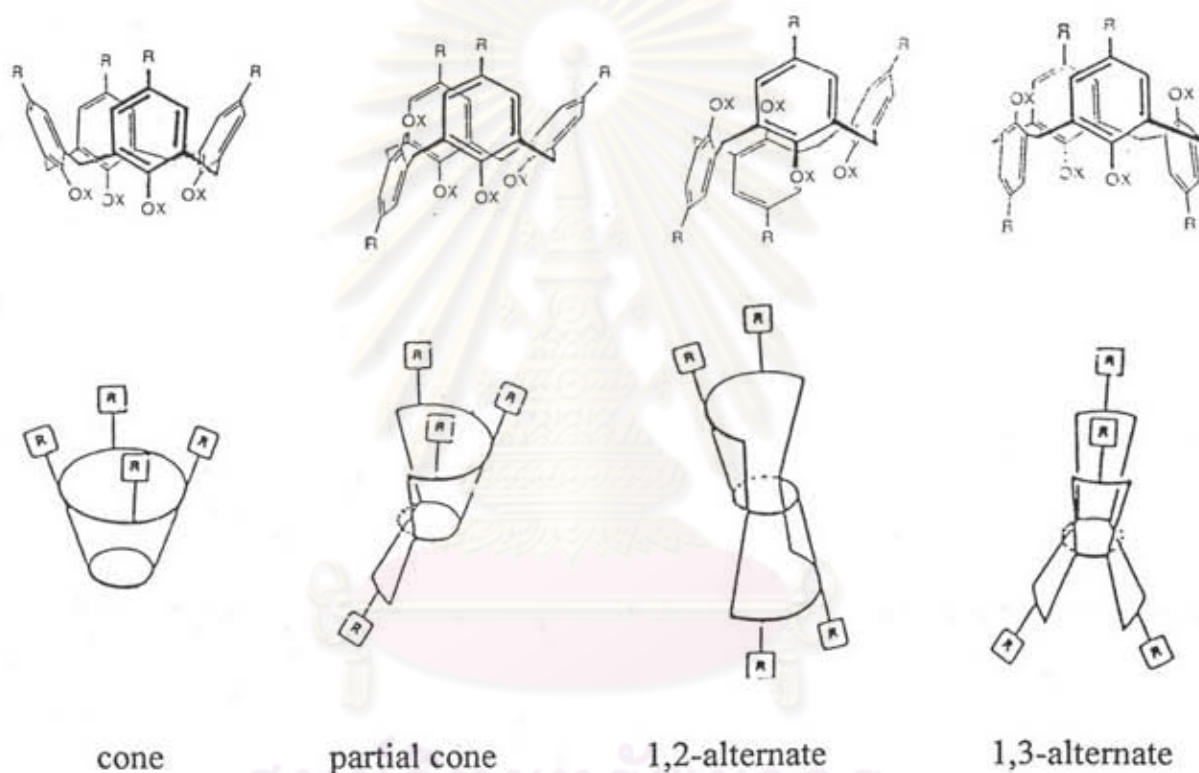


Figure 1.17 The conformations of calix[4]arenes

By choosing the reaction conditions, the control of the stereochemistry has been achieved especially in alkylation reactions.

Chemically Modified Calix[4]arenes for Host-guest Chemistry

Calix[4]arenes are readily converted into a wide variety of derivatives at the lower rim by alkylation of the phenolic groups. This type of chemical modification was first introduced by Gustche as part of his study of conformational change in calix[4]arenes and since then it has been used widely by several groups to produce derivatives with pendant ether [31], carboxylate [32], ester [33], amide [34] and keto [35] groups. The vast majority of these modified calixarenes exist in the cone conformation in which the mutually syn pendant groups possess a considerable degree of preorganisation and define the boundaries of a hydrophilic cavity suitable for ion reception. Indeed, the most significant feature of the chemistry of these molecules is their ability to bind selectively alkali and alkaline earth cations inside the cavity. Although less extensively studied, chemically modified calix[6]arenes and calix[8]arenes also possess receptor properties for selected inorganic and organic cations [36].

Calix[4]arenes are easily modified at the 1,3-difunctional hydroxyl groups at the lower rim (Figure 1.18). This form is the most appropriate form for preorganisation of potential binding sites, making possible the synthesis of several mixed ligand receptors.

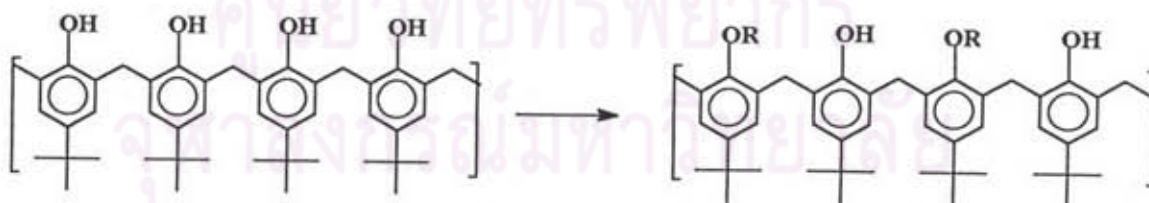


Figure 1.18 Chemical modification of calix[4]arenes at the 1,3-dihydroxyl group at lower rim

After modification, some calix[4]arene derivatives can complex with guests selectively. Calix[4]arene-crown-5 [37] is one example of this model, being 1,3-distal capping of calix[4]arene at lower rim. The superiority of this calix[4]arene ether over crown ether is ascribed to the ionophoric cavity size exactly fit to the size of Na^+ and to the rigid calix[4]arene skeleton supporting the cavities (Figure 1.19).

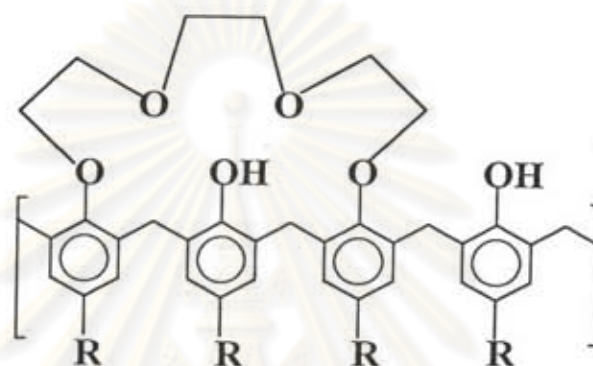


Figure 1.19 Calix[4]arene-crown-5

In 1994, Schiff base *p*-*tert*-butylcalix[4]arenes [38], Figure 1.20, were synthesized. Alkali and alkaline earth cations are very poorly extracted by ligands (g-k). However, the better extraction of Li^+ and Na^+ ions with ligand (i) may be explained by the greater flexibility of its bridge which is due to an additional carbon that allows the chain to adopt a more convenient geometry for complexation. In the transition metal series, Fe^{2+} and Cu^{2+} ions were extracted more efficiently. Heavy metal cations are extracted with ligand (g), with higher preference for Pb^{2+} ion. In the lanthanide series, there is an extraction selectivity for Nd^{3+} and Eu^{3+} ions with (h) and for Eu^{3+} with (i).

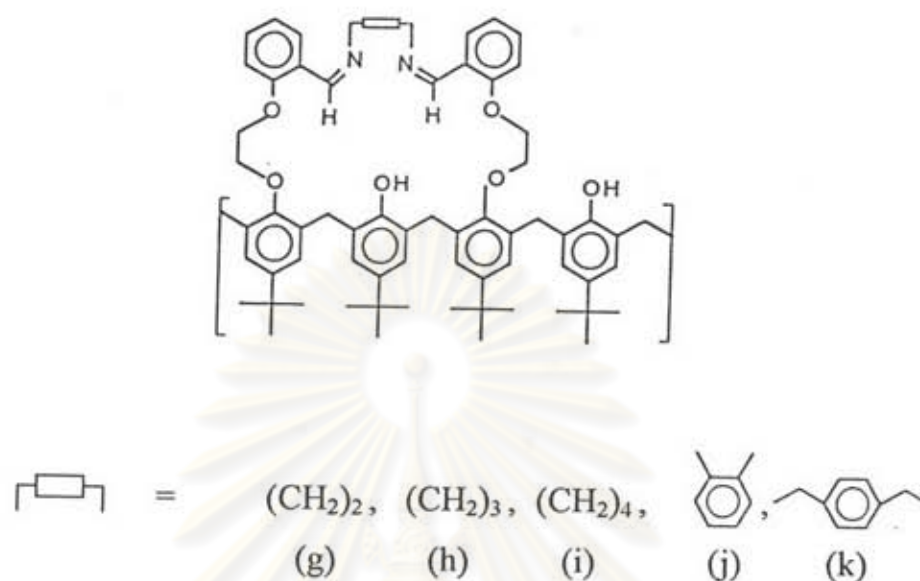


Figure 1.20 Schiff base *p*-*tert*-butylcalix[4]arenes

Not only the examples of above but 1,3-distal capping of calix[4]arenes at lower rim were also achieved with salophane moieties to yield calix-salophane crown ethers (Figure 1.21) as receptors for neutral molecules [39]. These hosts are highly lipophilic, making them useful as carriers for urea in supported liquid membranes. Furthermore, they have a phenolic group on either side of the crown ether ring, which can be used for the incorporation of functional groups either as additional binding sites for the substrate molecule or for catalyzing reactions of the complexed substrate.

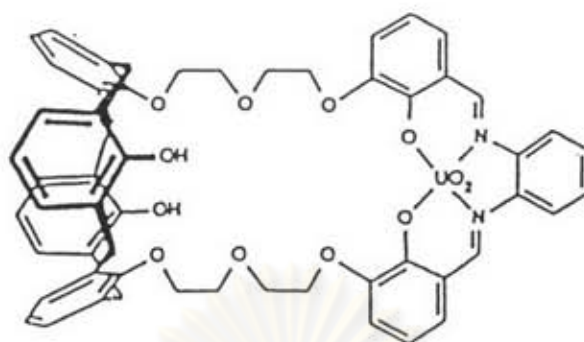


Figure 1.21 Calix salophane crown ethers

Moreover, the calix[4]arene has been displayed in double-calix-crown form in Figure 1.22. This is in the 1,3-alternate conformation and can complex with potassium and rubidium picrates forming 1:1 complex in deuterated chloroform [40]. All the results were accounted for by locating the metal cation in the central cavity of the potential tritopic receptor.

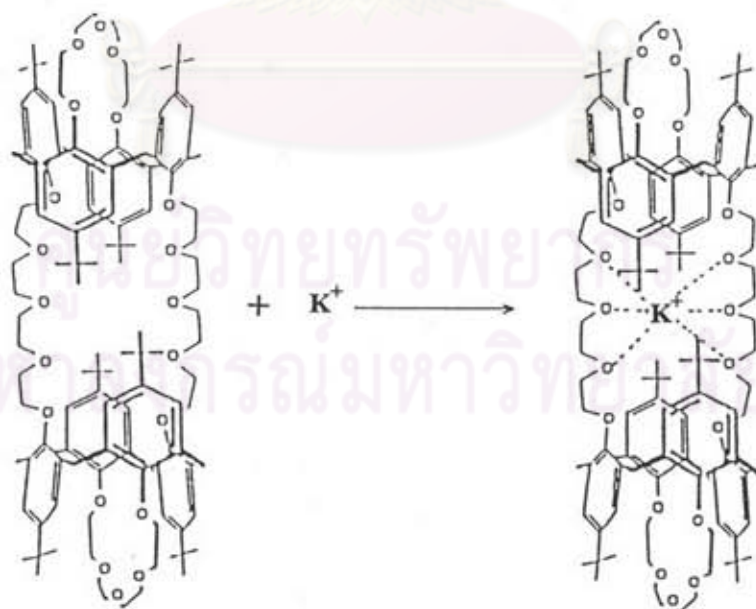


Figure 1.22 Double-calix-crown

For anionic guest species, Beer and co-workers synthesized a calixarene derivative that could bind with anionic guest. This ligand is a novel *bis*-calix[4]arene receptor (Figure 1.23) in which the upper rim of one calix[4]arene moiety is covalently linked *via* amide bonds to the lower rim of another in head to tail fashion [41]. This ligand can form 1:1 stoichiometric solution complexes with various anions, with an order of magnitude selectivity preference for fluoride over chloride. Relatively much weaker complexes were formed with HSO_4^- and H_2PO_4^- anions which may be attributable to anion size.

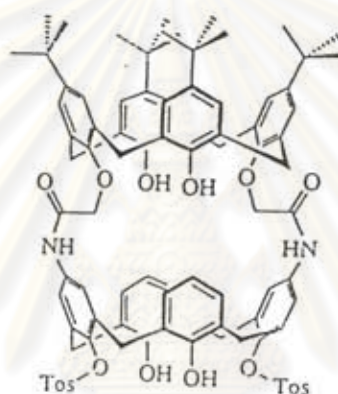


Figure 1.23 A novel neutral fluoride anion selective *bis*-calix[4]arene receptor

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Reason for Undertaking This Study

Eventhough the development in host-guest chemistry of calix[4]arenes towards cationic guests has progressed rapidly, the study of anionic complexation of such molecules is not as extensive. Only a few reports on such subject have been discussed. It is the intention of this study to synthesize anion receptors and to investigate their anion complexation properties. The anionic receiving sites will be of ammonium cations, yielding from hydrogenating the Schiff-base derivatives [38]. The number of positive sites on the calix[4]arene will be varied to give different cavity sizes, 2, 3, 4 and 5 sites, and the complexing ability with certain anions, NO_3^- (neutral anion) and CO_3^{2-} (basic anion) will be studied in order to be able to conclude the anionic guest chemistry of such aza-crown-*p-tert*-butylcalix[4]arenes. The results of this study should lead to an application for anion separation in the future.



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