CHAPTER I

INTRODUCTION

1.1   Review of Macrocyclic Compounds and Supramolecular Chemistry

The metal ion and host-guest chemistry of macrocyclic ligands have 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 complexes are involved in a number of fundamental biological systems and have long been recognized.

A considerable amount of research involving synthetic macrocycles has been directed towards the preparation of model compounds for the natural macrocycles. The development of new macrocyclic ligands 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 and the stability and specificity of macrocyclic ligands with metal ion or other guests depend on some important properties of the ligand 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 (-thio compounds)

    3. The oxidation number and the size of cation or other guests

    4. Steric hindrance

    5. Solvent effect.

The stability constant of complexation relies on the interaction between ion or guest with ligand such as ion-dipole and charge-induced dipole. Each type of macrocyclic compound is different in structure, some types have one ring in the molecule, some types have a three dimensional ring. Macrocyclic compounds consist of different donor atoms in the molecule. Basicity of the oxygen, nitrogen, and oxygen/nitrogen mixed donor macrocyclic ligands and their complexes with divalent metals have been widely studied.[1-10]

In 1990 Supramolecular chemistry[11] was implies the developments of new synthetic methods directed to research areas referred as host-guest chemistry, molecular and ionic recognition, supramolecular catalysis, self-organization, aggregation, signal transfer, allosteric effects, etc. In this respect, attention was paid to the search for molecular structures with three dimension geometries offering starting building blocks for the production of sophisticated molecules by anchoring functional groups oriented in such a way that they delineate a suitable binding site. This was achieved by developing the chemistry of new families of macrocyclic molecules such as synthetic crown-ethers, cryptands, spherands, cyclophanes, and natural cyclodextrins. A relatively new class of synthetic macrocyclic building blocks is the calixarenes.

1.2   Calixarenes

Calixarenes are macrocycles made up of phenolic units meta-linked by methylene bridge and possessing basket-shape cavities. The name "calixarene" has been given by Gutsche[12] 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.

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 provide several-size π-rich cavities for including guest compounds. Calixarene can form complexes with both ionic and neutral guests. 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.

For specifying the size of the macrocycle, one intercalculates between brackets a number of phenolic units constituting the calixarene. The most practical way to prepare calix[4]arene, calix[6]arene and calix[8]arene is to condense formaldehyde with *para*-substituted phenol under basic condition. Generally, the selectivity of cyclization decreases as follow 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 1.1).
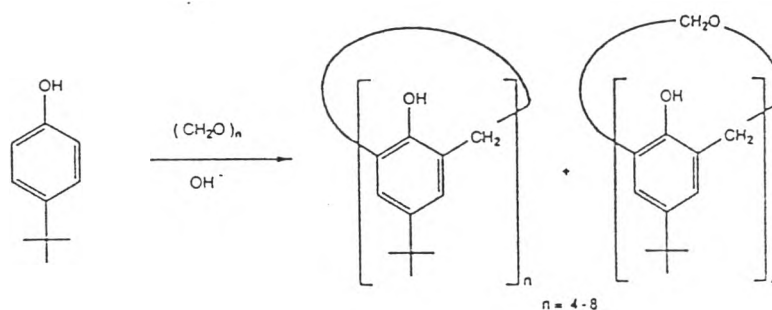

Figure 1.1 Products of basic condensation of *p-tert*-butylphenol with formaldehyde.

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 such as reactions of hydroxyl group, reactions of aromatic rings and reaction of methylene bridges. As calixarene are made up of phenolic units, the reactions of hydroxyl groups are usually those performed on phenols[13].

1.3 Calix[4]arenes

Calix[4]arenes are one type of calixarene and they are very useful building blocks as receptors for cations, anions and neutral molecules. The introduction of bulky substituents at the lower rim of the calixarene prevents the interconversion among the four possible stereoisomers. Those four possible stereoisomers are cone, partial-cone, 1,2- alternate and 1,3- alternate as shown in Figure 1.2[14].

cone   partial-cone

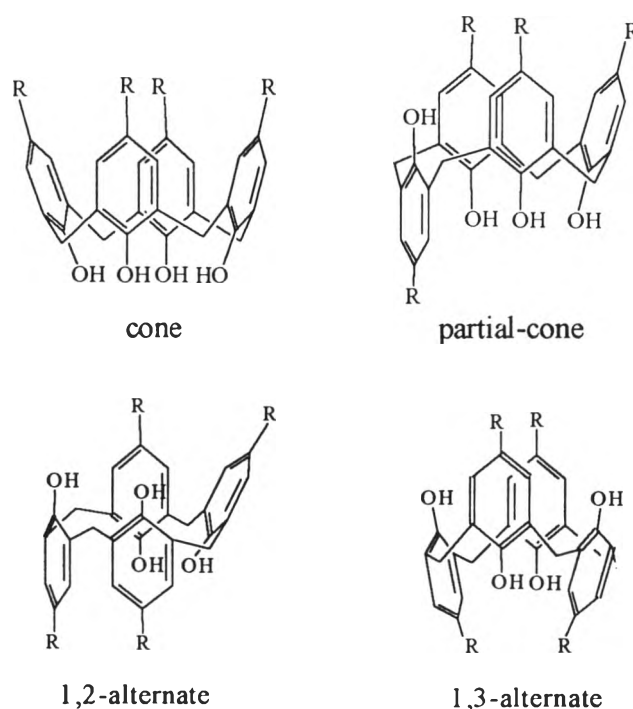1,2-alternate   1,3-alternate

Figure 1.2 The possible conformation of calix [4]arene.

By choosing the reaction conditions, the control of the stereochemistry has been achieved especially in alkylation reactions. The *p-tert*-butylcalix[4]arene, which is the cyclic tetramer of the series, has been shown to be the most important starting building block because (a) it is produced in large quantities from cheap commercial starting materials, (b) it is easily chemically modified at the phenolic oxygens (lower rim) and at the *para*-positions (upper rim) and (c) the chemical modifications associated to the conformational properties lead to a large variety of tailor-made receptors.

1.4   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 modifications were first introduced by Gustche as part of his study of conformational change in calix[4]arenes. Chemical modification at lower rim of *p-tert*-butylcalix[4]arenes and more generally of calix[4]arenes, with ester, amide, keto, carboxylic acid, hydroxamic acid, pyridine, pyridyl and bipyridyl, alkyl thio ether, ether and phosphinite donor pendent group have been described in connection with their metal complexing properties (binding ability, ionophoric behavior, complex formation, etc.). The vast majority of these modified calixarenes exist in the cone conformation in which the mutually syn pendant groups possess a considerable degree of preorganization 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. For the study acid-base characteristics of chemically modified calix[4]arenes and their complexation properties towards alkali and alkaline-earth metal were reported by Arnaud-Nue and co-worker[15]. The results of these studies showed that under appropriate acidic conditions, calix[4]arene carboxylic acids were very sufficient complexing agents for these cations and were much stronger binders than calix[4]arene ester, amides or ketones. Although less extensively studied, chemically modified calix[6]arenes and

calix[8]arenes also possess receptor properties for selected inorganic and organic cations.

Since Alfieri et al.[16] reported on the synthesis of the first member of a new class of macrocyclic crown compounds with *two opposite* OH group of *p-tert*-butyl calix[4]arenes bridged by a pentaethylene glycol chain, extensive work has been devoted to the synthesis of 1,3-bridged calix[4]arenes used as preorganized ligands. Calix[4]arenes are easily modified at the 1,3-difunctional hydroxyl groups (two opposite OH) at lower rim (Figure1.3). This form is the most appropriate form for preorganization of potential binding sites, making possible the synthesis of several mixed ligand receptors.
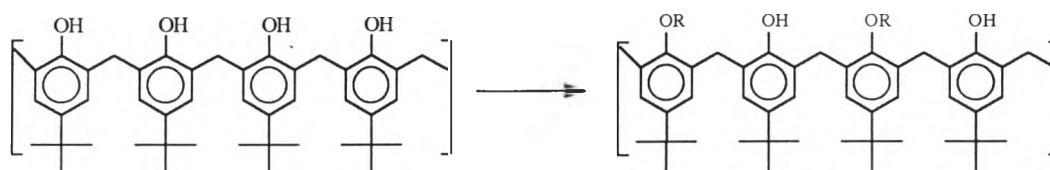

Figure 1.3 Chemical modification of calix[4]arene at the 1,3-dihydroxyl group at lower rim.

After modification, some calix[4]arene derivatives can form complex with guests selectively. For example, the 1,3-distal selective capping of *p-tert*-butyl calix[4]arene at lower rim has been achieved with poly(oxyethylene) chains, e.g. calix crowns ether, calix doubly crowned, double calix crown, with terphenyl units (calixspherands), with salophene units, with a metallocene unit (metallocene calix[4]arene), with disulphonyl and diacetyl dichloride, with diaza crown units (calixcryptand), and phosphorus atoms (phosphorus polybridged calixarenes). Furthermore, calix(aza-)crowns[17] and Schiff-base calix[4]arenes[18] are another examples of this model, being 1,3-distal capping of *p-tert*-butyl calix[4]arene at lower rim. These macrocyclic receptors were mainly used for the coordination of alkali and

alkaline earth metals except for calix(aza-)crowns which showed interactions with softer di- and tri-valent cations and Schiff-base calix[4]arenes which formed complexes with lanthanide, heavy and transition metals.

In 1992-1994, Diaza benzo crown ether-*p-tert*-butylcalix[4]arene[19] (Figure 1.4) were synthesized and were studied complexation with Zn^{2+}, where the counter anions are Cl^-, Br^-, I^-, ClO_4^-, NO_3^- by ^1H NMR spectroscopy. This study showed this ligand could bind Zn^{2+} to a different extent depending on the counter anions and the cavity size of the ligands. The stability of the anion complexation of this ligand, therefore, varied as follow : $NO_3^- > ClO_4^- > I^- > Br^- > Cl^-$. Recently, the protonation of this ligand and its complexation with Zn (II) perchlorate were studied by potentiometric and ultraviolet spectroscopic titrations[20]. The obtained complex formation constants are compared with values obtained from a previous study by nuclear magnetic resonance[21].
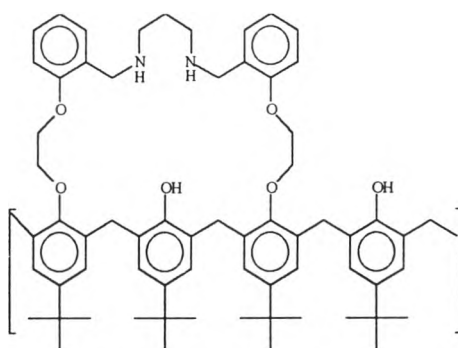

Figure 1.4 Diaza benzo crown ether-*p-tert*-butylcalix[4]arene.

In 1994, Schiff base *p-tert*-butylcalix[4]arenes[18], (Figure 1.5) were synthesized. Alkali and alkaline earth cations were very poorly extracted by ligands (I-III). However, the better extraction of Li^+ and Na^+ with ligand (III) 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+} were extracted more efficiently. Heavy metal cations were extracted with ligand (II) and (III), with a higher preference for Pb^{2+}. In the lanthanide series, there was an extraction selectivity for Nd^{3+} and Eu^{3+} with (II) and for Eu^{3+} with (III).

$$\boxed{} = (CH_2)_2, \ (CH_2)_3, \ (CH_2)_4, \ \text{(IV)} \ \text{(V)}$$
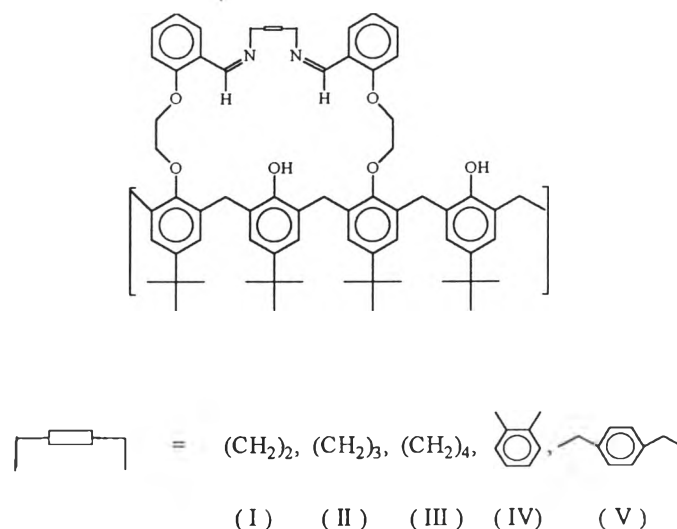
(I)   (II)   (III)   (IV)   (V)

Figure 1.5 Schiff base *p-tert*-butylcalix[4]arenes.

In 1994, the ammonium derivative of diaza benzo-crown ether-*p-tert*-butyl calix[4]arene[22], (Figure 1.6) were synthesized and were studied complexation with NO_3^-, CO_3^{2-}, PO_4^{3-}, CH_3COO^-, $C_2O_4^{2-}$ by NMR spectroscopy. This study showed that only NO_3^- can form complex. Other anions can not bind with this ligand because they could be hydrolyzed in aqueous solution and generated OH^- which reacted with NH_2^+ and changed the ligand to neutral form which can not form complex with these anions. In 1995, the ammonium derivative of triaza benzo-crown ether-*p-tert*-butyl calix[4]arene[23], (Figure 1.7) were synthesized and were studied complexation with a series of anions by NMR spectroscopy. This study implied that only anions that have suitable size (1.71-1.75 $^{\circ}A$) can fit in the cavity of nitrogen donor of this ligand. The anion selectivity of this ligand varies as follows: $CO_3^{2-} > NO_3^- > AsO_2^- > Cl^-$.
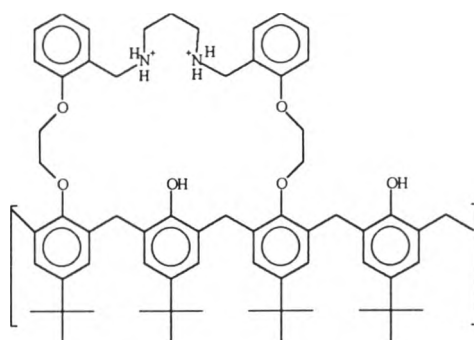
Figure 1.6 Ammonium derivative of diaza benzo-crown ether-*p*-*tert*-butyl calix[4]arene.
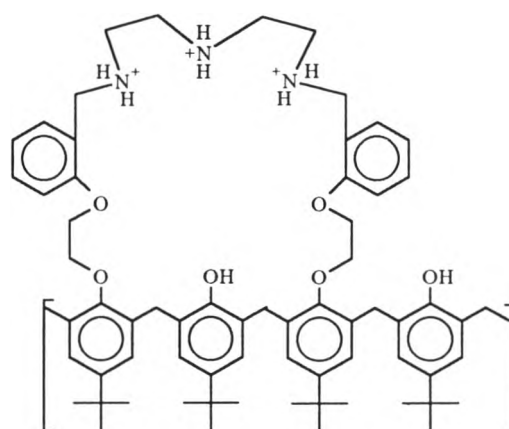

Figure 1.7 Ammonium derivative of triaza benzo-crown ether-*p*-*tert*-butyl calix[4]arene.

In 1996, the tripodal-amine capped benzo crown-*p*-*tert*-butylcalix[4]arene (Figure 1.8)[24] was synthesized. The basicity of the tripodal-amine capped benzo crown-*p*-*tert*-butylcalix[4]arene was evaluated in terms of the protonation constants and was studied complexation with Zn^{2+}, where the counter anions are Br^-, NO_3^- by ^1H NMR titration experiment. This study showed this ligand could bind with $ZnBr_2$ in

1:1 complex formation. One Zn^{2+} may reside in the cavity of the amine nitrogen donors while one of Br^- may be induced into cavity of the phenolic oxygen. However this ligand bind with $Zn(NO_3)_2$ to give another possible species, a 2:1 complex, in which two Zn^{2+} reside in this ligand, one Zn^{2+} must reside in the amine nitrogen cavity while the other is in the phenolic oxygen cavity. The basicity of the nitrogen donors in this ligand was investigated by determining protonation constants in methanolic solution with potentiometric titration in same time.
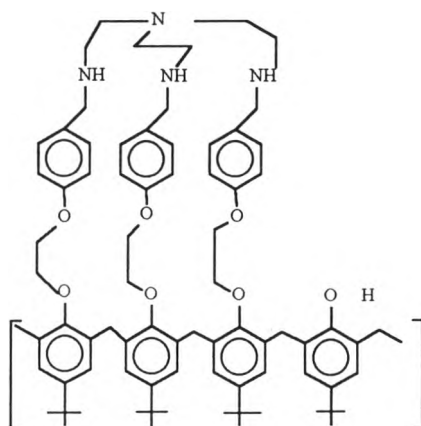

Figure 1.8   Tripodal-amine capped benzo crown-*p-tert*-butylcalix[4]arene.

1.5   Systematic Investigation of Solution Chemistry

The process by which the nature of the species present in a solution at equilibrium is systematically investigated can be divided into a number of steps:

(a)   The nature of each of the species present in solution is first identified by using a mixture of 'chemical intuition' and a number of physicochemical techniques which determine either the stoichiometry of the species present (that is, the values of m and n in M_mL_n) or the number of different species present.

(b)   Expressions relating the concentrations of the initial reactants and final products such as the basicity and the stability constants are set up.

(c)   As many quantitative observations as possible are made on the solution, using one or more suitable methods for determining basicity constants such as potentiometry, nuclear magnetic resonance and stability constants such as ultraviolet and visible spectrophotometry.

(d)   The errors inherent in these measurements such as systematic errors and random errors are discussed.

(e)   The equilibrium concentrations of all the species present in solution are calculated.

1.6   Complexes

Complexes are compounds containing a central atom or ion, which is usually a metal but may be any electron acceptor (Lewis acid), and which is surrounded by several electron donor group (Lewis bases) that are generally referred to as ligands. The complex, which may be either charged or neutral, tends to retain its identity even in solution, although of course both dissociation and replacement of the original ligands may occur. Since a number of different types of complex are referred to in the literature let us look at each of these in turn.

1.6.1 Inner- and Outer-Sphere Complexes

When a ligand binds covalently to a metal the resulting complex is sometimes referred to as an inner-sphere complex. In such a complex the ligand occupies a clearly defined site within the coordination shell of the metal. An outer-sphere complex is formed when an inner-sphere complex is formed and weakly linked through electrostatic, Van der Waals' or hydrogen-bonding to further groups. In general these groups do not occupy specific sites around the metal.

1.6.2 Chelate Complexes

When a ligand such as EDTA or ethylenediamine, which can potentially coordinate to a metal ion through more than one position acts as a multidentate ligand, the resulting complex is said to be a chelate complex. Chelate complexes are of particular importance because of their generally greater stability than the complexes of the corresponding unidentate ligands. This greater stability, known as the chelate effect, gives rise to their widespread applications in analytical chemistry, for example in complexometric titrations such as EDTA titrations. It is also responsible for the ligands which nature has chosen to surround metals in biological systems.

1.6.3 Mononuclear and Polynuclear Complexes

Mononuclear complexes have only one metal ion in each complex unit. When M and L denote the metal ion and ligand respectively, thus ML, ML_2, ML_n are all mononuclear complexes. By contrast, complexes in which more than one metal ion is present, such as M_2L and M_mL_m ($m > 1$), are described as polynuclear. Polynuclear complexes are of particular importance in the hydrolysis of metal ions.

1.7   Objective and Scope of the Research

Aza-crown-*p-tert*-butylcalix[4]arene is one type of 1,3- selective distal capping of -*p-tert*-butylcalix[4]arene which show interactions with softer di and trivalent transition metal ions. The 25,27-{2,2′-[2,2′-((2,5,8-triaza)nonyl)diphenoxy]diethyl}-*p-tert*-butylcalix[4]arene is a new synthetic aza-crown-*p-tert*-butylcalix[4]arene [25] and contains three nitrogen donor atoms (Figure 1.9). The basicity study of the 25,27-{2,2′-[2,2′-((2,5,8-triaza)nonyl)diphenoxy]diethyl}-*p-tert*-butylcalix[4]arene and its complexation with certain transition metal ions by potentiometric titration are, therefore, the goal of the research. The results of this research should lead to protonation ability of the 25,27-{2,2′-[2,2′-((2,5,8-triaza)nonyl)diphenoxy]diethyl}-*p-tert*-butylcalix[4]arene and complexing ability of its complexes with certain divalent transition metal ions. The species distribution of the ligand alone and its complexes with transition metal ions over the varied pH values of the methanolic solutions will also be obtained.

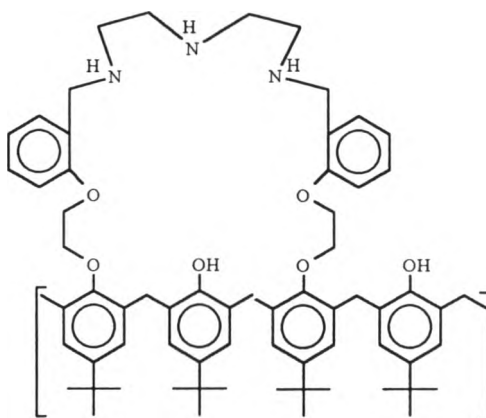**Figure 1.9**   25,27-{2,2′-[2,2′-((2,5,8-triaza)nonyl)diphenoxy]diethyl}-*p-tert*-butylcalix[4]arene.