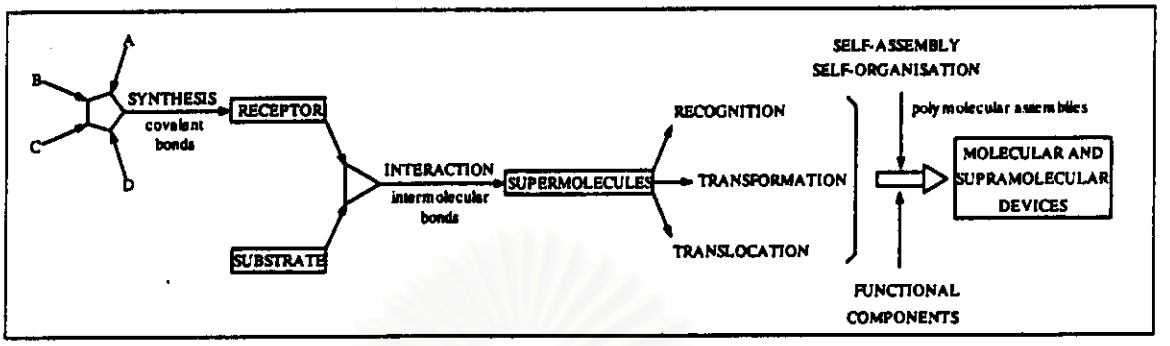
CHAPTER I

INTRODUCTION

1.1 Supramolecular Chemistry

In modern information technology, the information can be stored as binary code, 0 and 1; on the other hand, in living organisms, the information is stored in the form of structural peculiarities. Efforts to understand how biomolecules organize their structures for specific functions lead to a new branch of chemistry called *Supramolecular Chemistry*. The area of supramolecular chemistry is still a young one. However, it becomes more and more fascinating topics because it is not only closely related to bioorganic and bioinorganic chemistry but also the basic knowledge for nanotechnology. Supramolecular chemistry is defined as "chemistry beyond the molecule" and as chemistry of tailor-shapes inter-molecular interaction[1]. Supermolecules are made up of two or more chemical species held together by weak intermolecular forces (non-covalent intermolecular bond) such as hydrogen bonding, Van der Waals interaction or electrostatic interaction. Moreover, supramolecular chemistry is composed of self-organization processes (self-assembly) and specific reaction of molecules. The relationship of molecular and supramolecular chemistry is shown in Scheme 1.1. A wide varieties of research topics in this field such as molecular recognition, molecular transformation and molecular translocation have been studied.



Scheme 1.1 The relationship of molecular and supramolecular chemistry[2]

1.2 Molecular Recognition

Molecular recognition is a large and fast growing field of supramolecular chemistry in which crystal structure analysis has played, and will continue to play the key role. Molecular recognition is defined by the energy and the information involved in the binding and selection of substrates by a given receptor molecule. It may also involve a specific function, so thus implied the (molecular) storage and (supramolecular) read out of molecular information. Several factors should be controlled in order to achieve high affinity in molecular recognition:

a.) steric complementarity: it depends on shapes and sizes of both receptor and substrate;

b.) interactional complementarities : electrostatic, hydrogen bonding and Van der Waals interaction such as positive/negative, charge/dipole, dipole/dipole or hydrogen bond donor/acceptor, hydrophobic/hydrophobic or hydrophilic/hydrophilic;

c.) large contact area between receptor molecule and substrate;

d.) multiple interaction sites due to non-covalent interaction;

e.) strong overall binding[3].

1.3 Molecular Receptors

Molecular recognition is composed of molecular receptors bound together with the substrate. Molecular receptors are defined as organic structures helded by covalent bonds, that are able to bind selectively ionic and/or molecular substrates by means of various intermolecular interactions, leading to an assembly of two or more species, a supermolecule. If the substrate is included into the cavity, we call the molecular receptors as endoreceptors. In case of exoreceptors, they possess externally oriented binding sites. The best receptor is the one designed for high selectivity, high stability, and high flexibility with substrate. Supramloecular chemistry is based both on the development of the chemistry of crown ethers and cryptands. Nevertheless a tremendous progress of the field has recently been made by the studies of calixarenes.

1.4 Calixarenes

Calixarenes have proved to be very useful building blocks in supramolecular chemistry. They are the cavity-containing-cyclic molecules made up of phenolic units linked *via* methylene bridges (Figure 1.1). The name *calixarenes* is chosen for this compounds because it clearly describes the shape of these cyclic molecules (calix: beaker, arene: aryl[4]) when they orientate in the cone conformation. Such conformation is a very stable conformation because of intramolecular hydrogen bondings of all phenolic hydroxy groups. Calixarenes possess an upper rim defined by the para substituents of the phenolic moieties and a lower rim defined by the phenolic hydroxy groups. One of the most important properties of calixarenes is their ability to include smaller molecules and ions reversibly and selectively. Calixarenes have many size of cavity for including substrates depending on the number of phenolic moieties. Calix[4]arene, the smallest number of this family, is a very popular one since it provides a cavity and can be prepared with ease. In addition they have different positions that can be selectively functionalized *i.e.*, the phenolic

oxygens at the lower rim and the aromatic *para* positions at the upper rim. Calix[4] arene can adopt four different conformations: cone, partial cone, 1,2-alternate and 1,3-alternate[5] (Figure 1.1). This enlarges the number of potentially useful geometries of these molecules as building blocks. Calixarenes and especially calix[4]arenes are widely used in supramolecular chemistry because they are useful in the design and synthesis of artificial receptors for the selective recognition of ions and neutral molecules. Some of the molecular complexes of calixarenes are a class of inclusion compounds in which the receptors enclose other molecules without the formation of covalent or ionic bonds. The molecules which do the enclosing are refered to as the hosts, while the inducing molecules are the guests. The hosts form a lattice type structure with voids which are large enough to accommodate the guests.

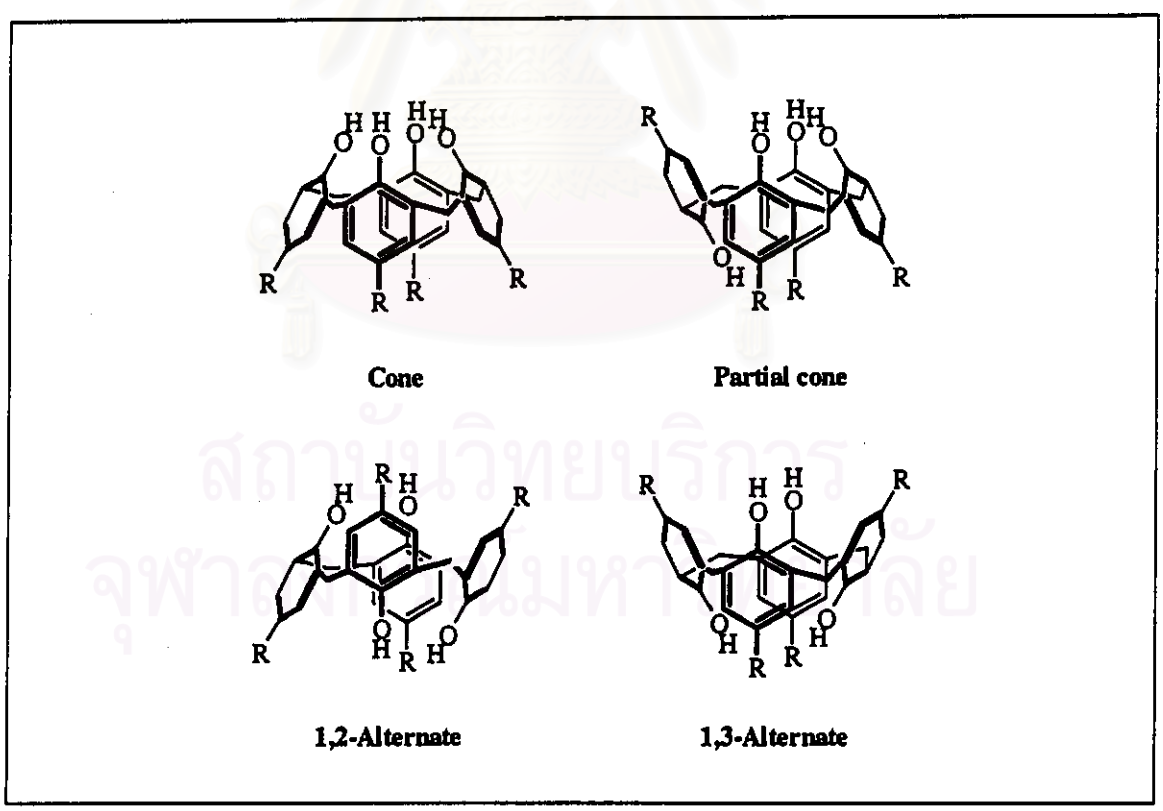


Figure 1.1. Structures and conformations of calix[4]arene.

1.5 Hydrogen Bonding Interaction

A main goal of supramolecular chemistry is the use of specific non-covalent binding forces to obtain selectively stable host-guest complexes. Hydrogen bonding is known to be one of the most important non-covalent interactions not merely in supramolecular chemistry but also in molecular biology. Hydrogen bondings have three different types of interaction, strong, moderate and weak, depending on the functional groups of donors and acceptors (Table 1.1); thus the properties of hydrogen bondings are classified into three classes (Table 1.2). All types of hydrogen bonding can be intramolecular when donor and acceptor groups are on the same molecule or intermolecular when they are on different molecules. Very strong hydrogen bonds resemble covalent bonds, while very weak hydrogen bonds are close to Van der Waals forces. A wide variety of both intermolecular and intramolecular hydrogen bonds is described having O-H or N-H as donor and O or N as acceptor atom. The nature of a hydrogen bond depends on the nature of the donors and acceptor groups. The inclusion compounds containing hydrogen bond are carried out not exclusively in metal cation guest molecules but also anion as well as neutral molecules. In comparison with the large variety of ligands which has been described for cations, the development of selective hosts for anions and neutral molecules is still in its infancy. This is also true for calixarenes-based receptors.

Table 1.1. Functional groups that form hydrogen bonds[6]

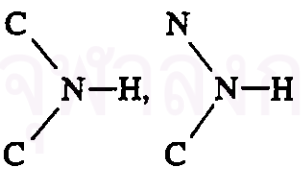
Strong hydrogen bonds	
Donors and acceptors	
$[F\text{----}H\text{----}F]^-$	Symmetrical hydrogen bifluoride ion
$[H—F—H]_n^-$	Anions in fluoride HF adducts
$[O—H\text{----}O^-]$	Organic hydrogen anions, hydrogen phosphates and sulfates, hydrogen carboxylate ions
$[O^+—H\text{----}O]$	Hydroxonium ions, pseudo hydrates
$[N^+—H\text{----}N]$	Proton sponges
$[N—H\text{----}N^+]$	
Moderate hydrogen bonds	
Donors and acceptors	
O—H, P—O—H, $H—O_w—H$	Water, hydrates, alcohols, carboxylic acids, phenols, carbohydrates, oligo- and polysaccharides, nucleosides, nucleotides, nucleic acid
	Secondary amines, amides, carbamates, hydrazides, purines, pyrimidines, barbiturates, nucleosides, nucleotides, peptides, proteins (main chain and side chains)

Table 1.1. *(continue)*

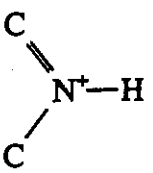
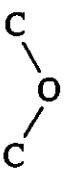
Moderate hydrogen bonds	
Donors only	
$N^+(H_3)H$	Ammonium salts
$—N^+(H_2)H$	Zwitterion amino acids
$>N^+(H)H$	
S—H	Cysteine
	Proteins (side chain, nucleic acids (low pH))
C—N(H)H	Primary amines, pyrimidines, purines, barbiturates
Acceptors only	
	Ethers, carbohydrates, oligo- and polysaccharides (ring and glycosidic oxygens)
$>C^-=O$	Carboxylates, zwitterion amino acids
>C=O	Carboxylic acids, ketones, esters, N-oxides, pyrimidines, purines, nucleosides, nucleotides, nucleic acids, peptides, proteins (main chain)
$X^-=O$	Oxyanions, nitrates, chlorates, sulfates, phosphates
>N	Tertiary amines
>N	Purines, pyrimidines, barbiturates, nucleosides, nucleotides, nucleic acid
N=O	Aromatic nitro compounds
>S	Methionine

Table 1.1. *(continue)*

Weak hydrogen bonds
Donors
C—H, Si—H
Acceptors
C≡H, F—C, 

Table 1.2. Properties of strong, moderate and weak hydrogen bonds[6]

	Strong	Moderate	Weak
A—H---B interaction	mostly covalent	mostly electrostatic	electrostatic
Bond lengths	A—H ≈ H----B	A—H < H----B	A—H << H----B
H----B (Å)	~ 1.2-1.5	~ 1.5-2.2	2.2-3.2
A----B (Å)	2.2-2.5	2.5-3.2	3.2-4.0
Bond angles (°)	175-180	130-180	90-150
Bond energy (kcal mol^{-1})[a]	14-40	4-15	< 4
Relative IR ν_s Vibration shift (cm^{-1})[b]	25%	10-25%	< 10%
^1H chemical shift downfield (ppm)	14-22	< 14	-
Examples	Gas phase dimers with strong acids or strong bases Acid salts Proton sponges Pseudohydrates HF complexes	Acids Alcohols Phenols Hydrates All biological molecules	Gas phase dimers with weak acids or weak bases Minor components of 3-center bonds C—H----O/N bonds O/N—H----π bonds

[a] Suggested by Emsley (1980)

[b] Observed ν_s relative to ν_s for a nonhydrogen bonded X H.

The methods for studying hydrogen bonding can be categorized into four techniques; spectroscopy, diffraction, thermochemical and theoritical methods. ^{1}H-NMR spectroscopy is a sensitive probe of hydrogen bonding, since the proton magnetic resonance is very sensitive to the electron environment around the proton. The chemical shift on hydrogen bond formation is one of the largest observed.

1.6 Anion Recognition

The molecular recognition and sensing of anionic guest species are the area of intense current research activity due to endeavors in studying and mimicking the important biological processes. The challenge in the field of anion complexation is to design the receptors with a high selectivity for biologically important anions like phosphates, (poly)carbonate and halides (especially chloride). The design of selective receptors for anions is more demanding than that of cations because of both wide variety of geometries and sizes (Table 1.3). The geometry is an important factor to account for the design of selective anion receptors, although it is not easy to synthesize receptor molecules with complementary binding sites in a proper three dimentional arrangement.

The synthetic anion receptors are devided into two classes : positively charged and neutral anion receptors[7]. The positively charged receptors, such as poly-ammonium receptors[8], guanidinium based receptors[9], porphyrins[10] and cobalticinium[11] based receptors are less selectively recognized anions than neutral anion receptors.

Table 1.3. The geometry and size of various anions[12]

Anions	Geometry	Size (Å)
F^-	spherical	1.33
Cl^-	spherical	1.81
Br^-	spherical	1.96
I^-	spherical	2.20
CO_3^{2-}	trigonal planar	1.78
NO_3^-	trigonal planar	1.79
$H_2PO_4^-$	tetrahedral	2.00
PO_4^{3-}	tetrahedral	2.38
SO_4^{2-}	tetrahedral	2.30
ClO_4^-	tetrahedral	2.50

The most interesting aspect of anion recognition studies is how to extract and transport particular anions. Extractors or carriers have to fulfil two requirements, namely to be good complexing agents and exhibit high lipophilicity. The large variety of anion receptors available will certainly induce further efforts in molecular catalysis and the construction of sensors.

Tetrasubstituted of four urea groups at the lower rim of *p-tert*-butylcalix[4] arene (Figure 1.2) was synthesized and the ^{1}H-NMR titrations were investigated by Scheerder *et al*[13]. This new class of neutral ligands was able to bind anions in a 1:1 stoichiometry exclusively through hydrogen bonding observed in downfield shift of all N-H protons. A good selectivity for spherical anions was obtained, in the order $Cl^- > Br^- > I^-$ (K_{ass} (M^{-1}) = 2660, 1735 and < 25 respectively). Since it is known that

chloride and bromide anion are good hydrogen bond acceptors and the hydrogen bond donor sites of the urea moiety act as hard Lewis acid. The selectivity of chloride over bromide and iodide may be attributed to the higher complementarity of the cavity of the host molecule.

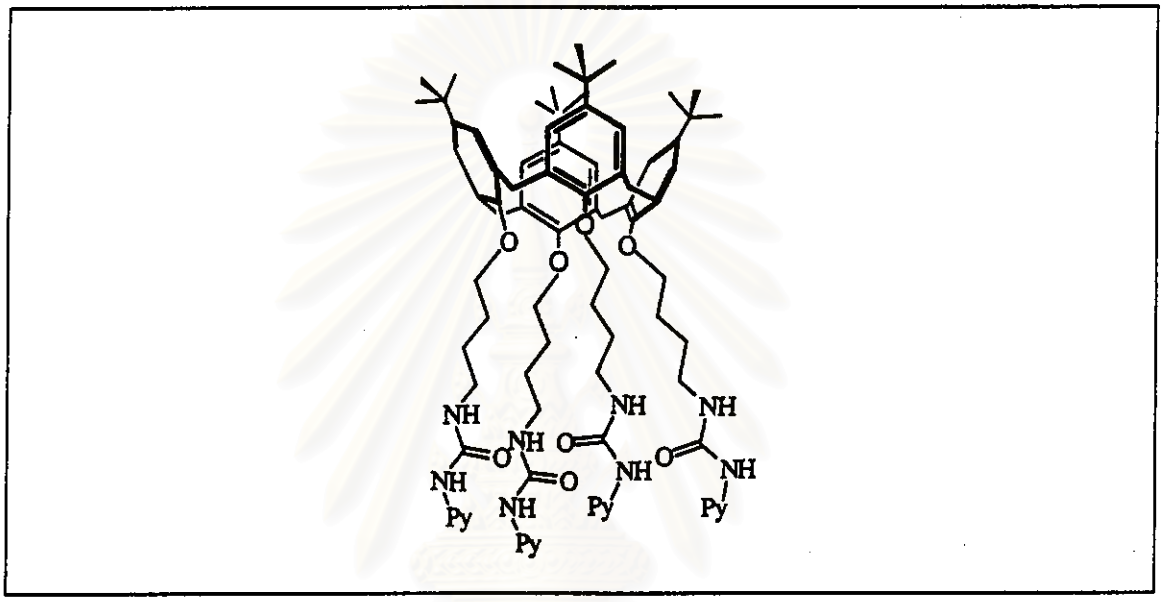


Figure 1.2. The *p-tert*-butylcalix[4]arene derivatized with four urea moieties at the lower rim.

The importance of favorable amide CO-NH hydrogen bonding interactions for anion binding has recently been exploited in the design of calix[4]arene anion receptors. Beer *et al* synthesized a novel *bis*-calix[4]arene receptor molecule (Figure 1.3) in which the upper rim of one calix[4]arene moiety was covalently linked *via* amide bonds to the lower rim of another[14]. The addition of tetrabutylammonium fluoride, chloride, hydrogen sulfate and dihydrogen phosphate to CD_2Cl_2 solutions of host molecule resulted in significant perturbations of the receptor's methylene, phenolic and amide protons. The resulting titration curves suggested 1:1 stoichiometric complexes with the various anions. The stability constant values exhibited an order of magnitude of the selectivity difference for fluoride (1330) and

chloride (172), and relatively much weaker complexes are formed with HSO_4^- (21) and $H_2PO_4^-$ (91) anions which may be attributed to anion size.

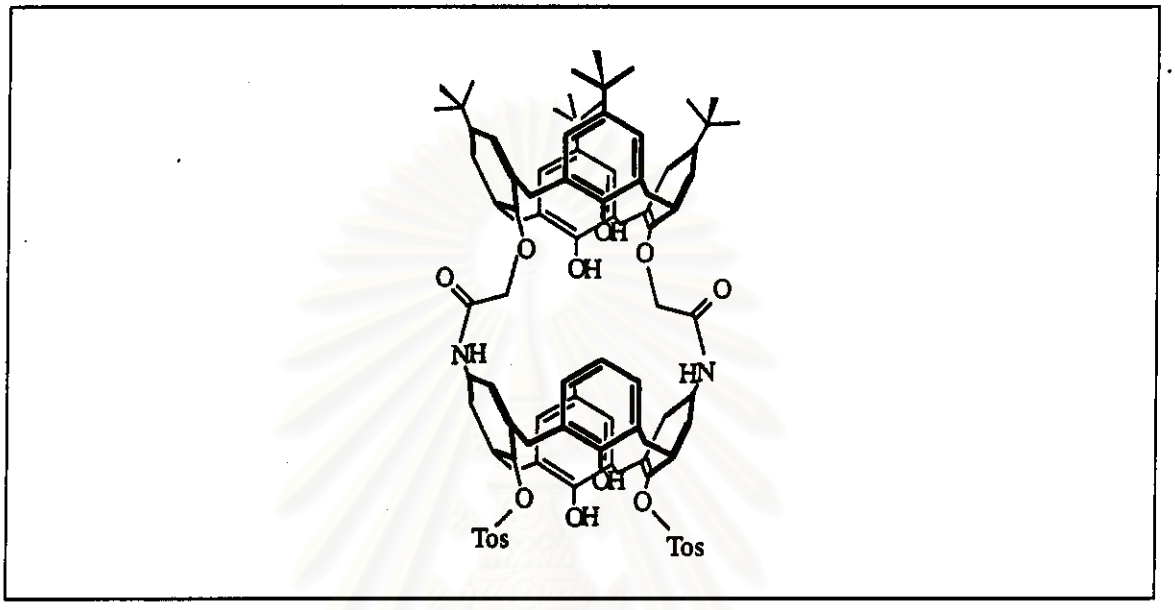


Figure 1.3. The *bis*-calix[4]arene receptor molecule.

Bis-(amido) calix[4]arene based anion receptors was synthesized by Cameron *et al*[15]. The pinched cone conformation is flexible enough to allow for the binding of a series of anions and the acceptor properties of the amido group could be tuned by varying the electron withdrawing nature of the terminal substituents. These new receptors are selective for Y-shaped carboxylate ions (K_s ($CH_3CO_2^-$) = 88 M^{-1}) over tetrahedral anions (K_s ($H_2PO_4^-$) = 22 M^{-1}, K_s (HSO_4^-) = 27 M^{-1} and K_s (ReO_4^-) < 10 M^{-1}) and show a particular preference for benzoate derivatives (K_s ($C_6H_5CO_2^-$) = 107 M^{-1}). In all cases, the anion:receptor stoichiometry was confirmed to be 1:1 (Figure 1.4) by a Job's plot. In contrast, for larger dicarboxylate anions (isophthalate, terephthalate and fumarate) were found to bind with the receptor in a 1:2 fashion (K_s (M^{-1}) > 10^6).

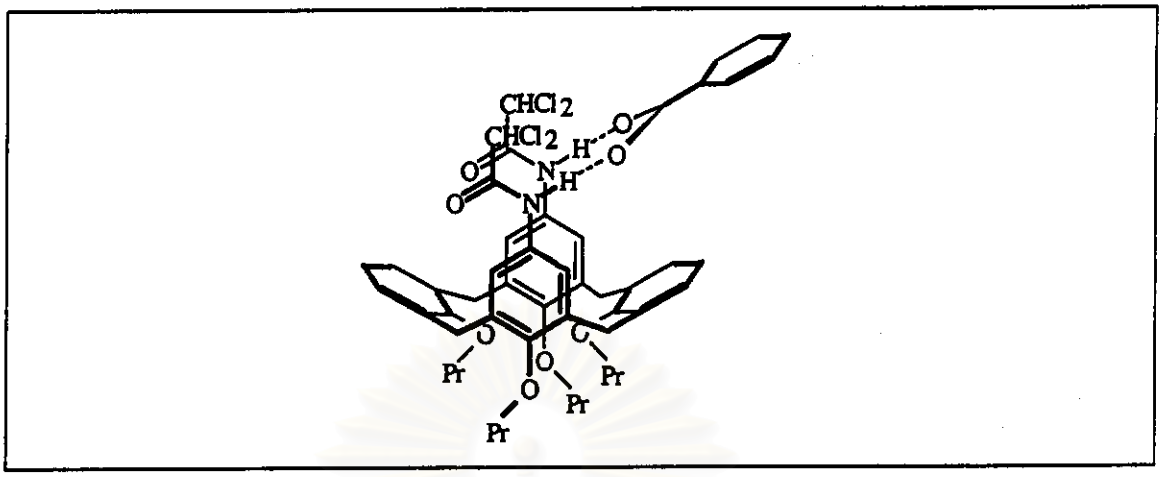


Figure 1.4. The structure of *bis*-(amido) calix[4]arene.

1.7 Neutral Molecule Recognition

The development of molecular receptors for neutral substrates, a possibility which is indicated by the first X-ray structural analysis of calixarenes, is basically still in its infancy. In addition, the design and synthesis of new ligands for neutral molecules is an area of current interest both in supramolecular chemistry and organic synthesis. Some receptors are designed for chiral recognition and catalysis. Thus the reaction center is often surrounded by a chiral moiety and a recognition site; the latter controls the substrate selectivity and the former has a strong influence on the stereoselectivity of the process. Noncovalent interaction between aromatic rings and neutral molecules is important in determining the structures and properties of molecular complexes in host-guest chemistry. Although calixarenes are interesting because they are able to form inclusion complexes with several organic neutral guest molecules, they have a low solubility in organic solvents. After introduction the fuctional groups such as alkyl, aryl or amine moiety, the solubility of calixarenes in non-aqueous media are enhanced. The substrate molecules are assemblied with large receptors using non-colavent interaction such as π-π stacking, CH-π interaction and hydrogen bonding.

Loon and co-workers synthesized calix[4]arene derivatives that contain α-pyridone moiety at the upper rim[16]. The ^{1}H-NMR spectra of the host molecule in $CDCl_3$ showed broad peaks for all protons indicating the reduced flexibility of calix [4]arene derivatives due to the formation of associates (K_D = 100 ± 20 M^{-1}). Although the urea derivatives were flexible in solution, the formation of a complex with imidazolidone *via* a complementary hydrogen bond pattern denatured the multi-calix[4]arene systems. Since the imidazolidone N-H proton became sharp and shifted downfield, indicating the formation of a well-defined hydrogen bond, and the broad signals of the methylene bridge protons in the receptor became sharper. Initially a 1:1 complex was formed (K_s = 5.6 ± 1.1 x 10^3 M^{-1}) (Figure 1.5), and it later converted into a 1:2 complex upon excessive addition of guest molecule. The structure was determined by ^{1}H-NMR spectroscopy and vapor pressure osmometry (VPO).

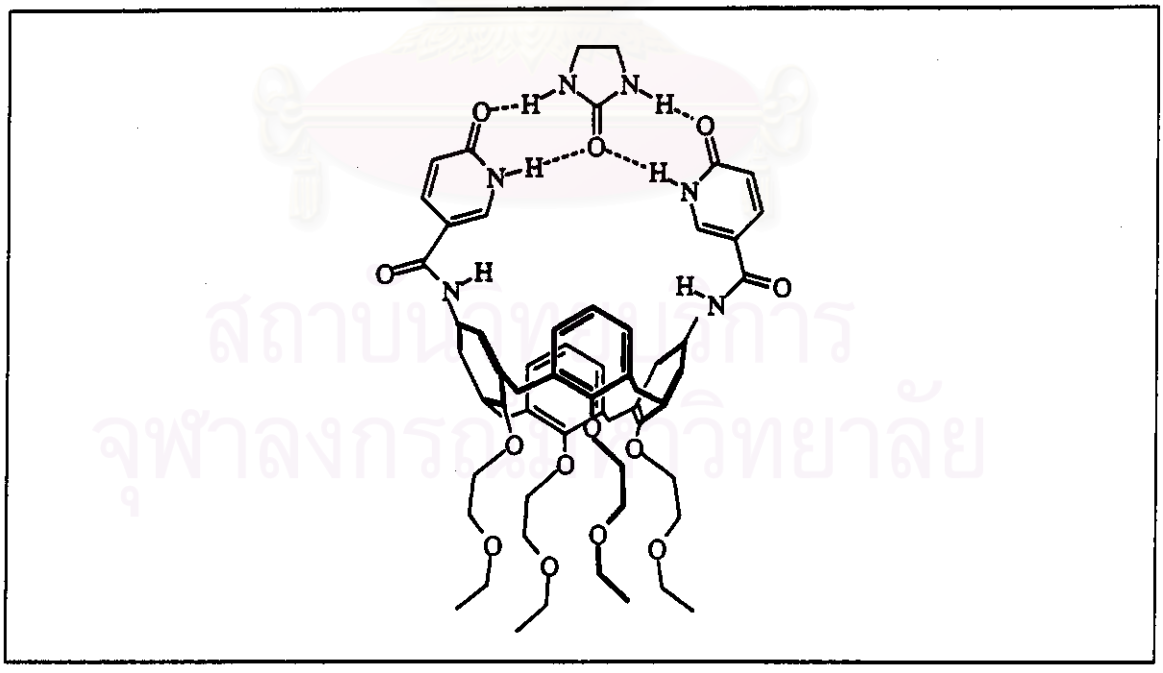


Figure 1.5. The calix[4]arene derivative containing α-pyridone moiety at the upper rim.

A calix[4]arene substituted with hydrogen bonding groups, carboxylic group, at the upper rim (calix[4]arene tetracarboxylic acid) interacted with calix[4]arenes substituted with pyridine moiety at the lower rim (tetra(4-pyridyl)calix[4]arene),(a) and tetra(3-pyridyl)calix[4]arene),(b) as reported by Vreekamp and co-workers[17]. The downfield shifts for the aromatic protons on pyridine moiety were observed on the ^{1}H-NMR spectra. Furthermore, the extraction series and VPO measurements indicated the formation of 1:1 adducts (K_{ass} = 7.6 x 10^3 and 1.3 x 10^3 M^{-1} for (a) and (b) respectively) (Figure 1.6).

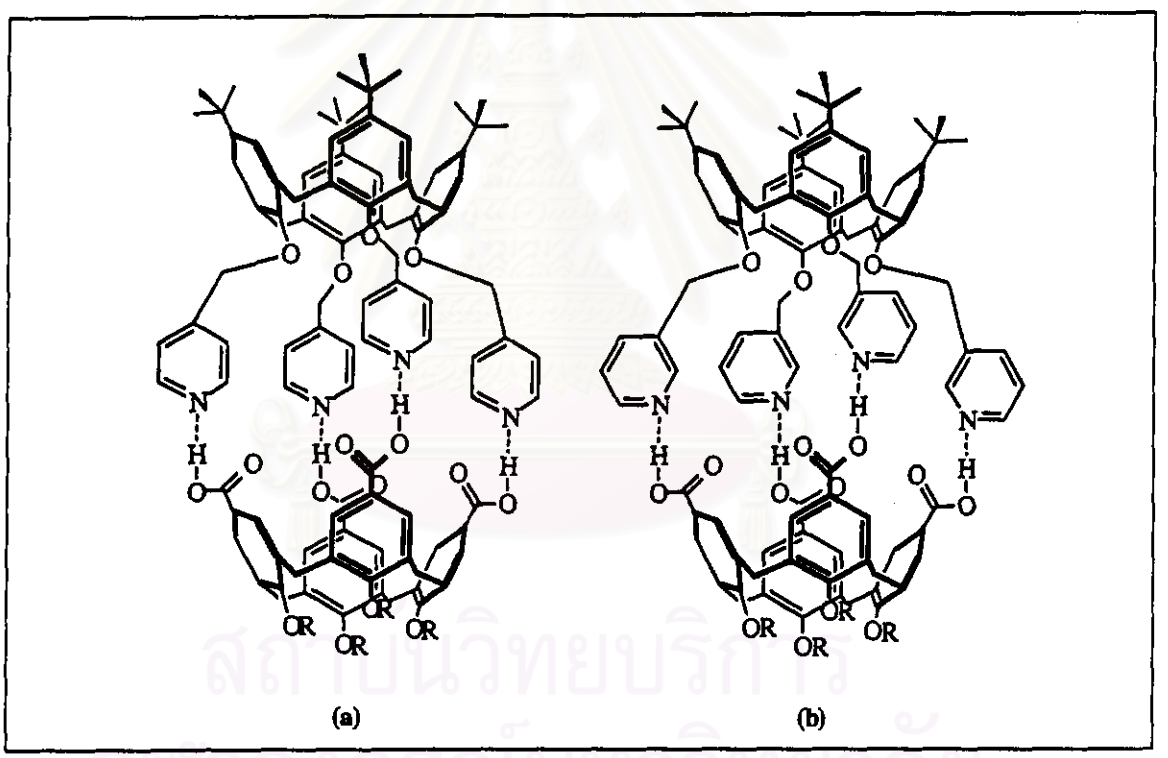


Figure 1.6. The adducts of calix[4]arene tetracarboxylic acid with (a) tetra(4-pyridyl) calix[4]arene or (b) tetra(3-pyridyl)calix[4]arene).

Corazza *et al.* have synthesized an interesting oxo-molybdenum calix[4] arene in which oxo-molybdenum binds four oxygen atoms from the cone conformation of a calix[4]arene[18]. The oxo-molibdenum calix[4]arene reacted with

calix[4]arene to give a product which could be crystallized in nitrobenzene. The crystal structure of the product depicted in Figure 1.7 shows that nitrobenzene is stabilized in the structure by both hydrogen bonding with a H_2O molecule and hydrophobic/hydrophilic interaction of the arene rings.

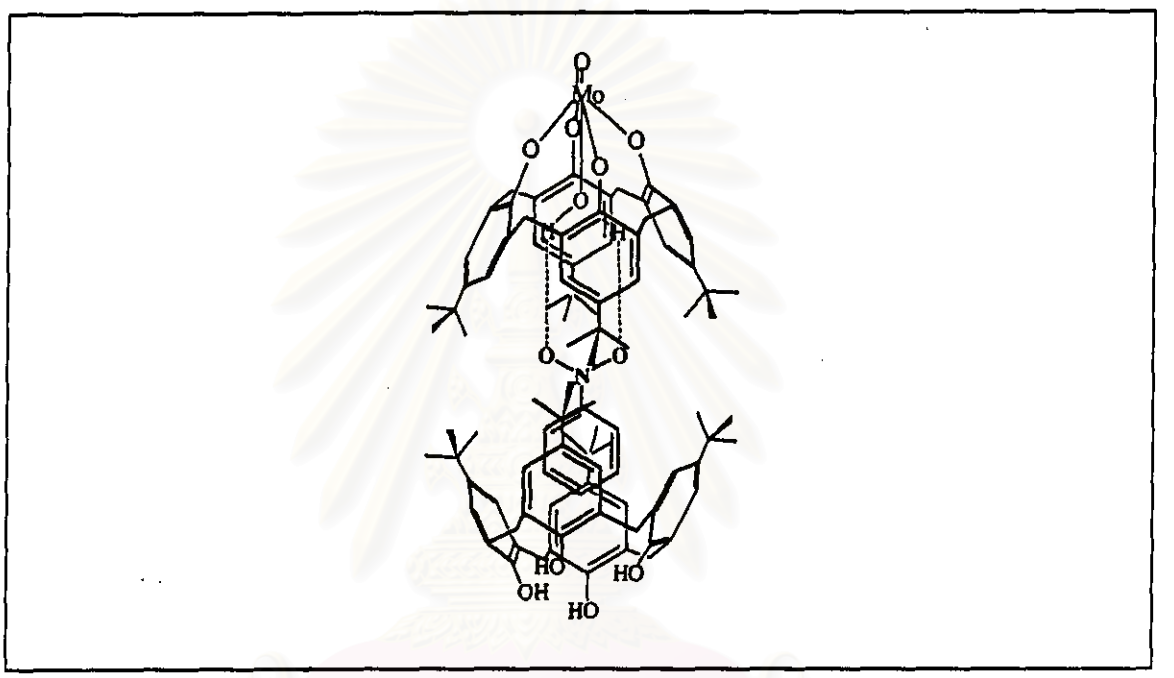


Figure 1.7. The structure of an oxo-molybdenum calix[4]arene derivative.

Flexible molecules can reversibly self-assemble to give a well-defined receptor cavity such as tetramethoxy calix[4]arene containing a wide variety of urea at the upper rim (Figure 1.8) as reported by Castellano and co-workers[19]. The monomeric molecule existed in a partial cone conformation. However ^{1}H-NMR spectrum showed the downfield shift of urea protons and indicated the dimerization of the ligand. Thus, the intermolecular hydrogen bonding can be used to drive the conformational equilibrium exclusively to cone conformation. The preliminary encapsulation studies of the ligand were performed and showed that benzene could be encapsulated into the cavity of the bowl-shape molecule. Finally, an additional evidence for dimerization and encapsulation can be obtained from ESI-MS studies.

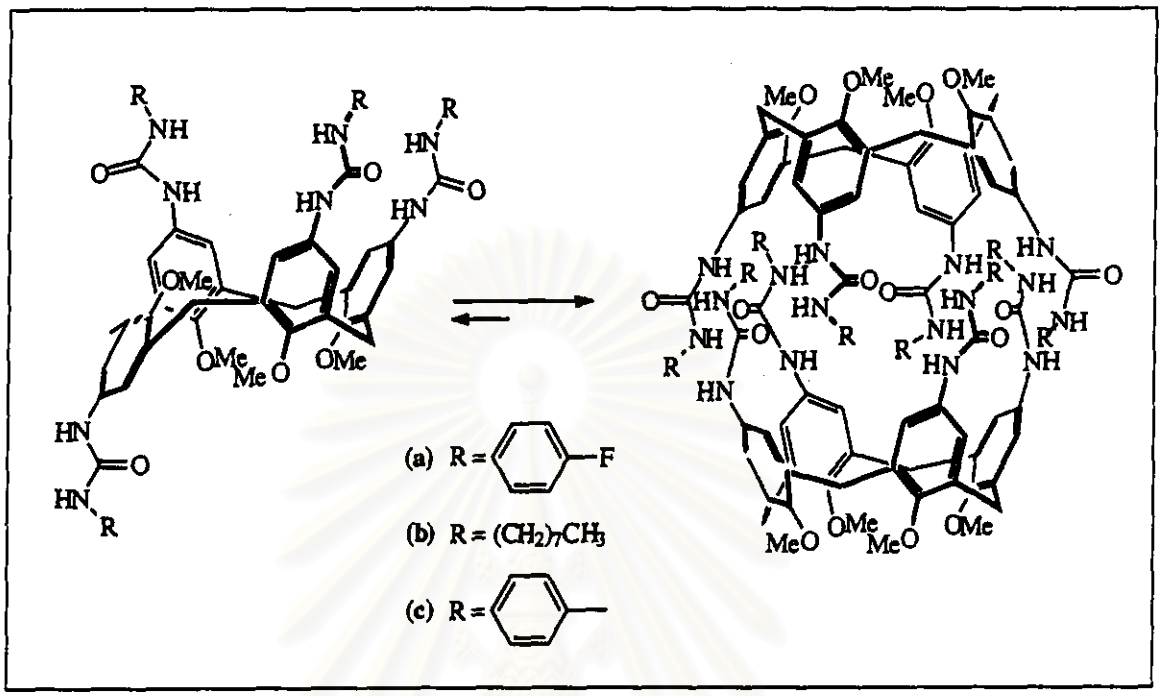


Figure 1.8. Dimerization of tetramethoxy calix[4]arene derivatives.

Haino *et al* focused their attention on the ether derivatives of monodeoxy calix[4]arene because of their increasing solubility and larger flexibility than calix[4] arene[20]. This receptor (Figure 1.9) was designed to have two benzoic acid moieties as the guest binding sites. The synthesis and binding behavior were reported. The binding ability of host molecule to a series of urea guests, tetrahydro-2-pyrimidone (K_a = 1900 ± 100 M^{-1}), 2-imidazolidone (K_a = 750 ± 130 M^{-1}) and N-ethylurea (K_a = 1300 ± 100 M^{-1}), was evaluated by ^{1}H-NMR titration in $CDCl_3$. The downfield shift of N-H signal of urea was observed suggesting the hydrogen bonding interaction between N-H of the guest and the carboxyl groups of host molecule. Job's plot analysis confirmed the 1:1 stoichiometry of all the complexes. These receptor molecules could strongly bind both the cyclic and acyclic ureas in solution. All guest molecules were effectively bound to host due to their conformation.

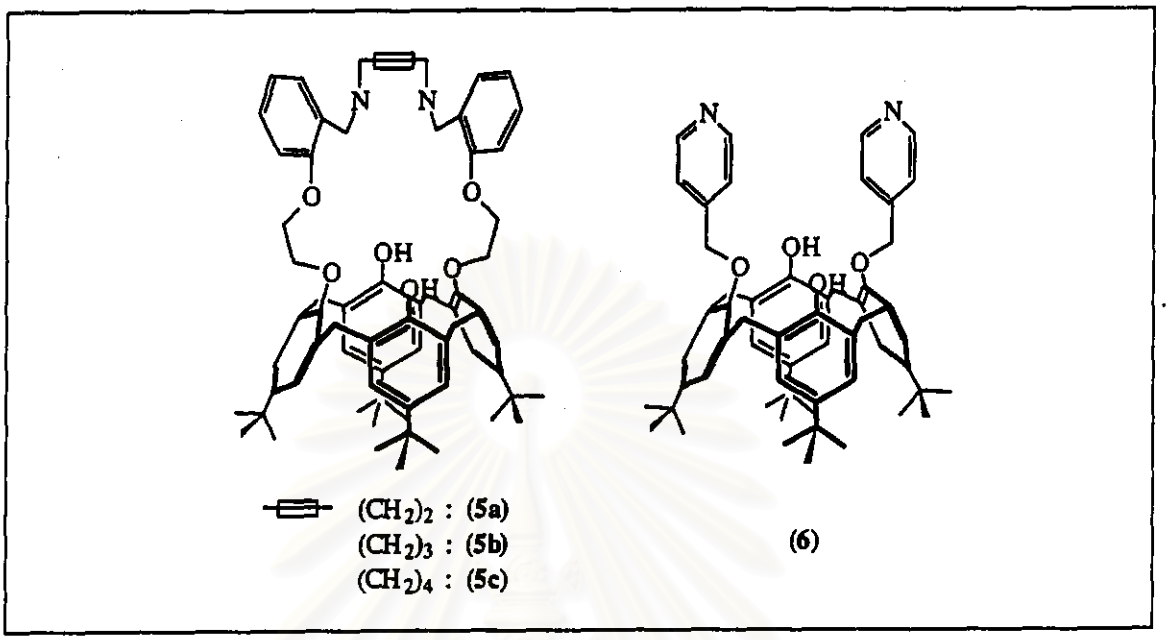


Figure 1.10. Receptor molecules used in this thesis.