# NOVEL MACROCYCLIC COMPOUNDS AS BUILDING BLOCKS IN SUPRAMOLECULAR CHEMISTRY

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By
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And herby certify that their opinion it is worthy of acceptance

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## LIST OF ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| 2-AP | 2-Aminopyrimidine |
| bpy | 2,2′-Bipyridyl |
| °C | Degree Celsius |
| d | Doublet |
| DMF | *N*,*N*′-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| δ | Chemical shift |
| K | Kelvin |
| NBS | *N*-Bromosuccinimide |
| NMP | 2-Methyl-1-pyrrolidinone or *N*-methylpyrrolidinone |
| ν | Wavenumber |
| ppm | Part per million |
| q | Quartet |
| s | Singlet |
| t | Triplet |
| THF | Tetrahydrofuran |
| THP | Tetrahydropyrimidine-2-one |

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## ABSTRACT

Resorcinarenes and pyrogallolarenes have been widely used as building blocks for novel synthetic receptors and supramolecular self-assemblies. To explore new chemistry of these compounds, new substituted macrocyclic arenes were synthesized. Introduction of functionalities such as nitro, cyano, and amido groups into the resorcin[4]arene molecule can significantly change the chemical properties of these macrocycles. The spectroscopic data and X-ray crystal structures of the new tetracyano resorcin[4]arenes show that these compounds adopt a crown conformation and that all alkyl substituents are in the axial position. No hydrogen-bonded self-assembly is observed suggesting that the presence of a cyano group inhibits the formation of the hydrogen bonds between the macrocycles. The complex of silver(I) ion and tetracyano resorcin[4]arene is a three-dimensional polymer in which the silver center is coordinated by three cyano groups of the macrocycle and possesses an unusual trigonal planar geometry. No new tetranitro and tetraamido resorcin[4]arenes were synthesized under the studied conditions.

Additionally, molecular hosts with a spacious inner cavity have also received a lot of interest because of their ability to encapsulate and stabilize several guest molecules. To obtain such valuable receptors, palladium-catalyzed Suzuki-Miyaura cross coupling and aldehyde-amine condensation are used as the synthetic pathways to functionalize calix[4]arenes and cavitands with a trimethoxyphenyl moiety. The Suzuki coupling attempts afford only mixtures of products and no pure desired macrocycles can be isolated. In a similar fashion, condensation reactions of tetraformyl- and tetraamino calix[4]arenes produce mixtures of imino calix[4]arene derivatives. The poor solubility of these calix[4]arenes could result in incompletion of the reactions.

Finally, a new calix[4]arene derivative possessing the versatile 2,4-diamino-1,3,5-triazine moieties has been prepared. Its ability to participate in a large hydrogen-bonded system and to serve as a potential ligand for transition metal complexes was examined by X-ray crystal structure analysis and $^{1}$H-NMR titration. The results from this study reveal that the new diamino-triazine calix[4]arene derivative has a poor solubility in most organic solvents except dimethylsulfoxide. No hydrogen-bonded network is detected for the hydrochloride salt of this new macrocycle. Very polar solvents such as dimethyl-sulfoxide probably disturb the formation of a hydrogen-bonded assembly, even in the presence of compatible barbituric acid. The complexation study of the new triazine calix[4]arene with zinc(II) trifluoromethanesulfonate also suggests that no complex is formed between the new calix[4]arene compound and a zinc ion.

# CHAPTER 1

# SUPRAMOLECULAR SELF-ASSEMBLY

## 1.1 Introduction to supramolecular chemistry

Supramolecular chemistry was established in late 1970, developed from the approach towards the understanding of chemistry found in many biological systems. Since biochemical systems normally comprise several large, complex biomolecules, the studies of these compounds are quite difficult. To simplify this problem, supramolecular chemists synthesize and investigate chemical systems which are less complicated but still similar to those biomolecules. Generally, the main theme of supramolecular chemistry is to study the intermolecular non-covalent bonds involved in many chemical systems, which are composed of the association of two or more chemical species.[1] Nevertheless, the term 'non-covalent bonds' must be used with great caution since chemists in the other research fields of study may use the different definitions with respect to chemical bonding. For example, metal-ligand interactions could be considered covalent (for inorganic chemists) or non-covalent bonds (for supramolecular chemists) depending on the perspective of an interpreter.

The simplest concept in supramolecular chemistry, in the sense of binding or complexation, could be host-guest chemistry. In this context, a host is generally defined as an entity that binds to another species by non-covalent interactions. A guest is smaller than a host in size.[2,3] It can be a cation, an anion, or a sophisticated molecule such as an enzyme substrate or a drug. The result of the binding between a host and a guest leads to

a complex. In supramolecular chemistry perspective, Cram[4,5] gave the definition of a complex as follows:

*Complexes are defined as two or more compounds bound to one another in a definable structural relationship by forces such as hydrogen bonding, ion-paring, metal-to-ligand attractions, π-acid-to-π-base attractions, van der Waals attractions, and the entropic component of desolvation*.

To understand the function and complexity of any supramolecular system, it is necessary to comprehend the non-covalent interactions used in the formation of a host-guest complex in detail.

## 1.2 Types of intermolecular interactions

As described in section 1.1, non-covalent interactions are essential tools for supramolecular architecture. These are composed of various forces, either attractive or repulsive.[6] A brief account of each interaction, as well as its approximate bond energy, are discussed below.

### 1.2.1 Ion-ion interactions

This type of interaction occurs between cationic and anionic species. The bond energies of ion-ion interactions are relatively as strong as those of covalent bonds (100-350 kJ $mol^{-1}$).[6] However, regarding the nature of this intermolecular force, it sometimes can be classified as an ionic bond like in most ionic compounds such as sodium chloride. Therefore, from the supramolecular perspective, each sodium ion in NaCl shows the ability to attract and organize 6 donor entities (chloride ions), resulting in the maximum overall interaction in the solid phase.

### 1.2.2 Ion-dipole interactions

The majority of instances of this force can be found between charged species and polar molecules. It has relatively high bond energy (50-200 kJ $mol^{-1}$). This also includes coordinative bonds, which are ordinarily electrostatic in the case of interactions between hard donor atoms and small, non-polarizable cations.[6,7] A good example is the attraction towards alkali metal ions of crown ether macrocyclic compounds (e.g. $Na^+$ ion bonded to 18-crown-6, Figure 1.1a). The oxygen lone pair electrons of the crown ether are drawn towards the positive charge of the $Na^+$ ion. In some cases, such as in the $[Ru(bpy)_3]^{2+}$ complex (Figure 1.1b), the bond between the ruthenium(II) ion and nitrogen atoms of bipyridyl has significant covalent character and is regarded as a dative bond. This is because the $Ru^{2+}$ ion can use available d-electrons to participate in the bonding, based on molecular orbital theory.

### 1.2.3 Dipole-dipole interactions

Polar molecules possess partial positive and negative charges, which are named the poles. Molecules such as carbonyl compounds align their poles in the fashion that result in a very weak intermolecular interaction (5-50 kJ $mol^{-1}$).[6] The arrangement of molecules can be either a pair of the opposite poles on adjacent molecules (Figure 1.1c) or the opposing parallel of one dipole with the other (Figure 1.1d). If a polar molecule interacts with a non-polar but polarizable molecule, the dipole of the polar molecule perturbs the electron density of the adjacent non-polar molecule. This produces a very tiny dipole moment that lasts just only an instant. Thus, this force is called dipole-induced dipole interaction.[7]

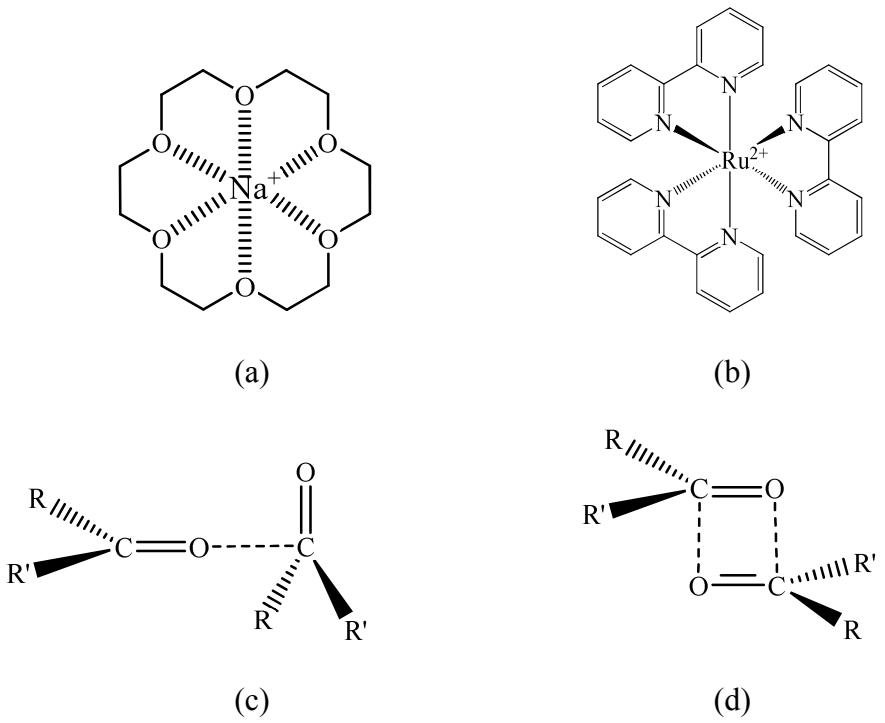



**Figure 1.1** Types of intermolecular forces: (a) & (b) ion dipole interaction; (c) & (d) dipole-dipole interaction.

### 1.2.4 van der Waals interactions

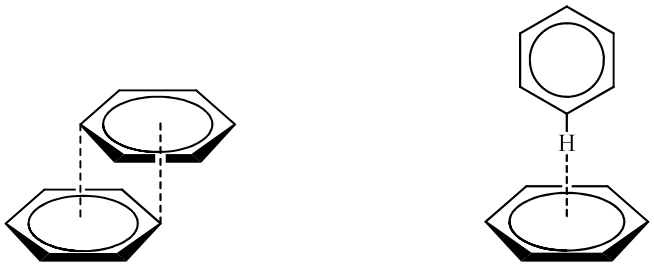
The origin of this force comes from the polarization of an electron cloud of a non-polar molecule, influenced by the presence of the adjacent molecules in proximity.[7] This usually occurs at distances larger than the summation of their electron clouds. Relatively weak (the bond energy depends on the overall structure), van der Waals interactions are typically non-directional and their effects are collective. Thus, their total contribution to the complex stability could be crucial.

One type of van der Waals interaction is called a dispersion force (or London force). It arises from the fluctuation of the electron density within the electron cloud of molecules.[6] The strength of dispersion forces varies with $r^{-6}$ (where $r$ = intranuclear distance) and is relatively small in the term of magnitude. Dispersion forces play an

important role in the attraction between long chain alkanes that can be observed as the increase of the boiling points when the chain of hydrocarbons is longer.

### 1.2.5 π-π Stacking

Interactions between π-systems (0-50 kJ $mol^{-1}$) have been observed in numerous aromatic compounds, by X-ray crystal structure determination. There are two basic types of π-π interactions: face-to-face and edge-to-face (Figure 1.2a, and Figure 1.2b). The former is the major factor in the stabilization of the DNA double helix structure,[8] whereas the latter is normally found between the slightly electron deficient hydrogen atom of one aromatic ring and the rich π-electrons of another ring.




(a) (b)

**Figure 1.2** Types of π-π interaction (a) face-to-face π-π stacking; (b) edge-to-face π-π stacking.

Sanders and Hunter[9] carefully proposed a simple yet successful model, which is based upon electrostatic and van der Waals forces, to explain the features of π-π interactions. The main concept of this approach is to consider the σ-framework and the π-electrons separately. It suggests that the overall π-π interactions do not stem from the

attractive electronic interaction but rather occur when the interaction between the π-electrons and the σ-framework overcomes the π-π repulsion. Moreover, this model can explain that the σ-π interactions also control the overall geometry of the interaction as being observed in both face-to-face and edge-to-face fashions.

### 1.2.6 Hydrogen bonding

Hydrogen bonds are arguably the most utilized non-covalent interactions within supramolecular systems. Originally used as a term to describe the internal structure of water,[10] it is necessary to state that the definition of hydrogen bond has been subject to change, based upon several criteria such as geometry, energy, and function.

According to Pimentel and McClellan,[11] the definition of a hydrogen bond is as follows:

> *A hydrogen bond exists between a functional group A-H and an atom or a group of atoms B in the same or a different molecule when:*
> *(a) there is evidence of bond formation (association or chelation)*
> *(b) there is evidence that this new bond linking A-H and B specifically involves the hydrogen atom already bonded to A.*

A-H is called a hydrogen bond donor whereas B is regarded as a hydrogen bond acceptor. Generally, both A and B possess greater electronegative character than the hydrogen atom and the proton involved in the hydrogen bond is shared between the electron pairs on A and B.[12] The most common hydrogen bond donors are C-H, N-H, O-H, S-H, P-H, and halogen-H while acceptors are the conjugate bases of those moieties, as well as π-systems, and in some cases, low-valent transition metal ions.[13]

The evidence of hydrogen bond existence is extremely significant for most supramolecular chemists. Various techniques are employed to investigate and study

hydrogen bonds,[14] including IR and NMR spectroscopy, mass spectrometry, X-ray diffraction, and neutron diffraction. Additionally, the thermodynamic stabilities and strength of hydrogen-bonded systems in solution are greatly affected by the nature of solvents. Any solvent which can participate in any hydrogen bonding will decrease the overall stability of a particular hydrogen-bonded system significantly.

Hydrogen bonds vary in the vast range of geometry, bond length and bond strength. However, based on the properties mentioned above, one can categorize hydrogen bonds into three different types: strong, moderate, and weak.[15] General parameters of those hydrogen bonds are given in Table 1.1.

**Table 1.1** General properties of hydrogen bonds.[15]

| | Strong | Moderate | Weak |
|---|---|---|---|
| A-H· · ·B interaction | Partially covalent | Mainly electrostatic | Electrostatic |
| Bond energy (kJ $mol^{-1}$) | 60-120 | 16-60 | <12 |
| Bond lengths (Å)<br>H· · · B<br>A · · · B | <br>1.2-1.5<br>2.2-2.5 | <br>1.5-2.2<br>2.5-3.2 | <br>2.2-3.2<br>3.2-4.0 |
| Bond angles (°) | 175-180 | 130-180 | 90-150 |
| Examples | HF complexes<br>Gas phase dimers of strong acids-bases | Acids<br>Alcohols<br>N-H···O<br>O-H···N | C-H···π<br>O-H···π<br>N-H···π |

### 1.2.7 Hydrophobic effect

This type of interaction can be observed in several systems in which the large, non-polar parts of host and guest molecules bind together and exclude the polar media, normally in aqueous or other protic solvents.[16] The hydrophobic effect is the major reason for the immiscibility of water and oil. Similar to hydrogen bonding, this non-covalent interaction is very dependent on the solvent properties. Decrease of the solvent polarity results in a weakening of hydrophobic binding, as the solvent molecules surround and interact with the non-polar region of the host-guest complex. Nevertheless, the effect of the hydrophobic effect is relatively weak. Other contributions in the overall interactions between those organic molecules are also from van der Waals and π-π stacking.

## 1.3 Building blocks: Fundamental components of construction

The early development of the supramolecular field relied heavily on the host-guest chemistry concept. In this context, various macrocyclic compounds such as crown ethers, cryptands, and spherands – synthesized and thoroughly studied by Pederson, Lehn, and Cram, respectively – are employed as hosts for positively charged, and neutral guests.[17] Later, numerous macrocycles, such as calixarenes, carcerands and other container molecules, were prepared and utilized as molecular receptors which can bind a large variety of guests, different in geometry, size and charge.

What follows in this section briefly describes examples of important macrocyclic compounds as building blocks in supramolecular systems. Moreover, some molecules show the potential to be used in much more sophisticated systems like self-assembly and molecular devices.

### 1.3.1 Crown ethers, cryptands, and spherands

The basic constructive entity for a supermolecule is a molecular receptor – an organic structure held by covalent bonds that exhibit the ability to selectively bind an ionic or molecular substrate by various intermolecular interactions.[18] The earliest synthetic receptors are undoubtedly crown ethers such as dibenzo-18-crown-6 (Figure 1.3a), accidentally discovered by C. J. Pederson. Most crown ethers have the ability to attract positively charged species such as alkali metal ions and alkyl ammonium ions. The main interactions towards those mentioned guests are ion-dipole and hydrogen bonds.[19,20]

To increase the binding ability of molecular hosts, Lehn designed three-dimensional macrocyclic polyethers called cryptands (e.g. [2.2.2]-cryptand, Figure 1.3b) to serve as sodium or potassium transporting agents.[21-23] Additionally, the replacement of oxygen donors by nitrogen atoms in the cryptands leads to new spherical receptors that can even bind negatively charged species after being protonated.[24]

Host-guest complexes of crown ethers and cryptands are relatively more stable than those of acyclic receptors; this phenomenon is referred to as the macrocyclic effect.[6,17] This effect is entropically favorable since when macrocyclic ligands bind to a guest, solvent molecules are expelled to the environment resulting in the increase of the entropy of reaction. Structures of cyclic compounds are less flexible and therefore lose fewer degrees of freedom upon complexation. In addition, in some cases, not only entropic factor but also enthalpic effect plays an important role in the net stability of host-guest binding.

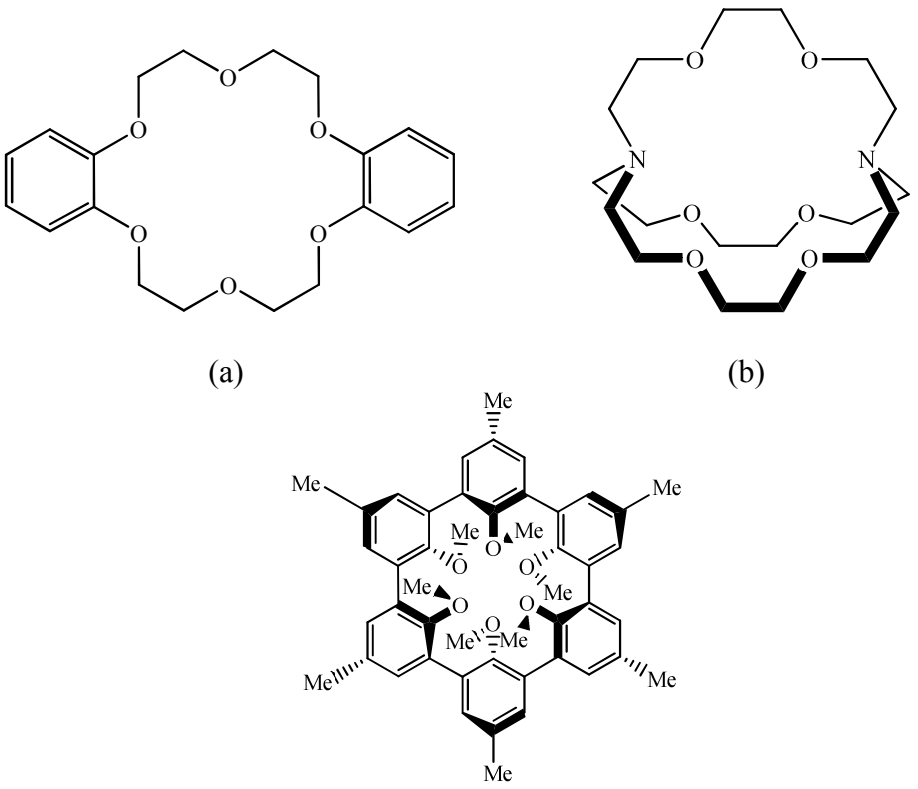



**Figure 1.3** (a) Dibenzo-18-crown-6; (b) [2.2.2]-cryptand; (c) spherand **1.1**

Donald J. Cram designed the new macrocycles that he termed as spherands (e.g. a molecule depicted in Figure 1.3c), a type of host molecules that were synthetically preorganized for guest binding.[25] Spherands have rigid intracavities which are less flexible than those of crown ethers or cryptands. Therefore, they can bind substrates selectively, for example spherand **1.1** interacts with $Li^+$ and $Na^+$ ions but not other alkali metal ions. This excellent accomplishment was the breakthrough to the concept of preorganization of molecular receptors.[26]

### 1.3.2 Calixarenes: Versatile building blocks

In the 1940s, Zinke and Ziegler discovered the novel cyclic tetramer from the base-catalyzed condensation reaction of *para*-substituted phenols with formaldehyde.[27,28] However, the certain structures of those compounds were not determined. Laters, Cornforth and coworkers[29] indicated that the products from Zinke's research were actually mixtures of various oligomers. It was not until mid 1970s that Gutsche. *et al*. extensively studied and characterized three of the components of the mixture as a tetramer, a hexamer, and an octamer.[30-32] Gutsche provided the nomenclature of this group of macrocycles as calix[*n*]arenes (based from the word *Calyx* in greek, which means a vase) whereas the *n* in the square bracket refers to the number of phenolic units within the structure. Some of the known calixarenes are depicted in Figure 1.4.

Calixarenes are categorized as $[1]_n$-metacyclophanes in which each phenolic unit is connected by the methylene bridge ($-CH_2-$) at the meta position.[33,34] The subscript n is the number of methylene bridges. In the past 30 years since their discovery, calixarenes have become one of the most utilized macrocycles in supramolecular chemistry. The functionalizations of their hydroxy groups and aromatic regions produce numerous molecular receptors for a vast variety of guests.[35] Further discussions regarding calixarenes and their chemistry are presented in Chapter 3.

Additionally, calixarenes themselves exhibit the ability to interact with other compounds without any further functionalization. Atwood and coworkers[36] found that *p-tert*-butylcalix[8]arene (Figure 1.4d) has the ability to bind $C_{60}$ specifically, leading to the possible separation of $C_{60}$ from fullerite. Further studies also showed that *p-tert*-butylcalix[8]arene can bind not only $C_{60}$ but also $C_{70}$.[37,38] Soon after that, crystalline

*p-tert*-butylcalix[4]arene (Figure 1.4a) was recognized as the compound for methane and freon gas storage. The bilayer arrangement of *p-tert*-butylcalix[4]arenes contain lattice voids of large size (approximately 235 $Å^3$). Volatile gases are stabilized in this void by mainly van der Waals interactions.[39,40]

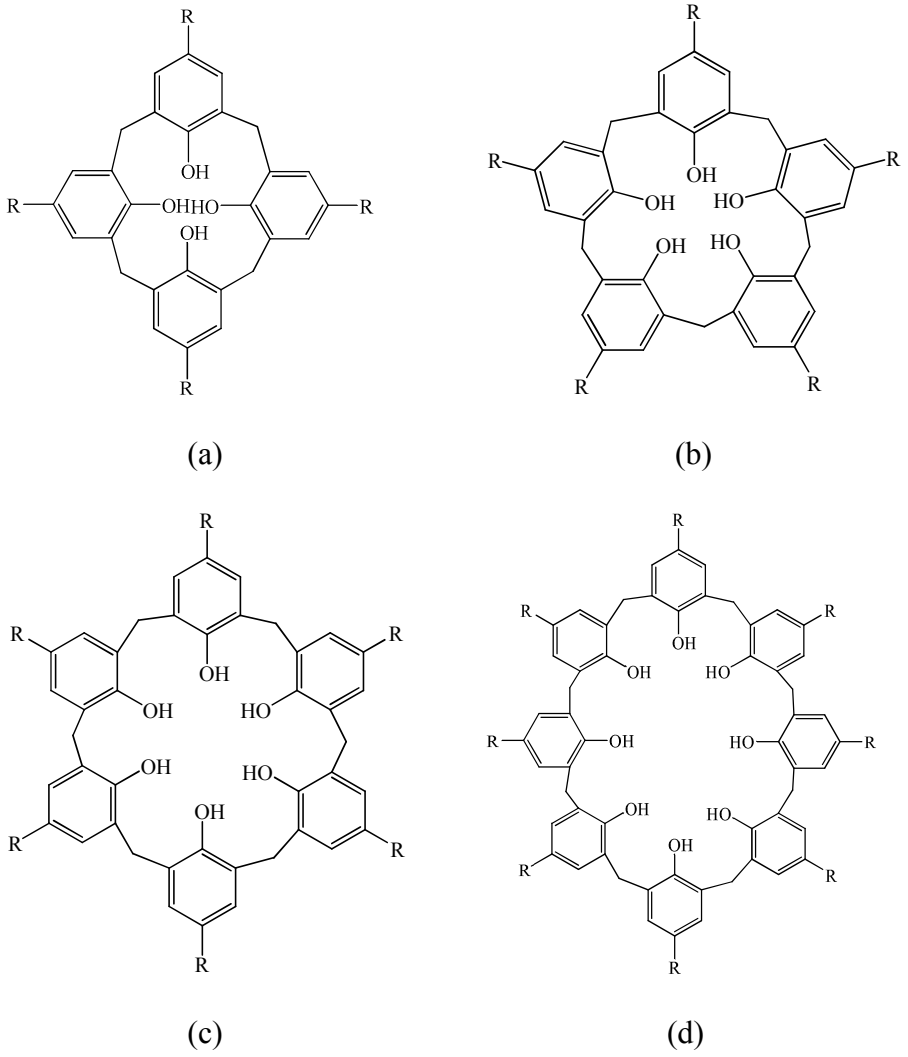



**Figure 1.4** Examples of the calixarene family: (a) calix[4]arene, (b) calix[5]arene, (c) calix[6]arene, and (d) calix[8]arene. R represents any functional group. For example, if R = *tert*-butyl, the calixarene is named *p-tert*-butyl calix[4]arene.

### 1.3.3 Cavitands: The molecular containers

Cavitands are defined as host molecules containing an intrinsic cavity that is present in both the solid state and in solution.[41,42] The cavity is normally accessible at one end of the molecule, allowing the inclusion of a guest molecule into the void. This intrinsically concave surface is present in both the solid state and in solution. Therefore, cavitands are considered as molecular containers, possessing the abilities to bind guest molecules, especially neutral, non-polar organic compounds.

In 1980, Högburg investigated the acid-catalyzed condensation reaction between resorcinol (1,3-dihydroxybenzene) and acetaldehyde , resulting in the cyclic tetramer called resorcin[4]arene.[43] Furthermore, the specific conditions that yield both cone ($C_{4v}$) and chair ($C_{2v}$) conformers (Figure **1.5a** and **b**, respectively).[44,45] were also elucidated. Several different aldehydes can be used in the syntheses of resorcin[4]arenes but not formaldehyde because it produces no cyclic tetramer.

Cram designed new rigid, bowl-shaped molecules derived from resorcin[4]arenes by bridging the hydroxy groups with linkages to form cavitands (linkage X = $CH_3$, $CH_2CH_2$, $CH_2CH_2CH_2$, $Si(CH_3)_2$, *etc*. see Figure 1.5c).[46] The formation of covalent bridges between hydroxy groups significantly reduces conformational flexibility of a molecule, producing a preorganized enforced cavity within a cavitand.[47] Cavitands show the ability to bind small neutral molecules. For example, cavitand **1.2** (with the $Si(CH_3)_2$ bridges) binds carbon disulfide in chloroform at 250 K with the association constant of 0.82 $M^{-1}$.[41,48] Cavitand **1.3** has a vase-shaped cavity and selectively binds fluorobenzene in acetone at 293K with the high binding constant ($K$ = 2300 $M^{-1}$).[49,50]

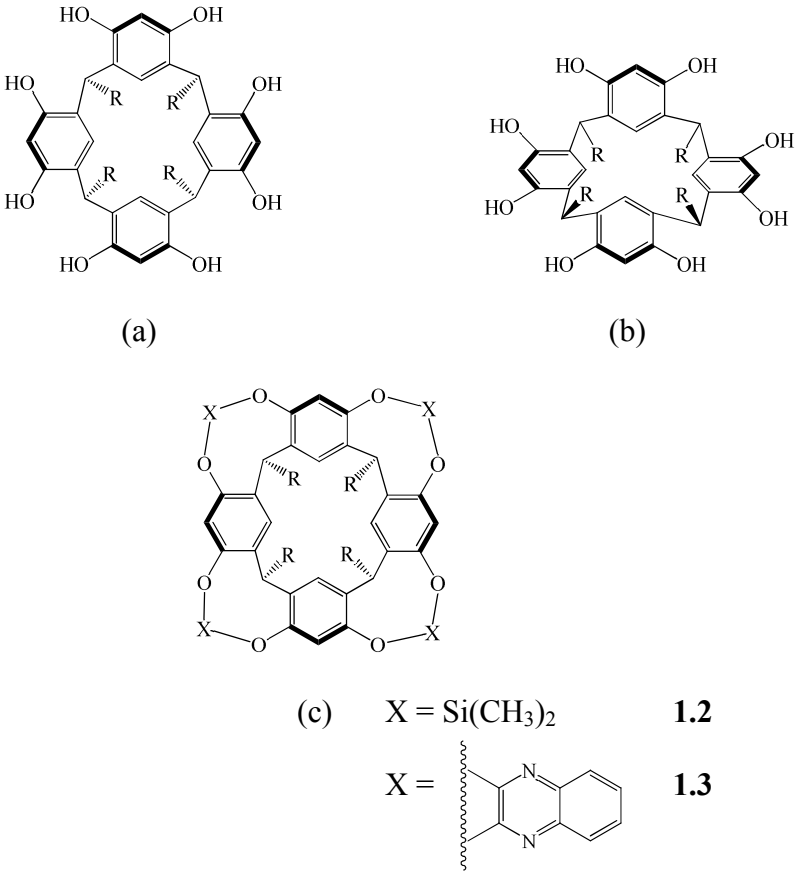


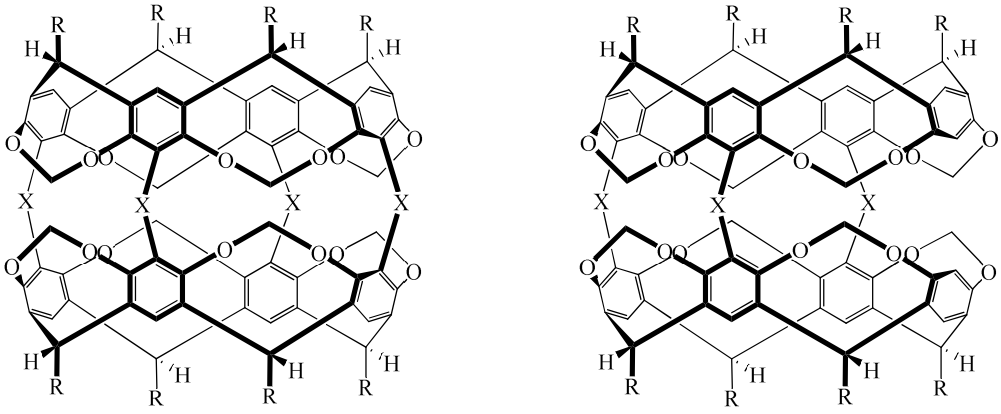

**Figure 1.5** Structure of resorcin[4]arene (a) cone or $C_{4v}$ conformer (b) boat or $C_{2v}$ conformer, and (c) general structure of cavitands, **1.2** and **1.3**. Here R = alkyl or aryl group.

### 1.3.4 Carcerands and other larger molecular containers

Cram and coworkers constructed dimeric three-dimensional host molecules by connecting two cavitands together *via* covalent bonds.[51-53] These new spheroid compounds can be classified into two different groups: carcerands and hemicarcerands.[54] A carcerand is described as a closed, well-defined molecular container that permanently traps the guest species within the internal volume. There is no guest exchange unless the covalent bonds in the carcerand structure are broken. Thus, carcerands themselves are not

adoptable to many applications except the possible usage in the field of molecular devices.

On the other hand, a hemicarcerand is defined as a closed molecule which allows the guest to enter or exit through asufficiently large entrance.[55,56] The guest exchange can be achieved without any covalent bond forming or breaking. Therefore, hemicarcerands are potential candidates for reactive species stabilization, drug delivery and catalysis because these applications require the ability to bind and release guest species in response to certain conditions. Examples of a carcerand and a hemicarcerand are shown in Figure 1.6.



(a) (b)

**Figure 1.6** General structures of (a) a carcerand, and (b) a hemicarcerand. X = any linkage group.

Hemicarcerands have relatively small cavities which accommodate just some organic guests such as solvent molecules.[42,57,58] To increase the intracavity space of the molecular container, Sherburn and coworkers[59] synthesized a container molecule with an internal cavity size of ca 1050 $Å^3$. This compound is composed of five cavitands

connected to one another by eight covalent bonds. Later, Sherburn[60] prepared a large molecular container that consists of six cavitands and can include seven guest molecules. Typically, the overall yields of those compounds are relatively low. This disadvantage stems from the multiple steps required to bond the cavitand molecules together. To avoid this problem, Warmuth *et al*.[61,62] demonstrated the one-step synthetic route for a new molecular container **1.4** from six formyl cavitands and 12 diamino linkages, resulting in the larger system held by 24 imino bonds with quantitative yield.

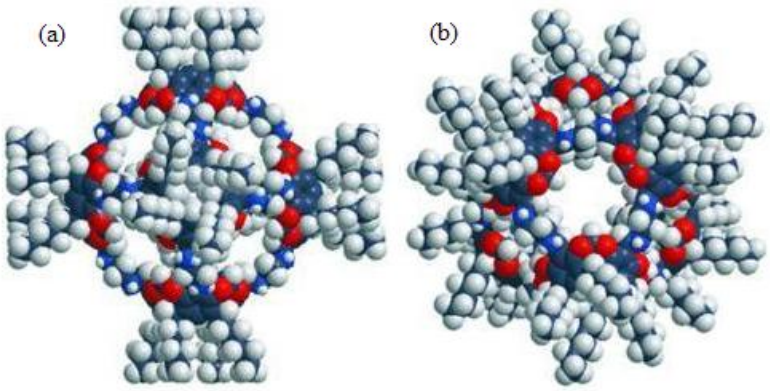



**Figure 1 7** The structure of molecular container **1.4** (a) view along $C_4$ axis, and (b) view along $C_3$ axis. Note for atoms and their colors: carbon-grey, hydrogen-white, nitrogen-blue, and oxygen-red.[61]

## 1.4 Self-assembly and design of supramolecular systems

### 1.4.1 General perspectives

Lehn defined self-assembly in supramolecular systems as the process involving the spontaneous association of either a few or many molecular components affording the formation of either discrete supramolecules or extended assemblies.[17] The formation of those superstructures is under the control of intermolecular interactions that connect them

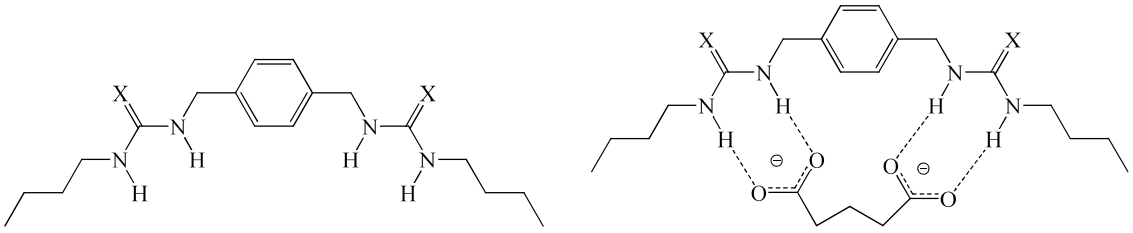
together in concert. A distinctive character of supramolecular assemblies is that the association of molecular species is typically reversible.[45] Thus, certainly, the results of self-assembly are thermodynamically stable. The components in such systems could undergo the "self-correction" sequence[63] which involves non-covalent bond breaking and bond forming until the most thermodynamically stable entity is obtained. This process is not normally observed for most covalently-bonded counterparts. Additionally, molecular assembly is a self-organizing process in which only specific components come together and result in a distinctive chemical entity. This progression is similar to the formation of DNA double helix in which only A-T and G-C base pairs are observed (purines form hydrogen bonds to pyrimidines). The important information encoded in the individual self-aggregation can be transferred and stored like genetic codes in DNA.[64]

With the concept of self-assembly, chemists can employ a strategy similar to that in biochemical systems, to construct larger, more complex, artificial structures without extensive utilization of organic synthesis.[65] The complicated connections by covalent bonds can be replaced by the efficient design of initial components and their self-assemblies. Moreover, Linsey[66] suggested that a self-assembly process involving intermolecular forces followed by covalent bond formation would be a very effective strategy to synthesize covalently-bonded superstructures.

### 1.4.2 Simple hydrogen-bond-directed self-assemblies

This section describes noncovalent self-assemblies that are formed by hydrogen bonding complementarity between a few components. This concept is apparently inspired by the nature of the DNA double helix structure. Intermolecular hydrogen bonds between

base pairs play an important role in the stabilization and genetic information storage of DNA. The simplest system for this type of self-assembly is the host-guest complexes between compounds **1.5a-b** (Figure 1.8) and glutamic acid, reported by Hamilton *et al*.[67] The complexes (Figure 1.8) are stable even in polar solvents like dimethyl sulfoxide. The urea and thiourea functional groups of compound **1.5** act as the hydrogen-bond donors whereas the dicarboxylate anion works as the hydrogen-bond acceptors.



(a) Compound **1.5a**: X = O
**1.5b**: X = S

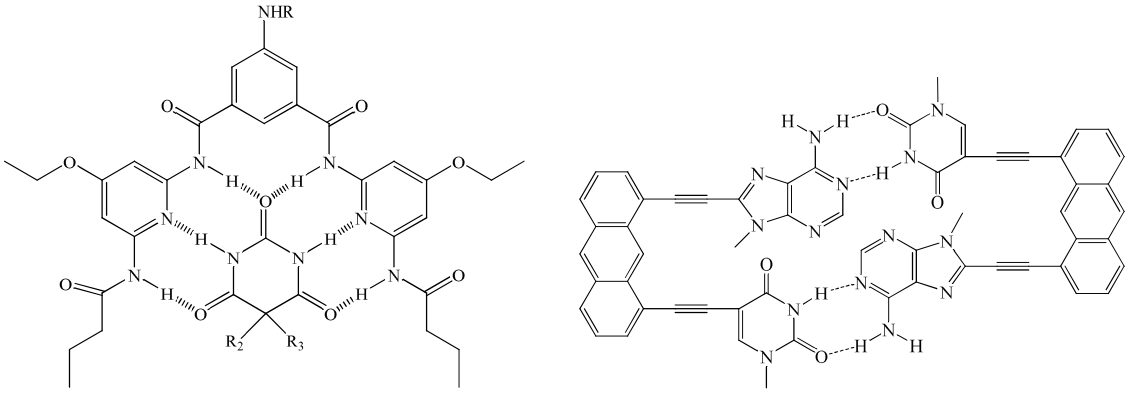
(b)

**Figure 1.8** (a) Compounds **1.5a** and **1.5b**, (b) the complexes between ligand **1.5** and glutamic acid

Hamilton and coworkers[68] designed the host molecule incorporating 2,6-pyridine-diamine groups for various barbiturate derivatives. (compound **1.6**, Figure 1.9a). The ligand possesses the functional groups that are complementary with the three carbonyl acceptors and two NH donors in a barbiturate guest. The resulting complex is held together by six intermolecular hydrogen bonds.

Some synthetic modules employed the base pair concept to demonstrate hydrogen-bonded self complimentarity. Sessler and coworkers[69] developed the artificial dinucleotide complex **1.7** (Figure 1.9b) which contains adenine and uracil base pairs. According to the results from $^{1}$H-NMR spectroscopy, the model shows a very high

stability constant compared to that of the monomeric base pair. Moreover, the diethynylanthracene linkage was also found to likely improve the overall stability of the complex. The subsequent work that utilized more flexible spacers suggested no increase in the dimeric complex stability.[70]

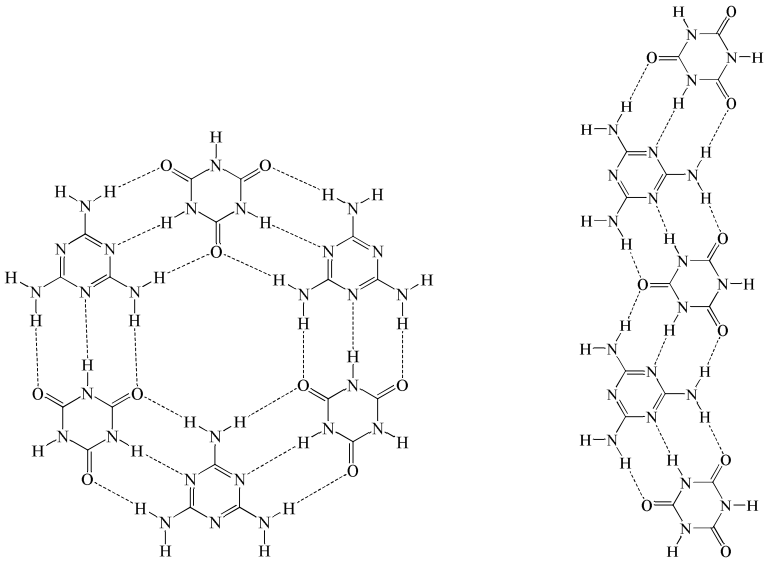


(a) (b)

**Figure 1.9** (a) Hydrogen-bonded complex **1.6**, (b) Dimeric complex **1.7**

### 1.4.3 Isocyanuric acid-melamine assemblies

Whitesides demonstrated the formation of large self aggregates by using the pair of disc-like compounds: melamine and isocyanuric acid.[71] Both molecules are rigid and possess complementary hydrogen bonding arrays. Isocyanuric acid has three orthogonal acceptor-donor-acceptor (abbreviated as ADA) groups, whereas melamine contains the donor-acceptor-donor (abbreviated as DAD) arrays. The X-ray crystal structure revealed that the ratio between melamine and isocyanuric acid is 1:1. Nonetheless, more remarkably, there are two major substructures[72]: finite hydrogen-bonded rings or "rosettes" (Figure 1.10a) and infinite hydrogen-bonded one dimensional chain or "tape" (Figure 1.10b).



(a) (b)

**Figure 1.10** The two structures of melamine-isocyanuric acid assembly: (a) ring or rosette, (b) linear chain or tape.

Later, the research groups of Whitesides[73] and Lehn[74] also found that blocking one of the hydrogen-bonding arrays of both components results in either one of the substructures. However, the linear, one dimensional structure of tapes is less useful for the synthesis of any nanostructure because of its lack of definite shape and size. On the other hand, the rosette structure has no such disadvantages, and consequently has been investigated extensively. To promote the formation of rosettes, covalent bonds were used to preorganize the melamine and cyanurate units. This strategy also results in the higher thermodynamic stability of the assembly. For example, compound **1.8** is the covalent preorganization of the melamine units by $C_3$-symmetrical spacer. After the addition of hexylcyanuric acid, the formation of a capsule-like assembly was observed with the 3:1 ratio of cyanuric acid to the ligand (Figure 1.11).

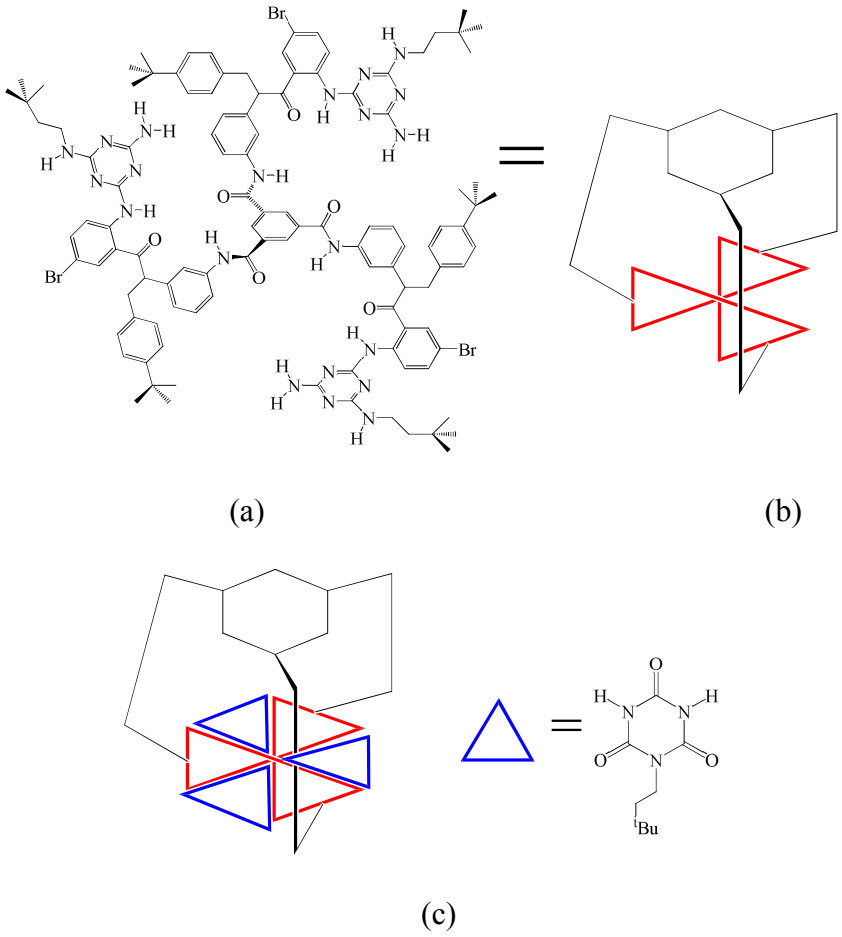


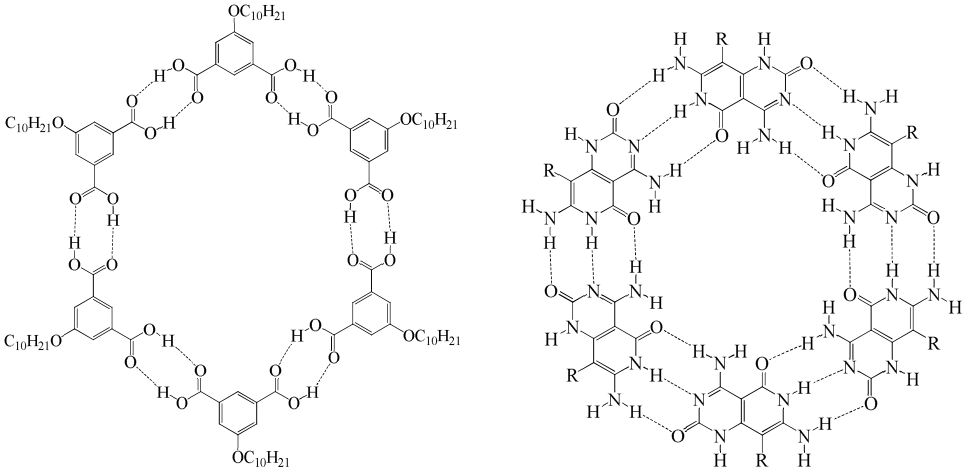

**Figure 1.11** (a) compound **1.8**, (b) cartoon representation of compound **1.8**, (c) cartoon representation of the self-assembly of compound 1.8 with hexyl cyanuric acid.

### 1.4.4 Cyclic hydrogen-bonded assemblies

Cyclophanes have been widely used in inclusion chemistry to bind a wide variety of guest types. Syntheses of those cyclophanes require covalent bonds to construct such molecules. With the similar aspect, hydrogen bonded self-assembly can be employed to produce cyclophane-like entities.

In 1994, Hamilton and coworkers[75] reported the assembly of 5-substituted isophthalic acid derivative. The self aggregate **1.9** is a cyclic hexameric structure, stabilized by 12 hydrogen bonds of carboxylic acids. The approximate diameter of the

cyclic hexamer is *ca* 14 Å. In the similar manner, Turkenburg and coworkers also prepared cyclic hexamer **1.10**.[76] The product was even formed in the polar solvent like dimethyl sulfoxide. The formation of hydrogen-bonded assembly incorporates the donor-acceptor array of cytosine and the complementary sequence of the guanine moiety.



(a) (b)

**Figure 1 12** The structures of cyclic hexamers (a) structure **1.9**, (b) structure **1.10.**

## 1.5 Spheroidal self-assemblies by hydrogen bonding

Besides the great discovery of carcerands and hemicarcerands by Cram in late 90s, most chemists are still impressed with the formation of closed-surface compounds. Therefore, the development of new molecular containers is constantly under extensive progress. Although carcerands and hemicarcerands can encapsulate guest species within their internal cavities, the uses of them are somewhat at the limit.[77] As mentioned in Section 1.3.4, carcerands permanently trap guest molecules without any exchange unless the covalent bonds are destroyed. Moreover, the synthesis of the desired product requires

a lot of effort and poses limits to the synthetic achievement.[78] The lack of symmetry in the hemicarcerand structures also establishes the crucial challenge of their syntheses.

On the contrary, hydrogen bonds are relatively weak when compared to covalent bonds yet robust and directional.[79] Formation and cleavage of hydrogen bonds are reversible and can be manipulated by changing the environmental conditions. Therefore, the utilization of hydrogen-bonded self-directing systems provides the intriguing, new approach for the increasing demands of molecular containers.

### 1.5.1 Glycouril-based molecular capsules

Julius Rebek Jr. *et al*. [80]were successful in constructing new hydrogen-bonded structures containing significant internal cavities. Compound **1.11** (Figure 1.13), possessing the glycoluril subunits, exhibits the dimeric self-assembly with a spherical shape in both non-polar and moderately polar solvents. The X-ray crystal structure showed that two identical subunits aggregated in the fashion resembling a tennis ball (Figure 1.14). Thus, Rebek adopted the term "tennis ball" to characterize this particular structure.

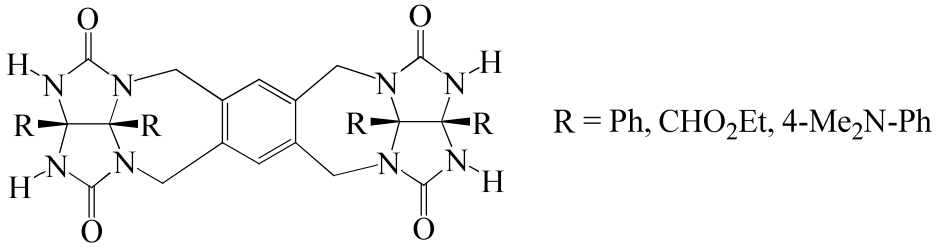



**Figure 1.13** The bisglycoluril derivatives **1.11** employed in the self-assembly of the tennis ball structures.

The tennis ball structure is stabilized by eight hydrogen bonds (N-H···O) and has an internal cavity volume of approximately 60 Å$^3$. The subsequent studies revealed that small guest molecules such as xenon, methane, and ethylene can be encapsulated within the void according to the $^1$H-NMR results.[81]

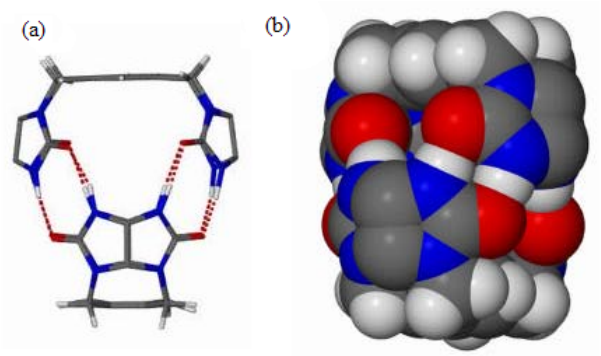
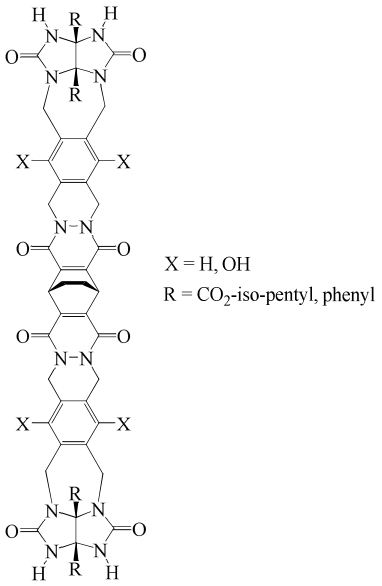



**Figure 1.14** (a) X-ray crystal structure of the tennis ball, showing only the core structure of a bisglycoluril monomer and its dimerization. (b) space filling representation of the tennis ball. Other substitutents are omitted for clarity.

To improve the intracavity size of the tennis ball structure, Rebek and coworkers extended the length of the spacer between two glycoluril subunits.[82] Self-complementary formation of compound **1.12** (Figure 1.15a) resulted in the dimeric capsule-like structure (Figure 1.15b) named the "soft ball". The approximate void of this assembly is in the range of 240 to 320 Å$^3$. The system is stabilized by multiple hydrogen bonds (N-H···O) akin to those of the analogous tennis ball. Rebek suggested that the internal void within the new capsular assembly is adequate enough to accommodate two guest molecules.[83,84] Under further investigation, benzene, *p*-quinone, and 1-adamantanecarboxylic acid were found to be encapsulated by the enlarged glycoluril-based compounds.



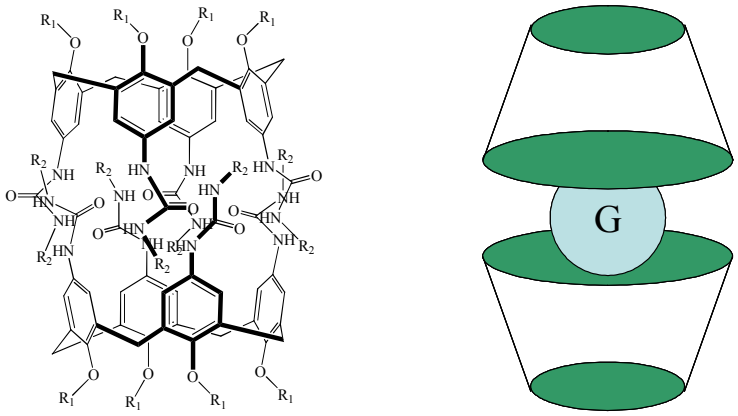

(a) (b)

**Figure 1.15** (a) The structure of extended bisglycoluril monomer **1.12**, (b) the presentation of the dimeric capsule composed of the subunit **1.12**.[85] R groups are omitted for clarity.

Interestingly, the soft ball dimeric self-assembly was found to accelerate the rates of Diels-Alder reactions.[86] The encapsulated adduct was observed by NMR spectroscopy within one day, whereas the half-life for the reaction under the given conditions is on the order of a year. Therefore, the resultant capsules were considered as eminent catalytic reaction chambers for various chemical reactions. However, this system is affected by apparent product inhibition, so the turnover could not be observed.[87] Moreover, the size of the guest molecule still poses the major obstacle. In accordance with the $^{1}$H-NMR study of the soft ball assembly, many large dienophiles were incapable of binding within the capsule, resulting in no observation of the adduct.[88]

### 1.5.2 Calixarene-based hydrogen-bonded capsules

Rebek *et al* introduced the tetraurea calix[4]arenes as the building blocks for hydrogen bonding, self-complementary products.[89] The dimeric structures are held together by 16 intramolecular hydrogen bonds in a head-to-tail topology (Figure 1.16). Carbonyl oxygen serves as the hydrogen bond acceptor for both N-H hydrogen atoms of a urea functional group.[89,90] The capsules existed in moderately polar solvents such as chloroform and toluene but not in solvents that can perturb the formation of hydrogen bonds (e.g. DMF, DMSO). The internal cavity of those assemblies is sufficiently large to accommodate various solvent molecules. The discrete capsule shows high affinity towards fluorobenzene, pyrazine, p-difluorobenzene but interacts weakly with phenol or aniline.[91] Interestingly, upon binding guest molecules such as (1R)-(+)-nopinone,[92] (1R)-(+)-camphor,[92] or dipentacyclodione,[93] the assemblies become chiral systems, characterized by $^1$H-NMR and NOESY techniques.

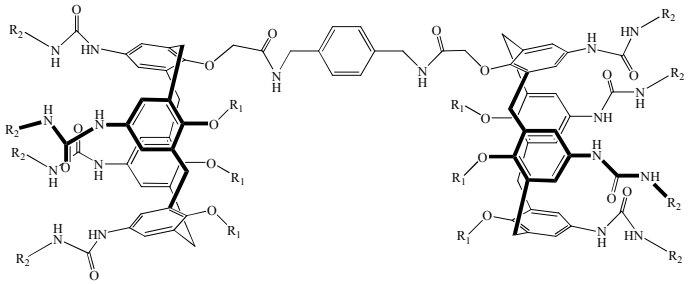



(a) (b)

**Figure 1.16** (a) general dimeric structure of tetraurea calix[4]arene **1.13**; $R_1$ = alkyl or other functional group, $R_2$ = alkyl or aryl group, (b) schematic depiction of dimeric capsule with the guest molecule encapsulated between two calixarene molecules.

When $R_1$ in the structure **1.13** is $CH_2C(O)$-$NH(CH_2)_7CH_3$, the amido groups at the lower rim of calix[4]arene can also form four intramolecular hydrogen bonds.[94] However, the carbonyl groups of acetamido and urea units are oriented in the opposite direction, making the chiral capsule. This behavior was confirmed by the existence of two enantiomers in the X-ray crystal structure determination.[95]

The hydrogen-bonded assembly of tetraurea calix[4]arene can be extended to the polymeric form. In 1997, Rebek and coworkers[96] connected two tetraurea calix[4]arenes with diamide linkage to afford compound **1.14**. The self-complementarity of compound **1.14** resulted in a chain-like polymer with the dimeric calix[4]arene capsules reminiscent of beads on the string (Figure 1.17). For the encapsulation studies, *p*-difluoro-benzene was employed to compete with $CDCl_3$ solvent. Increasing the concentration of *p*-difluorobenzene caused the downfield shift of the amide-NH protons of the spacer. The deduction of the $^1$H-NMR studies suggested that the *para* subsitituents are perpendicularly aligned at the urea region while the ortho and meta hydrogens face the aromatic rings of calix[4]arene



**1.14**

**Figure 1.17** The structure of bistetraureacalix[4]arene **1.14** and the schematic representation of the polymer capsule formation. Guest molecules are stabilized between two tetraurea calix[4]arene subunits.[96]

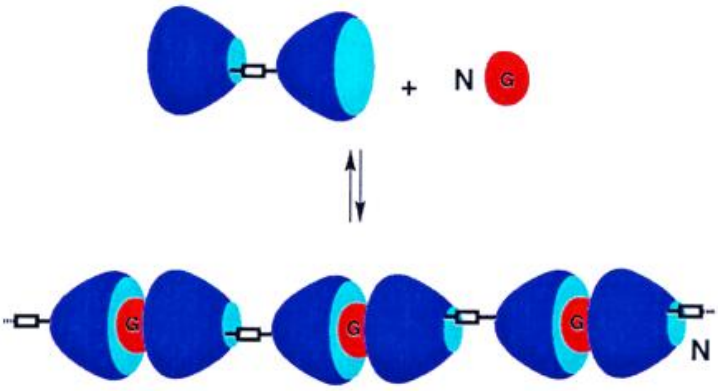



**Figure 1.17** (continued) The structure of bistetraureacalix[4]arene **1.14** and the schematic representation of the polymer capsule formation. Guest molecules are stabilized between two tetraurea calix[4]arene subunits.[96]

Formation of hydrogen-bonded capsules of calix[4]arenes can be achieved without the presence of amido or urea groups. Reinhoudt and coworkers[97] synthesized the heterodimeric adducts from the assembly between calix[4]arene tetracarboxylic acid and three tetrapyridyl calix[4]arenes (Figure 1.18). Remarkably, only tetra(4-pyridyl)- and tetra(3-pyridyl)-calix[4]arenes showed the ability to bind towards calix[4]arene tetracarboxylic acid. The dimeric structures **1.15** are held together via four hydrogen bonds between pyridyl and carboxylic acid groups of calix[4]arenes. The aggregation of tetra(2-pyridyl)calix[4]arene was not observed due to the unfavorable geometry of the hydrogen bonds. The association constants for the 4-pyridyl and 3-pyridyl derivatives, determined by $^{1}$H-NMR dilution experiments, are 7.6 x $10^{3}$ and 1.3 x $10^{3}$ $M^{-1}$, respectively.

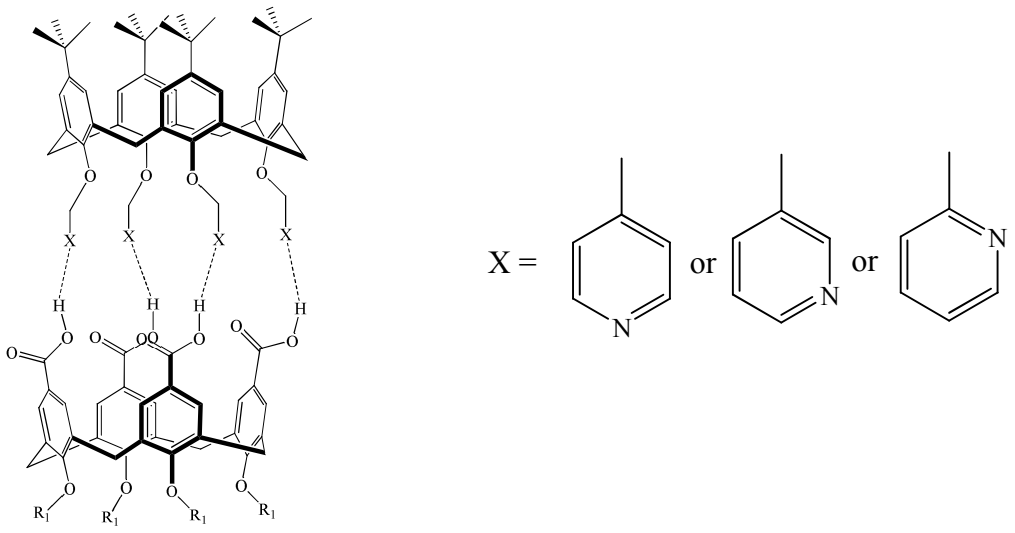
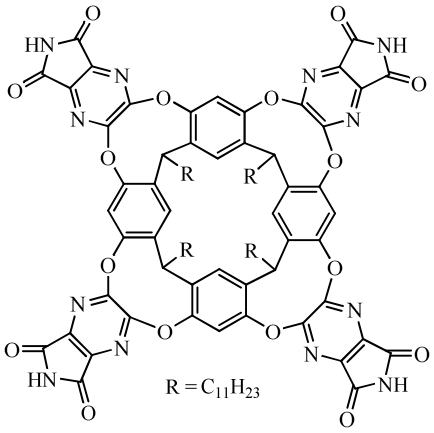


**Figure 1.18** The heterodimeric capsule **1.15** ($R_1 = C_8H_{17}$) between tetra(pyridyl)-calix[4]arene and calix[4]arene tetracarboxylic acid.

### 1.5.3 Cavitands as molecular capsules

Calix[4]arene-based capsules have some disadvantages preventing them to become the ideal building blocks for hydrogen-bonded self assembly. Calixarenes have relatively high conformational flexibility which causes either a collapse of an internal cavity [98,99] or an aggregation of undefined species.[96,100] Therefore, cavitands seem to be the better choice of macrocycles for a self-assembly process. The conformation of cavitands is relatively rigid because of the covalent linkage between adjacent aromatic rings. Additionally, long, bulky alkyl or aryl side chains of cavitands also play an important role in retaining the curvature surface of the molecules.

Rebek and coworkers[101] successfully synthesized tetraimide cavitands **1.16** (Fig. 1.18) , using the resorcin[4]arene platform. The shape of a compound is vase-like and self-assembly takes place at the imide region to produce a cylindrical capsule. The approximate size of the hydrogen-bonded assembly is 10 x 18 Å.




**1.16**

**1.17**

**Figure 1.19** The tetraimide cavitand **1.16** ($R = C_{11}H_{23}$) and the model for its dimeric capsule **1.17**.[101] Peripheral alkyl and aryl groups are omitted for clarity.

Capsule **1.17** shows interesting properties upon interaction with various guest molecules, primarily monitored by $^1$H-NMR spectroscopy.[102] It selectively encapsulates *E*-stilbene but not the analogous *Z*-stilbene.[103] Moreover, when there is more than one guest species available in the solution, capsule **1.17** can accommodate two guests within its void, which may or may not be two identical molecules.[104-107] For example, 4-ethyl-toluene is coencapsulated with chloroform or carbon tetrachloride but not with another 4-ethyltoluene molecule while two picoline guests can be stabilized by the internal cavity of capsule **1.17**. This characteristic feature is regulated by the combination of the two different guest molecules that provides the lowest energy stabilization.[104]

Furthermore, the orientation and movement of guests are strictly controlled by the closed environment of capsule, observed by the isotope effect experiment.[108,109] One guest molecule can tumble in their occupied void but cannot exchange with the other molecule inside the capsule. In 1994, Reinhoudt introduced the term “carceroisomerism” to describe two different guests adopting two distinct orientations in the small cavity

lacking a center of symmetry.[110] With the related context, Rebek employed "social isomerism" to illustrate how the orientation of the guest molecule is related to the existence of the other guest(s).[104,105] Besides, the size of guest molecules and temperature also affect the overall motion of the encapsulated guests.[111]

The studies of encapsulation complexes with various chiral molecules[112,113] revealed remarkable results. For capsule **1.17**, if one of the guest molecules is chiral, it induces the space inside the self-assembly to become chiral, indeed. For this reason, only compatible chiral molecules can be coencapsulated in the closed environment, resulting in the diasteromeric form of the specific assembly.[112,114] Additionally, capsule **1.17** also exhibits the enantiomeric selectivity towards some chiral acids, resulting in homochiral or heterochiral encapsulation.[115]

In the case of small guest molecules, tetraamide assembly **1.17** shows the ability to encapsulate three guest species.[116] Regarding this general idea, there are six possible distributions in the capsule structure if there are two different guests (Figure 1.20). Rebek and coworkers described this characteristic feature as "isomeric constellation" or "constellational isomerism".[117] The unique arrangement of three chiral guest molecules within assembly **1.17** results in the organization of constellational diastereomers.[118,119]

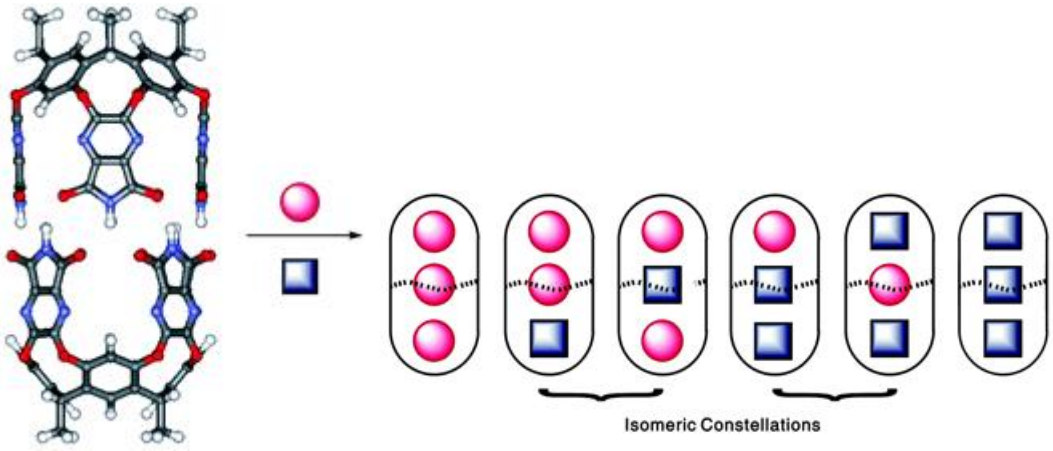



**Figure 1.20** A ball-and-stick representation of the self-assembled cylindrical capsule **1.17** and six possible distributions of two different guests in the capsule.[117]

Long hydrophobic chain alkanes are the other type of guests found to be encapsulated by capsule **1.17**.[120] Extraordinarily, the conformation of the alkyl chains is induced into helical folding in the presence of the well-confined wall of assembly **1.17**, especially for *n*-decane, *n*-undecane, and *n*-tetradecane.[120,121] When the guest molecules were changed from n-alkanes to oligoethylene glycols, the folding behavior was still observed. In contrast, the perfluoro-*n*-alkanes efficiently occupy the void in their original conformations without any change.[122]

A promising application of the self-assembled cavitand **1.16** is to serve as a catalytic reaction chamber for some chemical reactions. Cycloaddition studies of capsule **1.17** showed that the reactions between phenylacetylene and phenyl azide afford only the 1,4-isomer adduct.[123] Thus, the presence of a well-defined cavity plays a significant role in the regioselective catalysis. Without capsule **1.17**, the reaction proceeded slowly at ambient temperature. Furthermore, a recent study also showed that the dimeric capsule of

tetraimide cavitand **1.16** can catalyze the reaction between carboxylic acid and isonitriles without using any external energy source. [124]

To extend the size of capsule **1.17**, Rebek *et. al* [125]reported the formation of extended self-assembly when excess glycoluril **1.18** was added. According to the $^{1}$H-NMR results, the new hydrogen-bonded capsule **1.19** was detected, when the ratio of compound **1.16** and glycoluril **1.18** is 2:4.[126] Four glycouril molecules form bifurcated hydrogen bonds with the imide region of cavitand **1.16**, resulting in the larger capsule with the approximate void of 620 Å$^3$. Surprisingly, the long chain *n*-alkanes like $C_{15}$-$C_{19}$ can induce the hyperextension of capsule **1.19** to the assemblies **1.20** and **1.21**, composed of 8 and 12 glycoluril spacers, respectively.[127] The schematic representations of assemblies **1.19-1.21** are depicted in Figure 1.21

Guest molecules also adapt themselves upon encapsulation, resulting in the observation of social isomerism of two identical guests.[128] Additionally, the formation of extended hydrogen-bonded capsules can be regulated by a change of the pH of the solution.[129] Large *n*-alkanes encapsulated within capsule **1.19** exhibit helical folding as detected in the complexation with capsule **1.17**. Nonetheless, the rotation of encapsulated species can be observed on the NMR time scale, suggesting a weaker interaction between the tetraimide cavitand and the glycoluril spacers.[130]

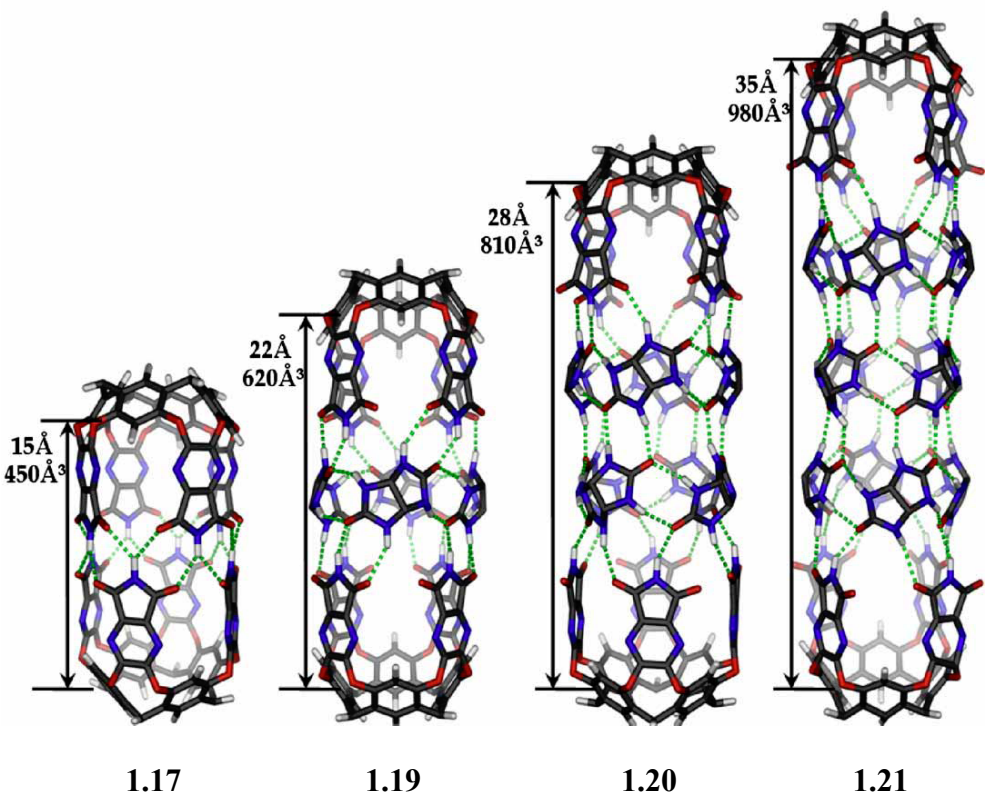



**Figure 1.21** Schematic representations of the tetraimide cavitand capsule **1.17** and its analogous extended capsules **1.19-1.21**. All peripheral alkyl and aryl groups are omitted for clarity.[129]

Other self-complementary cavitand (compound **1.22**, Figure 1.22), synthesized by Rebek and coworkers, utilizes the octaamide functional group on the wide rim of the core structure.[131-134] The secondary amido groups provide hydrogen bonds that connect the adjacent aromatic rings –interannular bonding – and are kept in position by the 7-membered intraannular hydrogen bonds.[131] The presence of intramolecular hydrogen bonding stabilizes the $C_{4v}$ conformation of a cavitand (all aromatic substituents on the wide rim of a cavitand side up), featuring a well-defined vase-like shape (Figure 1.22a). In contrast, the other conformer with $C_{2v}$ symmetry has all upper rim moieties flipping

outwards in a kite-like structure (Figure 1.22b). The latter is the dominant species when there is no intramolecular hydrogen bonding.[132]

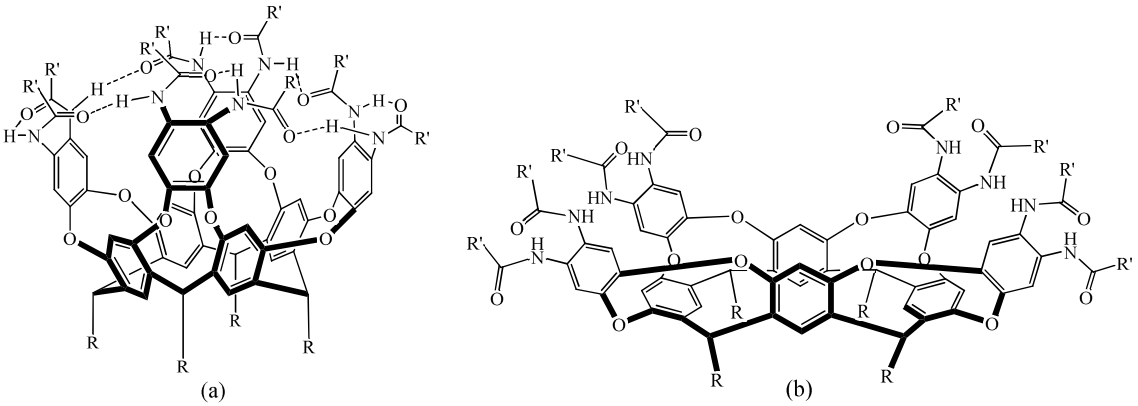



**Figure 1.22** Two possible conformational structures of octaamide cavitand **1.22** (a) vase-like shape ($C_{4v}$) and (b) kite-like shape ($C_{2v}$). R, R′ = alkyl group; R ≠ R′

The interchange between the two conformers of the octaamide cavitand is controlled by solvent and temperature.[133] Interestingly, the inclusion of guest molecules into the cavity of the host can induce the change of conformation from kite to vase-like shape. Rebek defined the "self folding" concept to elaborate the host-guest chemistry of these functionalized upper rim cavitands.[135] Indeed, it is suggested that the mechanism of encapsulation and release of guest molecules within the cavitand molecule involves the folding and unfolding of upper rim moieties.

Moreover, many derivatives of cavitand **1.22** [136-138] were synthesized and used in the investigation of the self-folding process. Guest molecules such as admantane, pyracene, and imidazole, which are covalently attached to the upper rim of the modified cavitand **1.22,** also promote the formation of self-folding structures. The inner space of self-folding cavitand derivatives is well-defined[139] and provides excellent environment

binding for various chemical reactions such as amine methylation,[140] Menschutkin reaction,[141] addition,[142,143] nucleophilic aromatic substitution,[144] Diels-Alder reaction,[145] and acylation.[146-148]

Recently, several water soluble cavitand derivatives containing tetraamino and tetracarboxylate benzimidazole moieties have been synthesized by Rebek and coworkers.[149-151] These novel cavitands show binding ability toward hydrophobic species even in the aqueous solution.[152-155] Therefore, it is promising to utilize these water soluble cavitands as phase-transfer catalysts and extractants for organic species in the environment.

## 1.6 Metal-ligand supramolecular assemblies

To synthesize well-constructed supramolecular self assemblies, hydrogen bonding can be replaced by much stronger metal-ligand coordination. Metal ions are extremely effective components for building large superstructures because of their three major properties.[156] Firstly, most metal ions have directional, specific coordination geometries. This provides a variety of geometries of the resultant structures. Secondly, the strength of metal-ligand interaction is regulated by the hard-soft acid-base compatibility. Change of donor atoms dramatically affects the overall stability of the metal complexes. Finally, several metal ions have distinctive, interesting electrochemical and photochemical properties, which are valuable for assembling new supramolecular devices.

Regarding the syntheses of metal-directed assemblies, most systems utilize the palladium-nitrogen (Pd-N) coordination bond as the principle component. The main reason is the Pd-N bond is relatively labile and reversible.[157] Consequently, the

supramolecular systems using Pd-N bonds are in equilibrium, resulting in the formation of thermodynamic products. The other advantage of a Pd-N bond is the system can undergo the self-correcting process as found within the hydrogen-bonded assemblies.

### 1.6.1 Discrete metal-directing assemblies

To synthesize any closed metal-containing supramolecular assembly, there are two significant building blocks: metal ion (with or without other ligands) and multidentate ligands. It is crucial that one of the components possesses the divergent binding site while another has the convergent complement. If both building blocks possess divergent binding sites, mostly polymeric assemblies could be obtained.

Both Stang[157] and Fujita[158] described a similar approach involving the usage of metal ion or ligand to function as the directing unit for the metal-ligand supramolecular systems. Usually, the metal unit contains inert ligands occupying some of the binding sites. The remaining, unsaturated binding sites are subsequently coordinated with the other multidentate ligand(s). The multidentate ligand must have a relatively rigid conformation to avoid an unfavorable entropy effect upon the formation of the supramolecular assembly.

Numerous publications have reported the synthesis and characterization of various metal-ligand coordination objects, as collected and described in many excellent reviews.[159-164] The following will briefly discuss some examples of many self-assemblies using metal-ligand interaction as the binding force.

Fujita *et al.*[165] prepared the molecular square **1.23** (Figure 1.23) by combining 4,4′-bipyridyl with the convergent *cis*-coordinated Pd(II) center. The metal subunits have

the turning angle of 90° and behave as edges of the molecular box. Assembly **1.23** can perform as a host for an aromatic guest such as napththalene with the association constant of 1800 $M^{-1}$.

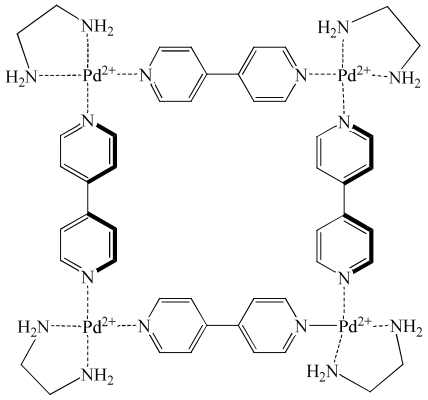
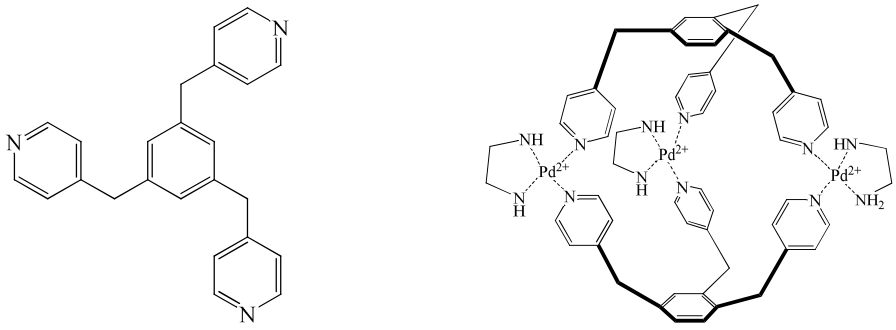


**Figure 1.23** The structure of molecular square **1.23**.

Replacement of the 4,4′-bipyridyl ligand from molecular square **1.23** with $\alpha,\alpha',\alpha''$-*tris*(4-pyridyl)mesitylene (Figure 1.24a) affords the new three-dimensional structure **1.24** (Figure 1.24b) akin to the cryptand topology.[166,167] The ratio between metal ion and ligand is 2:3. The tripodal ligand not only acts as a spacer but also as a protective surface for the assembly.



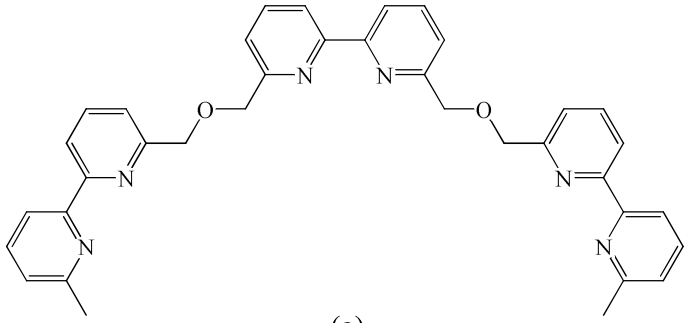
(a) (b)

**Figure 1.24** (a) α,α′,α″-*Tris*(4-pyridyl)mesitylene, and (b) the metal-directing cryptand **1.24**.

## 1.6.2 Metal-directing helicate self-assemblies

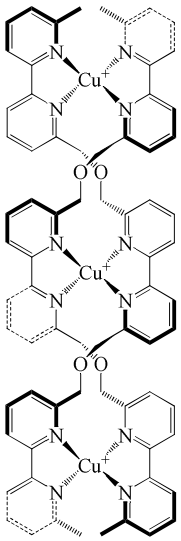
Preparation of s self-assembly resembling the DNA structure *via* metal-ligand interaction was firstly reported by Lehn and coworkers.[168,169] Oligobispyridyl compound **1.25**, as shown in Figure 1.25 has a binding site similar to 2,2′-bipyridyl. In the presence of $Cu^{+}$ [170] or $Ag^{+}$ [171] ion, the ligand **1.25** arranges around the metal center to create the double helix structure **1.26**. (Figure 1.25) The tetrahedral geometry of Ag(I) and Cu(I) plays an important role here in organizing the ligand **1.25** to form the double helix structure.

When Cu(I) is replaced by a Cu(II) ion, the coordination mode of the Cu(II) ion changes to the trigonal bipyramidal geometry. Therefore, when one strand of ligand **1.25** was replaced by a ligand similar to compound **1.25** but containing 2,2′: 6′,2″ -terpyridine groups instead of the bipyridine moiety, a heteroduplex helicate was formed.[172,173] Thus, the design of new helicate structures can be achieved by changing the type of ligand, in combination with the choice of different metal ions.

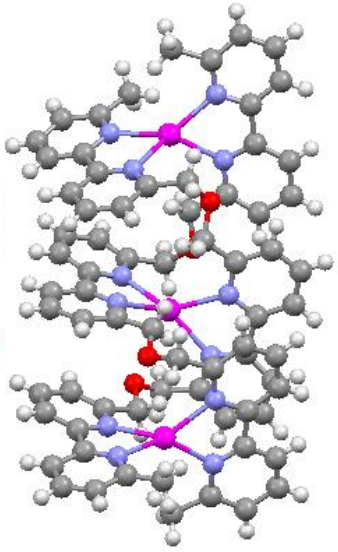


(a)

**1.25**



**1.26**



**1.27**

**Figure 1.25** (a) The chemical structure of ligand **1.25**, (b) representation of Cu(I) complex **1.26**, and (c) the X-ray crystal structure of Ag(I) complex **1.27**.

## 1.7 Dissertation Overview

The following chapters of this dissertation present a summary of the work with which the author has been engaged throughout his doctorate study. It comprises three chapters regarding the syntheses and studies of new macrocycles, which are based on resorcin[4]arene and calix[4]arene building blocks. The general aim of this dissertation is to understand the chemistry of new macrocyclic compounds when compared to the well-established pyrogallol[4]arene molecular capsules, which will be discussed in the subsequent chapters.

Chapter 2 discusses the development and preparation of new macrocycles from the resorcin[4]arene moiety. The main goal is to introduce other functional groups on the aromatic rings of the resorcin[4]arene structure. Those functionalities of interest are amino, cyano and amido groups. Novel macrocyclic compounds are subject to study for any possibility of hydrogen-bonded and metal-directing superstructures. Moreover, similarities and differences from those resorcin[4]arenes and pyrogallol[4]arenes will be described.

The theme of chapter 3 is the attempts to synthesize new macrocyclic compounds which have similar features to pyrogallol[4]arenes. The key step is to introduce four 3,4,5-trimethoxyphenyl groups on the cavitand and calix[4]arene platforms by Suzuki-Miyaura cross-coupling and aldehyde-amine condensation reactions. Regarding this strategy, the deprotection of methoxy groups could lead to new 3,4,5-trihydroxyphenyl tetrasubstituted macrocycles, which resemble pyrogallol[4]arenes but contain larger internal cavities. The usage of new building blocks for the formation of molecular capsules could provide more spacious room for bulky, complex guest molecules.

The last chapter concerns the syntheses and chemical properties of 2,4-diamino-1,3,5-triazine functionalized macrocycles. Diaminotriazine has been used in many chemical systems as the hydrogen bonding moiety and binding site for a metal ion. Therefore, by using tetramer macrocycles such as calix[4]arene and resorcin[4]arene as the platforms, novel 2,4-diamio-1,3,5-triazine substituted macrocycles could be prepared. Additionally, the preliminary complexation studies of those ligands will be reported.

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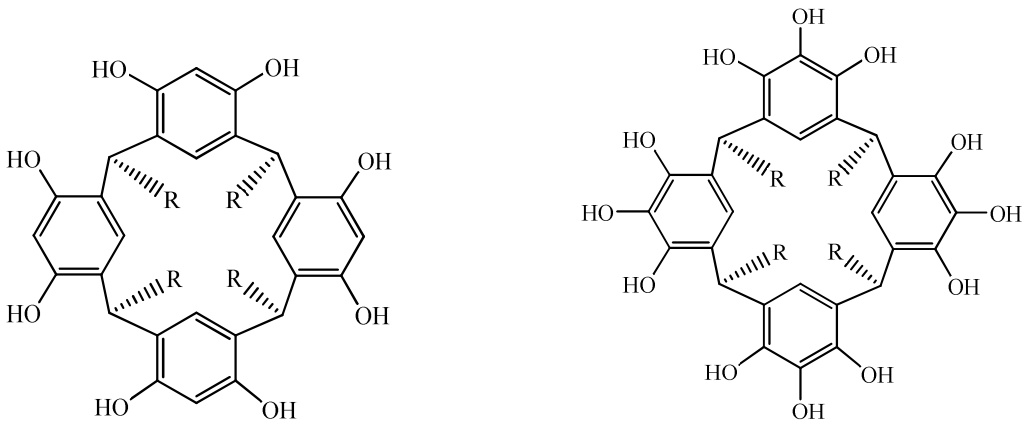
# CHAPTER 2

# FUNCTIONALIZED RESORCIN[4]ARENE DERIVATIVES

## 2.1 Resorcin[4]arene: Excellent scaffold in supramolecular chemistry

The acid-catalyzed condensation reaction of resorcinol with aldehydes was firstly reported in the late 1800 by von Baeyer[1] but the structures of the products had not been determined. Decade later, Michael[2] successfully deduced the elemental composition of the crystalline product and its acetyl derivatives. He suggested that the product is formed by an equal number of aldehyde and resorcinol molecules. In 1940, Niederl and coworkers[3] studied several condensation reactions between aliphatic aldehydes and resorcinol. After analyzing the results of molecular weight determinations, they concluded that the ratio between the aldehyde and resorcinol should be 4:4, which corresponds to the chemical structure shown in Figure 2.1.




(a) **2.1** (b) **2.2**

**Figure 2.1** The chemical structure of (a) resorcin[4]arene **2.1** and (b) pyrogallol[4]arene **2.2**. R group is any alkyl or aryl group.

The official IUPAC-name for compound 2.1 (R1 = alkyl or aryl group) is 2,8,14,20-tetraalkyl(or tetraryl)pentacyclo[19.3.1.13,7].19,13.115,19]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol.[4] This name is too complicated to be used when referring to this type of compound regularly. The trivial name resorcin[4]arene was suggested by Schneider and coworkers[5], which will be used throughout this dissertation.

### 2.1.1 Syntheses of resorcin[4]arenes and related compounds

Resorcin[4]arenes can be synthesized in moderate to high yield *via* a one-step procedure without using templates or high dilution techniques. Generally, the preparation can be performed by mixing appropriate aldehyde (except formaldehyde, which yields a mixture of polymers) with resorcinol in the 1:1 ratio.[6-9] The mixture is dissolved in ethanol (95% or absolute) in the presence of concentrated hydrochloric acid, and subsequently refluxed for several hours.[7,10] Recently, the reaction time can be accelerated by utilizing a microwave-assisted technique.[11] The reaction time dramatically reduces from several hours to just a mere 5-6 minutes. Regarding the isolation of pure compound, products occasionally crystallize from the solution but in most cases, excess water should be added to precipitate the product.

Not only mineral acids but also several Lewis acids are capable of catalyzing the condensation reaction between resorcinol and aldehydes. Ytterbium(III) triflate,[12] bismuth(III) triflate,[13] scandium(III) triflate,[14,15] and many lanthanide(III) nitrobenzene-sulfonates and *p*-toluenesulfonate complexes[16] are excellent catalysts for the syntheses of resorcin[4]arenes. The yields are the same degree of that of the hydrochloric acid-

promoted reaction. The great advantage of using metal triflates over mineral acids is that reactive or acid-sensitive aldehydes can be used in the preparation of desired resorcin[4]arenes.

Other electron donating resorcinol derivatives such as 2-methylresorcinol or pyrogallol (1,2,3-trihydroxybenzene) yield similar tetrameric compounds.[17,18] Notably, in the case of pyrogallol, the product is colloquially called pyrogallol[4]arene (Fig. 2.1b), and will be used throughout this dissertation as well. On the other hand, resorcinol derivatives containing electron-withdrawing substituents like nitro (-$NO_2$) or bromo (-Br)[7] or cyano (-CN) at the 2-position do not afford any cyclic compound. Only dimerized products are obtained as reported by Cram and coworkers.[7]

Octamethoxyresorcin[4]arene derivatives are prepared in excellent yields by different starting materials such as 2,4-dimethoxybenzyl alcohol[19] and 2,4-dimethoxy-cinnamates.[20,21] Moreover, the reaction between 1,3-dimethoxybenzene and aldehyde in the presence of Lewis acids like $SOCl_2$ and $SnCl_4$ also produces octamethoxyresorcin[4]arene derivatives in high yield.[22]

### 2.1.2 Stereochemistry of resorcin[4]arenes and pyrogallol[4]arene

As described in section 2.1, since the ratio of resorcinol (or pyrogallol) and aldehyde units in both resorcin[4]arenes and pyrogallol[4]arenes are 4:4 and they are non-planar, resorcin[4]arenes and pyrogallol[4]arenes can exist in many isomers. Högberg[23] categorized the stereochemistry of resorcin[4]arenes into three stereochemical elements as follows.

(1) The conformation of the aromatic rings, which can adopt five distinctive conformers: the crown ($C_{4v}$), boat ($C_{2v}$), chair ($C_{2h}$), diamond ($C_s$), and saddle ($D_{2d}$) conformation. (Figure **2.2**)

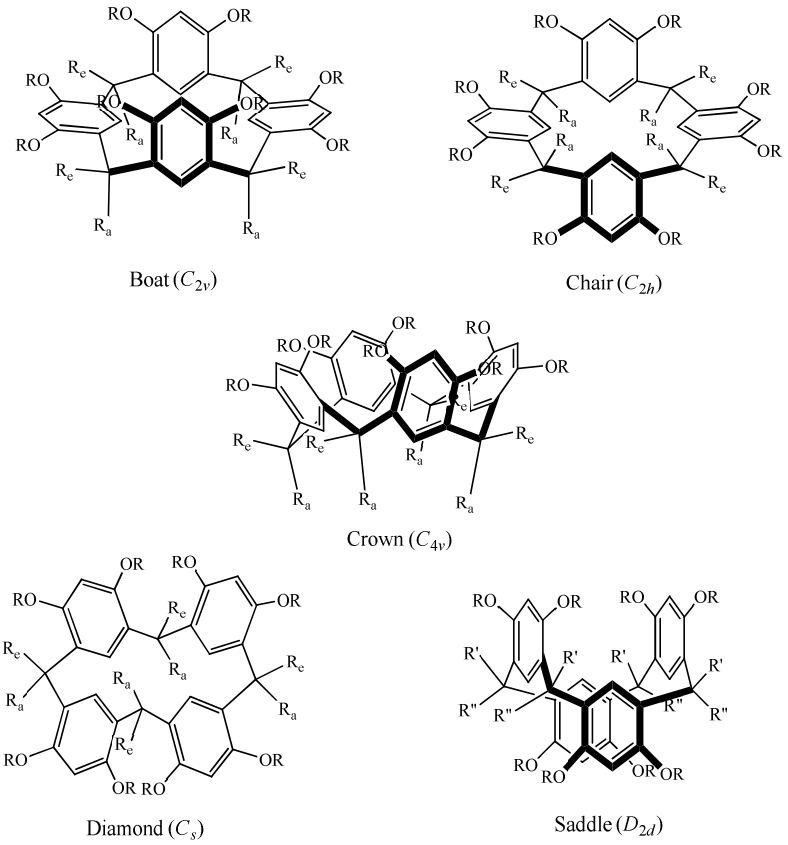



**Figure 2.2** The structures of five possible conformers of resorcin[4]arene.

(2) The relative configuration of the substituents at the methine bridges, producing the all-*cis* (*ccc*), *cis*-*cis*-*trans* (*cct*), *cis*-*trans*-*trans* (*ctt*), and *trans*-*cis*-*trans* (*tct*) configurations. (Figure 2.3) To describe this type of stereochemical element, one side chain group is designated as a reference group. For example, if the other three substituents are in the *cis*-*trans*-*trans*

arrangement with respect to the reference group, the configuration is denoted as *rctt*.[24]

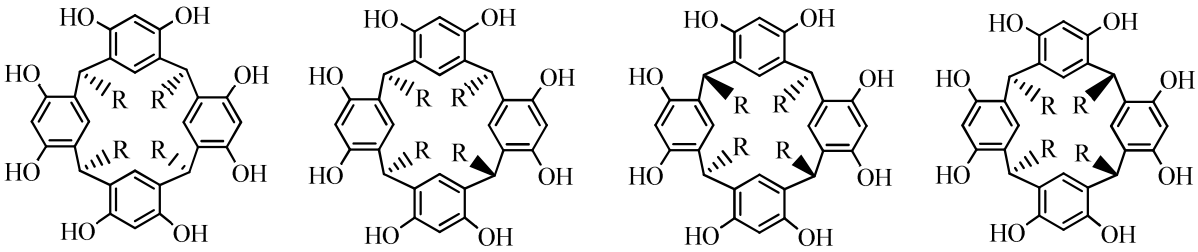



**Figure 2.3** The four possible configurational arrangements of resorcin[4]arene.

(3) The particular configuration of the groups at the methane carbon atoms. If the substituents are chiral, the macrocycle becomes chiral too.

(4) The orientation of a substituent on the methine bridges in which can be in either the axial or the equatorial position with respect to the macrocycle core structure.

With the many combinations of the aforementioned stereochemical components, resorcin[4]arenes and their derivatives can adopt a great number of possible stereoisomers. One would expect them to be interconvertible like calixarenes.[4] However, the inversion between stereoisomers of resorcin[4]arene is very complicated and there is still no clear explanation regarding this aspect. The rotation through the annulus of one (or more) aromatic ring(s) alters not only the stereochemistry of the aromatic region but also the individual configuration of the adjacent substituents at the methine carbon atom.

Therefore, the interconversion process with the retention of configuration could happen only when there are bond breaking and bond forming within the macrocycle molecules.[4]

Many research groups have studied the dynamic behavior in solution of resorcin[4]arenes and octaester derivatives by temperature-variable $^{1}$H-NMR spectroscopy.[23,25,26] The results suggest that the existence of a particular conformation of resorcin[4]arene is principally controlled by two factors. Firstly, conformations with the maximum number of hydrogen bonds are favorable. Secondly, the substituents strongly prefer axial to equatorial orientations because the steric effect between the phenolic hydroxy groups and the side chain moieties is at minimum.[4,23] However, if all phenolic hydroxyl groups are converted to the respective ester groups, the conversion between each stereoisomer is likely more probable because of the decrease in the energy barrier for interconversion by breaking the intramolecular hydrogen bonds. Additionally, the polarity of solvent also plays an important role in governing the stereoisomeric conversion in solution as well.[25] For example, the conversion between boat or chair conformers of *C*-hexylresorcin[4]arene to the respective crown arrangement was observed in acetone-$d_6$ but not in DMSO-$d_6$. Interestingly, the interconversion led to the formation of *C*-hexylresorcin[4]arene in the crown conformer but with one or two substituents in an equatorial orientation.[26]

## 2.2 Functionalization of resorcin[4]arenes and pyrogallol[4]arenes

Generally, there are three possible positions on the resorcin[4]arene molecule that can be functionalized: Aromatic carbons (exclusively at the 2-position), phenolic hydroxy groups, and the side chain substituents. For pyrogallol[4]arene, the aromatic substitution

reaction at the 2-position carbon of an aromatic ring is unlikely. Each of these functionalizations is briefly discussed in the following section.

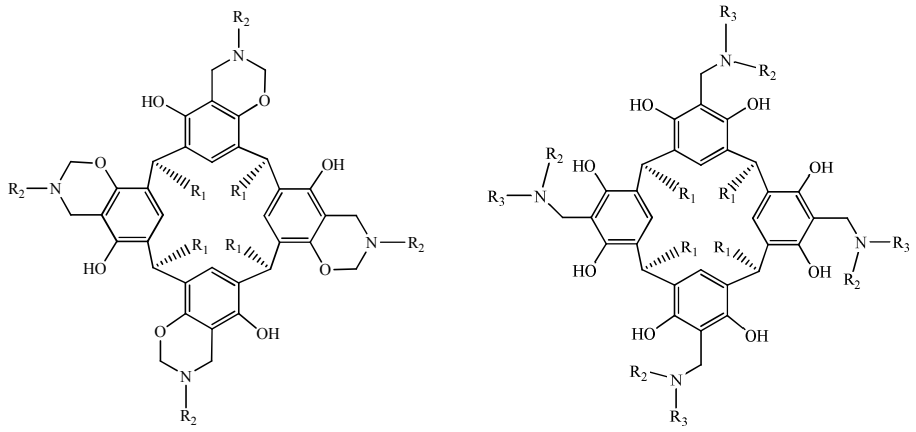
### 2.2.1 Electrophilic aromatic substitution of resorcin[4]arenes

The presence of hydroxy groups on the aromatic rings of resorcin[4]arenes makes them electron rich and highly active for an electrophilic aromatic substitution reaction. Several examples of this type of substitution reaction at all four carbon positions between the hydroxyl groups have been reported.

The most common reaction is bromination, which can be successfully performed by reacting *N*-bromosuccinimide (NBS) with the appropriate resorcin[4]arene.[8,27] The reaction occurs exclusively at the 2-position of an aromatic ring, resulting in tetrabromo resorcin[4]arenes. Since NBS and a brominated product are light-sensitive, exclusion of light during synthesis is necessary. When excess NBS is used, there is no effect on an aromatic carbon which is between two methine bridges. However, 1,3-distal dibromination of resorcin[4]arene can be achieved by limiting the equivalence of NBS to only two with respect to the resorcin[4]arene.[28]

Mannich reaction of resorcin[4]arenes is the other common approach of preparing several aminomethylated derivatives (Figure **2.4**).[29-34] The appropriate resorcin[4]arene is reacted with formaldehyde in the presence of a primary or secondary amine (both aliphatic and aromatic). The products are tetrabenzooxazine derivatives (when primary amines are used) and tetraaminomethylated compounds (when secondary amines are used). This type of reaction can be extended to numerous nucleophiles such as amino

alcohols,[35,36] amino acids,[37-39] thiols,[40] sodium sulfite,[41] and combination of amines and alcohols or alcohol and amino alcohols.[42]



(a) **2.3** (b) **2.4**

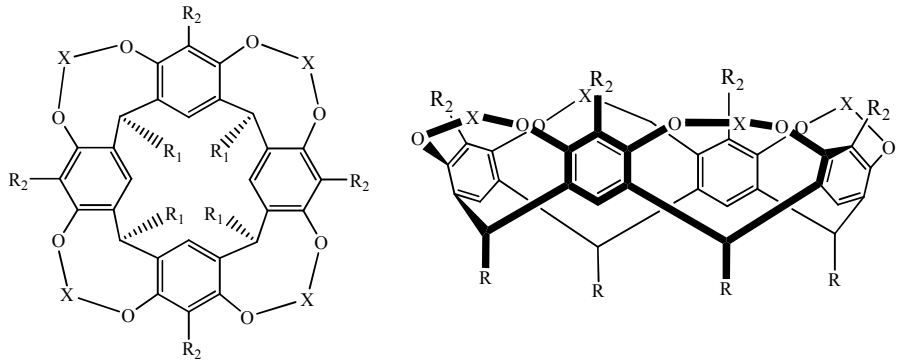
**Figure 2.4** The chemical structures of (a) tetrabenzooxazine resorcin[4]arene **2.3** and (b) tetra aminomethylated resorcin[4]arene **2.4**.

## 2.2.2 Formation of covalent linkages on hydroxy groups

This approach is arguably the significant reason that makes resorcin[4]arene one of the most utilized macrocycles in supramolecular chemistry. The well-defined, bowl-shaped structure of resorcin[4]arene is suitable for the syntheses of cavitands.[8] Typically, cavitands can be synthesized by covalently connecting two hydroxyl groups of each adjacent aromatic ring with a suitable linking group.[7,8,43,44] The chemical structure of general cavitands is shown in Figure 2.5.

Compared to the parent resorcin[4]arenes, cavitands are very rigid molecules. They adopt a crown conformation with $C_{4v}$ symmetry in both solid state and solution.[44] The flexibility of the cavitands depends on the linkage group and the substituents at the methine carbon atoms. If long, less rigid linker groups are used to build cavitands, the

molecules become more flexible and a boat conformation can be observed in the solid state.[7,8,27]



**2.5**

**Figure 2.5** The general structure of a cavitand **2.5** and its crown-liked conformation. $R_1$, $R_2$ = any functional group; X = any linkage group.

#### 2.2.2.1 Alkylenedioxy-bridged cavitands

The first preparation of a cavitand was reported in 1982 by Cram *et al*.[27] Reaction between resorcin[4]arene with excess $CH_2BrCl$ and base in a mixture of DMSO and DMF produced unsubstituted cavitand in quite low yield (23%). Nevertheless, the use of resorcin[4]arenes with functional groups like bromine and methyl groups between two hydroxy moieties gave relatively higher yields ( *ca*. 55-70%).[43] The methylene bridge (from $CH_2BrCl$) is, by far, the most common linker of cavitand derivatives.[45] Furthermore, DMF is the most effective solvent in the synthesis of fully substituted cavitands.[46] The general structure of alkylene-bridged cavitand is depicted in Figure 2.6a.

Tetrabromo cavitands are excellent starting materials for synthesizing other types of cavitands.[47-49] Treatment of tetrabromocavitands with *n*-BuLi at -78°C followed by reaction with an appropriate electrophile, affords novel cavitands with other substituents.

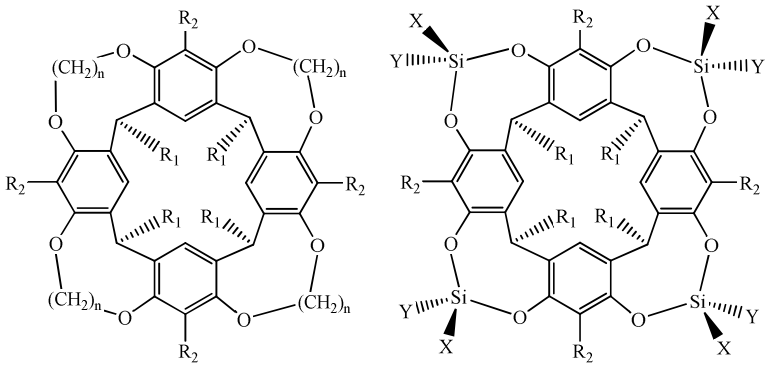
This approach is extremely valuable when the desired functional groups are not compatible with the reaction conditions for preparing resorcin[4]arene and cavitand.[7] Several functional groups such as iodo,[8] carboxylate ester,[50] hydroxy,[48,49] and formyl[51-54] can be introduced into the cavitand scaffold by this strategy. Reduction of tetraester cavitand results in tetramethyl-hydroxy cavitands, which can be chlorinated with *N*-chlorosuccinimide to give a tetramethylchloro cavitand.[50]

Sherburn and coworkers established the method for selective functionalization of cavitands by varying the number of equivalents of *n*-BuLi in the lithiation step.[55-58] A tribromocavitand can be synthesized by treatment of a tetrabromocavitand with 1.1 molar equivalents of *n*-BuLi, followed by reaction with excess methanol.[55] For an *A*,*B*-dibromo-cavitand (bromine atoms are on the adjacent aromatic rings), 1.1 molar equivalents of *n*-BuLi is added twice to produce the desired compound (36%).[56] On the other hand, an *A*,*C*-dibromocavitand (bromine atoms are on the opposite aromatic rings) is the major product when 2.1 molar equivalents of *n*-BuLi is added at once (61%).[57]

Recently, the synthesis of a cavitand *via* ring closure metathesis was remarkably demonstrated by Bisht and coworkers.[59] 2-Methylresorcin[4]arenes and bromoresorcin[4]-arenes were treated with allyl bromide to give octaallylated resorcin[4]arene derivatives. In the presence of Grubbs' generation I catalyst, all allylated resorcin[4]arenes underwent the ring-closure metathesis to afford alkene-bridged cavitands.

### 2.2.2.2 Alkylsilicon-bridged cavitands

Reaction of resorcin[4]arene with the appropriate dialkyldichlorosilanes in the presence of triethylamine ($NEt_3$) under high dilution conditions afforded the tetrasilylated cavitands in quite low yield (< 40%).[60,61] Changing $NEt_3$ to pyridine significantly improves the yield of tetrasilylated products. The silyl bridges are highly base-sensitive; therefore the use of a weaker base like pyridine prevents the unexpected side reaction which may occur at the silyl bridges. The silyl group serves as a protecting group for the synthesis of highly-ordered cavitands. HF is an excellent reagent to remove the silyl groups from the cavitand scaffold. The general structure of silyl-bridged cavitand is shown in Figure 2.6b.



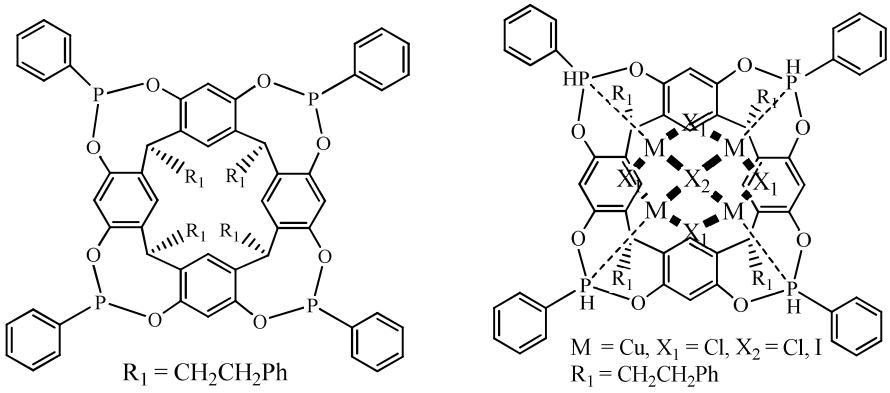
(a) **2.6** (b) **2.7**

**Figure 2.6** The chemical structures of (a) alkylene-bridged cavitand **2.6,** and (b) dialkylsilyl-bridged cavitand **2.7**. $R_1$ = alkyl or aryl group. $R_2$ = any functional group. X, Y = alkyl group.

### 2.2.2.3 Phosphoryl-bridged cavitands

The first phosphoryl-bridged cavitand derivative was synthesized by Puddephatt and coworkers by reacting *C*-phenylethylresorcin[4]arene with phenyldichlorophosphine

in the presence of pyridine as a base.[62] All four phenyl groups attached to phosphorous atoms arrange in the equatorial position, as confirmed by the X-ray crystal structure. Interestingly, all phosphorous atoms still have lone-pair electrons which participate in metal-ligand interaction.[63] Treatment of the compound with $[(CuC{\equiv}CPh)_n]$ in the presence of pyridinium chloride resulted in a complex in which a cluster of $Cu_4(\mu\text{-}Cl)_4$ is located on the top of the cavitand structure. Another chloride ion is in the middle of the tetranuclear Cu(I) cluster. Moreover, Puddephatt *et al*.[64] also attempted to synthesize the analogue of the complex with iodides as counter ions. Surprisingly, the result revealed that not all chloride could be substituted by iodides. Only the chloride ion in the middle of the tetranuclear Cu(I) cluster was replaced by an iodide ion. This result stems from the fact that an iodide ion is more fitted to the cavity of the cavitands and binds all four copper(I) ions.




(a) **2.8** (b) **2.9**

**Figure 2.7** (a) Chemical structure of cavitand **2.8**, and (b) the metal complex **2.9**.

#### 2.2.2.4 Phenylene-bridged cavitands

The intrinsic cavity of resorcinarenes can be expanded by connecting the phenolic hydroxy groups with aromatic spacers. This strategy leads to the formation of cylindrical-shaped cavitands which have been widely used in the field of hydrogen-bonded capsules as previously discussed in section 1.5.

### 2.2.3 Functionalization of hydroxy groups

Hydroxy group of resorcin[4]arenes and pyrogallol[4]arenes are very good nucleophiles in the $S_N2$ nucleophilic substitution. However, unlike calixarenes, there is no general standard procedure for selective functionalization of resorcin[4]arenes and pyrogallol[4]arenes. Macrocycles such as octasubstituted resorcin[4]arenes and dodecasubstituted pyrogallol[4]arenes are among the most common derivatives because all hydroxy groups are fully substituted and their syntheses are practically straightforward.

Alkylation is an effective way to modify the parental resorcin[4]arenes. The examples of functional groups introduced *via* this strategy are methyl, hydroxamic acid[65], ethyl ester,[66] ethyl hydrazine,[66] *tert*-butyldimethylsilyl,[67] and *N*,*N*′-dialkylacetamide.[68] Weak inorganic bases such as $Na_2CO_3$ and $K_2CO_3$ are sufficiently effective to abstract hydroxy protons. In a similar approach, reactions of resorcin[4]arenes with several reagents such as acetic anhydride,[69-71] benzyl chloroformate, [72]3-bromopropionyl chloride,[73] and dansyl chloride,[74] gave a new variety of acylated and sulfonated derivatives. In most acylation reactions of resorcin[4]arenes, weak organic bases like $NEt_3$ and pyridine are strong enough to deprotonate hydroxy groups.[75]

### 2.2.4 Functionalization of side chain groups of resorcin[4]arenes

Generally, this methodology requires the synthesis of functionalized aldehydes prior to the acid-catalyzed condensation reaction with resorcinol or pyrogallol. It is very crucial that those functional groups be acid tolerant and do not interact with the aldehyde or its related functional groups. There are several publications devoted to discussing the details of synthesis of resorcin[4]arenes and pyrogallol[4]arenes containing side chain moieties of halide,[76] alcohol,[43] perfluoroalkane,[77] citronellal and carvone,[78] aldose sugars,[79] dialkoxyphosphonate,[80,81] crown ether,[82] cyanide,[83] amines and ammonium salts,[84-87] and thiophene.[88] These functionalized macrocyclic compounds are potential candidates for further studies as molecular devices.

As briefly discussed throughout section 2.2.2, syntheses of new resorcin[4]arene-based macrocycles may require the combination of methodologies to obtain desired compounds. A well-planned retrosynthesis procedure is extremely crucial in the preparation of this type of compound. For example, acylated resorcin[4]arenes are sensitive to acidic and basic hydrolysis. Therefore ester groups are not ideal protecting groups in reaction conditions containing water and strong acids or bases. The true difficulty is, however, that not all functional groups can be introduced on the resorcin[4]arene core structure because of the unique reactivity and stability of each functional group. For instance, tetrabromo-resorcin[4]arenes are synthesized from the reaction between *N*-bromosuccinimide with parental resorcin[4]arenes but there is no example of the direct synthesis of tetraiodo-resorcin[4]arene using the analogous *N*-iodosuccinimide or any iodating reagent to date.

## 2.3 Complexation of resorcin[4]arenes and pyrogallol[4]arenes

The hydroxy groups of resorcin[4]arenes and pyrogallol[4]arenes participate in hydrogen bonds as both hydrogen bond donor and acceptor because of the availability of two sets of lone pair electrons on an oxygen atom. Moreover, the internal cavity of resorcin[4]arenes is electron rich and can also form cation-π interaction with various cations. The following in this section discusses the complexation studies of resorcin[4]arenes with some cationic and neutral species.

### 2.3.1 Interaction between resorcin[4]arenes and alkylammonium cations

Resorcin[4]arenes co-crystallize with several trialkylammonium and tetraalkyl-ammonium cations. Shivanyuk and Rissanen[89] reported the X-ray crystal structure of triethylammonium bromide with *C*-ethylresorcin[4]arene **2.10**. Interestingly, the ammonium cation is encapsulated between two resorcin[4]arene molecules, stabilized by one water molecule. The hydrogen bond distance between the nitrogen atom of the ammonium ion and the oxygen atom of water is about 2.735 Å. Another 8 water molecules act as the bridging edges for the dimeric structure. All bromide ions are excluded from encapsulation. The similar structures with larger diquaternary ammonium ions were observed by Rissanen and coworkers.[90] However, there was evidence of a C-H··π interaction of length 3.24-3.27 Å between the ethylene bridges of the cation and the centroid of the aromatic ring of the hosts. The encapsulation of cationic guests was confirmed by $^{1}$H-NMR titration[91] and ESI mass spectra.[92-94] The X-ray crystal structures of *C*-alkylresorcin[4]arenes and tetraalkyl-ammonium cation are shown in Figure 2.8.

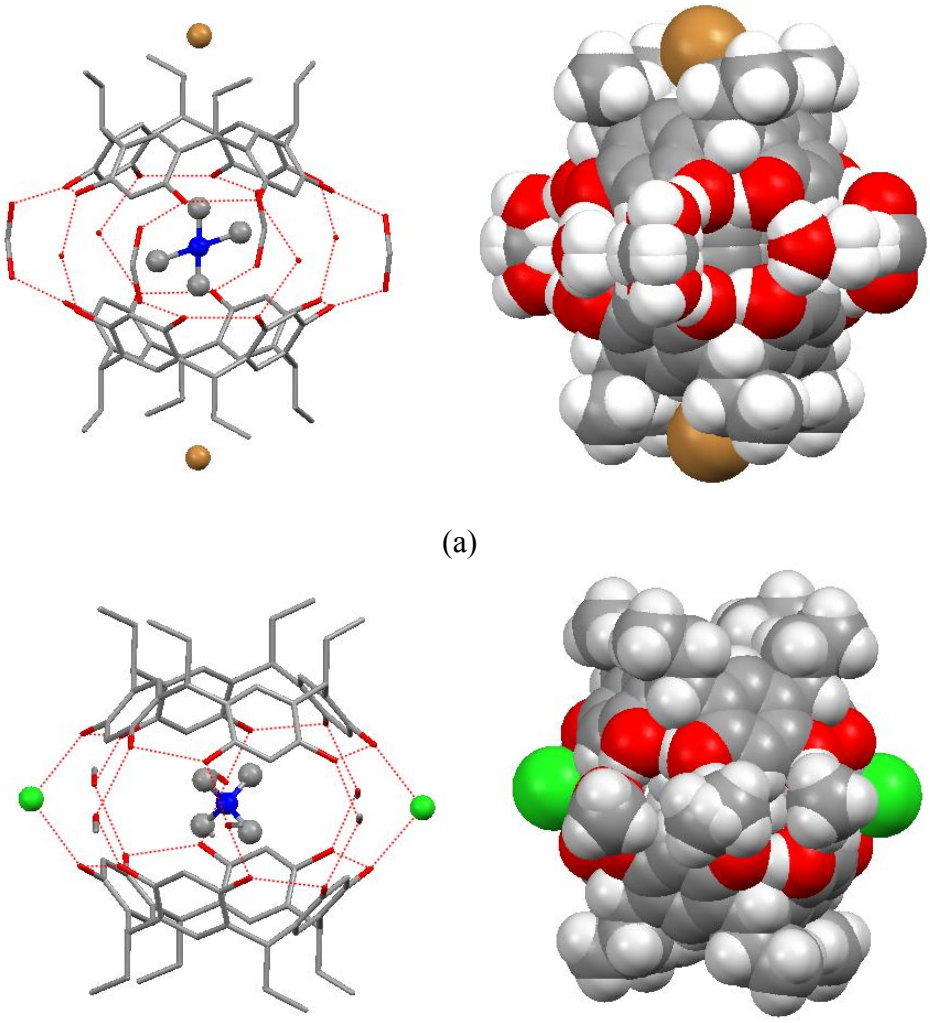
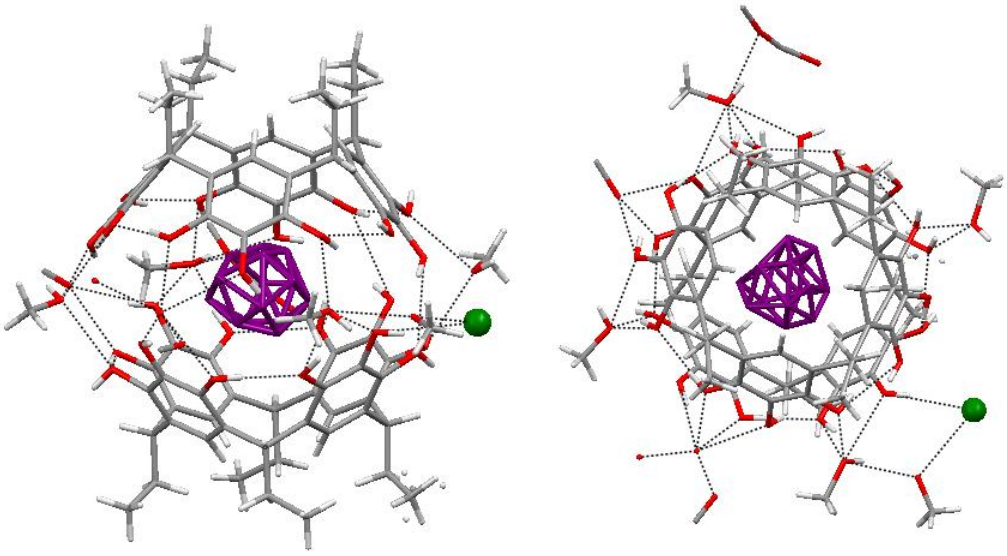


**Figure 2.8** X-ray crystal structures and their respective space filling representation of (a) $[(NMe_4)^+(\mathbf{2.10})_2]\cdot Br^-\cdot 8MeOH$ and (b) $[(NMe_4)^+(\mathbf{2.10})_2]\cdot Cl^-\ 6MeOH\cdot H_2O$. All hydrogen atoms are omitted for clarity. The hydrogen bonds are shown as dashed lines.[92]

For pyrogallol[4]arenes, alkylammonium cations also induce the formation of dimeric capsules. Rebek *et al*. recrystallized *C*-ethylpyrogallol[4]arene **2.11** from methanol in the presence of quinuclidine hydrochloride.[95] The X-ray crystal structure showed that a quinuclidinium cation is encapsulated between two molecules of pyrogallol[4]arene. The crown (*rccc*) conformation of pyrogallol[4]arene is stabilized by

4 intramolecular hydrogen bonds between hydroxy groups of adjacent aromatic rings. Furthermore, 7 molecules of methanol and one molecule of water are involved in the intermolecular hydrogen bonds, stabilizing the capsule. The guest occupies about 82% of available space in the cavity, higher than the optimal 55% value for encapsulated neutral molecules. The X-ray crystal structure of the complex is shown in Figure 2.9.



(a) (b)

**Figure 2.9** X-ray crystal structure of [(**2.11**)$_2$⊂ quinuclidine ion]·$Cl^-$·7MeOH·$H_2O$. Hydrogen bonds are shown as dashed lines. Chloride ion is shown as a green sphere.The purple cluster in the middle of the structure is distorted cation. (a) the view from the side and (b) the view from the top.[95]

Complexation studies of **2.11** with trimethylammonium bromide and trimethyl-phosphonium bromide by $^1$H-NMR spectroscopy also indicated the formation of dimeric capsules.[95] At 303 K the $^1$H-NMR spectra have very broad signals, indicating a fast equilibrium on the NMR time scale. Lowering the temperature resulted in the upfield shift of the resonance of the encapsulated cations. However, after excess salt was added,

the signal of cation on the spectra broadened and depended on the amount of salt. This indicates the formation of a kinetically unstable open complex.

In 2009, Mattey and coworkers[96] published an article regarding complexation studies of *C*-isobutylresorcin[4]arene **2.12** and *C*-isobutylpyrogallol[4]arene **2.13** with several alkylammonium cations. By using the calorimetric investigation, interestingly, the results revealed that the tetramethylammonium complex of **2.13** is more stable than that of **2.12** ($K_a$ = 1900 $M^{-1}$ vs 350 $M^{-1}$) Furthermore, **2.13** forms a complex with several tetraalkylammonium chloride salts with stability constants in the range of 850-7500 $M^{-1}$. When the alkyl group of the ammonium salt is larger than the propyl group, no thermodynamic data could be obtained.

Tetraesters and tetrasulfonate resorcin[4]arenes also exhibit affinity towards alkylammonium cations, reported by Vainiotalo[97] and Shivanyuk.[98] Unfortunately, no X-ray crystal structures were obtained. However, the ESI mass spectra showed that the ratio between tetrasulfonated resorcin[4]arene and triethylammonium cation is 1:2,[99] similar to those of parental resorcin[4]arenes. Additionally, H-D exchange experiments suggested that the steric effect of the alkyl group of alkylammonium cation disturbs the intramolecular hydrogen bonds of the host. Unfortunately, there is no clear correlation between the stability and steric factors for these resorcin[4]arene derivatives.

In 1998, Mattey and coworkers[100] found that *C*-methylresorcin[4]arene **2.14** forms complexes with various amines, amino alcohols and pyridine. The compositions of the complexes were determined by $^1$H-NMR experiments and spectrophotometric methods. There was evidence of a hydrogen bond between the nitrogen atom of the amines and a hydroxy group of the resorcin[4]arene. The ratio between **2.14** and

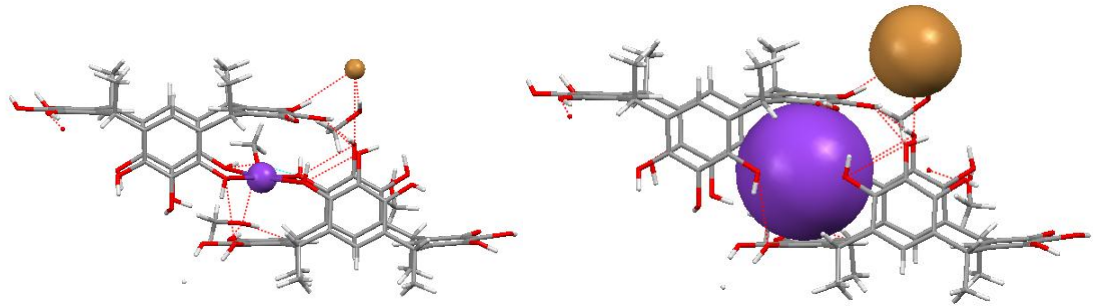
secondary amines is generally 1:2. The stability constants of the secondary amine complexes are of the magnitude $10^7$ and $10^8$ $M^{-2}$. However, when pyridine was used in the complexation study, the X-ray single crystal results showed that 6 pyridine molecules interact with one resorcin[4]arene. Pyridine's nitrogen atom acts as hydrogen bond acceptor, interacting with hydroxy protons from the –OH groups of resorcin[4]arene molecule. The N···H bond lengths range from 1.84-1.86 Å and the N···H-O bond angles are close to 180°.

### 2.3.2 Complexation of resorcin[4]arenes and alkali metal ions

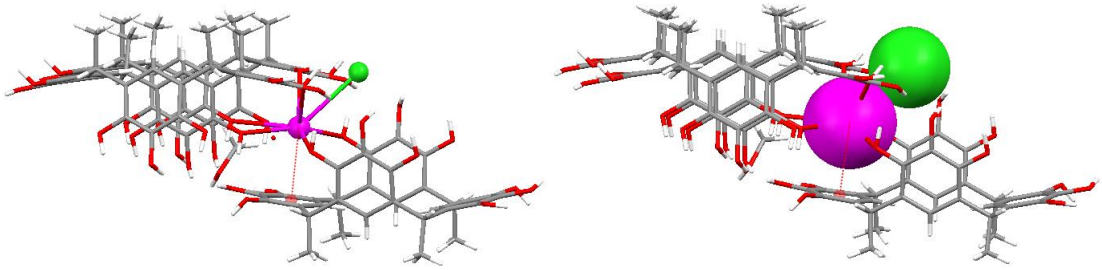
The electron rich cavity of resorcin[4]arene and pyrogallol[4]arene is also suitable for complexation with various alkali metal ions. Mattey and coworkers[101] utilized ESI mass spectrometry to determine the evidence of the alkali metal complexes of resorcin[4]arenes and pyrogallol[4]arenes. The results showed that *C*-octyl and *C*-undecylpyrogallol[4]arenes (**2.15** and **2.16**) have affinities toward $Cs^+$ ion over the other alkali metal ions. On the basis of the hard-soft acid-base concept, the basic π-electron rich cavity of pyrogallol[4]arene is suitable for interaction with a soft alkali metal ion such as $Cs^+$ ion.

Later in 2006, Nissanen[102] demonstrated that *C*-methylpyrogallol[4]arene **2.17** interacts with several alkali metal salts such as KBr, RbCl and CsBr in the solid state. KBr forms a 1:1 complex with the host. Potassium ion is coordinated to four hydroxy oxygens, two from each pyrogallol[4]arene. The bond lengths of $K^+$···O are in the range of 2.76-2.85 Å. Most importantly, the cation is $\eta^6$-coordinated to two aromatic rings of the host forcing the boat conformation as shown in Figure 2.10. In contrast, no

complexation is observed in the case of compound **2.14**. The lack of additional hydroxy groups at the 2-positions results in the intermolecular hydrogen bonds between two host molecules and close π···π contact between the opposing aromatic rings. The examples of X-ray crystal structures of **2.17** with alkali metal ions are shown in Figure 2.10.



(a)



(b)

**Figure 2.10** Crystal structures of (a) KBr complex of **2.17**, and (b) RbCl complex of **2.17**, drawn as the capped stick diagram with the ball and stick (left) and space filling representation (right) for cations and anions. Note for the colors: $K^+$ = purple, $Br^-$ = gold, $Rb^+$ = magenta, $Cl^-$ = green.[102]

Recently, Dalgarno and Atwood[103] studied the complexation of pyrogallol[4]-arenes with CsCl. X-ray crystal structures revealed that the Cs ion is coordinated to hydroxy groups of the pyrogallol[4]arene as well as to part of one aromatic ring in a dimeric head-to head fashion. In addition, the Cs center is also bound to an acetonitrile

molecule (through the C-N triple bond) and three water molecules. The counter chloride ion is located at the periphery of the capsule structure.

### 2.3.3 Complexation of resorcin[4]arenes and polar organic molecules

Aoyama and coworkers[71,104] were the first to recognize this feature and have studied this phenomenon exclusively with several polar guest species. Remarkably, they suggested that in the presence of water molecules in apolar organic solvents such as $CCl_4$ and $CHCl_3$, *C*-undecylresorcin[4]arene **2.18** can form intermolecular hydrogen bonds with four water molecules.[105] The $H_2O$ complex possesses four binding sites, each between two hydroxy groups of the adjacent resorcinol moieties. This startling result is also observed in the formation of larger resorcin[4]arene-based molecular capsules, which will be discussed in section 2.4.

Resorcin[4]arenes form various complexes with several cyclohexanediols *via* intermolecular hydrogen bonding between the hydroxy groups of resorcinol and those of the cyclic diols.[106] Interestingly, *cis*-1,4-cyclohexanediol is by far bound most tighly ($K$ = 103 $M^{-1}$ in $CDCl_3$ at 25°C). Open chain diols are bound less strongly than their cyclic counterparts, suggesting the significance of preorganization on the host and guest molecules. Moreover, the complexation experiments of macrocycle **2.18** with the pyranose and furanose forms of *D*-ribose revealed that the host selectively binds α-pyranose, which contains a *cis* orientation of the hydroxy groups on $C_1$ and $C_4$ of the pyranose molecule.[107]

Dicarboxylic acids can also bind to compound **2.18** in $CDCl_3$ by hydrogen bonds.[108] Indeed, water molecules are an integral part of these complexes, similar to the observations found in the case of cyclic diols. The stability of the dicarboxylate complexes depends on the length of the spacer connecting the two carboxylic ends. Additionally, compound **2.14** and *C*-nonylresorcin[4]arene **2.19** form 1:1 complexes with caffeine in 1% water in methanol *via* hydrogen bond formation with the carbonyl oxygen of caffeine.[109]

## 2.4 Hydrogen-bonded multi-component capsules

### 2.4.1 Resorcinarene-based hexameric capsules

As mentioned in sections 1.5, 2.2.2 and 2.3, resorcin[4]arenes and pyrogallol[4]arenes are typically considered as the platforms for syntheses of numerous molecular receptors. Most complexes of resorcin[4]arenes and their derivatives are either monomeric or dimeric in nature. No research group had considered this bowl-shaped macrocycle as a basic component of any self-assembled system until MacGillivray and Atwood[110] reported the synthesis of a chiral hexameric capsule assembled by *C*-methylresorcin[4]arene **2.14** in 1997. The assembly is stabilized by 60 hydrogen bonds (36 of which are intermolecular, all are O-H···O type) and 8 water molecules are an integral part of this superstructure. The capsule possesses an internal cavity volume of approximately 1,375 $Å^3$ and a diameter of 17.7 Å.

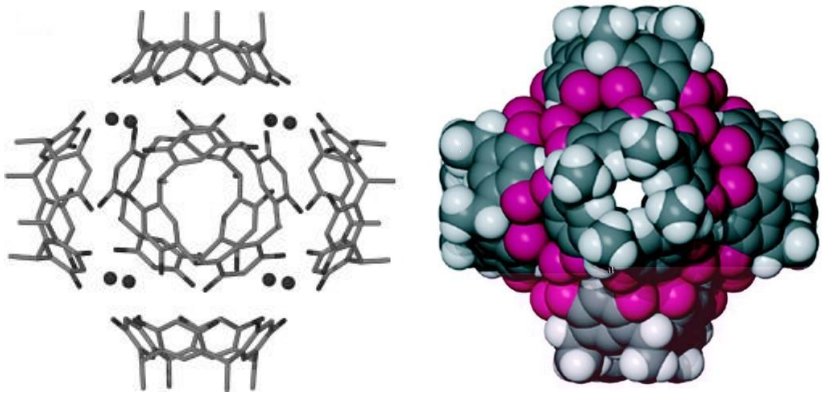


**Figure 2.11** Crystal structure of the $(\mathbf{2.14})_6(H_2O)_8$ capsule, with the capped stick diagram (left) and space filling representation (right). For the capped stick diagram, hydrogen atoms are omitted for clarity.[111]

The hexameric capsule $[(\mathbf{2.14})_6(H_2O)_8]$ resembles the topology of a snub cube, one of the 13 Archimedian solids.[112] Water molecules occupy the vertices of the cube, whereas the six macrocycles arrange themselves as the faces. The hydrogen bond pattern of the hexamer is similar to that of Aoyama's **2.18** hydrate complex.[105] Recent studies by Holman and coworkers[113] showed that the replacement of water molecules with several alcohols such as 2-ethylbutanol and (±)-2-butanol results in the formation of dimeric species. Only in the presence of (±)-2-ethylhexanol (2EH) is the achiral molecular capsule formed. The formula of this structure is $[(\mathbf{2.14})_6(H_2O)_2(2EH)_6]$, where four alcohol molecules substitute four water molecules (see Figure 2.12). This new structure is held together by 58 hydrogen bonds and the two opposing resorcin[4]arenes are perfectly eclipsed.

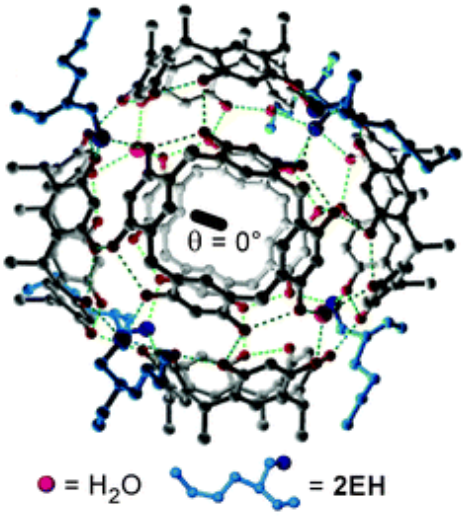



**Figure 2.12** X-ray crystal structure of [(**2.14**)$_6$($H_2O$)$_2$(2-ethylhexanol)$_6$]. The hydrogen bonds are shown as dashed lines. All hydrogen atoms are omitted for clarity.[113]

### 2.4.2 Solution and complexation properties of *C*-alkylresorcin[4]-arene hexameric capsules

Compound **2.18** was chosen in complexation studies with many quaternary ammonium and phosphonium salts.[114] The $^1$H-NMR results revealed that tetrahexyl- and tetraheptylammonium cations are encapsulated within the cavity of the hexamer. The complexes are stable in water-saturated $CDCl_3$. For small tetraalkylammonium ions (methyl, ethyl groups), there is no evidence of hexameric capsule formation under any conditions. Therefore, it is strongly believed that the presence of the tetraalkyl ammonium cation induces the formation of a hexameric capsule in solution. Moreover, when $Bu_4SbBr$ is a guest, it can be coencapsulated with several aromatic molecules such as benzene and *p*-xylene.[115] Interestingly, no encapsulation of aromatic compounds could be detected in the absence of $Bu_4SbBr$.

Later, Rebek and coworkers[116] discovered that the hexameric capsule of compound **2.18** encapsulates 6 $CHCl_3$ or 8 benzene molecules within the cavity. On the basis of the NOESY technique, the cross relaxation constants of the $CHCl_3$/benzene-encapsulated capsule and that of the complex of **2.18** with $Bu_4SnBr$ are similar in magnitude. Consequently, it is clear that the formation of a hexamer structure is spontaneous in water-saturated solvents.

Kinetics and thermodynamic studies of hexameric capsule formation were performed by Rebek and coworkers.[117] The results suggested that tetraalklyammonium cations are coencapsulated with solvent molecules. The equilibrium constant and entropy of the exchange between salt-occupied and solvent-filled capsules gradually decrease as the size of the cation increase. On the kinetics aspect, the rate constants of the guest exchange are temperature dependent. Additionally, the size of the cation and the type of anions also affect the rate constants of these experiments greatly.

In 2002, Cohen and coworkers[118] utilized the pulse gradient spin-echo (PGSE) NMR technique to determine the diffusion coefficients of the relevant species in solution. The results showed that a hexameric capsule of **2.18** spontaneously forms in water-saturated $CDCl_3$ without any presence of a guest molecule. The diffusion coefficients of hexameric capsules and its complex with tetrahexylammonium bromide are the same in magnitude (*ca*. $0.28 \pm 0.02 \times 10^5$ $cm^2$ $s^{-1}$).[119] Addition of polar solvents such as DMSO-$d_6$ and $CD_3CN$ into the capsule solution resulted in the increase of the diffusion coefficient indicating the decompostion of the hexamer species.

Additionally, the water/resorcin[4]arene ratio dramatically affects the diffusion coefficients of water molecules.[120] When the resorcin[4]arene/$H_2O$ ratio was higher, the

diffusion coefficient of water increased more than that of the resorcin[4]arene. This observation implies that the water molecules experience faster diffusion as expected from bulk water in $CDCl_3$. This strongly suggests the exchange of water molecules between free water and water incorporated within the capsule are fast on NMR time scale. Therefore, the hexameric species is the major species in the solution as found in the solid state.

The hexameric resorcin[4]arene capsule is also capable of including electrochemically active species such as ferrocene within the cavity.[121] Cyclic voltammetric experiments showed that there was a new cyclic voltammetric wave after the addition of **2.18** into $CH_2Cl_2$ solution containing ferrocene and tetradececyl-ammonium bromide as supporting electrolyte. This unusual behavior suggests that ferrocenium ion is stabilized by the presence of resorcin[4]arene molecule, as reflected by the lower potential observed in the cyclic voltammogram when ferrocene is oxidized to ferrocenium ion. On the contrary, the reduction back to ferrocene molecule requires extra potential approximately 500 mV, indicating the high stability of the ferrocence·**2.18** complex. Further electrochemical studies with cobaltocenium as a probe also suggested that an encapsulated cobaltocenium exhibits no electrochemical signal when compared to the free cobaltocenium in $CH_2Cl_2$ using tetradececylammonium bromide as supporting electrolyte.

### 2.4.3 Pyrogallol[4]arene-based hexameric capsules

In 1999, there was an article regarding the synthesis of a large self-assembly related to that of *C*-methylresorcin[4]arene hexameric **2.14** capsule by replacing resorcinarene with *C*-isobutylpyrogallol[4]arene **2.13**.[122] The new supramolecular entity is composed of 6 pyrogallol[4]arene molecules held together *via* 72 hydrogen bonds (O-H···O). Interestingly, 48 of these hydrogen bonds are intermolecular and there is no water molecule as an integral part of the superstructure. The presence of 4 extra hydroxy groups per pyrogallol[4]arene results in an achiral capsule in which two opposing pyrogallol[4]-arene molecules are totally eclipsed. Unfortunately, this great discovery was overshadowed by the irreproducibility of the hexamer entity out of many attempts. The X-ray crystal structure of the hexameric capsule of **2.13** is shown in Figure 2.13.

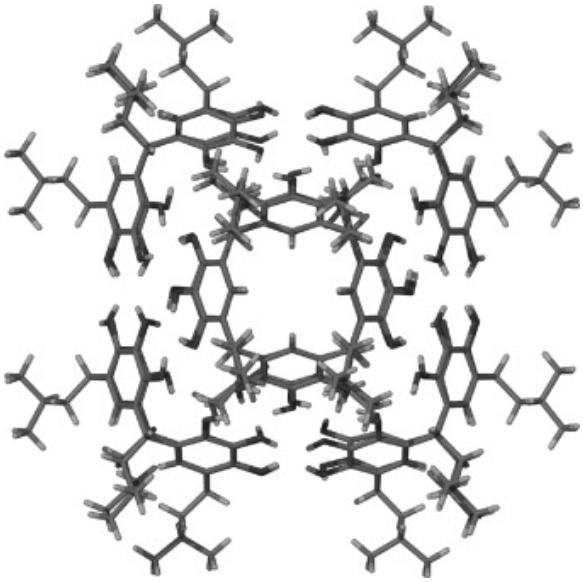
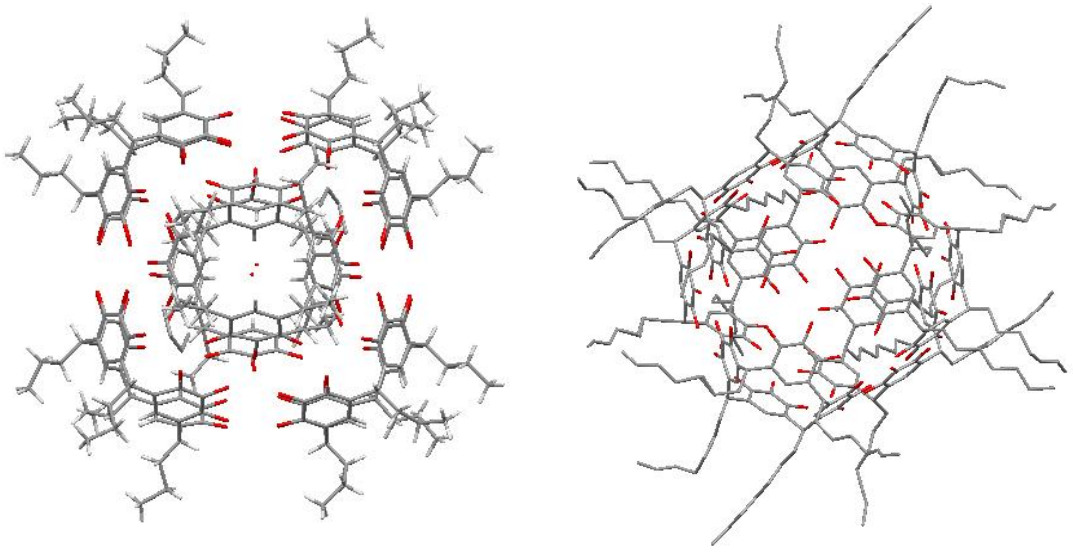


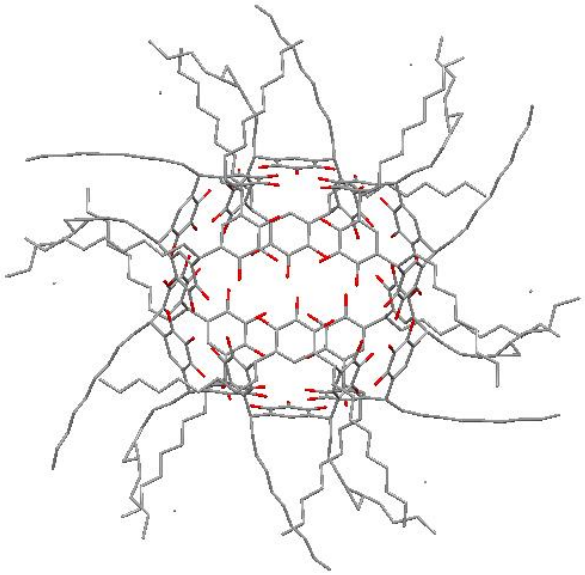
**Figure 2.13** X-ray crystal structure of [(**2.13**)$_6$].[122]

Nevertheless, Atwood and coworkers[111,123-126] have recognized the importance of the structure in the formation of novel molecular capsules. A variety of pyrogallol[4]arenes were synthesized and the yields are moderate to high. Several X-ray crystal structures of hexameric pyrogallol[4]arene assemblies with different side-chain alkyl groups (R = ethyl to heptyl groups) have been reported (see Figure 2.14). Ethyl acetate is the most suitable solvent to recrystallize these hexameric nanocapsules.[125] X-ray structure analysis showed that six ethyl acetate molecules are encapsulated inside the enclosed space of a hexameric structure.



(a) (b)

**Figure 2.14** Views of some hexameric capsules of (a) *C*-propylpyrogallol[4]arene **2.20**, (b) *C*-heptylpyrogallol[4]arene **2.21**, and (c) *C*-nonylpyrogallol[4]arene **2.22**. Hydrogen atoms of **2.21** and **2.22** capsules are omitted for clarity.



(c)

**Figure 2.14** (continued) Views of some hexameric capsules of (a) *C*-propyl-pyrogallol[4]arene **2.20**, (b) *C*-heptylpyrogallol[4]arene **2.21**, and (c) *C*-nonyl-pyrogallol[4]arene **2.22**. Hydrogen atoms of **2.21** and **2.22** capsules are omitted for clarity.

Additionally, the stability of the **2.13** hexameric capsule was tested by adding water into the crystals of the compound and sonicating for several minutes.[123] The X-ray powder pattern of the compound after the exposure to water was identical to that of the compound before the treatment. This experiment confirmed that a hexameric capsule is not decomposed by the addition of polar, protic solvents.

For R = hexyl (compound **2.23**), the packing of the hexamers shows evidence of interesting hydrogen bond pattern between spherical capsules. Four OH groups on the opposite side of each capsule form hydrogen bonds with two adjacent hexameric moieties.[124] Therefore, the surface of an individual capsule is distorted by these interactions. Atwood and coworkers regarded this observation as 'the communication' between each hexameric capsule throughout the entire packing array.[127] The evidence

was the reorientation of the ethyl acetate molecules inside the cavity of **2.23**.[124] Typically, an ethyl acetate molecule forms a hydrogen bond to the wall of a pyrogallol[4]arene capsule through the carbonyl group. The methyl group of ethyl acetate is located at the base of a macrocycle. However, in the case of compound **2.23**, ethyl acetate rearranges its methyl group towards the center of a capsule while the ethyl group is located at the base of the pyrogallol[4]arene molecule. The structure of the **2.23** hexameric capsule is depicted in Figure 2.15.

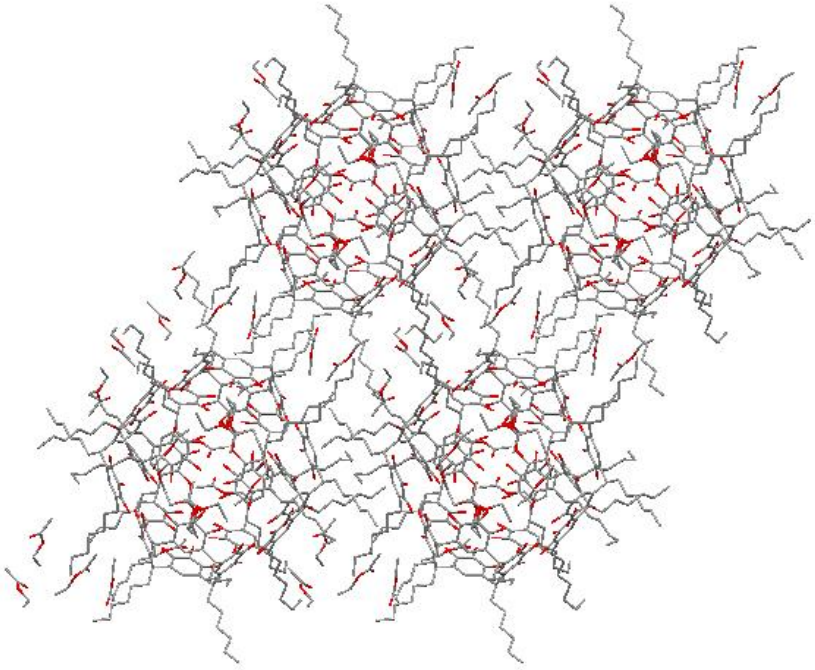


**Figure 2.15** Orthogonal view of the crystal packing showing neighboring capsules of compound **2.23**. All hydrogen atoms are omitted for clarity.

To explore and understand the nature of the internal cavity of the *C*-alkyl-pyrogallol[4]arene capsule, Tucker and Atwood[128] examined the encapsulation of probe molecules in the assembly of compound **2.23**. The saturated solution of **2.23** and excess

pyrenebutyric acid (PBA) in acetonitrile was heated and then sonicated for several minutes to afford crystals that were subject to X-ray crystallography analysis. The results showed that two PBA are included within the cavity of the **2.23** hexameric structure. PBA molecules are bound to the inner wall of the capsule through π-π stacking and CH···π interactions. The distance between two PBA molecules is about 7.843 Å. The X-ray crystal structure of *C*-hexylpyrogallol[4]arene capsule with encapsulated PBA is represented in Figure 2.16.

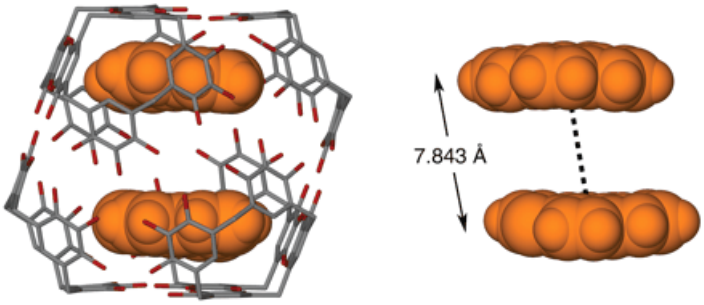



**Figure 2.16** The side view of [(**2.23**)$_6$⊂2PBA] complex. Alkyl substituents and hydrogen atoms are omitted for clarity. Two PBA molecules are in space filling representation.[128]

### 2.4.4 Structural studies of pyrogallol[4]arene nanocapsules in solution

Avram and Cohen[129] studied the behavior of compound **2.16** in $CDCl_3$ by using diffusion NMR experiments. The diffusion coefficient of **2.16** was similar to that of **2.18**, so it is obvious that the hexameric capsule of **2.16** exists in solution as well as in the solid state. By integration, it is clear that 6-7 molecules of $CDCl_3$ are encapsulated in the inner part of the capsule and therefore both guest molecules and capsule diffuse as a single entity. Addition of $CD_3OD$ or DMSO-$d_6$ into the solution of **2.16** in $CDCl_3$ resulted in an

increase of the diffusion coefficient, indicating the decomposition of the hexameric structure.[130] However, interestingly, the diffusion coefficient of **2.16** does not change until the equivalents of $CD_3OD$ exceed 300 fold with respect to **2.16**. On the contrary, the same experiment on compound **2.18** caused an increase in the diffusion coefficient after the addition of only 6 equivalents of $CD_3OD$. This indicates that the capsule of **2.16** is more stable than that of **2.18**.[131] Moreover, both compounds **2.16** and **2.18** do not form heterohexameric capsules even when mixed together. Thus, it is obvious that both resorcin[4]arene and pyrogallol[4]arene exhibit the self-recognition properties.

In comparison with resorcin[4]arene, pyrogallol[4]arene hexameric capsules exhibit significant difference regarding guest complexation.[130,132] No tetraalkyl-ammonium salts are encapsulated in the cavity of pyrogallol[4]arene hexamers.[133] Only neutral compounds such as tertiary alkylamines[130] and hydrocarbons[134] are found to form inclusion complexes with the hexameric pyrogallol[4]arene capsule.

Philip and Kaifer[135] studied the complexation between **2.16** and cobaltocenium cation ($Cob^+$) in $CD_2Cl_2$ by $^1$H-NMR spectroscopy. Surprisingly, 6 equivalents of **2.16** do not yield total encapsulation of $Cob^+$, unlike that of compound **2.18**. This suggests that complex [(**2.16**)$_6$⊂ $Cob^+$] is less stable than [(**2.18**)$_6$⊂$Cob^+$]. Additionally, the presence of 6 equivalents of **2.16** suppresses the voltammetric signal of $Cob^+$ completely, signifying the incorporation of $Cob^+$ inside the hexameric structure of **2.16**.

## 2.5 Hypothesis and objectives

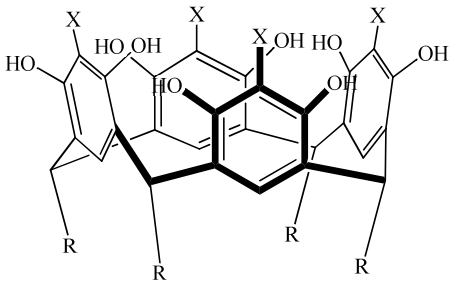
As discussed in Sections 2.1-2.5, resorcin[4]arenes and pyrogallol[4]arenes have received a lot of interest from many research groups as the basic components for hydrogen-bonded capsules. Both solid state and solution investigations have been in progress extensively. However, other derivatives of these macrocycles have not been studied for the same purpose. The only difference between resorcinarene and pyrogallolarene is an extra OH group at the 2-position of an aromatic ring. Therefore, if other functional groups could be introduced at the 2-position instead of the hydroxyl group, it could possibly lead to new macrocyclic compounds which might be capable of forming interesting superstructures in the nano-scale level.

This research has generally focused on three potential functional groups: amino ($-NH_2$), cyano (-CN) and amido ($-C(=O)NH_2$). An amino group can act as a hydrogen bond donor for hydrogen bonding interactions. Moreover, it contains a lone pair of electrons which could participate in metal-ligand coordination bonds. Unfortunately, 2-aminoresorcinol is not commercially available from any major chemical company. So the reaction between 2-nitroresorcinol with appropriate aldehyde in the presence of a catalytic amount of HCl could be a reasonable first step of the synthetic route. However, Cram and coworkers[7] discovered that only dimeric product was obtained from such a reaction. Therefore, the alternative synthetic route for amino-resorcin[4]arene is proposed. Firstly, *C*-alkylresorcin[4]arene is subject to nitration with appropriate nitrating reagents. Subsequently, the reduction of nitroresorcin[4]arene would afford the respective aminoresorcin[4]arene.

There are several publications that have reported the observation of metal-directed self-assemblies involving the usage of cyano-functionalized cavitands as the building blocks. Nonetheless, only a few articles have discussed cyanoresorcin[4]arenes and their complexation properties. To explore the chemistry of cyanoresorcin[4]arene in further detail, new cyanoresorcin[4]arene derivatives have been synthesized and complexation studies with some transition metal ions of these novel macrocycles will be discussed.

Cyanoresorcin[4]arenes could be useful starting materials for the preparation of amido-functionalized derivatives. Hydrolysis of a cyano group in the presence of hydrogen peroxide affords amido functionality in reasonable yield. It is well known in supramolecular chemistry that a primary amide group can serve as both hydrogen bond donor and hydrogen bond accepter *via* the $-NH_2$ and carbonyl groups, respectively. Consequently, the presence of an amido group on the 2-position combining with two hydroxy groups on the aromatic ring of resorcin[4]arene could provide the alternate possibility of a hydrogen-bonded self-assembly. Moreover, some macrocycles containing amido functionality show affinity toward several anions such as halides, phosphate, sulfate and carboxylates. Therefore, these novel amidoresorcin[4]arenes might form complexes with some anionic species through intermolecular hydrogen bonding.

To simplify the stereochemical complexity of novel synthetic macrocycles, this work will focus on only the tetrasubstituted derivatives of resorcin[4]arene. All the 2-positions of the four aromatic rings will be functionalized by those aforementioned moieties. All four aromatic rings are chemically identical. The general structure of the target molecules in this research is depicted in Figure 2.17.




X = -$NO_2$,-$NH_2$,-CN, -$CONH_2$; R = *n*-alkyl group

**Figure 2.17** Target functionalized resorcin[4]arenes in this chapter.

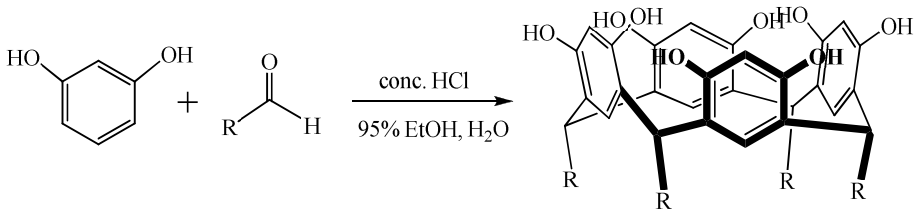
## 2.6 Results and discussion

### 2.6.1 Nitration of resorcin[4]arene attempts

At the beginning, given the poor solubility of most short to moderate-length side chain resorcin[4]arenes in apolar organic solvents such as $CH_2Cl_2$ and $CHCl_3$, there were attempts to derivatize some *C*-alkylresorcin[4]arenes to their octamethoxy derivatives to cope with this difficulty. Later, parental resorcin[4]arenes were directly subject to the nitration reaction without any derivatization. The results from both sets of the attempts were reported as follows.

#### 2.6.1.1 Synthesis of *C*-alkylresorcin[4]arenes

*C*-alkylresorcin[4]arenes with different alkyl side chain lengths (R = $CH_3$ – $C_{10}H_{23}$) (compounds **2.10**, **2.12**, **2.14**, **2.18**, **2.19**, **2.24-2.30**) were synthesized and characterized as described in the experimental section of this chapter. In general, all *C*-alkylresorcin[4]arenes used in this research were synthesized from the acid-catalyzed condensation reaction between resorcinol (1,3-dihydroxybenzene) with appropriate *n*-alkyl aldehydes in the presence of conc. HCl as shown in Scheme 2.1.



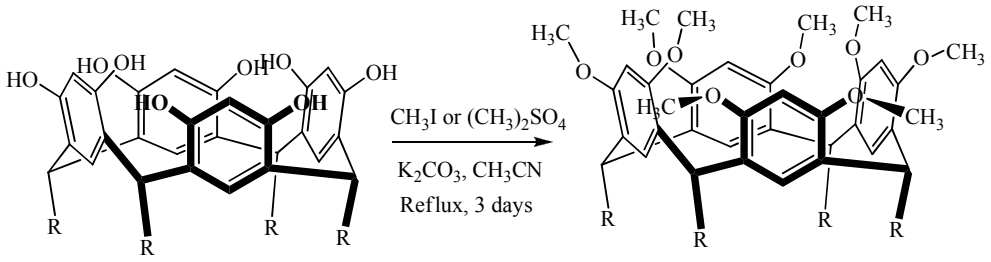

**Scheme 2.1** The general synthetic route for *C*-alkylresorcin[4]arene. R is any alkyl group.

Although many articles regarding the synthetic aspect of resorcin[4]arenes suggested the ratio of 95% ethanol: water: conc. HCl as 2: 2: 1, the author discovered that this procedure yielded only a polymeric mixture which no product crystallizes or precipitates. Given the lack of success, only a catalytic amount of conc. HCl was used in the later synthetic attempts. Indeed, all desired resorcin[4]arenes were precipitated from the reaction mixture after adding a large amount of water (1-2 L).

All $^{1}$H-NMR spectra of *C*-alkylresorcin[4]arenes in acetone-$d_6$ show a characteristic peak of –O*H* protons around 8.40-8.60 ppm. This indicates two magnetically identical –OH protons involved in intramolecular hydrogen bonds between two adjacent resorcinol moieties. Moreover, only one Ar-C*H*-Ar signal is observed around 4.10-4.30 ppm. This also confirms that all synthetic resorcin[4]arenes are in the crown (*rccc*) conformation in which all alkyl groups are oriented in the axial position. $^{13}$C-NMR spectra also exhibit only one peak of Ar*C*HAr at $\delta$ = 31.0-34.0 ppm, indicating only one type of methine bridging carbon. All mass spectra results are consistent with the masses of the anticipated cyclic tetramers.

### 2.6.1.2 Synthesis of octamethoxy resorcin[4]arenes

*C*-Methyl, *C*-ethyl, *C*-propyl, and *C*-pentylresorcin[4]arenes (**2.10**, **2.14**, **2.24**, and **2.26**) were subjected to reaction with methyl iodide or dimethyl sufate using anhydrous $K_2CO_3$ as base in $CH_3CN$. The reactions were complete after refluxing under nitrogen atmosphere for 3 days. After purification by column chromatography using $CH_2Cl_2$ or $CH_2Cl_2$:EtOAc (98:2 to 96:4) as the eluent, corresponding octamethoxy resorcin[4]arenes (**2.31** - **2.34**) were obtained in low yields (13-35 %) The procedure for the synthesis of octamethoxy resorcin[4]arene is depicted in Scheme 2.2 as follows:




**Scheme 2.2** The synthetic procedure for octamethoxy *C*-alkylresorcin[4]arene **2.31**-**2.34**.

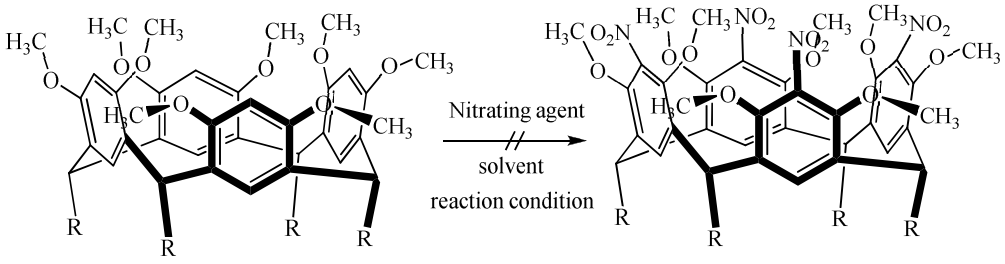
Substitution of –OH groups with methoxy groups literally destroys the intramolecular hydrogen bonds of resorcin[4]arene. This results in the conformational flexibility of the octamethoxy resorcin[4]arene derivatives. The reaction mixture after methylation is composed of several products which could not be completely purified by flash column chromatography. Only crown (*rccc*) conformers of compounds **2.31**-**2.34** were obtained in collectable amounts.

Crown conformers of octamethoxy resorcin[4]arenes were characterized by $^1H$ and $^{13}C$-NMR spectra. All –OH signals in the $^1H$-NMR spectra were replaced by the

–OC$H_3$ chemical shift at 3.59-3.60 ppm. Aromatic protons signals show a slight peak shift from those of C-alkylresorcin[4]arenes due to the effect of the –$CH_3$ group. For the $^{13}$C-NMR results, the new peak of –O*C*$H_3$ appears around δ = 60.0-61.0 ppm. Additionally, there was no observation of conformational flexibility of compounds **2.31-2.34** on the $^{1}$H-NMR time scale at 300K. This also suggested that the conformation of methylated resorcin[4]arene may be immobilized during the synthetic process and could not undergo conformational interchange at the ambient temperature.

### 2.6.1.3 Nitration attempts of octamethoxy resorcin[4]arenes

Reactions between octamethoxy resorcin[4]arenes and some nitrating agents were investigated according to the procedure shown in Scheme 2.3. The starting materials, reaction conditions, nitrating agents and results of the nitration of octamethoxy resorcin[4]arenes are summarized in Table 2.1.




**Scheme 2.3** The proposed synthetic procedure of octamethoxy tetranitro *C*-alkyl-resorcin[4]arene.

**Table 2.1** Starting materials, reagents, reaction conditions and results from the synthetic attempts of octamethoxy tetranitro *C*-alkylresorcin[4]arene.

| Starting material | Nitrating agents and reaction condition | Result |
|---|---|---|
| **2.31** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA), $CH_2Cl_2$, RT[136] | complex mixture |
| **2.31** | conc $HNO_3$, conc. $H_2SO_4$, 0°C to RT[137] | complex mixture |
| **2.32** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA), $CH_2Cl_2$, RT | complex mixture |
| **2.32** | $NaNO_2$, Trifluroacetic acid, RT[138] | complex mixture |
| **2.32** | conc $HNO_3$, conc. $H_2SO_4$, 0°C to RT | complex mixture |
| **2.33** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA), $CH_2Cl_2$, RT | complex mixture |
| **2.33** | $NaNO_2$, Trifluroacetic acid, RT | complex mixture |
| **2.34** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA), $CH_2Cl_2$, RT | complex mixture |
| **2.34** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA), $CH_3CN$, RT | complex mixture |
| **2.34** | $NaNO_2$, Trifluroacetic acid, RT | complex mixture |

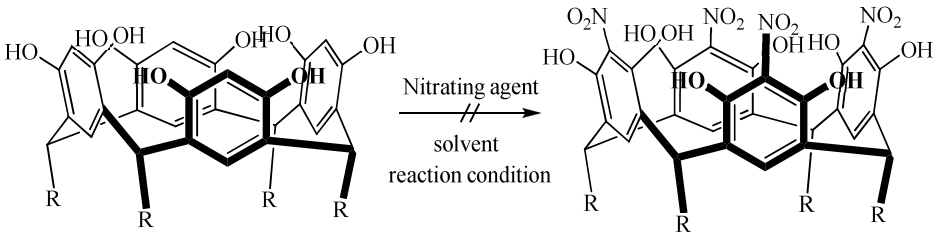
Given the results shown in Table 2.1, it was clear that none of the synthetic attempts afforded desired tetranitro octamethoxy resorcin[4]arenes. The products are complex mixtures, as characterized by $^1$H-NMR spectra. Using a traditional nitrating agent such as the combination of conc. $HNO_3$ and conc. $H_2SO_4$ resulted in a complex mixture, which might be partially nitrated product, oxidized compounds or decomposed starting material.[139] During the reaction, the solution turned from colorless to black or brown after the addition of a nitrating reagent. The use of strong acidic reagents such as conc $HNO_3$, conc $H_2SO_4$, trifluoroacetic acid or trifluoroacetic anhydride may possibly

result in the formation of unexpected oxidized products and unidentified resinous materials from over-oxidation of the substrate.

#### 2.6.1.4 Direct nitration attempts of resorcin[4]arenes

Given the lack of success in the attempts regarding the nitration of octamethoxy resorcin[4]arenes, it is quite worthwhile to investigate the nitration of parental resorcin[4]-arenes to establish the similarity and contrast of this type of reaction. Unfortunately, there is no research article describing the direct nitration of *C*-alkyl-resorcin[4]arenes to date. Consequently, all nitrating agents and conditions utilized in this section were based on the literature reports pertaining to the nitration of substituted phenolic compounds. Recently, several chemicals such as $Bi(NO_3)_3 \cdot 5H_2O$,[140] $ZrO(NO_3)_3 \cdot xH_2O$,[141] $Ni(NO_3)_2 \cdot 6H_2O$,[142] $NaNO_3$,[143-145] $VO(NO_3)_3$,[146] and $Fe(NO_3)_3 \cdot 9H_2O$[143] have been reported as a nitrating agent of phenolic compounds without utilizing a protecting group.

Reactions between *C*-alkylresorcin[4]arenes and some nitrating agents were investigated according to the procedure shown in Scheme 2.4. The starting materials, reaction conditions, nitrating agents and results of the nitration of octamethoxy resorcin[4]arenes are summarized in Table 2.2.




**Scheme 2.4** The proposed synthetic procedure of tetranitro *C*-alkylresorcin[4]arene.

**Table 2.2** Starting materials, nitrating agents, reaction conditions and results from the synthetic attempts of tetranitro *C*-alkylresorcin[4]arenes.

| Starting material | Nitrating agent | Solvent and condition | Result |
|---|---|---|---|
| **2.14** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.14** | $ZrO(NO_3)_2 \cdot xH_2O$ | $CH_3CN$, RT | complex mixture |
| **2.12** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.24** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.24** | $ZrO(NO_3)_2 \cdot xH_2O$ | $CH_3CN$, RT | complex mixture |
| **2.25** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.26** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.27** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.28** | $ZrO(NO_3)_2 \cdot xH_2O$ | Acetone, RT | complex mixture |
| **2.14** | $Ni(NO_3)_2 \cdot 6H_2O$; *p*-toluenesulfonic acid (TsOH) | Acetone, reflux | starting material |
| **2.12** | $Ni(NO_3)_2 \cdot 6H_2O$ *p*-toluenesulfonic acid (TsOH) | Acetone, reflux | starting material |
| **2.14** | $Bi(NO_3)_3 \cdot 5H_2O$ | Acetone, reflux | starting material |
| **2.12** | $Bi(NO_3)_3 \cdot 5H_2O$ | Acetone, RT | starting material |
| **2.14** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA) | $CH_3CN$, RT | complex mixture |

**Table 2.2** (continued) Starting materials, nitrating agents, reaction conditions and results from the synthetic attempts of tetranitro *C*-alkylresorcin[4]arenes.

| | | | |
|---|---|---|---|
| **2.24** | $NH_4NO_3$, Trifluoroacetic anhydride (TFAA) | $CH_3CN$, RT | complex mixture |
| **2.14** | $Fe(NO_3)_3 \cdot 9H_2O$ | $CH_3CN$, reflux | starting material |
| **2.24** | $Fe(NO_3)_3 \cdot 9H_2O$ | $CH_3CN$, reflux | starting material |
| **2.26** | $VO(NO_3)_3$ | Acetone-$CH_2Cl_2$, reflux | starting material |
| **2.27** | $VO(NO_3)_3$ | Acetone-$CH_2Cl_2$, reflux | starting material |
| **2.14** | conc. $HNO_3$, conc. $H_2SO_4$ | 0°C to RT | complex mixture |

As the results show in Table 2.2, unfortunately, none of nitrating agents used in these attempts afford the desired tetranitro resorcin[4]arenes. Isolated products from some reactions were either dark brown (or black) solid or tar-like material. The solubility of the dark brown (or black) powder in most organic solvents is extremely poor even in hot DMF and DMSO. Additionally, sonication of this residue for several hours did not improve its solubility as expected. It dissolves only in aqueous alkali solutions such as aq. NaOH or aq. KOH and the resulting solution turned purple or dark red after the addition of alkali solution. This observation shows that the mixture is composed of phenolic compounds. Hydroxide ion deprotonates the proton of a hydroxy group resulting in a phonoxide ion and increases the solubility of the mixture in aqueous solution.

The $^1$H-NMR spectra of these solutions showed numerous signals, generally broad and complicated. Consequently, no reasonable chemical structure could be elucidated. This suggests that starting resorcin[4]arene may undergo further oxidation

reaction or be polymerized under these conditions. In some cases, only starting materials were recovered. It is very interesting that although the size of the nitronium ion ($NO_2^+$) is similar to that of the bromine cation ($Br^+$) (1.15 Å, and 1.14 Å, respectively), resorcin[4]arenes preferably undergo bromination reaction. The linear geometry of $NO_2^+$ may be the reason why nitration of resorcin[4]arene was not successful as originally expected. Two adjacent hydroxy groups to the carbon atom at the 2-position may hinder the electrophilic aromatic substitution, resulting in no nitrated aromatic ring.

In conclusion, all attempts to synthesize tetranitro resorcin[4]arene from normal *C*-alkylresorcin[4]arene were practically unsuccessful. Nevertheless, this does not mean that resorcin[4]arene could not undergo a nitration reaction since only some of the nitrating agents were examined in this research (*vide supra*). It might be possible to perform direct nitration of resorcin[4]arene and its derivatives but not under the previously described conditions.

### 2.6.2 Synthesis of tetracyano resorcin[4]arenes

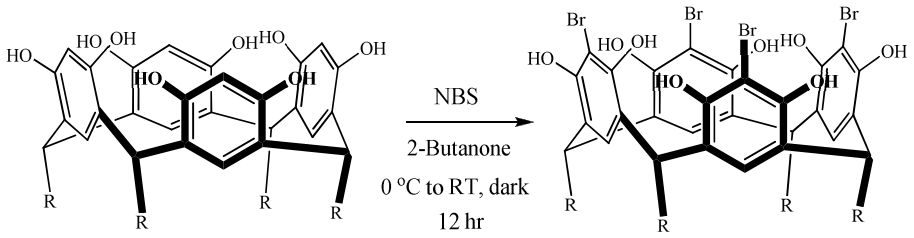
Tetracyanoresorcin[4]arenes with ethyl and tridecyl side chains were firstly synthesized by Yoshiali Kobuke and coworkers[147,148] to be used as an acetylcholine receptor. For the synthetic aspects, tetrabromoresorcin[4]arenes were prepared *via* bromination with *N*-bromosuccimide. The corresponding tetrabromoresorcin[4]arenes were subjected to methylation with methyl iodide to afford tetrabromo octamethoxy-resorcin[4]arenes. Cyanation reactions were performed by using the typical Rosemund-von Braun reagent (CuCN) in refluxing DMF. Finally, demethylation of tetracyano octamethoxyresorcin[4]arenes was successfully accomplished by LiI in a mixture of

pyridine – 2,4,6-trimethylpyridine (γ-collodine). The overall yields for tetracyano *C*-ethyl and *C*-tridecylresorcin[4]arenes were 5 and 15%, respectively.

Given the previous reports regarding the syntheses of tetracyanoresorcin[4]arenes, the usage of the methoxy group as a protecting group requires harsh conditions to cleave the O-$CH_3$ bond. Therefore, at the beginning, a benzyl group was selected as a protecting group for tetrabromoresorcin[4]arenes since the cleavage of the benzyl group can be performed by simple hydrogenation at room temperature.

#### 2.6.2.1 Synthesis of tetrabromo resorcin[4]arenes

Tetrabromo *C*-methyl, *C*-ethyl, and *C*-hexylresorcin[4]arenes were obtained from the reactions between corresponding resorcin[4]arenes and NBS in 2-butanone (see Scheme 2.5) in high yields (73-82%). The exclusion of light from these reactions is crucial since NBS is light-sensitive. Compounds **2.35**-**2.37** are less soluble in acetone, acetonitrile and methanol than their parental compounds **2.10**, **2.14**, and **2.27**. The $^1$H-NMR spectra of compounds **2.35**-**2.37** in DMSO-$d_6$ showed only one signal for the aromatic proton at 6.8-7.4 ppm, indicating the bromine substitution at the 2-position of an aromatic ring. The methine proton appears at δ = 4.23-4.62 ppm as one peak. This suggests that the tetrabromo *C*-alkylresorcin[4]arenes **2.35**-**2.37** are crown (*rccc*) conformers. The mass spectra of **2.35**-**2.37** are consistent with the calculated masses of tetrabromo resorcin[4]arene derivatives.

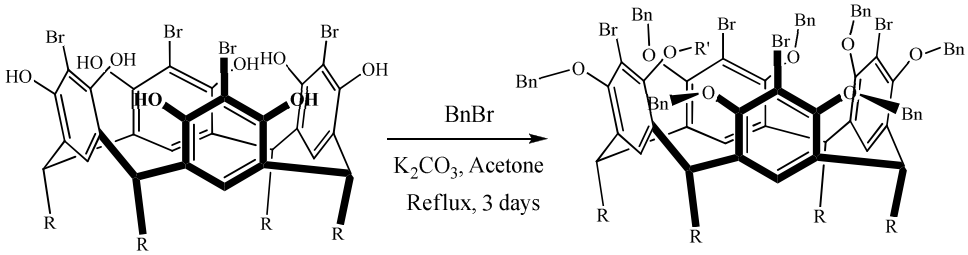



R = -$CH_3$, **2.35**; -$CH_2CH_3$, **2.36**, -$(CH_2)_5CH_3$, **2.37**

**Scheme 2.5** The synthetic procedure of tetrabromo *C*-alkylresorcin[4]arenes.

### 2.6.2.2 Synthesis of octabenzylated tetrabromo resorcin[4]arenes

The chemical reaction for the preparation of octabenzylated tetrabromo *C*-methyl and *C*-ethylresorcin[4]arenes (**2.38** and **2.39**) is shown in Scheme 2.6.




R = -$CH_3$, **2.38**; -$CH_2CH_3$, **2.39**

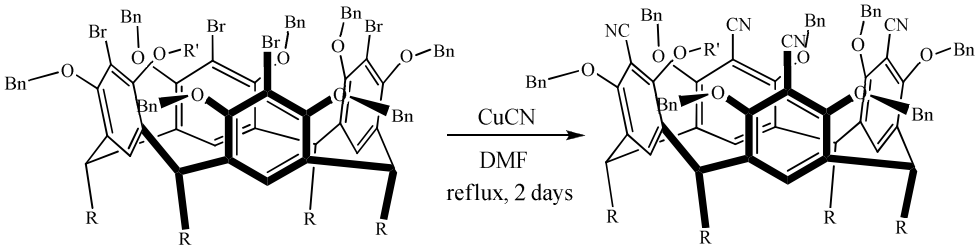
**Scheme 2.6** The synthetic procedure of octabenzyloxy tetrabromo *C*-alkylresorcin[4]-arenes.

After purification by column chromatography ($CH_2Cl_2$ as eluent) and recrystallization from methanol, compounds **2.38** and **2.39** were obtained in high yields (89% and 80%, respectively). The $^1$H-NMR spectra of **2.38** and **2.39** showed the characteristic peaks of O-C$H_2$-Bn protons as 2 pairs of doublets ($^2J$ = 11.4 and 10.8 Hz). This suggests that both **2.38** and **2.39** are not in crown (*rccc*) but rather boat (*rccc*)

conformations. The benzyl group provides too much steric hindrance between adjacent aromatic rings so the octabenzylated derivatives prefer a boat to a crown conformation. However, all four alkyl side chains still adopt an axial orientation. The evidence is only one signal for Ar-C*H*-Ar at 4.83-4.85 ppm. The $^{13}$C-NMR spectra also showed two peaks for O-*C*$H_2$-Ar at 74.3 and 74.1 ppm, indicating two magnetically different carbon atoms. The aromatic carbon peaks of the benzyl group are at δ =127.0-128.5 ppm whereas the aromatic carbons of resorcin[4]arene exhibit two sets of chemical shifts, consistent with the boat conformer pattern.

### 2.6.2.3 Cyanation attempts of octabenzylated tetrabromo resorcin[4]arenes

The proposed cyanation reaction of compounds **2.38** and **2.39** is depicted in Scheme 2.7.




R = -$CH_3$, **2.38**; -$CH_2CH_3$, **2.39**

**Scheme 2.7** The proposed cyanation reaction of octabenzyloxy tetrabromoresorcin[4]-arenes.

The reaction between compounds **2.38** and **2.39** with CuCN in refluxed DMF yielded a complex mixture of products. TLC experiments showed multiple closed spots when observed under an UV lamp at the wavelength of 254 nm. There was no clear separation between those spots. There were several attempts to purify the mixture but the

results were unsatisfactory. The complex crude material might come from the decomposition of DMF when refluxed for a long period of time. At the boiling point, DMF tends to decompose and produces carbon monoxide and dimethylamine which might result in an unexpected side reaction. The other explanation is a benzyl group provides too much steric hindrance and prevents the complete substitution reaction of bromine with cyanide ion.

#### 2.6.2.4 Synthesis of tetracyano *C*-hexylresorcin[4]arene

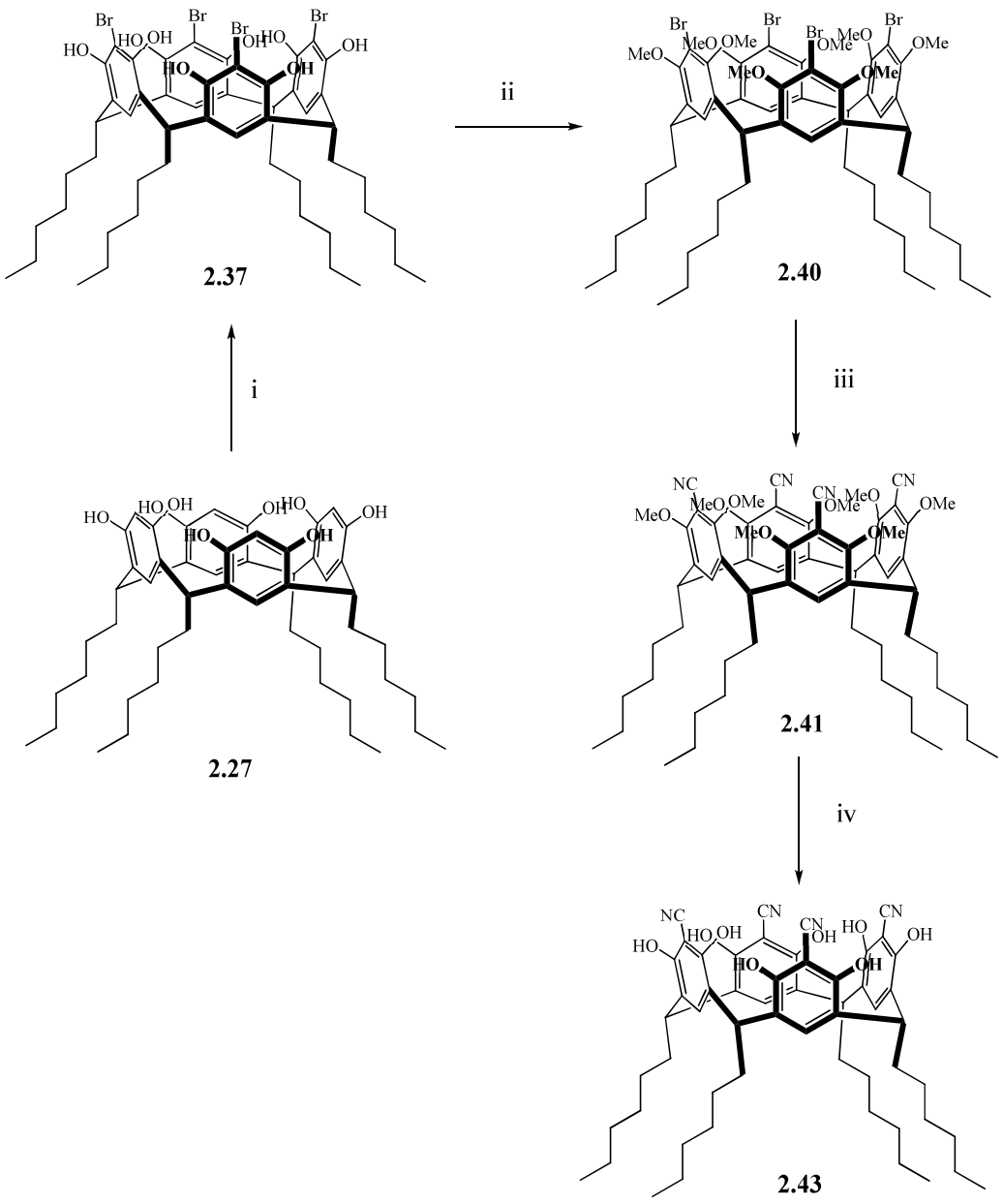
Given the lack of success on the attempts at the cyanation reaction of octabenzyloxy tetrabromo resorcin[4]arenes, a new approach was designed to obtain the desired products. Firstly, the hydroxy groups of tetrabromo resorcin[4]arene are protected with methoxy groups. Even though a methoxy group is hard to cleave, it is robust under most reaction conditions.[149] Moreover, the size of a methoxy group does not cause too much steric hindrance and obstruct the substitution on the 2-position of the resorcinarene's aromatic rings. Then, the octamethoxy derivative is subjected to cyanation using CuCN as a cyanide source. The resulting octamethoxy tetracyano resorcin[4]arene is demethylated to produce the target molecule of tetracyano resorcin[4]arene.

At the beginning, tetrabromo *C*-methyl and *C*-hexylresorcin[4]arenes were subjected to the methylation reaction with dimethyl sulfate in the presence of anhydrous $K_2CO_3$. However, the very poor solubility of tetrabromo *C*-methylresorcin[4]arene in acetonitrile resulted in the very low yield of tetrabromo octamethoxy *C*-methylresorcin[4]arene. Hence, only tetrabromo octamethoxy *C*-hexylresorcin[4]arene

**2.40** was used for the next step. The synthetic procedure of tetracyano *C*-hexylresorcin[4]arene is shown in Scheme 2.8.

Tetrabromo octamethoxy *C*-hexylresorcin[4]arene was obtained in 62% yield. The $^{1}$H-NMR spectrum showed only one peak for the aromatic protons and methine bridge protons at $\delta$ = 6.52 and 4.41 ppm, respectively. Besides, there is only the peak for the $-OCH_3$ protons with the total number of 24. These results suggest that compound **2.40** adopts a crown conformation and all alkyl side chains are oriented in the axial position. The $^{13}$C-NMR spectrum of **2.40** also revealed one signal for the methine carbons (Ar*C*HAr) as a confirmation of a crown (*rccc*) conformer.

Cyanations of compound **2.40** were tested in both DMF and *N*-methyl-pyrrolidinone (NMP). Again, DMF seems to produce a complex mixture as observed when octabenzylated tetrabromo resorcin[4]arenes were used in the ation reactions. Further investigation using (*l*)-proline as an auxiliary ligand[150] yielded the same complex residue. On the contrary, cyanation of **2.40** in NMP resulted in only two major products as observed from TLC experiments (silica gel; $CH_2Cl_2$:EtOAc = 97:3).




**Scheme 2.8** The synthetic procedure of tetracyano *C*-hexylresorcin[4]arene
(i) NBS, 2-Butanone; 0ºC to RT; 73% yield.
(ii) $(CH_3)_2SO_4$, anhydrous $K_2CO_3$, $CH_3CN$; reflux, 72 hr; 62% yield.
(iii) CuCN, NMP; reflux, 72 hr; 46% yield.
(iv) $AlCl_3$, thiourea, $CH_2Cl_2$; reflux, 24 hr; 72% yield.

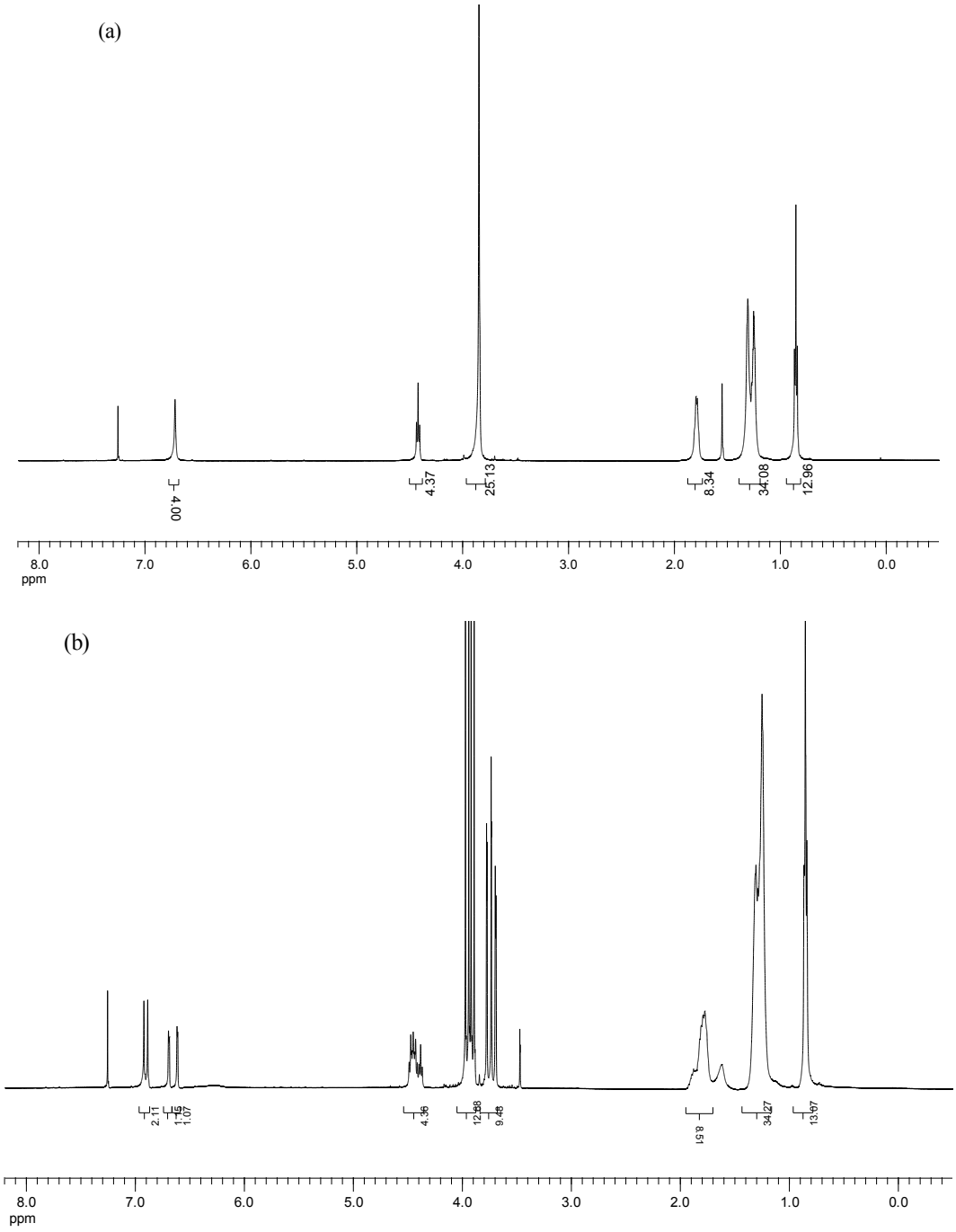



**Figure 2.18** $^{1}$H-NMR spectra of (a) compounds **2.41** and (b) compound **2.42.** (FID files were modified and operated by program MestRe-C).[151]

Purification of the residue by silica gel column chromatography using the gradient mobile phase ($CH_2Cl_2$:EtOAc = 97:3 to 95:5 as eluents) afforded two products, **2.41** and **2.42**. Surprisingly, both of them are tetracyano resorcin[4]arene derivatives. The $^1$H-NMR spectra of compounds **2.41** and **2.42** are shown in Figure 2.18.

Obviously, compound **2.41** is tetracyano octamethoxy *C*-hexylresorcin[4]arene (46% yield). The pattern of proton chemical shifts is similar to that of compound **2.40**. A slight downfield shift is observed due to the change of bromo to cyano group. The $^{13}$C-NMR spectrum of compound **2.41** also showed one signal for the –O*C*H$_3$ carbons as well as four chemical shifts for the four different aromatic carbons.

For compound **2.42**, its $^1$H-NMR spectrum has 4 magnetically inequivalent aromatic protons. This suggests that compound **2.42** might adopt another conformation rather than the expected crown isomer. There are 7 peaks belong to –$OCH_3$ protons around $\delta$ = 3.98-3.71 ppm. From integration, each signal has three protons, giving the total of 21 protons for the –$OCH_3$ group. Consequently, it implies that one methoxy group is missing from compound **2.42** resulting in an unsymmetric macrocycle. The $^{13}$C-NMR spectrum of **2.42** showed multiple chemical shifts especially for the $C_{ar}$–$OCH_3$ and $C_{ar}$–OH (three peaks) and –O*C*H$_3$ (7 peaks) signals. HMQC results confirmed that each peak for the –$OCH_3$ carbons is correlated to one proton signal for the –$OCH_3$ peaks. The mass spectrum and elemental analysis result are also consistent with the expected structure. Therefore, the formula of compound **2.42** should be tetrabromo heptamethoxy *C*-hexylresorcin[4]arene.

Cleavage of the methoxy groups of both compounds **2.41** and **2.42** was successfully accomplished by the reagent pair $AlCl_3$-thiourea in dry $CH_2Cl_2$.[152] This

demethylation procedure gave a higher yield of tetracyano *C*-hexylresorcin[4]arene **2.43** (72%) compared to the use of LiI in a mixture of pyridine and γ-collidine (49%).[148] Usage of the $AlCl_3$-thiourea reagent pair is much more convenient and does not require excessive heating or dry LiI, pyridine and 2,4,6-collidine.

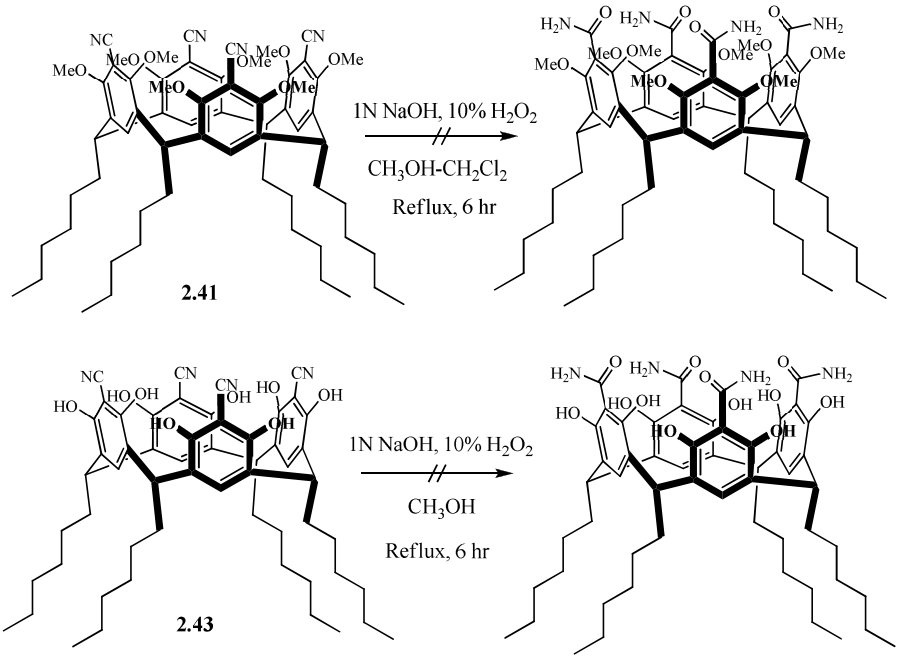
Compound **2.43** was characterized by $^1$H- and $^{13}$C-NMR spectroscopy, MALDI-TOF MS, FT-IR spectroscopy and microanalysis. The $^1$H-NMR spectrum of tetracyano *C*-hexylresorcin[4]arene showed a broad signal for the –OH group (exchanged with $H_2O$ in acetone-$d_6$). Only one set of aromatic protons (*para* to the –CN group) is observed. The methine proton signal appears at δ = 4.47 ppm implying that tetracyano *C*-hexyl-resorcin[4]arene exhibits a crown (*rccc*) conformation. The IR spectrum of compound **2.43** shows the peak for the C-N triple bond stretching at ν = 2243 $cm^{-1}$. The mass spectrum and elemental analysis results are also in good agreement with the calculated exact mass and chemical formula.

### 2.6.3 Attempts on the hydrolysis reaction of tetracyano *C*-hexyl-resorcin[4]arene derivatives.

As previously mentioned in section 2.6, amido substituted resorcin[4]arenes may be building block candidates for new hydrogen-bonded self-assembly systems. With the availability of compounds **2.41** and **2.43**, attempts to synthesize their amido derivatives were carried out. The proposed hydrolysis procedure for compounds **2.41** and **2.43** is depicted in Scheme 2.9.

Typically, basic hydrolysis of aromatic nitriles to aromatic primary amides requires $H_2O_2$. In these attempts, 10% $H_2O_2$ aqueous solution was used as the reagent

together with an aqueous sodium hydroxide solution.[153] Moreover, because of the insolubility of compound **2.41** in methanol, dry $CH_2Cl_2$ was employed as a co-solvent in the hydrolysis reaction.




**Scheme 2.9** The proposed hydrolysis reactions for compound **2.41** (top) and compound **2.43** (bottom).

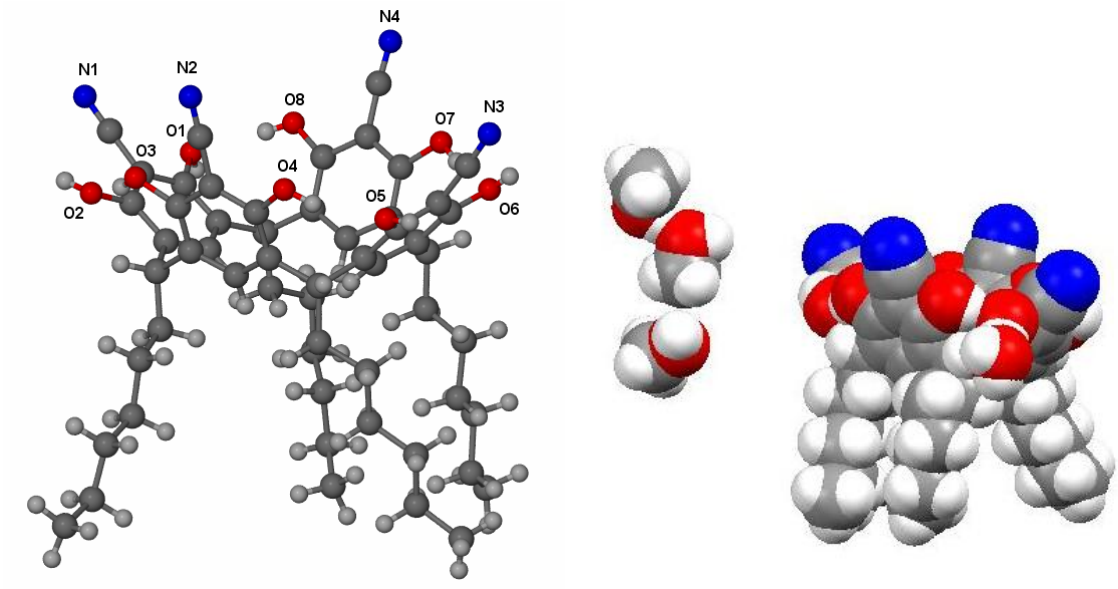
Hydrolysis of compound **2.41** gave only recovered starting material after workup. This observation suggests that compound **2.41** is not hydrolyzed by NaOH. The possible explanation is compound **2.41** has very poor solubility in methanol, even in the presence of a co-solvent like dichloromethane. Since 10% $H_2O_2$ solution contains water, the reaction mixture may become separated, resulting in heterogeneous reaction condition. Therefore, the reaction did not proceed as expected.

On the contrary, tetracyano *C*-hexylresorcin[4]arene dissolves very well in methanol and did not require a co-solvent in the reaction like its octamethoxy analog **2.41**. After the workup process with dilute HCl and extraction with ethyl acetate, an oily residue was obtained. The $^{1}$H-NMR of the residue revealed several broad signals but there was no trace of methine or alkyl side chain proton peaks. There is a possibility that compound **2.43** undergoes unexpected over-oxidation which might result in tetracarboxyl *C*-hexylresorcin[4]arene (soluble in water and may be removed after extraction) or other unknown compounds. Purification of the residue from hydrolysis of **2.43** is impractical with normal silica gel column chromatography because the resorcin[4]arene derivative has eight hydroxy groups causing a tailing effect on the TLC experiments. However, there is no conclusive result showing that hydrolysis of tetracyano resorcin[4]arene derivatives could not be achieved since these attempts were carried out with only two compounds (**2.41** and **2.43**). Other tetracyano resorcin[4]arene derivatives protected with other functional groups, such as the tetrahydropyranyl (THP) group, could possibly undergo hydrolysis without any side reaction.

### 2.6.4 Solid state structure of tetracyano *C*-hexylresorcin[4]arene

A single crystal of tetracyano *C*-hexylresorcin[4]arene suitable for X-ray crystallography was obtained from slow evaporation of the solution of compound **2.43** in methanol:$H_2O$ = 8:1. Crystals of compound **2.43** are orange in color. The X-ray crystal structure revealed that the asymmetric unit contains one molecule of macrocycle, 3 methanol and one water molecules. Unfortunately, neither a capsule-like structure nor a self-assembly entity was found. Furthermore, the structure shows that there is no solvent molecule encapsulated in the aromatic cavity of compound **2.43**.

Compound **2.43** recrystallized in the point group $P2_1/n$ which belongs to a monoclinic crystal system. The stereochemistry of tetracyano *C*-hexylresorcin[4]arene is clearly a crown (*rccc*) conformation where all hexyl groups orient in the axial position. The asymmetric unit of **2.43** with labeled nitrogen and oxygen atoms is shown in Figure 2.19.




(a) (b)

**Figure 2.19** Crystal structure of compound **2.43** in different representation (a) the capped stick (3 methanol molecules are removed for clarity) and (b) the space filling diagram with a water and three MeOH molecules.

Bond distances of the C-N triple bonds (1.141-1.146 Å) are in the expected range Angles between $C_{ar}$ and CN group are almost 180º (176.34º – 178.54º). There is evidence of intramolecular hydrogen bonds in compound **2.43**. Hydroxy groups of adjacent aromatic rings participate in these hydrogen bonding interactions. O···O bond distances are 2.700-2.831 Å and the bond angles are in the range of 152.36º-178.29º. Interestingly, only one hydroxy group (O1) forms a hydrogen bond to a water molecule (O···O = 2.707 Å, O(1)-H(1)-O(4S) = 165.02 º). Three methanol entities are distant from the macrocycle and there is no evidence of hydrogen bonds between them and the resorcin[4]arene molecule. X-ray crystal data and refinement methods are shown in Table 2.3. Selected bond angles and bond distances are presented in Table 2.4.

**Table 2.3** X-ray crystal data and refinement methods for compound **2.43**.

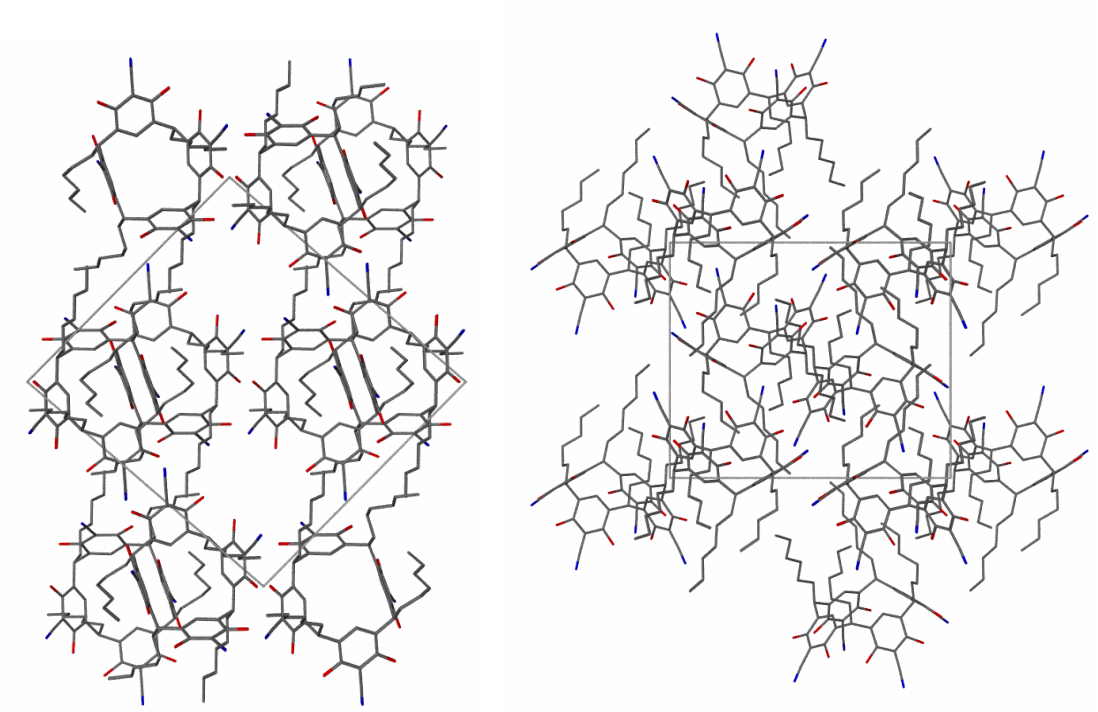
| | |
|---|---|
| Chemical Formula | $C_{59}H_{82}N_4O_{12}$ |
| Formula Weight (g· $mol^{-1}$) | 1039.29 |
| Crystal System | Monoclinic |
| Space Group | $P2_1/n$ |
| Temperature (K) | 173(2) |
| $a$ (Å) | 18.167(5) |
| $b$ (Å) | 16.430(4) |
| $c$ (Å) | 19.731(5) |
| $\alpha, \beta, \gamma$ (°) | 90.00, 93.477(3), 90.00 |
| $V$ ($Å^3$) | 5879(3) |
| $Z$ | 4 |
| $\rho_{calc}$ (g·$cm^{-3}$) | 1.174 |
| Mo-Kα radiation (λ, Å) | 0.71073 |
| Adsorption coefficient ($mm^{-1}$) | 0.082 |
| $F_{000}$ | 2240 |
| $2\theta_{max}$ (°) | 54.98 |
| Crystal size | 0.50 x 0.35 x 0.20 $mm^3$ |
| Index ranges | -23<=$h$<=23, -21<=$k$<=21, -25<=$l$<=25 |
| Reflection collected | 68252 |
| Independent reflections to θ = 27.49º | 13444 ($R_{int}$ = 0.0376) |
| Data/restraints/parameters | 13444/0/754 |
| Goodness-of-fit on $F^2$ | 1.035 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0566, ω$R_2$ = 0.1569 |
| R indices (all data) | $R_1$ = 0.0749, ω$R_2$ = 0.1722 |

**Table 2.4** Selected bond distances (Å) and bond angles (º) of compound **2.43**.

| | |
|---|---|
| N(1)-C(53) | 1.141(2) |
| N(2)-C(54) | 1.143(3) |
| N(3)-C(55) | 1.141(3) |
| N(4)-C(56) | 1.146(2) |
| C(4)-C(53)-N(1) | 178.54 |
| C(11)-C(54)-N(2) | 177.08 |
| C(18)-C(55)-N(3) | 176.22 |
| C(25)-C(56)-N(4) | 176.34 |
| O(1)-O(8) | 2.831 |
| O(2)-O(3) | 2.700 |
| O(4)-O(5) | 2.772 |
| O(6)-O(7) | 2.729 |
| O(1)-O(4S) | 2.707 |
| O(8)-H(8O)-O(1) | 178.29 |
| O(3)-H(3O)-O(2) | 167.85 |
| O(4)-H(4O)-O(5) | 161.20 |
| O(7)-H(70)-O(6) | 152.36 |
| O(1)-H(1)-O(4S) | 165.02 |

Compound **2.43** forms two arrays of packed resorcin[4]arene subunits which are anti-parallel to each other. For each array, two resorcin[4]arene molecules orient in the head-to-tail arrangement. One hexyl group side chain of tetracyano *C*-hexylresorcin[4]-arene is located in the cavity of another macrocycle. Obviously, there is neither π-π interaction nor hydrogen bonding between the two arrays of macrocycles. Moreover, it is not conclusive that the methyl group of a hexyl side chain has a C-H···π interaction with

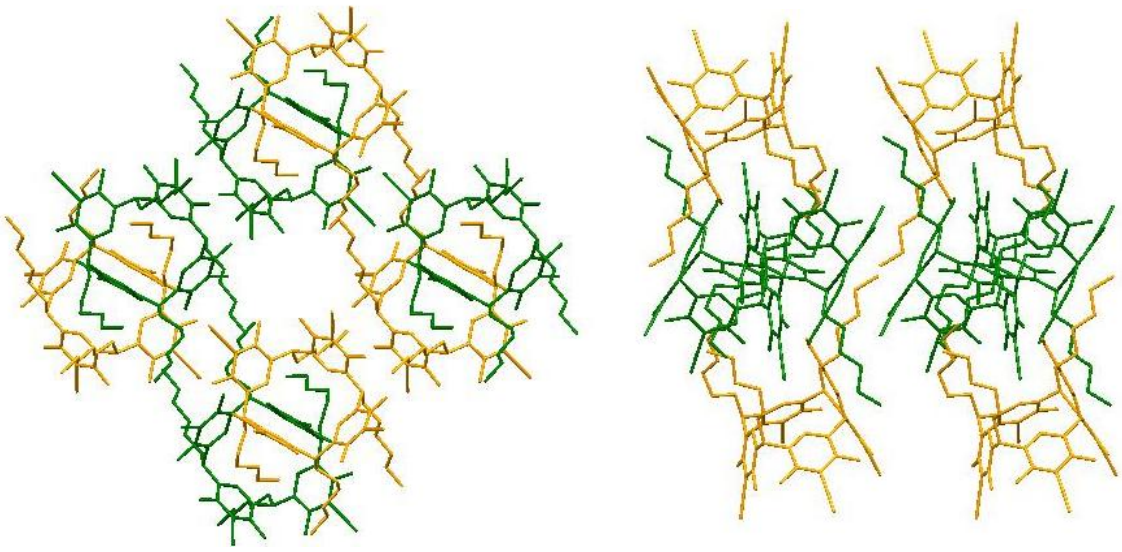
the electron-aromatic region of another macrocycle (C-H···centroid = 3.720 Å). Views of the crystal packing of compound **2.43** are shown in Figure 2.20.



(a) (b)

**Figure 2.20** The crystal packing of compound **2.43** in different views**.** (a) a view along the [001] plane, and (b) a view along the [010] plane. All hydrogen atoms are omitted for clarity.

To enhance the view of **2.43** crystal packing, color contrast representations are used to show the two different types of resorcin[4]arene molecules.(Figure 2.21) The yellow one represents a macrocycle for which one of its hexyl side chains points into the cavity of another resorcin[4]arene molecule (green). For each array, two molecules of **2.43** stack to each other with the angle about 75º. One cyano group of a green resorcin[4]arene is located in the middle of four hexyl groups of a yellow macrocycle.



(a) (b)

**Figure 2.21** Views of compound **2.43** packing arrangement represented in a color contrast to differentiate two types of macrocycle (yellow and green). (a) the view perpendicular to the *ac* plane. (b) the view down the crystallographic *c* axis. All hydrogen atoms are omitted for clarity.

The reason that tetracyano *C*-hexylresorcin[4]arene does not form a hydrogen-bonded assembly might come from the additional cyano group when compared to its cousins, resorcin[4]arenes and pyrogallol[4]arenes. The nitrogen atom of a cyano group extends the distance from the aromatic ring in the linear alignment and might prohibit the formation of stable hydrogen bonding between the molecules of **2.43**. Moreover, methanol and water molecules are capable of forming hydrogen bonds with hydroxy groups of compound **2.43**. It is also probable that these solvent molecules disturb the stable hydrogen bonding pattern of compound **2.43** resulting in the lack of a hydrogen-bonded entity observed in this condition.

### 2.6.5 Ag(I) complex of tetracyano *C*-hexylresorcin[4]arene: X-ray crystal structure study

In 2005, Chen and coworkers studied the complexation of tetracyano *C*-ethyl-resorcin[4]arene **2.44** (Figure 2.22) with several quaternary ammonium cations by ESI-MS, fluorescence and NMR spectrometries.[154] Compound **2.44** forms 1:1 inclusion complexes not only with small quaternary ammonium cations such as $Me_4N^+$ and $Et_4N^+$ but also bulky ones like $Pr_4N^+$ and $Bu_4N^+$ (which cannot be encapsulated by normal resorcin[4]arenes). Association constants determination by $^1$H-NMR showed that compound **2.44** has the highest affinity toward $Pr_4N^+$ and $Et_4N^+$ cations.

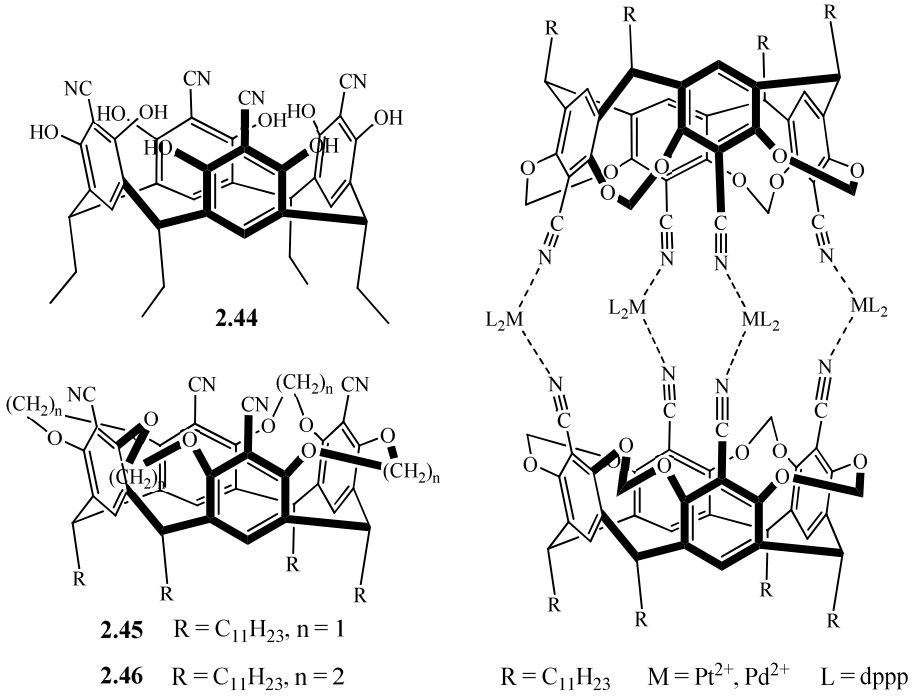



**Figure 2.22** Chemical structure of compounds **2.44-2.46** (left) and the metal-directed dimeric capsule of compound **2.45** (right).

Dalcanale *et al.*[155] extensively investigated metal-directed self-assemblies of tetracyano cavitands (compounds **2.45** and **2.46**) by X-ray crystallography and NMR spectroscopy. They discovered that the major factor controlling the formation of metal-coordinated dimeric capsules is the chelate angle between chelating ligand and the metal center. The ideal bond angle must be close to 90º. Therefore, square planar $d^8$ metal complexes such as Pt(dppp)$(OTf)_2$ and Pd(dppp)$(OTf)_2$ (dppp = 1,3-*bis*(diphenyl-phosphinopropane)) are most suitable to enforce the formation of dimeric cages.

Compound **2.45** forms dimeric Pt(II) capsules at room temperature in $C_2D_2Cl_4$ but coordination cage species of compound **2.46** were observed only as partial capsules at 300 K.[155] This phenomenon may come from the less rigid structure of compound **2.46**. However, elevation of the temperature from 300K to 353 K facilitates the complete association of Pt(II) capsules. Moreover, only non-coordinating anions such as triflate ($CF_3SO_3^-$), tetrafluoroborate ($BF_4^-$), and hexafluorophosphate ($PF_6^-$) can stabilize the coordination capsules. The presence of a basic anion like acetate or trifluoroacetate can dissemble the cages.

Recently, the Pd(II) complex of compound **2.45** was subjected to solution studies with various NMR techniques such as PGSE, NOE, and EXSY.[156] The results showed that all counteranions are located around the cage not only in the four equatorial sites close to the metal centers but also in the alkyl pockets formed by the side chains. The latter observation suggests a stabilization of anion through C-H···$X^-$ interactions. Stability of the $[Pd(dppp)_2(\mathbf{2.45})_2]^{7+}$ depends on the polarity of the solution. Addition of polar solvent $CD_3NO_2$ into $CDCl_3$ reduces the rate of the complex $[Pd(dppp)_2(\mathbf{2.45})_2]^{7+}$ formation.

A 1 x $10^{-3}$ M solution of tetracyano *C*-hexylresorcin[4]arene in methanol (9 mL) was added to a 0.1 M solution of $AgNO_3$ in water (1 mL). A light brown precipitate formed immediately after the addition. This is totally different from other metal salts such as $Cu(NO_3)_2$ which need pyridine to form precipitate. Slow evaporation of the solution containing compound **2.43** and $AgNO_3$ after 24 hours afforded yellow rod-like crystals suitable for X-ray single crystal determination.

Complex [Ag(**2.43**)MeOH] recrystallized in a space group of $P2_12_12_1$ in the monoclinic crystal system. The asymmetric unit is composed of a macrocycle, a silver(I) ion, a methanol molecule, and two unidentified oxygen atoms (could not be identified as methanol or water). Hydrogen atoms of methanol and some hydrogen atoms of the hydroxy groups could not be located due to the high thermal parameters. There is no evidence of $NO_3^-$ in the proximity of the complex. It may imply that nitrate ion is not required to balance the positive charge of the Ag(I) ion. Therefore, it is possible that one –OH group is deprotonated during the complex formation resulting in a neutral entity. In the solid state, macrocycle **2.43** in the [Ag(**2.43**)(MeOH)] adopts a crown (*rccc*) conformation like free tetracyano *C*-hexyl- resorcin[4]arene. This observation also implies that intramolecular hydrogen bonds between adjacent aromatic rings are not completely destroyed. The asymmetric unit with labeled hetero atoms is depicted in Figure 2.23.

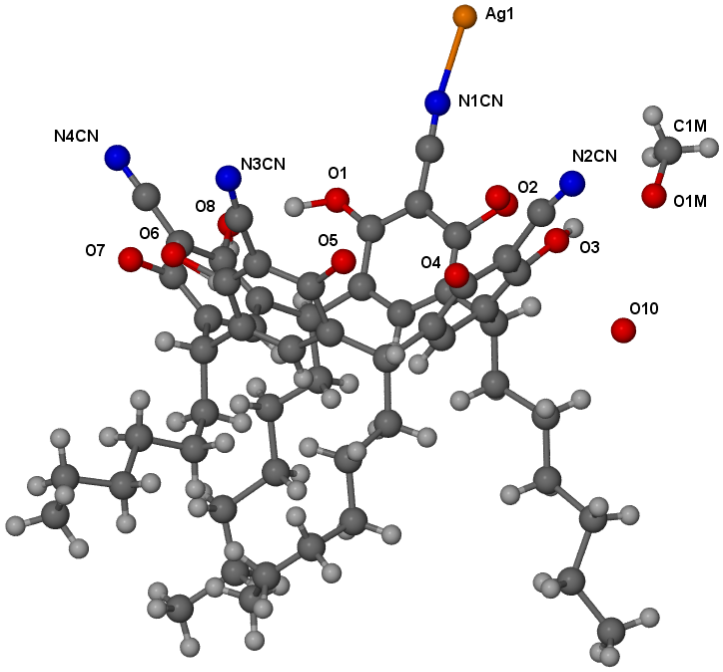



**Figure 2.23** The asymmetric unit of Ag(I) complex of tetracyano *C*-hexylresorcin[4]-arene. Heteroatoms are labeled.

Unfortunately, the Ag(I) complex of compound **2.43** is not a dimeric structure or one-dimensional head-to-head polymer as first hypothesized. However, the complex is clearly a polymer. Three cyano groups of tetracyano *C*-hexylresorcin[4]arene participate in metal-coordination interaction *via* the nitrogen atom of a cyano group. One cyano group does not coordinate to any Ag(I) ion. The coordination number of Ag(I) is three and the geometry of the Ag(I) center resembles distorted trigonal planar. Crystal data and the refinement method of the [Ag(**2.43**)MeOH] complex are shown in Table 2.5 and its selected bond distances and bond angles are represented in Table 2.6.

**Table 2.5** Crystal data and refinement methods of the [Ag(**2.43**)(MeOH)] complex.

| | |
|---|---|
| Chemical Formula | $C_{57}H_{67}AgN_4O_{11}$ |
| Formula Weight (g· mol$^{-1}$) | 1092.02 |
| Crystal System | Orthorhombic |
| Space Group | $P2_12_12_1$ |
| Temperature (K) | 173(2) |
| $a$ (Å) | 15.749(4) |
| $b$ (Å) | 15.874(4) |
| $c$ (Å) | 26.308(7) |
| $\alpha, \beta, \gamma$ (°) | 90.00, 90.00, 90.00 |
| $V$ (Å$^3$) | 6577(3) |
| $Z$ | 4 |
| $\rho_{calc}$ (g·cm$^{-3}$) | 1.103 |
| Mo-Kα radiation (λ, Å) | 0.71073 |
| Adsorption coefficient (mm$^{-1}$) | 0.358 |
| $F_{000}$ | 2288 |
| $2\theta_{max}$ (°) | 41.72 |
| Crystal size | 0.40 x 0.10 x 0.0.5 mm$^3$ |
| Index ranges | -15<=$h$<=15, -15<=$k$<=15, -26<=$l$<=26 |
| Reflection collected | 42328 |
| Independent reflections to $\theta$ = 20.86 | 6928 ($R_{int}$ = 0.1057) |
| Data/restraints/parameters | 6928/4/634 |
| Goodness-of-fit on F$^2$ | 1.239 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.1166, ω$R_2$ = 0.2985 |
| R indices (all data) | $R_1$ = 0.1676, ω$R_2$ = 0.3433 |

**Table 2.6** Selected bond lengths and bond angles of Ag(I) complex of compound **2.43**

| | |
|---|---|
| Ag(1)-N(4CN) | 2.17(2) |
| Ag(1)-N(1CN) | 2.207(18) |
| Ag(1)-N(2CN) | 2.212(18) |
| N(1CN)-C(1CN) | 1.13(2) |
| N(2CN)-C(2CN) | 1.10(3) |
| N(3CN)-C(3CN) | 1.20(2) |
| N(4CN)-C(4CN) | 1.18(3) |
| O(1)-O(8) | 2.622 |
| O(2)-O(3) | 2.609 |
| O(4)-O(5) | 2.738 |
| O(6)-O(7) | 2.771 |
| O(3)-O(1M) | 2.671 |
| O(4)-O(9) | 2.631 |
| N(4CN)-Ag(1)-N(1CN) | 136.8(7) |
| N(4CN)-Ag(1)-N(2CN) | 107.4(7) |
| N(1CN)-Ag(1)-N(2CN) | 115.6(7) |
| C(1CN)-N(1CN)-Ag1 | 172.5(17) |
| C(2CN)-N(2CN)-Ag1 | 151(2) |
| C(4CN)-N(4CN)-Ag1 | 173(2) |
| N(1CN)-C(1CN)-C4 | 179(2) |
| N(2CN)-C(2CN)-C25 | 170(2) |
| N(3CN)-C(3CN)-C18 | 173.8(18) |
| N(4CN)-C(4CN)-C11 | 175(3) |
| O(1)-H(1O)-O(8) | 151.69 |

A silver(I) center is coordinated by three cyano groups, each from a different macrycycle **2.43**. Two macrocycles orient in a head-to-head fashion using one of their cyano groups to interact with the metal center. The other molecule of **2.43** joins the

complex in a head-to-head fashion with one macrocycle and aligns parallel to the other one. Two head-to-head oriented macrocycles are linked by two metal centers (see Figure 2.24). Ag-N and N-C bond distances of this complex are in the range of 2.17-2.21 Å and 1.10-1.20 Å, respectively. The change of C-N bond length is not the same for all cyano groups. Two of them decrease when compared to those of free compound **2.43** (see Table 2.4), whereas the other two bonds increase their distances (0.04-0.06 Å). Additionally, a metal center adopts a distorted trigonal planar geometry with the N-Ag-N bond angles of 136.8, 115.6, and 107.4º, respectively.

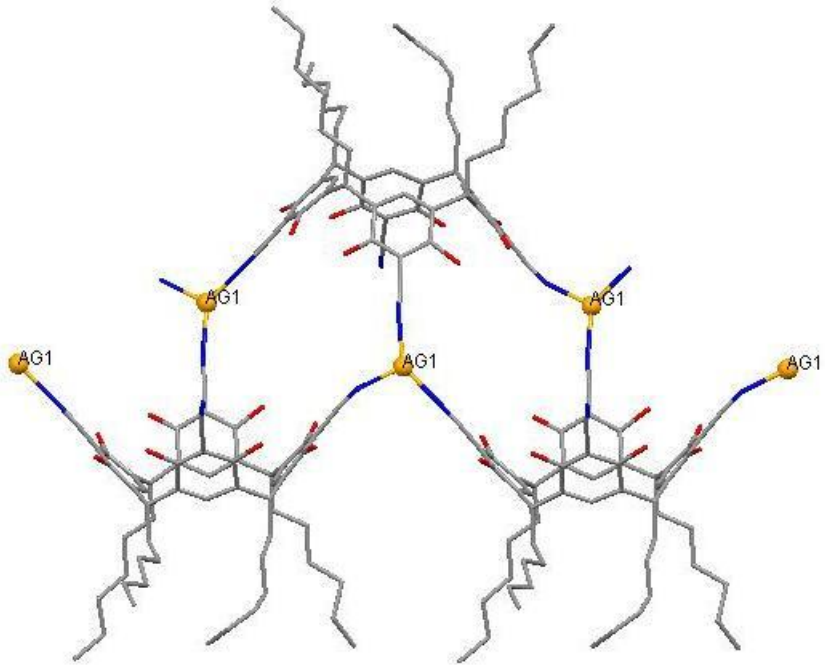
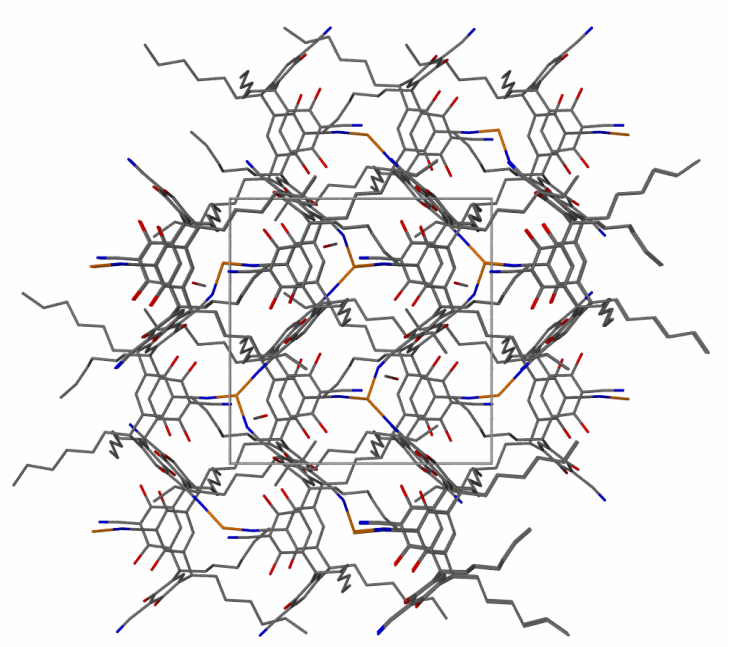



**Figure 2.24** X-ray crystal structure of [Ag(**2.43**)MeOH] complex showing 3-coordinated silver(I) ion (yellow) in a distorted trigonal planar geometry.

The non-participant cyano group of a macrocycle **2.43** is located under the alkyl side chain region of the adjacent molecule which is aligned in a head-to-tail fashion. Like

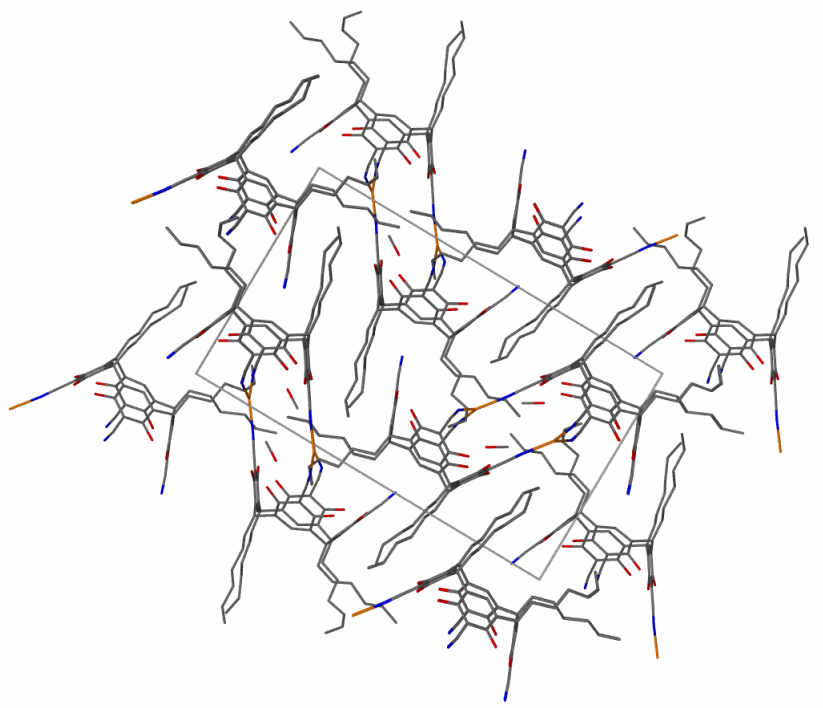
the solid state structure of compound **2.43**, one hexyl side chain of the [Ag(**2.43**)MeOH] complex is located in the aromatic cavity of another macrocycle. Again, there is no clear evidence of C-H···π interaction (C-H···centroid = 3.714 Å) between the end methyl group and an aromatic ring of tetracyano *C*-hexylresorcin[4]arene. Additionally, methanol and water molecules do not participate in any particularly interesting hydrogen bonding system.

The arrangement of the [Ag(**2.43**)MeOH] complex is clearly one type of metal-organic frameworks (MOF). However, this MOF does not exhibit any remarkable channel-like or porous structure which could be a potential candidate for several applications such as catalytic material or gas storage. Several views of [Ag(**2.43**)MeOH] complex crystal packing are shown in Figure 2.25.

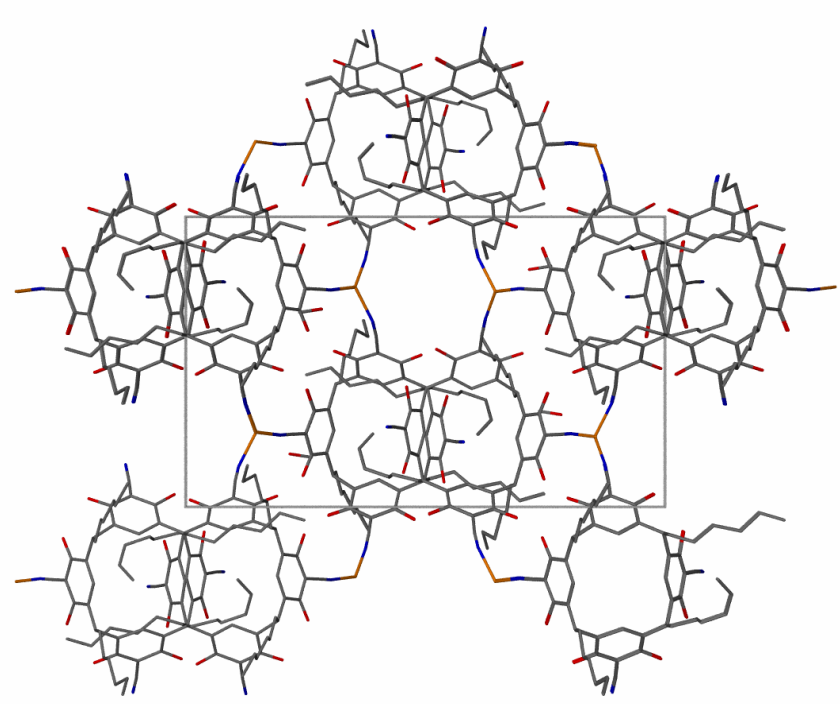


(a) View along *ac* plane

**Figure 2.25** The packing arrangement of the [Ag(**2.43**)MeOH] complex in many different views.



(b) View along *bc* plane



(c) View along *ab* plane

**Figure 2.25** (continued) The packing arrangement of the [Ag(**2.43**)MeOH] complex in many different views.

## 2.7 Experimental Section

### 2.7.1 General Procedures

All reagent grade chemicals and solvents were purchased from Sigma-Aldrich, Acros, Fisher-Scientific or Strem and used without further purification unless stated in the corresponding procedures. Tetrahydrofuran (THF) was dried over Na-benzophenone ketyl under $N_2$ and freshly distilled prior to use.[157] Toluene, $CH_2Cl_2$, and acetonitrile were dried over $CaH_2$ under $N_2$ and freshly distilled before use.[157] Acetone was dried over drierite for at least 48 hours and freshly distilled prior to use. Anhydrous $K_2CO_3$ and $Na_2CO_3$ were dried at 120ºC for 2 hours and allowed to cool down to room temperature in a desiccator (drierite) before use. Manipulations of dry solvents from distillation reservoirs were performed by syringes with interchangeable luer-lock needles or cannula. All glassware, needles, and syringes were dried in an oven for at least 6 hours prior to use in any reaction.

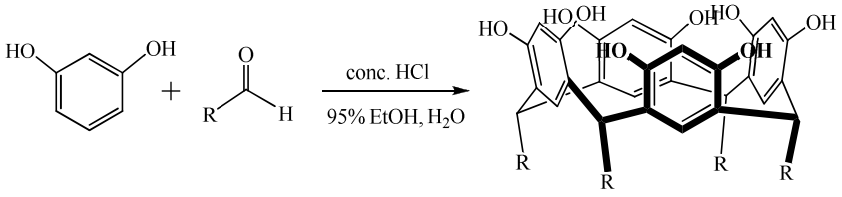
All reactions were conducted under $N_2$ or Ar atmosphere using the standard Schlenk techniques unless otherwise stated. Flash column chromatography was performed with silica gel 60 (Merck, 240-400 mesh, particle size 0.040-0.063 mm). Analytical thin-layer chromatography was conducted on Macherey-Nagel silica gel coated-aluminum plates $F_{254}$ (0.2 mm thickness). Melting points were recorded on a Fischer-Temp apparatus and are uncorrected.

### 2.7.2 Instrumentation

All $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Bruker ARX 250MHz, Bruker DRX 300MHz or Bruker DRX 500MHz. The chemical shifts were expressed

relative to the residual peaks of deuterated solvents ($CDCl_3$, acetone-$d_6$, methanol-$d_4$, DMSO-$d_6$) as internal standard. DMSO-$d_6$ was dried by passing the deuterated solvent through a short column containing neutral alumina ($Al_2O_3$) before use. Infrared spectra were recorded as a pellet of the mixture with IR-grade KBr using a Nicolet Magna-IR 550 spectrophotometer. Electrospray Ionization (ESI, both positive and negative modes) mass spectra were recorded on a Thermo-Finnigan TSQ7000 triple-quadrupole mass spectrometer and performed by Dr. Nathan Leigh of the Mass Spectrometry Facility. MALDI-TOF mass spectra were recorded on an Applied Biosystems 4700 MALDI TOF-TOF mass spectrometer using dithranol as external matrix at the MU Proteomics Center. All MALDI-TOF experiments were conducted by Andrew K. Maerz, a graduate student from the Department of Chemistry at the University of Missouri-Columbia. Elemental Analyses were performed at Galbraith Laboratories, Inc. Knoxville, TN.

### 2.7.3 Synthesis of *C*-alkylresorcin[4]arenes




A solution of resorcinol (44.04 g, 0.400 mol) in 95% ethanol (200 mL) and water (200 mL) was cooled to 0ºC in an ice bath. Conc. HCl (5 mL) was added dropwise with constant stirring. Then, appropriate aldehyde (0.410-0.420 mol) was added to the solution via an adding funnel over 1 hr at 0-5ºC. The reaction mixture was then heated to 70ºC for

48-72 hr. During this period, the solution turned from colorless to cloudy yellow or orange solution. After cooling to room temperature, the mixture was poured over deionized water (2 L) ans stirred vigorously for 2-3 hr. The precipitate was then collected by vacuum filtration on Buchner funnel and washed with hot water until the filtrate was neutral to pH paper. The product was dried under vacuum for 48 hr to afford yellow or orange or brownish yellow powder.

*C*-methylresorcin[4]arene **2.14** 46.39 g (85% yield)

$^{1}$H-NMR (300 MHz, acetone-$d_6$, 300 K): δ = 8.46 (s, 8H, -O*H*), 7.65 (s, 4H, -Ar*H meta* to –OH), 6.22 (s, 4H, -Ar*H ortho* to –OH), 4.54 (q, 4H, $^{3}J$ = 7.3 Hz, ArC*H*Ar), 1.76 (d, 12H, $^{3}J$ = 7.3 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, acetone-$d_6$): δ = 152.3 (*C*-OH), 125.7 ($C_{ar}$H *meta* to COH), 123.5 ($C_q$ *ortho* to COH), 102.5 ($C_{ar}$H *ortho* to COH), 29.0 (Ar*C*HAr), 22.0 (-*C*$H_3$) ppm.

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{32}H_{32}O_8$ - $H^+$] m/z = 543.20, Found m/z = 543.16 (100%).

*C*-ethylresorcin[4]arene **2.10** 48.77 g ( 81% yield)

$^{1}$H-NMR (300 MHz, acetone-$d_6$, 300 K): δ = 8.46 (s, 8H, -OH), 7.54 (s, 4H, -Ar*H meta* to –OH), 6.23 (s, 4H, Ar*H ortho* to –OH), 4.19 (t, 4H, $^{3}J$ = 7.9 Hz, ArC*H*Ar), 2.31 (qt, 8H, $^{3}J$ = 7.4 Hz, -C$H_2$CH$_3$), 0.90 (t, 12H, $^{3}J$ = 7.2 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, acetone-$d_6$): δ 152.2 (*C*-OH), 125.6 ($C_{ar}$H *meta* to COH), 123.3 ($C_q$ *ortho* to COH), 102.5 ($C_{ar}$H *ortho* to COH), 33.3 (Ar*C*HAr), 22.8 (-*C*$H_2$-), 14.2 (-*C*$H_3$) ppm.

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{36}H_{40}O_8$ - $H^+$] m/z = 599.26, Found m/z = 599.47 (100%).

*C*-propylresorcin[4]arene **2.24** 51.67 g (79% yield)

$^1$H-NMR (300 MHz, acetone-$d_6$, 300 K): δ = 8.45 (s, 8H, -O*H*), 7.57 (s, 4H, -Ar*H meta* to –OH), 6.23 (s, 4H, Ar*H ortho* to –OH), 4.32 (t, 4H, $^3J$ = 7.8 Hz, ArC*H*Ar), 2.28 (q, 8H, $^3J$ = 7.5 Hz, -CHC$H_2$CH$_2$-), 1.31 (m, 8H, -C$H_2$CH$_3$), 0.94 (t, 12H, $^3J$ = 7.4 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, acetone-$d_6$): δ = 152.2 (*C*-OH), 124.9 ($C_{ar}$H *meta* to COH), 124.0 ($C_q$ *ortho* to COH), 102.4 ($C_{ar}$H *ortho* to COH), 34.9 (-CH*C*H$_2$-), 33.8 (Ar*C*HAr), 20.9 (-*C*H$_2$CH$_3$), 14.40 (-*C*H$_3$) ppm.

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{40}H_{48}O_8$·- $H^+$] m/z = 655.33, Found m/z = 655.41 (100%).

*C*-butylresorcin[4]arene **2.25** 49.91 g (70% yield)

$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.47 (s, 8H, -O*H*), 7.55 (s, 4H, -Ar*H meta* to –OH), 6.22 (s, 4H, Ar*H ortho* to –OH), 4.29 (t, 4H, $^3J$ = 7.8 Hz, ArC*H*Ar), 2.29 (q, 8H, $^3J$ = 7.5 Hz, -CHC$H_2$CH$_2$-), 1.37 (m, 8H, -CH$_2$C$H_2$CH$_2$), 1.27 (m, 8H, -C$H_2$CH$_3$), 0.89 (t, 12H, $^3J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (175 MHz, acetone-$d_6$): δ = 152.2 (*C*-OH), 124.5 ($C_{ar}$H *meta* to COH), 123.6 ($C_q$ *ortho* to COH), 102.4 ($C_{ar}$H *ortho* to COH), 34.0 (-CH*C*H$_2$-), 32.6 (Ar*C*HAr), 30.3, 22.4 (-*C*H$_2$), 13.6 (-*C*H$_3$) ppm.

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{44}H_{56}O_8$ - $H^+$] m/z = 711.39, Found m/z = 711.28 (100%).

*C*-isobutylresorcin[4]arene **2.12** 61.60 g (80% yield)

$^{1}$H-NMR (300 MHz, acetone-$d_6$, 300 K): δ = 8.45 (s, 8H, -O*H*), 7.57 (s, 4H, -Ar*H meta* to –OH), 6.23 (s, 4H, Ar*H ortho* to –OH), 4.32 (t, 4H, $^{3}J$ = 7.8 Hz, ArC*H*Ar), 2.25 (q, 8H, $^{3}J$ = 7.5 Hz, -CHC$H_2$CH$_2$-), 1.38 (m, 4H, -C*H*(CH$_3$)$_2$), 0.94 (d, 24H, $^{3}J$ = 7.4 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, acetone-$d_6$): δ = 152.2 (*C*-OH), 124.4 ($C_{ar}$H *meta* to COH), 123.9 ($C_q$ *ortho* to COH), 102.6 ($C_{ar}$H *ortho* to COH), 42.4 (-CH*C*H$_2$-), 34.0 (-Ar*C*HAr-), 31.6 (-CH$_2$-), 25.9 (-*C*H(CH$_3$)$_2$-), 22.9 (-CH$_3$) ppm.

(-)-ESI-MS (CH$_3$OH): calculated for [C$_{48}$H$_{64}$O$_8$ - H$^+$] m/z = 767.45, Found m/z = 767.61 (100%).

*C*-pentylresorcin[4]arene **2.26** 51.88 g (67% yield)

$^{1}$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.54 (s, 8H, -O*H*), 7.53 (s, 4H, -Ar*H meta* to –OH), 6.23 (s, 4H, Ar*H ortho* to –OH), 4.28 (t, 4H, $^{3}J$ = 8.0 Hz, ArC*H*Ar), 2.28 (q, 8H, $^{3}J$ = 8.0 Hz, -CHC$H_2$CH$_2$-), 1.33 (m, 16H, -C$H_2$-), 0.88 (t, 12H, $^{3}J$ = 7.1 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, acetone-$d_6$): δ = 152.1 (*C*-OH), 124.1 ($C_{ar}$H *meta* to COH), 123.7 ($C_q$ *ortho* to COH), 102.4 ($C_{ar}$H *ortho* to COH), 33.2 (-CH*C*H$_2$-), 31.5 (-Ar*C*HAr-), 28.5, 27.8, 22.2 (-*C*H$_2$-), 13.4 (-*C*H$_3$) ppm.

(-)-ESI-MS (CH$_3$OH): calculated for [C$_{48}$H$_{64}$O$_8$ - H$^+$] m/z = 767.45, Found m/z = 767.41 (100%).

*C*-hexylresorcin[4]arene **2.27** 68.13 g (82% yield)

$^{1}$H-NMR (300 MHz, acetone-$d_6$, 300 K): δ = 8.67 (s, 8H, -O*H*), 7.53 (s, 4H, -Ar*H meta* to –OH), 6.26 (s, 4H, Ar*H ortho* to –OH), 4.32 (t, 4H, $^{3}J$ = 7.9 Hz, ArC*H*Ar), 2.31 (q, 8H, $^{3}J$

= 7.9 Hz, -CHC$H_2$CH$_2$-), 1.40-1.31 (m, 24H, -C$H_2$-), 0.90 (t, 12H, $^3J$ = 6.7 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, acetone-$d_6$): δ = 151.8 (*C*-OH), 124.5 ($C_{ar}$H *meta* to COH), 124.1 ($C_q$ *ortho* to COH), 102.4 ($C_{ar}$H *ortho* to COH), 33.4 (-CH*C*H$_2$-), 31.6 (-Ar*C*HAr-), 28.7, 28.2, 24.5, 22.2 (-*C*H$_2$-), 17.6 (-*C*H$_3$) ppm.

(-)-ESI-MS (CH$_3$OH): calculated for [$C_{52}H_{72}O_8$ - H$^+$] m/z = 823.51, Found m/z = 823.84 (100%).

*C*-heptylresorcin[4]arene **2.28** 42.22 g (48% yield)

$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.45 (s, 8H, -O*H*), 7.53 (s, 4H, -Ar*H meta* to –OH), 6.21 (s, 4H, Ar*H ortho* to –OH), 4.30 (t, 4H, $^3J$ = 8.0 Hz, ArC*H*Ar), 2.27 (m, 8H, -CHC$H_2$CH$_2$-), 1.31-1.28 (m, 32H, -C$H_2$-), 0.94 (t, 12H, $^3J$ = 7.0 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, acetone-$d_6$): δ = 152.1 (*C*-OH), 124.4 ($C_{ar}$H *meta* to COH), 123.8 ($C_q$ *ortho* to COH), 102.8 ($C_{ar}$H *ortho* to COH), 34.8 (-CH*C*H$_2$-), 34.0 (-Ar*C*HAr-), 31.8, 29.7, 29.3, 28.1, 22.6 (-*C*H$_2$-), 14.0 (-*C*H$_3$) ppm

(-)-ESI-MS (CH$_3$OH): calculated for [$C_{56}H_{80}O_8$ - H$^+$] m/z = 879.58, Found m/z = 879.31 (100%).

*C*-octylresorcin[4]arene **2.29** 56.84 g (61% yield)

$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.46 (s, 8H, -O*H*), 7.53 (s, 4H, -Ar*H meta* to –OH), 6.22 (s, 4H, Ar*H ortho* to –OH), 4.30 (t, 4H, $^3J$ = 8.0 Hz, ArC*H*Ar), 2.28 (q, 8H, $^3J$ = 8.0 Hz, -CHC$H_2$CH$_2$-), 1.37-1.31 (m, 40H, -C$H_2$-), 0.90 (t, 12H, $^3J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, acetone-$d_6$): δ = 152.6 (*C*-OH), 125.3 ($C_{ar}$H *meta* to COH), 125.1

($C_q$ *ortho* to COH), 103.6 ($C_{ar}$H *ortho* to COH), 34.3 (-CH*C*$H_2$-), 34.2 (-Ar*C*HAr-), 32.6, 30.5, 30.4, 30.1, 29.0, 23.3 (-*C*$H_2$-), 14.4 (-*C*$H_3$) ppm

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{60}H_{88}O_8$ - $H^+$] m/z = 935.64, Found m/z = 935.29 (100%).

*C*-nonylresorcin[4]arene **2.19** 69.85 g (70% yield)

$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.48 (s, 8H, -O*H*), 7.55 (s, 4H, -Ar*H meta* to –OH), 6.26 (s, 4H, Ar*H ortho* to –OH), 4.34 (t, 4H, $^3J$ = 7.8 Hz, ArC*H*Ar), 2.25 (q, 8H, $^3J$ = 7.8 Hz, -CHC*H*$_2$CH$_2$-), 1.34-1.29 (m, 48H, -C*H*$_2$CH$_3$), 0.86 (t, 12H, $^3J$ = 6.8 Hz, -C*H*$_3$); $^{13}$C-NMR (125 MHz, acetone-$d_6$): δ = 152.2 (*C*-OH), 124.4 ($C_{ar}$H *meta* to COH), 123.9 ($C_q$ *ortho* to COH), 102.7 ($C_{ar}$H *ortho* to COH), 34.0 (-CH*C*$H_2$-), 33.1 (-Ar*C*HAr-), 31.9, 29.8, 29.7, 29.6, 29.3, 28.2, 22.6 (-*C*$H_2$-), 14.0 (-*C*$H_3$) ppm.

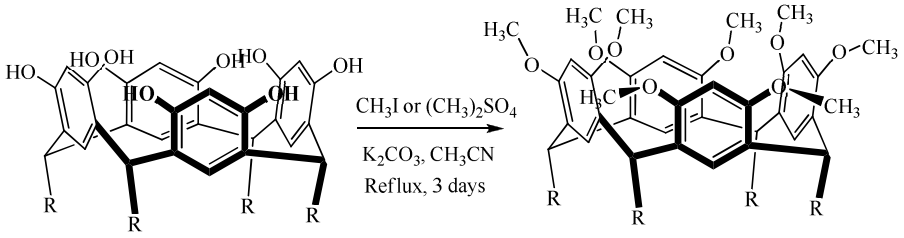
(-)-ESI-MS ($CH_3OH$): calculated for [$C_{64}H_{96}O_8$ - $H^+$] m/z = 991.70, Found m/z = 991.62 (100%).

*C*-decylresorcin[4]arene **2.30** 61.09 g (58% yield)

$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 8.45 (s, 8H, -O*H*), 7.53 (s, 4H, -Ar*H meta* to –OH), 6.25 (s, 4H, Ar*H ortho* to –OH), 4.37 (t, 4H, $^3J$ = 7.8 Hz, ArC*H*Ar), 2.26 (q, 8H, $^3J$ = 7.8 Hz, -CHC*H*$_2$CH$_2$-), 1.33-1.29 (m, 52H, -C*H*$_2$CH$_3$), 0.85 (t, 12H, $^3J$ = 6.8 Hz, -C*H*$_3$); $^{13}$C-NMR (acetone-$d_6$): δ = 151.9 (*C*-OH), 124.2 ($C_{ar}$H *meta* to COH), 123.6 ($C_q$ *ortho* to COH), 102.5 ($C_{ar}$H *ortho* to COH), 34.0 (-CH*C*$H_2$-), 33.1 (-Ar*C*HAr-), 31.9, 29.8, 29.7, 29.6, 29.4, 28.2, 22.6, 18.4 (-*C*$H_2$-), 14.0 (-*C*$H_3$) ppm.

(-)-ESI-MS ($CH_3OH$): calculated for [$C_{68}H_{104}O_8$ - $H^+$] m/z = 1047.77, Found m/z = 1047.86 (100%).

### 2.7.4 Synthesis of octamethoxy *C*-alkylresorcin[4]arenes




To a mixture of appropriate *C*-alkylresorcin[4]arene (5.00 mmol) and anhydrous $K_2CO_3$ (3.455 g, 25.0 mmol) in a 250 mL three-necked round bottom flask was added dry acetonitrile(50 mL). The reaction mixture was stirred at room temperature for an hour. $CH_3I$ or $(CH_3)_2SO_4$ (60.0 mmol) in dry acetonitrile (30 mL) was then added dropwise *via* an adding funnel over 30 min. After the addition was completed, the mixture was heated at reflux for 3 days. After cooling to room temperature, solvent was evaporated to dryness under vacuum to afford a brown or dark yellow oily residue. The residue was dissolved in $CH_2Cl_2$ and deionized water (150 mL) was added. The biphasic solution was stirred for 30 min and the organic layer was separated, washed with water (3 x 50 mL) and dried over anhydrous $Na_2SO_4$. The solution was concentrated on a rotary evaporator to give a yellow residue. The crude product was subjected to column chromatography on silica gel eluted with $CH_2Cl_2$ and a mixture of $CH_2Cl_2$:EtOAc (96:4 or 94:6). Combined organic phase was evaporated to dryness under reduced pressure to give the yellow oily

residue. Recrystallization from methanol afforded corresponding octamethoxy *C*-alkylresorcin[4]arene as a white solid.

4,6,10,12,16,18,22,24-Octamethoxy *C*-methylresorcin[4]arene **2.31** 1.15 g (35% yield) $^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.66 (s, 4H, -Ar*H meta* to $-OCH_3$), 6.31 (s, 4H, -Ar*H ortho* to $-OCH_3$), 4.41 (q, 4H, $^{3}J$ = 7.5 Hz, ArC*H*Ar), 3.60 (s, 24H, -OC*H*$_3$), 1.64 (d, 12H, $^{3}J$ = 7.5 Hz, -C*H*$_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 154.2 (*C*-$OCH_3$), 126.2 ($C_{ar}$H *meta* to $COCH_3$), 125.3 ($C_q$ *ortho* to $COCH_3$), 98.8 ($C_{ar}$H *ortho* to $COCH_3$), 55.3 (-O*C*H$_3$), 29.7 (Ar*C*HAr), 21.2 (-*C*H$_3$) ppm.

4,6,10,12,16,18,22,24-Octamethoxy *C*-ethylresorcin[4]arene **2.32** 0.80 g (22% yield) $^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): 6.66 (s, 4H, -Ar*H meta* to $-OCH_3$), 6.33 (s, 4H, Ar*H ortho* to $-OCH_3$), 4.39 (t, 4H, $^{3}J$ = 7.5 Hz, ArC*H*Ar), 3.59 (s, 24H, -OC*H*$_3$), 1.87 (quintet, 8H, $^{3}J$ = 7.5 Hz, -C*H*$_2$CH$_3$), 0.93 (t, 12H, $^{3}J$ = 7.0 Hz, -C*H*$_3$); $^{13}$C-NMR (175 MHz, $CDCl_3$): δ = 154.8 (*C*-$OCH_3$), 126.2 ($C_{ar}$H *meta* to $COCH_3$), 125.8 ($C_q$ *ortho* to $COCH_3$), 96.9 ($C_{ar}$H *ortho* to $COCH_3$), 56.1 (-O*C*H$_3$), 33.3 (Ar*C*HAr), 22.8 (-*C*H$_2$CH$_3$), 14.2 (-*C*H$_3$) ppm.

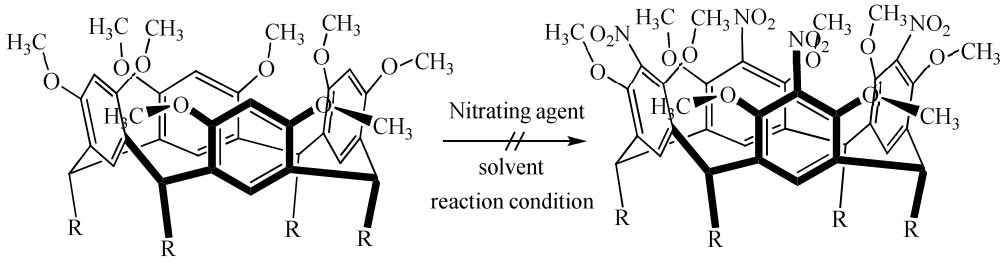
4,6,10,12,16,18,22,24-Octamethoxy *C*-propylresorcin[4]arene **2.33** 0.72 g (19% yield) $^{1}$H-NMR (300 MHz, $CDCl_3$, 300 K): δ = 6.64 (s, 4H, -Ar*H meta* to $-OCH_3$), 6.32 (s, 4H, Ar*H ortho* to $-OCH_3$), 4.48 (t, 4H, $^{3}J$ = 7.3 Hz, ArC*H*Ar), 3.61 (s, 24H, -OC*H*$_3$), 1.81 (q, 8H, $^{3}J$ = 7.6 Hz, -CHC*H*$_2$CH$_2$-), 1.38-1.30 (m, 8H, -C*H*$_2$CH$_3$), 0.96 (t, 12H, $^{3}J$ = 7.3 Hz, -C*H*$_3$); $^{13}$C-NMR (75.1 MHz, $CDCl_3$): δ = 154.7 (*C*-$OCH_3$), 126.2 ($C_{ar}$H *meta* to $COCH_3$),

124.9 ($C_q$ *ortho* to $COCH_3$), 95.8 ($C_{ar}H$ *ortho* to $COCH_3$), 56.4 (-O$CH_3$), 33.8 (Ar*C*HAr), 31.6, 20.9 (-*C*$H_2CH_3$), 14.4 (-*C*$H_3$) ppm.

4,6,10,12,16,18,22,24-Octamethoxy *C*-pentylresorcin[4]arene **2.34** 0.59 g (13% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.62 (s, 4H, -Ar*H meta* to –$OCH_3$), 6.32 (s, 4H, Ar*H ortho* to –$OCH_3$), 4.45 (t, 4H, $^3J$ = 7.1 Hz, ArC*H*Ar), 3.60 (s, 24H, -OC$H_3$), 1.83-1.80 (m, 8H, -CHC$H_2CH_2$-), 1.30-1.27 (m, 16H, -C$H_2$-), 0.88 (t, 12H, $^3J$ = 7.2 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, acetone-$d_6$): δ = 154.48 (*C*-$OCH_3$), 126.31 ($C_{ar}H$ *meta* to $COCH_3$), 125.66 ($C_q$ *ortho* to $COCH_3$), 96.05 ($C_{ar}H$ *ortho* to $COCH_3$), 56.49 (-O$CH_3$), 33.23 (Ar*C*HAr), 31.47, 28.54, 27.78, 22.25 (-*C*$H_2CH_3$), 13.39 (-*C*$H_3$) ppm.

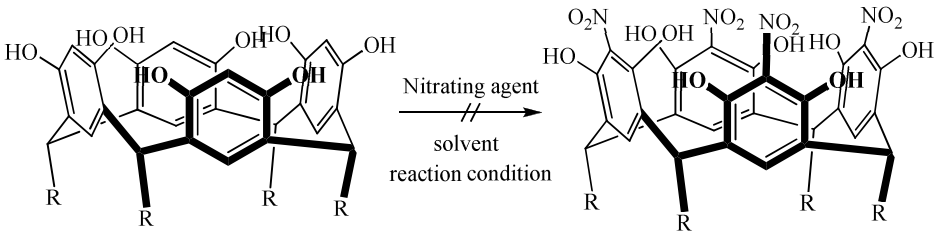
## 2.7.5 Synthetic attempts of tetranitro octamethoxy *C*-alkyl-resorcin[4]arenes




Appropriate octamethoxy *C*-alkylresorcin[4]arene (1.00 mmol) and nitrating agent (6.00-8.00 mmol) was dissolved in dry selected solvent (100 mL). The reaction mixture was stirred at room temperature or reflux for 24-72 hr. After cooling to room

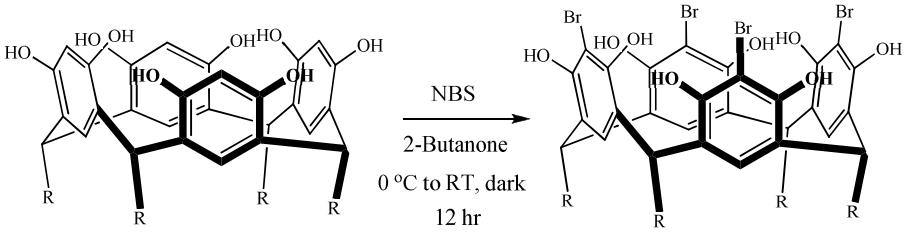
temperature (for reflux condition), organic solvent was evaporated to dryness on a rotary evaporator. The residue was added with deionized water (100 mL) and stirred for an hour. The suspension was then filtered, washed with water (3 x 50 mL) and air dried. If the residue dissolves in ethyl acetate, 100 mL of ethyl acetate was added and extracted with water (2 x 50 mL). The combined organic layer was concentrated under reduce pressure to give a dark solid or an oily residue. Characterization of a product was performed by $^{1}$H-NMR spectroscopy if it was soluble in any organic solvent.

### 2.7.6 Synthetic attempts of tetranitro *C*-alkylresorcin[4]arenes




Appropriate octamethoxy *C*-alkylresorcin[4]arene (2.00 mmol) and nitrating agent (10.0-12.0 mmol) was dissolved in dry selected solvent (100 mL). The reaction mixture was stirred at room temperature or reflux for 24-72 hr. After cooling to room temperature (for reflux condition), organic solvent was evaporated to dryness on a rotary evaporator. The residue was added with deionized water (100 mL) and stirred for an hour. The suspension was then filtered, washed with water (3 x 50 mL) and air dried. Characterization of a product was performed by $^{1}$H-NMR spectroscopy if it was soluble in a common organic solvent.

## 2.7.7 Synthesis of tetrabromo *C*-alkylresorcin[4]arenes




Appropriate *C*-alkylresorcin[4]arene (40.0 mmol) was dissolved in 2-butanone (180 mL). The solution was excluded from any light source by wrapping a round bottom flask with aluminum foil and cooled to 0ºC on an ice bath. *N*-bromosuccinimide (42.71 g, 0.240 mol) was added in portions over 30 minutes. The resulting solution was stirred at this temperature and allowed to warm to room temperature over 12 hr. The reaction mixture was concentrated on a rotary evaporator and subsequently filtered under vacuum. The precipitate was washed with cold methanol several times and dried in *vacuo* to afford the corresponding tetrabromo *C*-alkylresorcin[4]arene as a white solid.

5,11,17,23-Tetrabromo *C*-methylresorcin[4]arene **2.35** 28.08 g (82 % yield)

$^{1}$H-NMR (500 MHz, DMSO-$d_6$, 300 K): δ = 8.37 (s, 8H, -O*H*), 6.81 (s, 4H, -Ar*H meta* to –OH), 4.61 (q, 4H, $^{3}J$ = 7.0 Hz, ArC*H*Ar), 1.39 (d, 12H, $^{3}J$ = 7.0 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 149.0 (-*C*OH), 125.8 ($C_q$ *ortho* to COH), 123.8 (CH *meta* to COH), 102.0 ($C_q$ *ipso* to Br), 29.7 (Ar*C*HAr), 21.2 (-*C*$H_3$) ppm.

(-)-ESI-MS (DMSO): calculated for [$C_{32}H_{28}Br_4O_8$ - $H^+$] m/z = 854.84, Found m/z = 854.79 (100%).

5,11,17,23-Tetrabromo *C*-ethylresorcin[4]arene **2.36** 29.58 g (81%)

$^{1}$H-NMR (500 MHz, DMSO-$d_6$, 300 K): δ = 9.16 (s, 8H, -O*H*), 7.43 (s, 4H, -Ar*H meta* to –OH), 4.24 (t, 4H, $^{3}J$ = 7.5 Hz, ArC*H*Ar), 2.26 (m, 8H, -C$H_2$CH$_3$), 0.87 (t, 12H, $^{3}J$ = 8.0 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 148.6 (-*C*OH), 125.5 ($C_q$ *ortho* to COH), 123.7 (CH *meta* to COH), 101.2 ($C_q$ *ipso* to Br), 35.9 (Ar*C*HAr), 29.5 (*C*H$_2$CH$_3$), 12.4 (-*C*H$_3$) ppm.

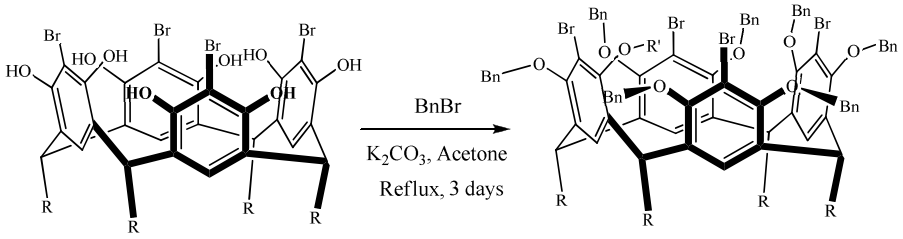
(-)-ESI-MS (DMSO): calculated for [$C_{36}H_{36}Br_4O_8$ - $H^+$] m/z = 910.91, Found m/z = 910.76 (90%).

5,11,17,23-Tetrabromo *C*-hexylresorcin[4]arene **2.37** 33.43 g (73% yield)

$^{1}$H-NMR (500 MHz, DMSO-$d_6$, 300 K): δ = 8.86 (s, 8H, -O*H*), 7.15 (s, 4H, -Ar*H meta* to –OH), 4.2 (t, 4H, $^{3}J$ = 7.6 Hz, ArC*H*Ar), 2.05-2.00 (m, 8H, ArCH-C$H_2$-), 1.24-1.18 (m, 32H, -C$H_2$CH$_3$), 0.83 (t, 12H, $^{3}J$ = 72 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 149.5 (-*C*OH), 124.9 ($C_q$ *ortho* to COH), 123.1 (CH *meta* to COH), 102.0 ($C_q$ *ipso* to Br), 34.0 (Ar*C*HAr), 33.7, 32.7, 29.4, 28.6, 23.3 (-*C*H$_2$-), 14.3 (-*C*H$_3$) ppm.

(-)-ESI-MS (DMSO): calculated for [$C_{52}H_{68}Br_4O_8$·- $H^+$] m/z = 1135.16, Found m/z = 1135.48 (100%).

### 2.7.8 Synthesis of octabenzyloxy tetrabromo *C*-alkyl-resorcin[4]arenes




To a mixture of appropriate tetrabromo *C*-alkylresorcin[4]arene (10.0 mmmol) and anhydrous $K_2CO_3$ (22.18 g, 0.160 mol) in a three-necked round bottom flask was charged with dry acetone (160 mL). The mixture was stirred at room temperature for an hour. Benzyl bromide (17.98 g, 12.50 mL, 0.105 mol) in dry acetone (30 mL) was added dropwise to the reaction mixture *via* an adding funnel over 30 min. The resultant mixture was then refluxed for 3 days under nitrogen atmosphere. After cooling to room temperature, acetone was removed under reduced pressure to afford a yellow oily residue. The residue was dissolved in $CH_2Cl_2$ and deionized water (150 mL) was added. The biphasic solution was stirred for 30 min and the organic layer was separated, washed with water (3 x 50 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated on a rotary evaporator to give a yellow residue. Recrystallization from methanol afforded the corresponding octabenzyloxy tetrabromo *C*-alkylresorcin[4]arene as a white solid.

4,6,10,12,16,18,22,24-Octabenzyloxy-5,11,17,23-tetrabromo *C*-methylresorcin[4]arene

**2.38**

14.07 g (89% yield)

$^{1}$H-NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.46 (s, 4H, -Ar*H* ), 7.42-7.30 (m, 20H, Ar*H*), 7.22-7.17 (m, 4H, Ar*H*), 7.13-7.05 (m, 6H, Ar*H*), 4.98 and 4.12 (dd, 8H, $^{2}J$ = 10.5 Hz, O-C$H_AH_B$-Bn), 4.87-4.82 (m, 8H, ArC*H*Ar and one of O-C$H_AH_B$-Bn), 4.73 (dd, 4H, $^{2}J$ = 11.4 Hz, one of O-C$H_AH_B$-Bn), 1.62 (d, 12H, $^{3}J$ = 7.2 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, $CDCl_3$): δ = 153.5, 152.2 (*C*-OBn), 138.7, 137.6, 136.6, 134.5, 128.3, 128.2, 128.0, 127.6, 127.0, 125.5, 125.2, 114.4 and 114.0 ($C_q$ *ipso* to Br), 74.3, 74.1 (-O*C*$H_2$Bn), 33.8 (Ar*C*HAr), 21.0 (-*C*$H_3$) ppm.

(+)-ESI-MS (acetone): calculated for [$C_{88}H_{76}Br_4O_8 + NH_4^+$] m/z = 1594.26, Found m/z = 1594.47 (100%). Analytical calculated for $C_{88}H_{76}Br_4O_8$: C, 66.85; H, 4.84. Found: C, 66.38; H, 4.72.

4,6,10,12,16,18,22,24-Octabenzyloxy-5,11,17,23-tetrabromo *C*-ethylresorcin[4]arene

**2.39**

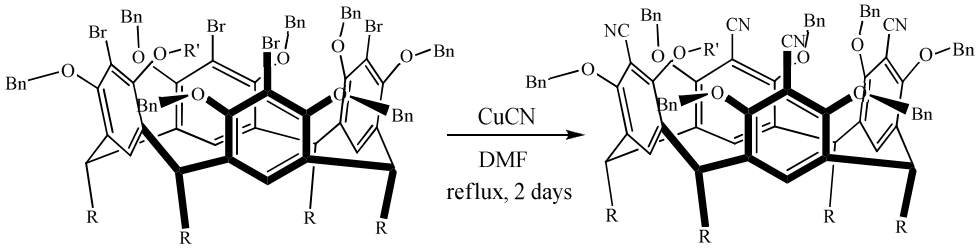
13.04 g (80% yield)

$^{1}$H-NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.46-7.27 (m, 24H, Ar*H*), 7.19-7.15 (m, 4H, Ar*H*), 7.09-7.02 (m, 16H, Ar*H*), 4.92 and 4.14 (dd, 8H, $^{2}J$ = 10.1 Hz, O-C$H_AH_B$-Bn), 4.83-4.79 (m, 8H, ArC*H*Ar and one of O-C$H_AH_B$-Bn), 4.73 (dd, 4H, $^{2}J$ = 12.0 Hz, one of O-C$H_AH_B$-Bn), 2.22 (m, 8H, -C$H_2$CH$_3$), 0.87 (t, 12H, $^{3}J$ = 7.2 Hz, -C$H_3$); $^{13}$C-NMR (75.1 MHz, $CDCl_3$): δ = 153.6, 152.7 (*C*-OBn), 138.8, 137.4, 136.6, 133.9, 128.6, 128.3, 128.1,

127.7, 127.2, 125.4, 125.2, 114.6 and 114.1 ($C_q$ *ipso* to Br), 74.3 and 74.1 (-O*C*$H_2$Bn), 34.9 (Ar*C*HAr), 28.8 (-*C*$H_2$$CH_3$), 12.6 (-*C*$H_3$) ppm.

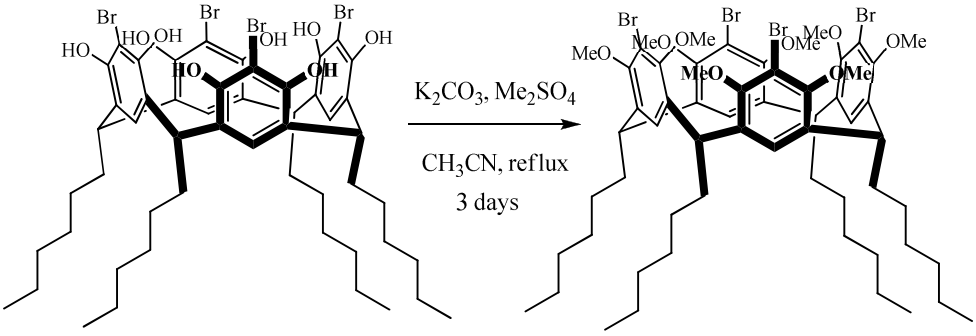
(+)-ESI-MS (acetone): calculated for [$C_{92}H_{84}Br_4O_8$ + $NH_4^+$] m/z = 1650.32, Found m/z = 1650.29 (100%). Analytical calculated for $C_{92}H_{84}Br_4O_8$·$CH_3OH$: C, 66.91; H, 5.31. Found: C, 66.77; H, 5.01.

### 2.7.9 Synthetic attempts of octabenzyloxy tetracyano *C*-alkyl-resorcin[4]arene




To a mixture of octabenzyloxy tetrabromo *C*-alkylresorcin[4]arene (1.00 mmol) and CuCN (1.86 g , 20.8 mmol) was added dry DMF (30 mL). The reaction mixture was rfluxed for 48 hours. After cooling to 100 ºC, a solution of $FeCl_3$ (5.12 g, 30.6 mmol) in 2M HCl (50 mL) was added and the mixture was stirred at this temperature for 2 hours. Dichloromethane (200 mL) was added to the mixture and organic phase was separated, washed with water (3 x 5o mL), brine (2 x 50 mL), and dried over anhydrous $Na_2SO_4$. The combined organic phase was concentrated under reduced pressure to give a dark brown residue. TLC experiments of the residue were performed to determine the components of the crude product.

### 2.7.10 Synthesis of tetrabromo octamethoxy *C*-hexyl-resorcin[4]arenes



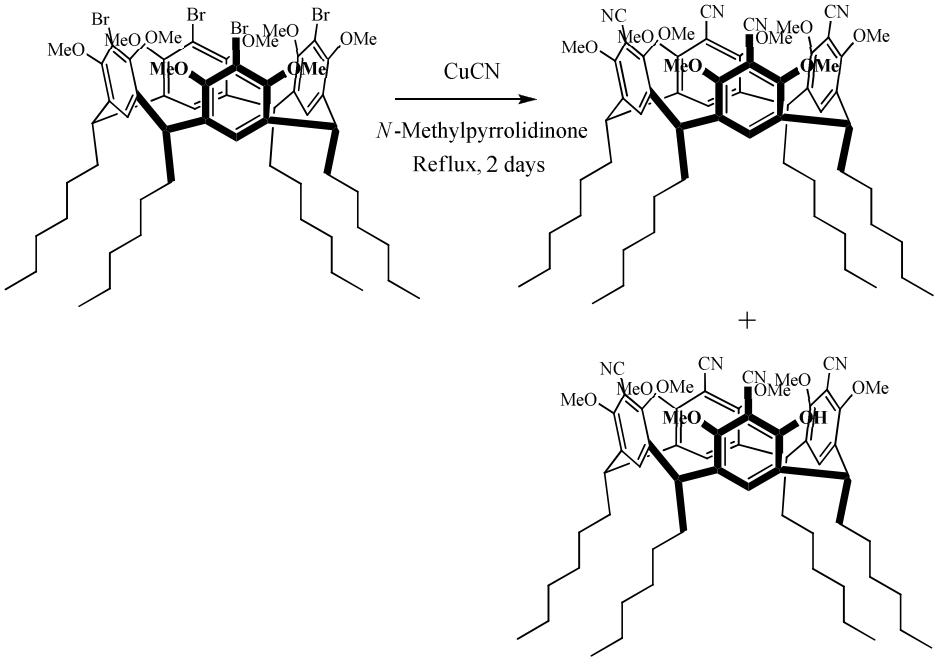

To a mixture of tetrabromo *C*-hexylresorcin[4]arene (17.28 g, 15.2 mmol) and anhydrous $K_2CO_3$ (19.02 g, 0.138 mol) in a 500 mL three-necked round bottom flask was charged with dry acetonitrile (250 mL). The mixture was stirred at room temperature for an hour. Dimethyl sulfate (26.66 g, 20.0 mL, 0.211 mol) in dry acetonitrile (50 mL) was added dropwise to the reaction mixture *via* an adding funnel over 30 min. The resultant mixture was then refluxed for 3 days under nitrogen atmosphere. After cooling to room temperature, acetone was removed under reduced pressure to afford a yellow oily residue. The residue was dissolved in $CH_2Cl_2$ and deionized water (150 mL) was added. The biphasic solution was stirred for 30 min and the organic layer was separated, washed with water (3 x 50 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated on a rotary evaporator to give a yellow residue which was subjected to silica gel column chromatography eluted with $CH_2Cl_2$. Combined organic solvent was evaporated to dryness to give white powder. Recrystallization from methanol afforded tetrabromo octamethoxy *C*-hexylresorcin[4]arene (11.81 g, 62% yield) as a colorless solid.

4,6,10,12,16,18,22,24-Octamethoxy-5,11,17,23-tetrabromo *C*-hexylresorcin[4]arene **2.40**

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.52 (s (broad), 4H, -Ar*H meta* to –$OCH_3$), 4.44 (t, 4H, $^{3}J$ = 7.0 Hz, ArC*H*Ar), 3.64 (s, 24H, -OC$H_3$), 1.84 (m, 8H, -CHC$H_2$C$H_2$-), 1.30 and 1.24 (m, 24H, -C$H_2$-), 0.83 (t, 12H, $^{3}J$ = 6.8 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 154.4 (*C*-$OCH_3$), 134.6 ($C_q$ *ortho* to $COCH_3$), 125.5 (*C*H *meta* to $COCH_3$), 113.1 ($C_q$ *ipso* to Br), 60.5 (-O*C*$H_3$), 38.6 (Ar*C*HAr), 35.0, 31.8, 29.4, 28.3 and 22.7 (-*C*$H_2$-), 14.0 (-*C*$H_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{60}H_{84}Br_4O_8$·2$CH_3OH$ + $H^+$] m/z = 1312.24, Found m/z =1311.66 (100%). Analytical calculated for $C_{60}H_{84}Br_4O_8$: C, 57.52; H, 6.76. Found: C, 57.30; H, 6.63.

## 2.7.11 Synthesis of tetracyano octamethoxy *C*-hexyl-resorcin[4]arenes



To a mixture of compound **2.40** (18.80 g, 15.0 mmmol) and CuCN (10.78 g, 0.120 mol) in a 500 mL three-necked round bottom flask was added dry 1-methyl-2-pyrollidinone (150 mL) under nitrogen. The reaction mixture was refluxed for 2 days. After reducing the heat to 100 ºC, a solution of $FeCl_3$ (20.10 g, 0.124 mol) in 2M HCl (150 mL) was added slowly and the resulting solution was vigorously stirred at this temperature for 2 hours. The solution mixture was filtered and washed with hot water until the filtrate was neutral to pH paper. The dark brown crude product was purified by silica gel column chromatography eluting with $CH_2Cl_2$ and then $CH_2Cl_2$: EtOAc (from 99:1 to 95:5). Macrocycle **2.41** came off a column first following by resorcin[4]arene **2.42**. Combined organic solvent was evaporated to dryness to give white semi-solid. Two pure compounds were obtained from separated fractions. The overall yield of compounds **2.41** and **2.42** is 82% yield.

4,6,10,12,16,18,22,24-Octamethoxy-5,11,17,23-tetracyano *C*-hexylresorcin[4]arene **2.41**

7.25 g (46% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.72 (s, 4H, -Ar*H meta* to –$OCH_3$), 4.43 (t, 4H, $^3J$ = 7.2 Hz, ArC*H*Ar), 3.85 (s, 24H, -OC$H_3$), 1.80 (m, 8H, -CHC$H_2$C$H_2$-), 1.32 and 1.27 (m, 24H, -C$H_2$-), 0.87 (t, 12H, $^3J$ = 6.7 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 159.5 (-*C*-$OCH_3$), 132.9 ($C_q$ *ortho* to $COCH_3$), 130.6 (-*C*H *para* to CN), 114.2 (-*C*N), 99.9 ($C_q$ *ipso* to CN), 61.7 (-O*C*$H_3$), 36.4 (Ar*C*HAr), 34.5, 31.7, 29.4, 27.8, 22.7 (-*C*$H_2$-), 14.0 (-*C*$H_3$) ppm.

FT-IR (KBr): ν (in $cm^{-1}$) 2241 (-C≡N)

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{64}H_{84}N_4O_8$ + $Na^+$] m/z = 1059.53, Found m/z = 1058.90 (88%). Analytical calculated for $C_{64}H_{84}N_4O_8$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.28; H, 8.20; N, 5.20.

4,6,10,12,16,18,22-Heptamethoxy-5,11,17,23-tetracyano *C*-hexylresorcin[4]arene **2.42**

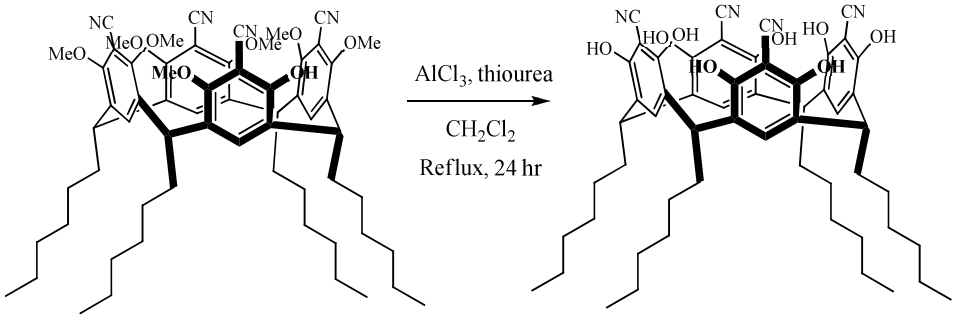
5.47 g (36% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.92 (s, 1H, -Ar*H meta* to –$OCH_3$), 6.89 (s, 1H, -Ar*H meta* to –$OCH_3$), 6.71 (s, 1H, -Ar*H meta* to –$OCH_3$), 6.63 (s, 1H, -Ar*H meta* to –$OCH_3$), 4.50-4.42 (m, 3H, ArC*H*Ar), 4.39 (t, 1H, $^3J$ = 7 Hz, ArC*H*Ar), 3.98, 3.95, 3.93, 3.90, 3.79, 3.75, 3.71 (each s, each 3H, total 21H, -OC$H_3$), 1.92-1.72 (m, 8H, -CHC$H_2$C$H_2$-), 1.32 and 1.27 (m, 24H, -C$H_2$-), 0.87 (t, 12H, $^3J$ = 6.8 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 159.8, 159.4 and 159.3 (-*C*-$OCH_3$, -*C*OH), 133.7, 132.5 and 132.4 ($C_q$ *ortho* to $COCH_3$), 130.8, 130.6, 130.5 and 130.4 ($C_{Ar}$H *para* to CN), 114.2 (-*C*N), 100.1, 100.0 and 99.9 ($C_q$ *ipso* to CN), 62.1, 61.8, 61.8, 61.7, 61.6, and 61.5 (-O*C*$H_3$), 36.2, 36.1, 35.9 and 35.8 (Ar*C*HAr), 35.0, 34.8, 34.6 and 34.2 (-CH*C*$H_2$C$H_2$), 31.7, 29.4, 27.8, and 22.7 (-*C*$H_2$-), 14.0 (-*C*$H_3$).

FT-IR (KBr): ν (in $cm^{-1}$) 2238 (-C≡N)

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{63}H_{82}N_4O_8$ + $Na^+$] m/z = 1045.60, Found m/z = 1044.84 (86%). Analytical calculated for $C_{63}H_{82}N_4O_8 \cdot H_2O$: C, 72.66; H, 8.13; N, 5.38. Found: C, 72.83; H, 8.01; N, 5.39.

## 2.7.12 Synthesis of tetracyano *C*-hexylresorcin[4]arenes




A mixture of $AlCl_3$ (15.18 g, 0.114 mol) and thiourea (4.91 g, 64.5 mmol) in a 250 mL three-necked round bottom flask was added tetracyano octamethoxy *C*-hexyl-resorcin[4]arene (2.65 g, 2.56 mmol). The solid mixture was added dry $CH_2Cl_2$ (60 mL) and stirred until all solid completely dissolved. Subsequently, the reaction mixture was refluxed for 24 hours. After cooling to room temperature, 1M HCl (150 mL) was added slowly to avoid the excessive exothermic reaction and the mixture was continuously stirred for 30 min. White precipitate was filtered off and washed with water until the filtrate became neutral to pH paper. A white solid was dried under vacuum for 24 hours to afford compound **2.43** (1.17 g, 72% yield).

5,11,17,23-Tetracyano *C*-hexylresorcin[4]arene **2.43**

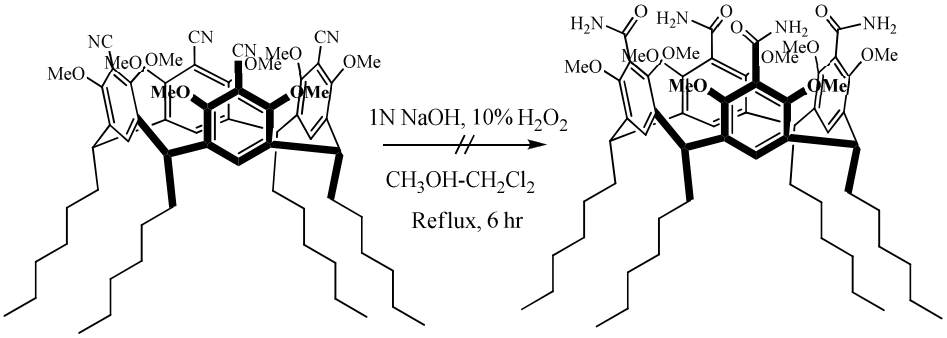
$^1$H-NMR (500 MHz, acetone-$d_6$, 300 K): δ = 9.26 (s (broad), 8H, -O*H*), 7.23 (s, 4H, -Ar*H* *meta* to –OH), 4.47 (t, 4H, $^3J$ = 8.0 Hz, ArC*H*Ar), 2.31 (q, 8H, $^3J$ = 7.5 MHz, -CHC$H_2$CH$_2$-), 1.36 and 1.26 (m, 24H, -C$H_2$-), 0.85 (t, 12H, $^3J$ = 6.8 Hz, -C$H_3$); $^{13}$C-NMR

(125 MHz, acetone-$d_6$): δ = 155.0 (-*C*-OH), 130.6 (-*C*H *para* to –CN), 126.1 ($C_q$ *ortho* to COH), 114.5 (-*C*N), 92.6 ($C_q$ *ipso* to –CN), 34.7 (Ar*C*HAr), 33.7, 32.7, 29.4, 28.6, 23.3 (-*C*$H_2$-), 14.3 (-*C*$H_3$) ppm.

FT-IR (KBr): ν (in $cm^{-1}$) 2243 (-C≡N).

(+)-MALDI-TOF MS (acetone): calculated for [$C_{56}H_{68}N_4O_8$ + $Na^+$] m/z = 947.49, Found m/z = 946.72 (100%). Analytical calculated for $C_{56}H_{68}N_4O_8 \cdot 2H_2O$: C, 69.98; H, 7.55; N, 5.83. Found: C, 70.07; H, 7.37; N, 5.94.

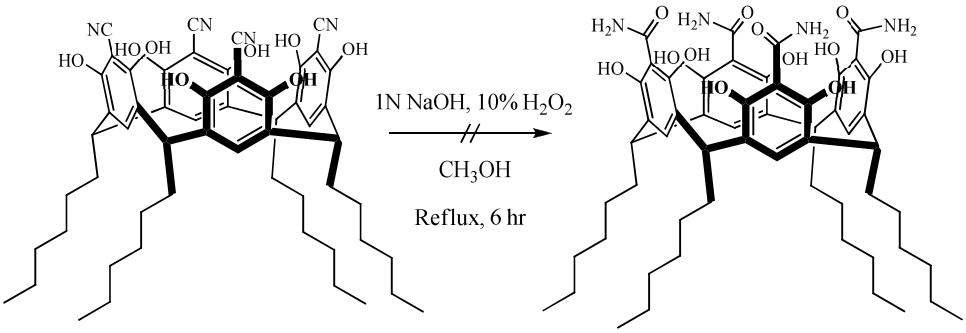
### 2.7.13 Synthetic attempts of tetracarbamyl octamethoxy *C*-hexyl resorcin[4]arene




To a solution of resorcin[4]arene **2.41** (2.62 g, 2.52 mmol) in the mixture of dry methanol (50 mL) and dry dichloromethane (15 mL), pre-heated to 40ºC, was added 20 mL of 1M NaOH and 20 mL of 10% $H_2O_2$. The reaction mixture was heated at 40ºC for 24 hours. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator to yield a yellow residue. $CH_2Cl_2$ (200 mL) was added to dissolve the residue and the organic layer was washed with water (3 x 50 mL), brine (50 mL), and

dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a light-yellow residue. Recrystallization from methanol afforded only starting material (compound **2.41**) in quantitive yield.

### 2.7.14 Synthetic attempts of tetracarbamyl *C*-hexyl-resorcin[4]arene




To a solution of compound **2.43** (2.36 g, 2.55 mmol) in 50 mL of dry methanol, pre-heated to 40ºC, was added 20 mL of 1M NaOH and 20 mL of 10% $H_2O_2$. The reaction mixture was heated at 40ºC for 12 hours. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator to yield a yellow residue. Ethyl acetate (200 mL) was added to dissolve the residue and the organic layer was washed with water (3 x 50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a dark brown residue. All recrystallization attempts failed to produce any solid from the ethyl acetate solution.

## 2.7.15 X-ray Crystallography

### 2.7.15.1 Acknowledgement on X-ray crystallography experiments

All X-ray crystal structure determination and refinements in this dissertation were performed by Andrew V. Mossine, a graduate student in the Department of Chemistry at the University of Missouri-Columbia. The author of this dissertation would like to give all credit on this part to Mr. Mossine for his excellent support.

### 2.7.15.2 General procedure for X-ray crystallographic experiments

X-ray single crystal studies were collected on a Bruker SMART CCD diffractometer. Crystals were mounted with epoxy on the end of a thin glass fiber and centered in the X-ray beam. A graphite-monochromatic Mo K$\alpha$ radiation (wavelength = 0.71073 Å) at -100ºC was employed. Full hemisphere data were collected and frames were integrated with the SAINT program. Additionally, the data were corrected for Lorentz, polarization and absorption effects and analyzed by the XPREP program. The crystal structures were solved using the direct methods option of the latest SHELXS program.[158,159] Refinement processes were performed by using conventional alternating cycles of least square refinement (SHELXL-97) on $F^2$. All non-hydrogen atoms were refined anisotropically on displacement parameters. Hydrogen atoms were fixed in idealized positions and given displacement parameters according to the atom to which they are attached. All diagrams and representations were created by the POV-Ray[160] and/or Mercury 2.3 programs.[161]

## 2.8 Conclusions

This chapter involves the attempts to synthesize new macrocyclic compounds using *C*-alkylresorcin[4]arenes as the scaffolds. Three functional groups of interest: amino-, cyano- and amido moieties, were chosen to being introduced on the 2-position of an aromatic ring of a resorcin[4]arene molecule. However, so far only a cyano group has been successfully functionalized on a resorcin[4]arene building block under the reported conditions in this chapter.

No tetranitro resorcin[4]arene is obtained from the nitration reaction of octamethoxy *C*-alkylresorcin[4]arenes or unsubstituted *C*-alkylresorcin[4]arenes. The nitrating agents and conditions employed in all nitration attempts may result in over-oxidation, polymerization or decomposition of starting materials. Consequently, it might be extremely challenging to synthesize aminoresorcin[4]arenes from their nitroresorcin[4]arene analogs.

Tetracyano *C*-hexylresorcin[4]arene is synthesized by substituting bromine atoms of tetrabromo octamethoxy *C*-hexylresorcin[4]arene with cyanide from CuCN in 46% yield. Surprisingly, another compound, tetracyano heptamethoxy *C*-hexylresorcin[4]-arene, was obtained from the same reaction. Both tetracyano derivatives can be used to prepare tetracyano *C*-hexylresorcin[4]arene through demethylation with an $AlCl_3$-thiourea reagent-pair without employing high temperature or harsh conditions. The overall percentage yield of the new macrocycle in 5 steps is 15% yield.

Solid state study shows that tetracyano *C*-hexylresorcin[4]arene crystallizes in a space group of $P2_1/n$ in the crystal system of monoclinic. The resorcin[4]arene backbone adopts a crown (*rccc*) conformation with all hexyl groups oriented in axial positions. A

crown conformer of tetracyano *C*-hexylresorcin[4]arene is stabilized by 4 intramolecular hydrogen bonds. No special aggregation or hydrogen-bonded self-assembly is observed.

Reaction of tetracyano *C*-hexylresorcin[4]arene with $AgNO_3$ affords a polymeric Ag(I) complex which crystallizes in a space group of $P2_12_12_1$ in the crystal system of orthorhombic. A silver(I) center is coordinated with nitrogen atoms of three cyano groups from three macrocycles. The geometry of a metal center in this complex is distorted trigonal planar. Two molecules of tetracyano *C*-hexylresorcin[4]arene arrange in the same orientation whereas the third one is in a head-to-head fashion. The polymer-like structure of this complex has no particular channel or porous-like feature for further application as a catalyst or a gas storage material.

Hydrolysis of tetracyano *C*-hexylresorcin[4]arene resulted in a complex mixture. There is a possibility that the starting material is over-hydrolyzed to its carboxylic acid derivative. Furthermore, hydrolysis of tetracyano octamethoxy *C*-hexylresorcin[4]arene does not afford any new macrocycle due to the poor solubility of starting material in the particular reaction conditions.

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# CHAPTER 3

# PYROGALLOL[4]ARENE-LIKE MACROCYCLES WITH AN EXTENDED CAVITY

## 3.1 Introduction to macrocycles with an extended internal cavity.

As previously described in section 2.4, self-assembly of preorganized molecules with a concave surface produces discrete supramolecular capsules containing a confined inner cavity.[1,2] These internal cavities can encapsulate several guest molecules of different size shape, charge, and stability. Generally, these trapped molecules behave differently from their counterparts in bulk phases.[3] This leads to the application of these nanospheroid entities in the fields of catalysis, drug delivery, and chemical storage.[4] Rebek and coworkers demonstrated the usage of a cavitand as a building block for the synthesis of larger cylindrical containers. These macrocycles are capable of encapsulating more than one guest within their nanometric cavities. The advantage of using extended-cavity molecular capsules is that larger guest molecules can be enclosed in this spacious void and stabilized from the external influences. This strategy may be very useful for a medical purpose in which a reactive drug can be kept inside the internal cavity of a capsule and released when the whole complex reaches the target.

Although the use of a cavitand as a scaffold for the preparation of a self-assembled entity has been extensively studied by many research groups, the functionalization of these compounds is mainly focused on the hydroxy groups of a resorcin[4]arene moiety using straightforward $S_N2$-type reactions. The other possible

approach is concerning the introduction of a desired chemical group on the aromatic rings of a cavitand. The latter strategy, nevertheless, requires the formation of a carbon-carbon bond between an aromatic ring of a cavitand and a new chemical group. The chemistry of a carbon-carbon bond formation has been a hot topic in the most recent research in organic chemistry since the demand for new bioactive molecules is on the rise. Suzuki-Miyaura cross coupling[5,6] is one of the most utilized C-C bond formation strategies in organic syntheses. Since its discovery in 1979 by Suzuki and Miyaura[7,8], this technique has explored the reaction between organic halides and boronic acid (and boronic esters) to form a new carbon-carbon bond in the presence of palladium catalysts and appropriate bases. This procedure has become very popular in both academic and industrial laboratories for many reasons.[5,9] Firstly, a variety of functional groups are tolerant of the mild conditions. Moreover, many boron compounds such as boronic acids and boronic esters are commercially available, stable at ambient atmosphere, and weakly toxic. Interestingly, some cross coupling processes can even be carried out in wet solvents since the reaction is not moisture sensitive. Additionally, several bases, from strong potassium *tert*-butoxide ($KOBu^t$) to weak CsF can be used to promote the reaction. Finally, a vast group of substrates, especially alkenyl- and aryl halides, can be employed in this cross-coupling reaction.

Nevertheless, the major drawback of Suzuki-Miyaura cross coupling is clearly the palladium catalysts.[10] A traditional catalyst, *tetrakis*(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), is extremely air-sensitive due to the oxidation of Pd(0) to Pd(II) ion. The reaction procedure needs complete evacuation of oxygen by flushing a reaction vessel with inert gases such as nitrogen and argon several times. The presence of a tiny amount

of $O_2$ can affect the overall reaction greatly. Therefore, to solve this problem, several palladium catalysts and phosphine ligands have been developed in the last few decades. Unfortunately, novel phosphine ligands are very expensive since the preparations of these compounds are somewhat painstaking. Many palladium compounds (both air-sensitive and air-stable) are also costly as well.

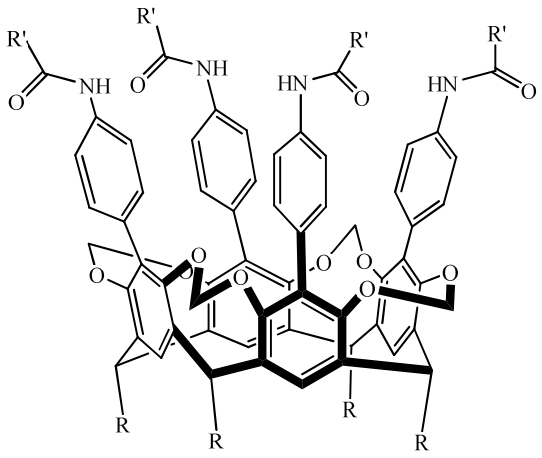
## 3.2 Hydrogen-bonded self-assemblies with extended-cavity macrocycles

### 3.2.1 Homodimeric capsules from macrocyclic compounds with enlarged-inner cavity.

Rudkevich and Rebek[11] successfully prepared a "deep-cavity" cavitand which self-aggregates to form a discrete dimeric capsule. Tetrabromo *C*-undecylcavitand was treated with 4-nitroboronic acid to afford *tetrakis*(4-nitrophenyl) *C*-undecylcavitand. Reduction of the nitro-substituted cavitand with Raney nickel/$H_2$ produced a tetraamine cavitand which was acylated with the appropriate acid chlorides to give tetraamide-substituted *C*-undecylcavitands (**3.1**-**3.2**) in excellent overall yields (60-70%). Compounds **3.1** and **3.2** form the homodimeric capsules in toluene-$d_8$ with the dimerization constants of *ca* 1700 ± 250 $M^{-1}$. The estimated size of a cavity of these capsules is 12 x 19 Å with an approximate volume of 440 $Å^3$. The structures of compounds **3.1** and **3.2** and their dimeric capsules are shown in Figure 3.1.

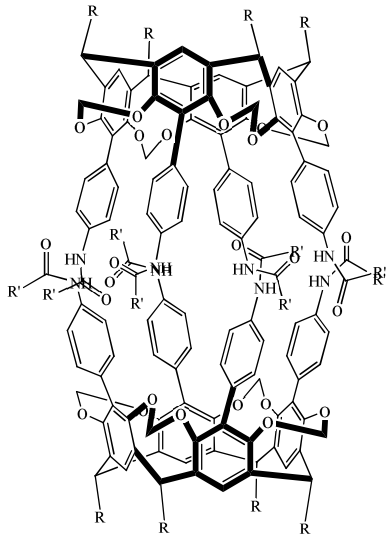
Urea functionality can be introduced on the upper rim of calix[4]arene in a similar fashion. Two calix[4]arene derivatives (**3.3** and **3.4**, see Figure 3.1c) were synthesized by reacting tetraamino calix[4]arenes with the appropriate isocyanates.[12] Tetraurea calix[4]arenes showed the ability to form dimeric entities in apolar solvents ($CDCl_3$ and

$CH_2Cl_2$) through 16 C=O···H-N intermolecular hydrogen bonds. The volume of these capsules is about 400 $Å^3$. Unfortunately, all attempts to encapsulate neutral guests such as 4,4′-dimethylbiphenyl and *N*-(4-tolyl)-benzamide failed.

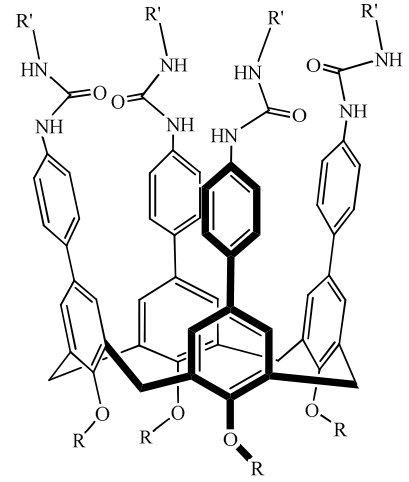


R = $C_{11}H_{23}$, R' = $C_7H_{15}$ **3.1**
R = $C_{11}H_{23}$, R' = $C_8H_{17}$ **3.2**

(a)



(b)



R = $CH_2CONEt_2$, R' = *p*-tolyl **3.3**
R = $CH_2CONEt_2$, R' = *p*-(*n*-hexyl)phenyl **3.4**

(c)

**Figure 3.1** (a) Chemical structures of compounds **3.1** and **3.2**. (b) Homodimeric capsules of compound **3.1** and **3.2**. (c) Chemical structures of compounds **3.3** and **3.4**.

Kobayashi *et al.*[13] studied the dimerization of an extended-cavity *tetrakis*(4-carboxyphenyl)- *C*-heptylcavitand (**3.5**). Compound **3.5** was synthesized by the Suzuki-Miyaura cross coupling of tetraiodo cavitand with 4-(methoxycarbonyl)phenyl boronic acid pinacol ester, followed by hydrolysis of the tetraester derivative. In the presence of linkers such as 2-aminopyrimidine (2-AP) and tetrahydropyrimidine-2-one(THP), homodimeric capsules of **3.5** were obtained *via* intermolecular hydrogen bonds between the carboxy groups of a cavitand and the hydrogen bond donors and acceptors of 2-AP and THP. (Figure 3.2) The cavity of novel capsules is large enough to accommodate a molecule of *hexakis*(4-methoxyphenyl)benzene.

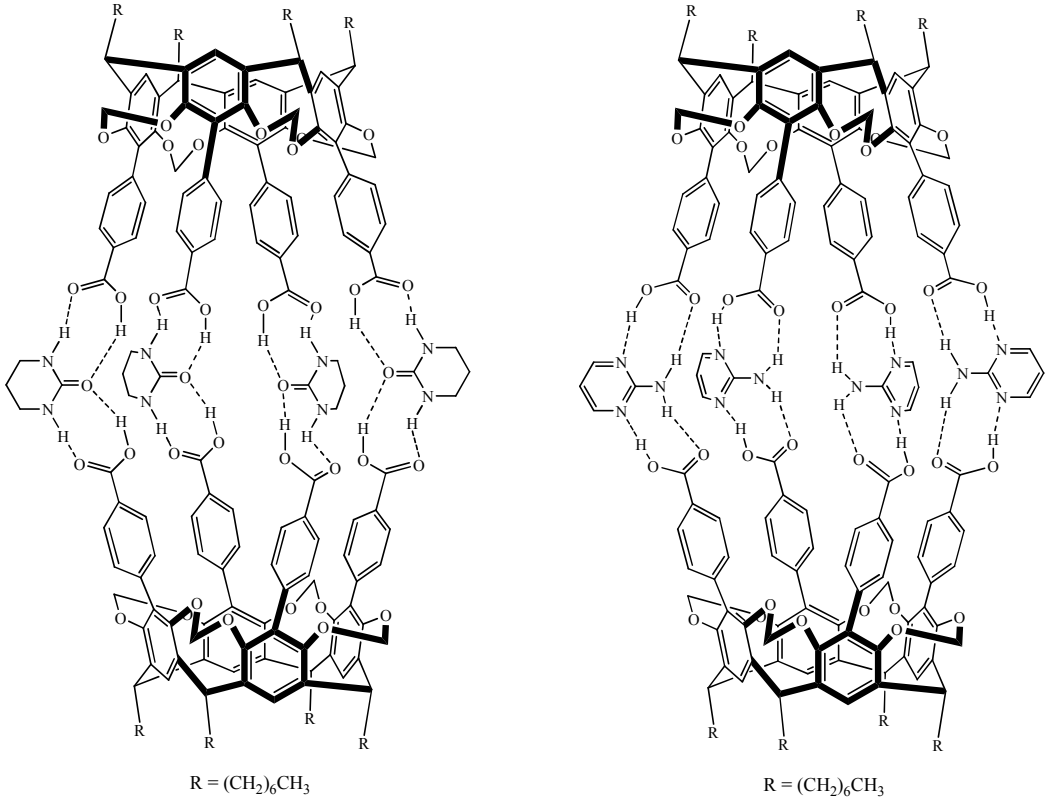
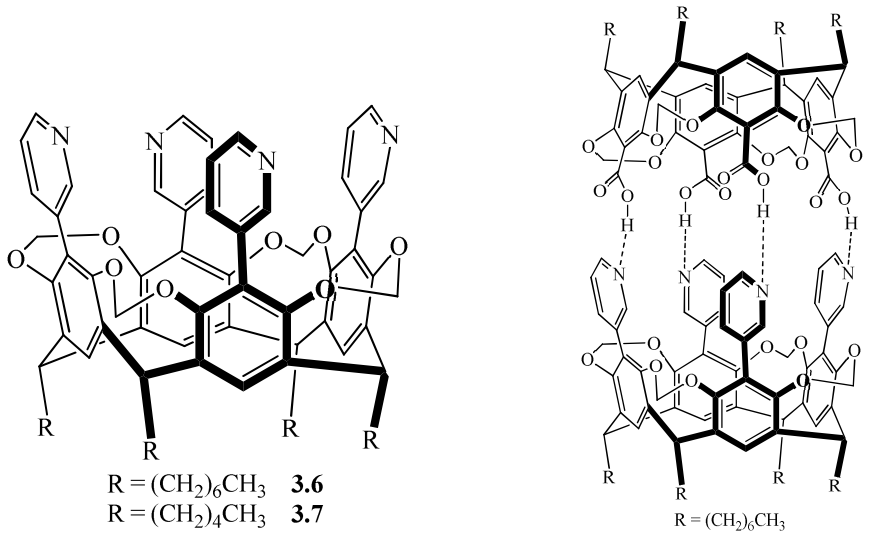



**Figure 3.2** Chemical structures of the dimeric capsules of compound **3.5** with THP (left) and 2-aminopyrimidine (right).

### 3.2.2 Formation of heterodimeric capsules using hydrogen bonds

Kobayashi *et al*.[14] synthesized tetra(3-pyridyl) *C*-heptylcavitand (**3.6**) through the Suzuki cross coupling of a corresponding tetraboronic acid cavitand with 3-bromopyridine. The similar tetra(3-pyridyl) *C*-pentylcavitand (**3.7**) was also prepared by Aakeröy and coworkers[15] by reacting tetrabromo *C*-pentylcavitand with 3-pyridyl boronic acid.

The mixture of compound **3.6** and tetracarboxy *C*-heptylcavitand (**3.8**) forms the heterodimeric capsule (**3.7**:**3.8** = 1:1, see Figure 3.3) stabilized by 4 hydrogen bonds (C-OH···N).[14] Polarity of the solvent plays an important role in the formation of a heterodimer. Decreasing in the polarity of the solvent from $CDCl_3$ to *p*-xylene-$d_{10}$ promotes the quantitative generation of a dimeric entity. Several 1,4-disubstituted benzenes are encapsulated along the long axis of the capsule. The inclusion complexes are stabilized by the CH-halogen or C-H···π interactions between the heterodimeric capsule and a guest.




(a) (b)

**Figure 3.3** (a) Chemical structures of compounds **3.6** and **3.7.** (b) Heterodimeric capsule between **3.6** and **3.8.**

Another 1:1 self-assembled capsule was prepared by mixing *tetrakis*(4-hydroxy-phenyl)-*C*-heptylcavitand (**3.9**) with tetra(4-pyridyl)-*C*-heptylcavitand (**3.10**).[16] This capsule (see Figure 3.4b) showed the orientational isomerism of an encapsulated unsymmetrical guest with high orientation selectivity. This feature comes from the difference between the electronic environment of **3.9** and **3.10**. Cavitand **3.9** with electron donating phenol groups is more electron-rich than cavitand **3.10** with electron withdrawing 3-pyridyl groups. Therefore, when guest molecules such as 4-ethoxyiodobenzene and 2-iodo-6-methoxynapthalene are encapsulated in this dimeric capsule, iodine atom is specifically oriented to the cavity of the **3.10** unit. Again, the stabilization of an encapsulated complex is based on C-H···halogen and C-H···π interactions.

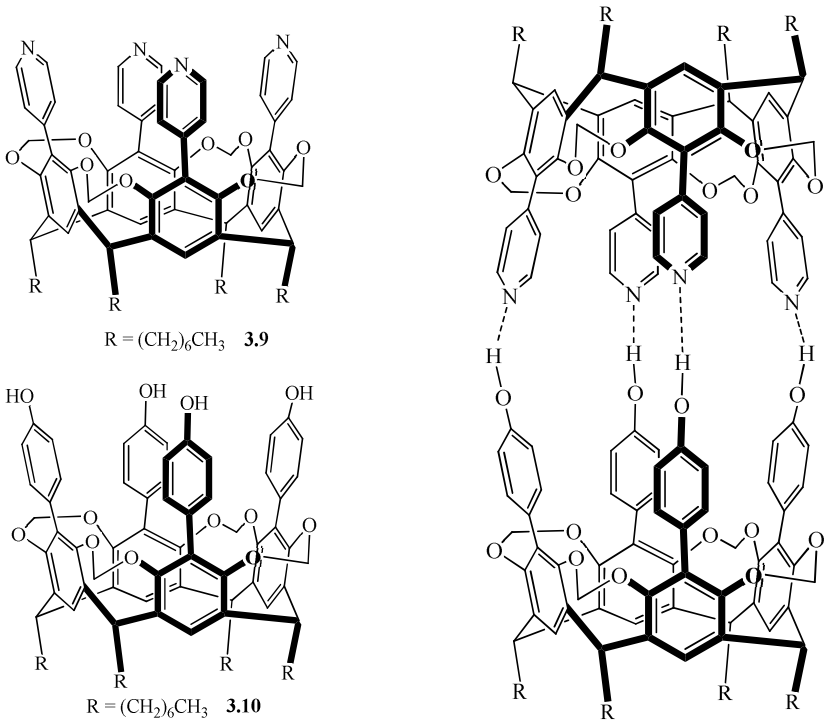


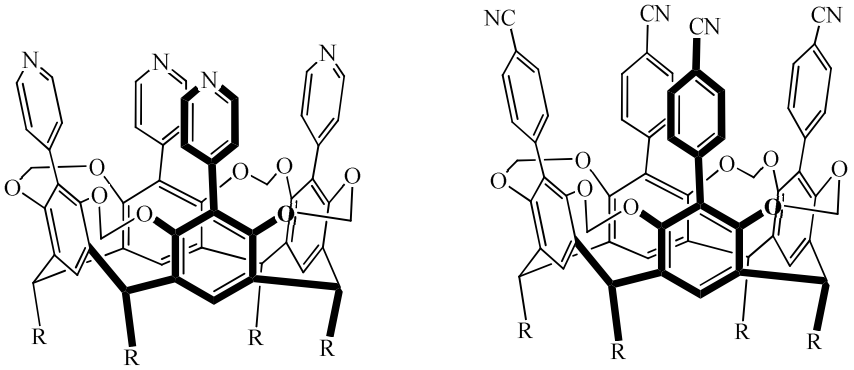

**Figure 3.4** Chemical structures of (a) compounds **3.9** and **3.10**, and (b) the hydrogen-bonded dimeric capsule of between **3.9** and **3.10** (the ratio of **3.9**:**3.10** = 1:1).

## 3.3 Metal-directing self-assembling coordination cages of enlarged-cavity macrocycles

### 3.3.1 Self-aggregation of homo- and hetero-cavitand capsules using metal-ligand interactions

Kobayashi and coworkers[17] investigated homo- and hetero-dimeric self-assembled capsules of tetra(4-pyridyl)-*C*-heptylcavitand (**3.11**) and *tetrakis*(4-cyano-phenyl)-*C*-heptylcavitand (**3.12**) (see Figure 3.5) which are formed *via* metal coordination to a [Pd(dppp)] fragment. Compound **3.12** forms a homodimeric cage-like structure held together *via* 8 Pd-N≡C- interactions, as observed in the $^{1}$H-NMR spectrum.

A dilution experiment of the [Pd(dppp)(**3.12**)$_2$] complex monitored by $^1$H-NMR showed that the difference in the chemical shits ($\Delta\delta$) of the complex gradually diminished upon the dilution. This indicates that the equilibrium between free and bound ligands is fast on the NMR time scale.[18] Additionally, the 1:1 mixture of **3.11**:**3.12** in the presence of a [Pd(dppp)] unit also underwent a self-assembly process to produce a heterodimeric metal cage.




(a) (b)

**Figure 3.5** Chemical structures of (a) compound **3.11,** and (b) compound **3.12.**

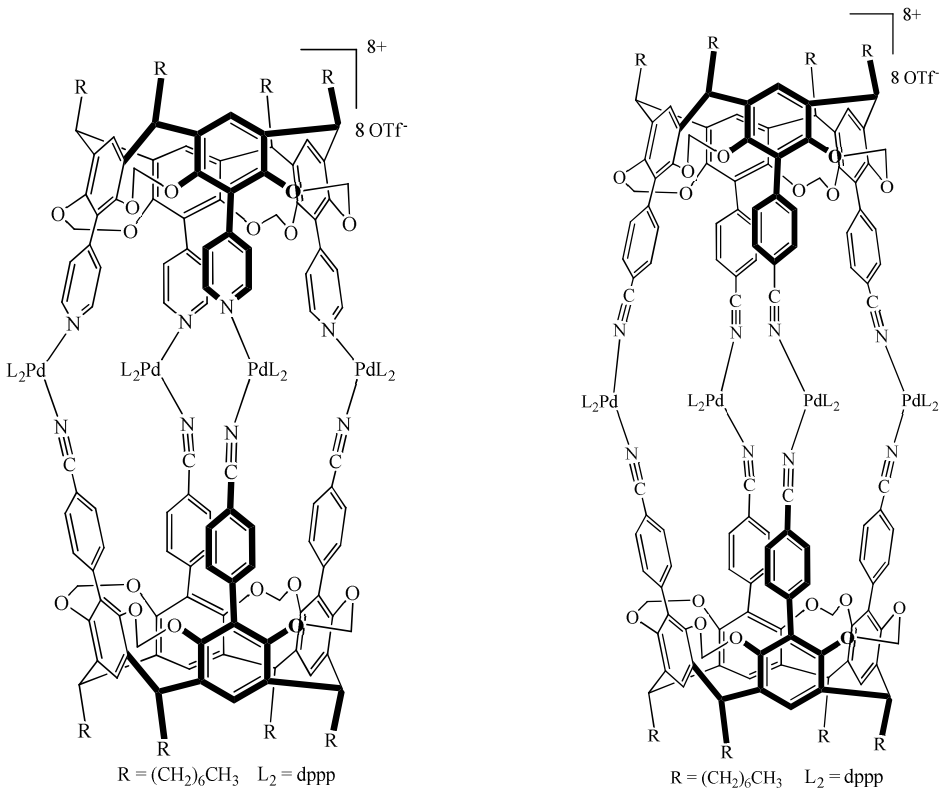



**Figure 3.6** (a) The heterodimeric capsule of **3.11** and **3.12** directed by $PdL_2$ fragments. (b) The homodimeric capsule of $[(PdL_2)_4(\mathbf{3.12})_2](OTf)8$, $L_2$ = dppp.

### 3.3.2 Formation of discrete metallosupramolecular cages with a large inner cavity.

*Tetrakis*(2,2-bipyridyl) *C*-undecylcavitand (**3.13**) was synthesized *via* the Suzuki-Miyaura cross coupling between tetraiodo *C*-undecylcavitand and 2,2-bipyridyl boronic ester in 80% yield.[19] This new cavitand specifically forms a dimeric coordination capsule with Ag(I) ion. $^1$H-NMR study of the $[Ag_4(\mathbf{3.13})_2][BF_4]_4$ complex revealed that this coordination cage adopts a $D_4$ symmetric form in which all bipyridyl groups are

magnetically equivalent.[20] The volume of this coordination cage calculated by a molecular modeling program is approximately 580 Å$^3$.

Recently, Mattey *et al*.[21] successfully prepared *tetrakis*(2,2′:6′,2″-terpyridyl)-*C*-isobutylcavitand (**3.14**) by using the Suzuki cross coupling. Addition of compound **3.14** to a solution of lipophilic $[Zn(NCMe)_6][TFBB]_2$ (TFBB = *tetrakis*-(3,5-*bis*(trifluoromethyl)-phenyl)borate) in THF-$d_8$ resulted in the formation of a hexameric coordination cage (**3.15,** Figure 3.7). The cage **3.15** is composed of 6 molecules of **3.14** and 12 $Zn^{2+}$ ions. The $^1$H-NMR spectrum of **3.15** indicates a high symmetry in which all cavitand subunits show only one set of signals. The point group of this cage is found to be $O_h$. Unfortunately, no crystals suitable for X-ray structure analysis of **3.15** could be obtained. By using a force field calculation model, it was suggested that a maximum of seven TFPB anions could be encapsulated in the cavity of **3.15**.

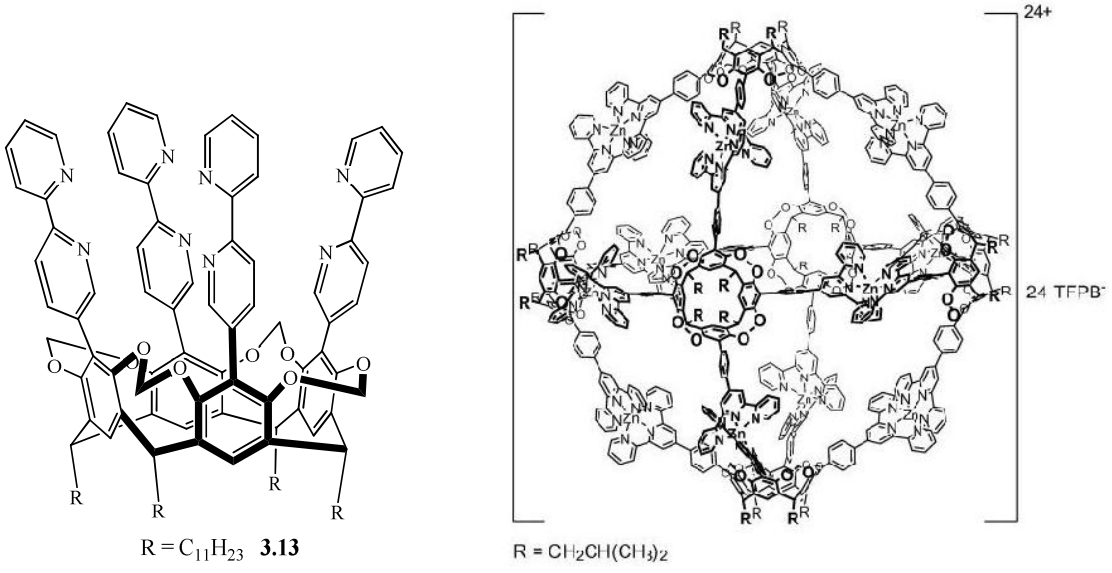



**Figure 3.7** The chemical structure of compound **3.13** (left) and the proposed coordination cage **3.15** (right) which is formed *via* the complexation of cavitand **3.14** and $[Zn(NCMe)_6][TFBB]_2$.

## 3.4 Hypothesis and objectives

As previously discussed in the early sections of this chapter, novel extended-cavity macrocycles with the ability to self-assemble through hydrogen bonds and metal-ligand interaction have become the main targets of many research groups around the world. However, there is no example of a macrocycle funtionalized by a 1,2,3-trihydroxyphenyl group in the literature survey (SciFinder, at the end of December 2009). A 1,2,3-trihydroxyphenyl group is identical to pyrogallol, which has been used in the synthesis of *C*-alkylpyrogallol[4]arenes. As previously discussed in Chapter 2, *C*-alkyl-pyrogallol[4]arenes show the great ability to form a hexameric hydrogen-bonded capsule and recently many publications have reported the preparation of metal-directed molecular capsules based on the pyrogallol[4]arene building block.[22-26] Therefore, the main objective of the work discussed in this chapter is to synthesize novel macrocycles possessing the functional groups of 1,2,3-trimethoxyphenyl on the upper rim of a building block. 1,2,3-trimethoxyphenyl can be demethylated to give a corresponding 1,2,3-trihydroxyphenyl which is the desired moiety.

There are two approaches that have been investigated in this section. The first strategy is to functionalize a 1,2,3-trimethoxyphenyl group on the 2-position of an aromatic ring of a suitable building block by using a Suzuki-Miyaura cross coupling reaction. There are four macrocycles used in this study: tetrabromo *C*-methylcavitand (**3.16**), tetrabromo *C*-hexylcavitand (**3.17**), 5,11,17,23-tetraiodo-25,26,27,28-tetrapropoxycalix[4]arene (**3.18**) and 5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxy-calix[4]arene (**3.19**). The palladium catalyst is *tetraki*s(triphenylphosphine)palladium(0)

($Pd(PPh_3)_4$). Several bases and solvent systems were studied to find the optimal condition for the synthesis of the target molecules.

The other methodology is to impart the 1,2,3-trimethoxyphenyl group to a calix[4]arene backbone by using the condensation reaction between an aldehyde and a primary amine. For many years, supramolecular chemists have utilized this reaction to prepare many new macrocyclic compounds such as 1,4,8,11-tetraazacyclotetradecane (cyclam) and its derivatives. To explore this strategy, 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxycalix[4]arene (**3.20**) and two tetraamino calix[4]arenes: 5,11,17,23-tetraamino-25,26,27,28-tetrahydroxycalix[4]arene (**3.21**) and 5,11,17,23-tetraamino-25,26,27,28-tetrapropoxycalix[4]arene (**3.22**), were used as the starting materials for the synthesis of novel macrocycles. Since Schiff bases or imines are moisture-sensitive, reduction of new imine calix[4]arene derivatives by $NaBH_4$ should produce more stable calix[4]arene tetraamines.

For novel synthesized macrocycles containing 1,2,3-trimethoxyphenyl moieties, the last step would be the demethylation of methoxy groups to produce hydroxy functionality. This would be convenient with the reagent pair of $AlCl_3$-thiourea[27] (see section 2.8.10). The target molecules in this chapter are shown in Figure 3.8 and Figure 3.9.

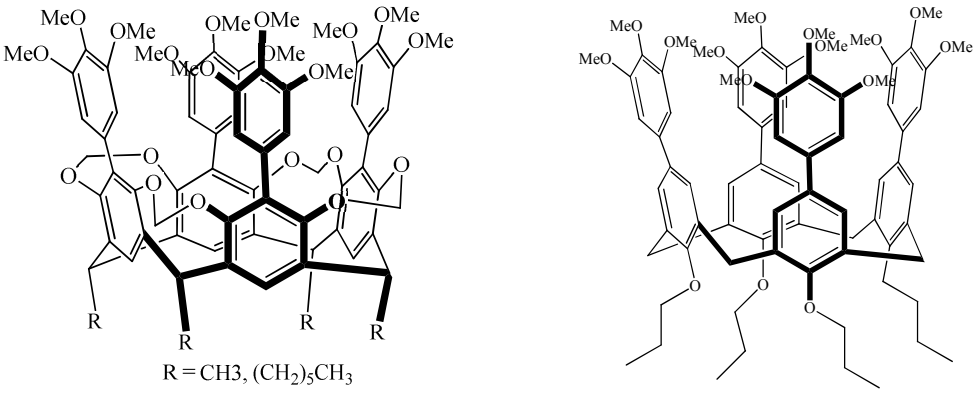



**Figure 3.8** Target molecules with an extended inner cavity synthesized *via* the Suzuki-Miyaura cross coupling.

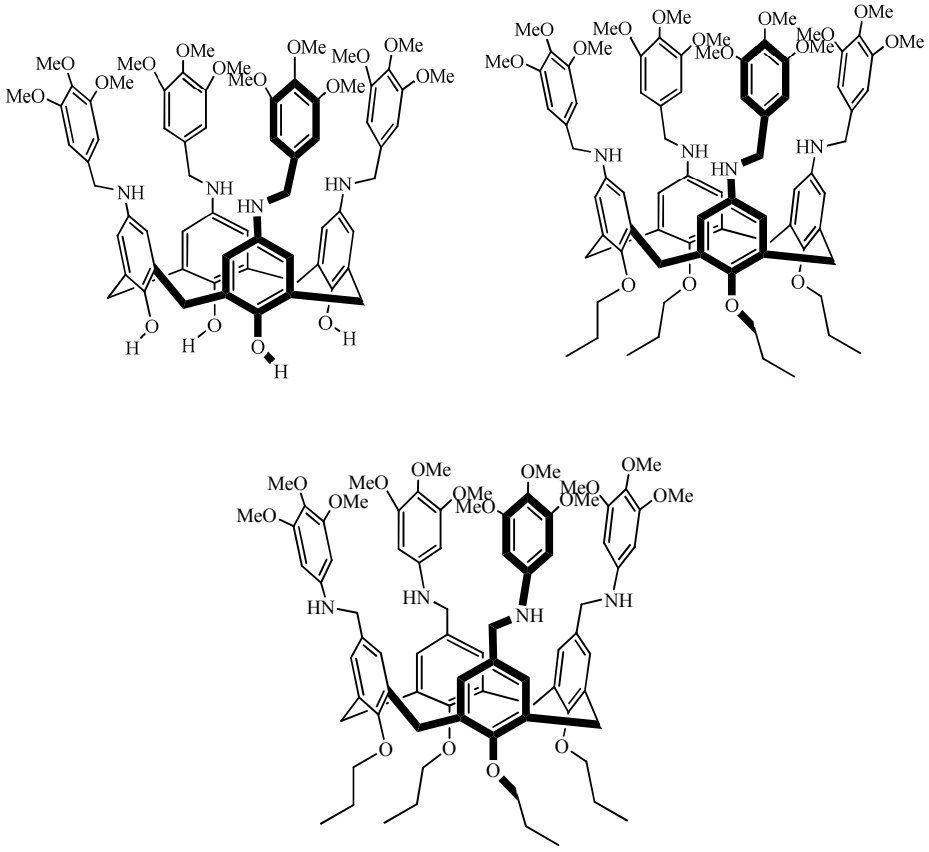


**Figure 3.9** Target molecules with an extended-cavity synthesized through the condensation reaction.

## 3.5 Results and discussion

### 3.5.1 Functionalization of macrocyclic compounds using Suzuki-Miyaura cross coupling reactions

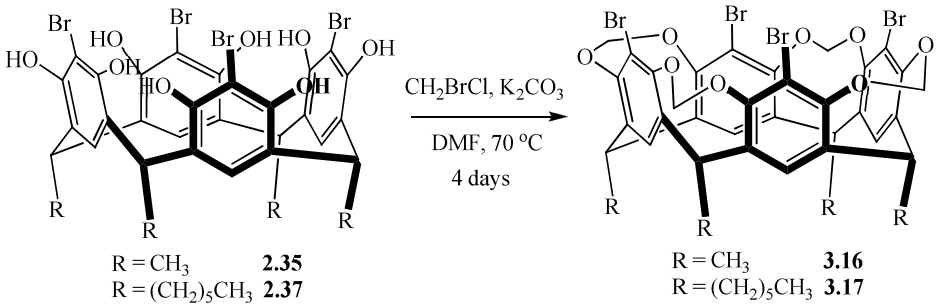
The key chemical in this experiment is 3,4,5-trimethoxyphenyl boronic acid (purchased from Frontier Scientific Inc.) and was used as received without any extra purification. For the building blocks, four macrocyclic compounds were utilized as the starting materials for this cross coupling process: tetrabromo *C*-methylcavitand (**3.16**), tetrabromo *C*-hexylcavitand (**3.17**), 5,11,17,23-tetraiodo-25,26,27,28-tetrapropoxy-calix[4]arene (**3.18**), and 5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxy-calix[4]arene (**3.19**).

#### 3.5.1.1 Synthesis of tetrabromo cavitands

Compounds **3.16** and **3.17** were synthesized from their corresponding tetrabromo resorcin[4]arenes **2.35** and **2.37**. Solutions of **2.35** and **2.37** in dry DMF were treated with anhydrous $K_2CO_3$ for an hour, followed by the addition of excess $CH_2BrCl$.[28] After heating at 65-70 ºC for 4 days, the desired tetrabromo cavitands **3.16** and **3.17** were obtained in moderate yields (64% yield for **3.16**, 74% yield for **3.17**) after purification by column chromatography ($CH_2Cl_2$:hexane = 60:40). The synthetic procedure for tetrabromo cavitands is shown in Scheme 3.1.

Solubility of compound **3.16** posed a major problem during the purification by column chromatography. Cavitand **3.16** does not dissolve very well in dichloromethane at room temperature. Addition of hexane into dichloromethane to prepare the eluent could crash out cavitand **3.16** from the solution. To solve this problem, a dry load

technique was performed on a chromatographic column to ensure the separation effectiveness.




R = $CH_3$ **2.35**
R = $(CH_2)_5CH_3$ **2.37**

R = $CH_3$ **3.16**
R = $(CH_2)_5CH_3$ **3.17**

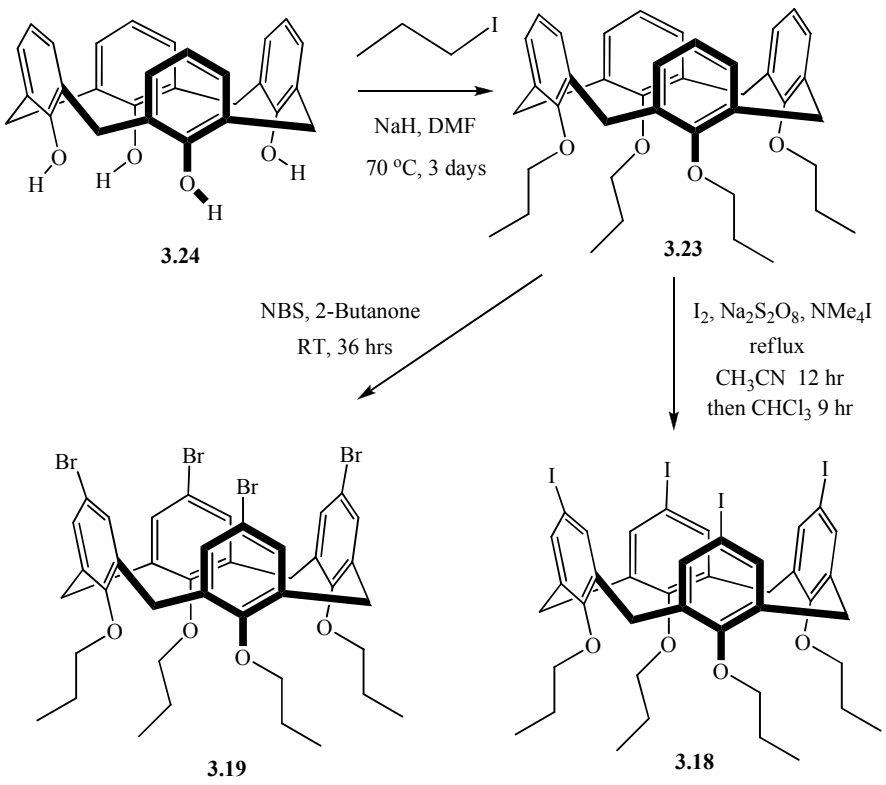
**Scheme 3.1** The synthetic procedure for tetrabromo cavitands **3.16** and **3.17**.

The $^1$H-NMR spectra of tetrabromo *C*-methyl- and *C*-hexylcavitands showed only one signal set of aromatic protons at 7.17 and 7.08 ppm, respectively. For the methine proton (ArC*H*Ar), the signals appear as a quartet at δ = 5.08 (for **3.16** with the $^3J$ = 7.5 Hz) and a triplet at δ = 4.86 (for **3.17** with the $^3J$ = 7.6 Hz) ppm. The proton signal of methylene bridges connected two adjacent aromatic rings appears as a pair of doublets around 5.98 and 4.42 ppm with the coupling constant ($^2J$) about 7.5 Hz. This indicates that two protons on a methylene bridge are magnetically inequivalent and so both tetrabromo cavitands adopt a crown conformation. The $^{13}$C-NMR spectra of **3.16** and **3.17** also showed four aromatic carbon signals and only one set of O-*C*$H_2$-O chemical shifts around 98.4 ppm indicating the $C_4$ symmetry of these macrocycles. Both the mass spectra and elemental analyses of compounds **3.16** and **3.17** are in the good agreement with the expected chemical formulas.

### 3.5.1.2 Synthesis of tetraiodo and tetrabromo tetrapropoxycalix[4]arenes

Both tetraiodo tetrapropoxycalix[4]arene (**3.18**) and its analogue, tetrabromo tetrapropoxycalix[4]arene (**3.19**) were synthesized from tetrapropoxycalix[4]arene (**3.23**). The synthetic route for compounds **3.18** and **3.19** is depicted in Scheme 3.2.

Iodination of calix[4]arene **3.23** with $I_2$ in the presence of $NaS_2O_8$ and $NMe_4I$ afforded tetraiodo tetrapropoxycalix[4]arene **3.18** in excellent yield (94%).[29] The $^1$H-NMR spectrum of **3.18** revealed one aromatic proton signal at $\delta$ = 6.98 ppm. The protons of the methylene bridge appear as a pair of doublets at 4.27 and 3.03 ppm with the coupling constant of 13.5 Hz. This confirms that calix[4]arene **3.18** possesses a cone conformation in solution.[30] The $^{13}$C-NMR spectrum also show only one set of chemical shifts belonging to the aromatic ($\delta$ = 156.3, 137.0, 136.8, and 86.0 ppm) and the methylene bridge (Ar*C*$H_2$Ar) ($\delta$ = 30.3 ppm) carbons.



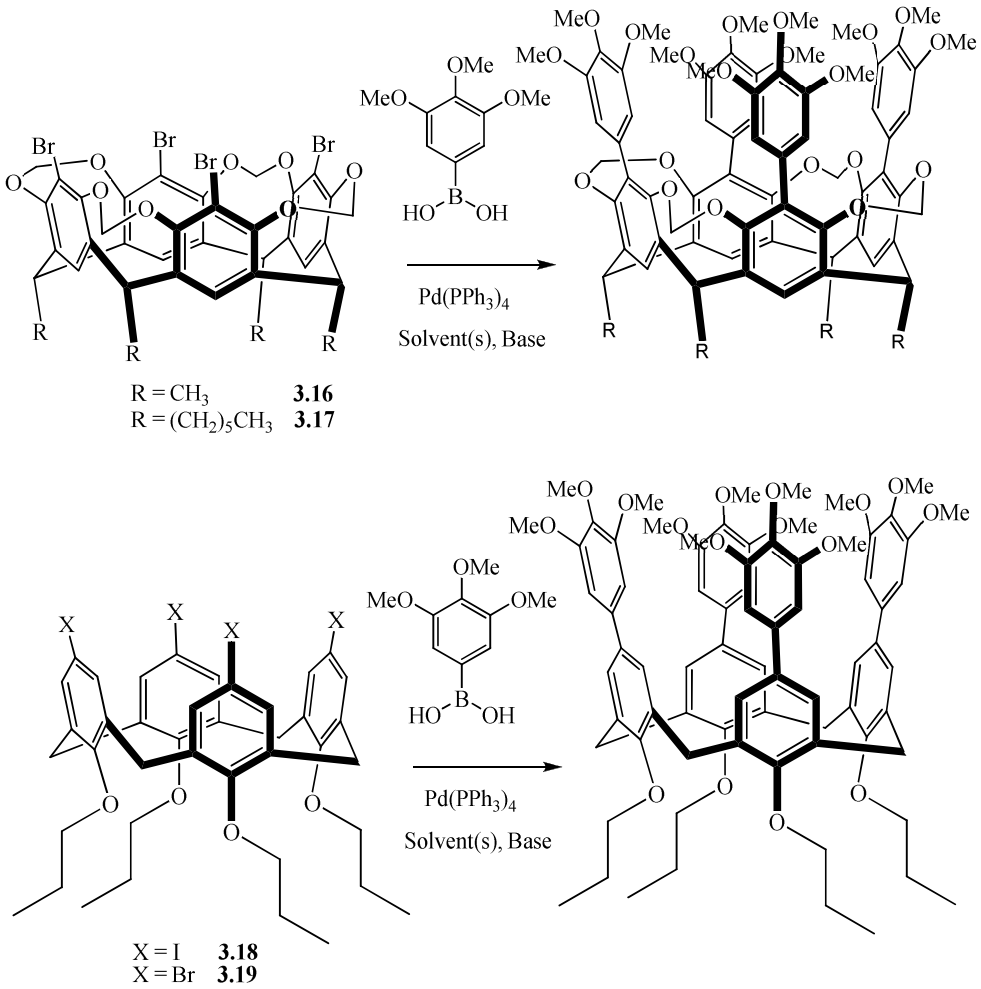

**Scheme 3.2** The synthetic procedure for tetrapropoxycalix[4]arene derivatives **3.18** and **3.19**.

Reaction between calix[4]arene **3.23** and NBS in 2-butanone at room temperature afforded calix[4]arene **3.19** in high yield (80%).[31,32] The $^{1}$H-NMR spectrum of compound **3.19** is similar to that of calix[4]arene **3.18**. Only one set of aromatic and methylene bridge protons appears at 6.78, 4.33 and 3.06 ppm. The coupling constant of the methylene-bridge protons is 13.5 Hz. The $^{13}$C-NMR spectrum of compound **3.19** also showed 4 peaks for the aromatic carbons (155.5, 136.4, 130.8 and 115.1 ppm). The Ar*C*H$_2$Ar signal appears at $\delta$ = 30.7 ppm at one peak, suggesting a cone conformational orientation.

#### 3.5.1.3 Attempts on the Suzuki-Miyaura cross coupling with 3,4,5-trimethoxyboronic acid

Because of the high $O_2$-sensitivity of $Pd(PPh_3)_4$, all reactions were carried out under nitrogen atmosphere. Solvents were degassed with nitrogen prior to use and the reaction mixture was evacuated and flushed with inert gas at least three times using a freeze-pump-thaw technique. The proposed synthetic pathway for macrocycles with an extended-cavity is shown in Scheme 3.3.

Since there is no direct example of the Suzuki-Miyaura cross coupling using 3,4,5-trimethoxyboronic acid on any macrocycle, the attempts are based on the articles regarding the synthesis of extended-cavity macrocycles discussed in early sections of this chapter. Additionally, the reaction conditions used in the attempts were also obtained from the articles involving the Suzuki-Miyaura cross coupling of 3,4,5-trimethoxyphenyl boronic acid with other aryl halides.[33-37]




**Scheme 3.3** The proposed synthetic procedure for the Suzuki-Miyaura cross coupling of macrocycles **3.16**, **3.17**, **3.18**, and **3.19** with 3,4,5-trimethoxyphenyl boronic acid.

The starting materials, bases, solvent systems, reaction conditions and results of the cross coupling attempts are shown in Table 3.1.

**Table 3.1** The reactants, bases, solvent systems, reaction conditions and results from the attempts of Suzuki-Miyaura cross coupling between tetrahalo macrocycles (**3.16-3.19**) with 3,4,5-trimethoxyphenylboronic acid.

| Reactant | Base | Solvent(s) and reaction condition | Result |
|---|---|---|---|
| **3.16** | $Na_2CO_3$ | Toluene, $H_2O$, ethanol, reflux | complex mixture |
| **3.16** | $Na_2CO_3$ | Toluene, $H_2O$, reflux | complex mixture |
| **3.16** | $Na_2CO_3$ | Toluene, $H_2O$, DMF, reflux | complex mixture |
| **3.16** | $KO^tBu$ | Toluene, MeOH, reflux | complex mixture |
| **3.16** | $KO^tBu$ | DME, $^t$BuOH, reflux | complex mixture |
| **3.16** | $KO^tBu$ | MeOH, DME, reflux | complex mixture |
| **3.17** | $KO^tBu$ | DME, $^t$BuOH, reflux | complex mixture |
| **3.17** | $KO^tBu$ | Toluene, MeOH, reflux | complex mixture |
| **3.17** | $KO^tBu$ | Toluene, DME, reflux | complex mixture |
| **3.17** | $KO^tBu$ | MeOH, DME, reflux | complex mixture |
| **3.18** | $K_2CO_3$ | Toluene, $H_2O$, reflux | complex mixture |
| **3.18** | $K_3PO_4$ | Toluene, $H_2O$, reflux | complex mixture |
| **3.18** | $K_3PO_4$ | DMF, reflux | complex mixture |
| **3.18** | $KO^tBu$ | Toluene, MeOH, reflux | complex mixture |
| **3.18** | $KO^tBu$ | DME, $^t$BuOH, reflux | complex mixture |
| **3.18** | $Cs_2CO_3$ | Toluene, ethanol, reflux | complex mixture |
| **3.19** | $Na_2CO_3$ | Toluene, $H_2O$, reflux | complex mixture |
| **3.19** | $K_2CO_3$ | Toluene, $H_2O$, reflux | complex mixture |
| **3.19** | $KO^tBu$ | Toluene, DME, reflux | complex mixture |

According to the results shown in Table 3.1, all crude products obtained from the Suzuki cross coupling attempts are complex mixtures. Purification by silica gel column chromatography using various eluents did not completely separate each compound found in the mixtures. However, one compound was successfully purified from some crude products. White powder of compound **3.25** was obtained from a column chromatography eluted with $CH_2Cl_2$:EtOAc (99:1). The $^1$H-NMR spectrum of this compound showed only two sets of peaks at $\delta$ = 6.63 (singlet), and two singlets at 3.81 and 3.77 ppm. There is no trace of a propyl group's protons which should be observed if this compound is a derivative of tetrapropoxycalix[4]arene. Therefore, compound **3.25** is obviously not an expected calix[4]arene derivative. From the integration, it was revealed that the ratio between the two proton signals is 1:4.6. This ratio is very similar to the ratio of protons found in 3,3′,4,4′,5,5′-hexamethoxybiphenyl. The proportion of aromatic protons and methoxy groups of 3,3′,4,4′,5,5′-hexamethoxybiphenyl is 4:18 which is relatively close to the 1:4.6 relative amount of protons found in compound **3.25**. With this information, it can be deduced that compound **3.25** is actually 3,3′,4,4′,5,5′-hexamethoxybiphenyl (Figure 3.10).

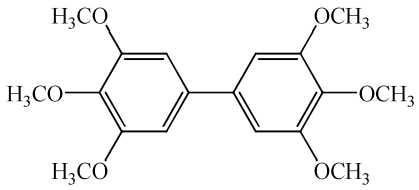



**Figure 3.10** Chemical structure of 3,3′,4,4′,5,5′-hexamethoxybiphenyl.

Formation of 3,3′,4,4′,5,5′-hexamethoxybiphenyl suggests that the Suzuki-Miyaura attempts were contaminated with a trace amount of $O_2$. The formation of self-coupled product such as **3.25** occurs when Pd(0) is oxidized to Pd(II) leading to the formation of peroxopalladium(II) complex.[38] In the presence of water, this complex could undergo further oxidation to produce a peroxyhydroxopalladium(II) complex which reacts with phenyl boronic acids to form a homocoupled product.[39] The proposed reaction pathway is depicted in Figure 3.11.

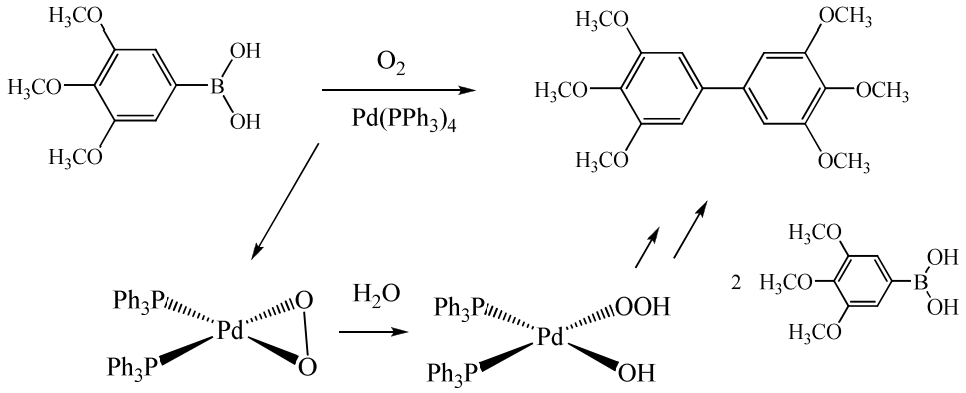



**Figure 3.11** Proposed reaction pathway for an oxygen-induced homocoupling of 3,4.5-trimethoxyphenyl boronic acid.

The other possible side reaction is dehalogenation of tetrabromocavitands and tetrahalocalix[4]arenes. In the attempts using alcohol (methanol or ethanol) as co-solvent, the intermediate Ar-Pd-OR′ (where Ar = cavitand or calix[4]arene; R′ = $CH_3$ or $CH_2CH_3$) can undergo $\beta$-hydride elimination to give Ar-Pd-H[40], followed by reductive elimination to afford undesired dehalogenated cavitand or calix[4]arene. Moreover, if the intermediate Ar-Pd-OH is formed during the reaction, it could be reduced by $PPh_3$ to produce Ar-Pd-H and triphenyl phospine oxide ($O=PPh_3$).[41]

With the lack of success on the Suzuki-Miyaura cross coupling reactions previously described, it seems that the reaction conditions and the catalyst are not suitable for the macrocycles and 3,4,5-trimethoxyboronic acid. There are several adjustments which could improve the overall cross coupling reaction as follows:

1. For cavitands **3.16** and **3.17**, the halogen-exchange from bromine to iodine[19] could promote better reaction because iodine is a better leaving group than bromine. Therefore, tetraiodo cavitands might be more appropriate starting materials.
2. Since $Pd(PPh_3)_4$ is not active enough for this coupling process, changing the catalyst to other Pd(II) catalysts such as $PdCl_2(PPh_3)_4$ or $Pd(OAc)_2$ may be worth trying. Additionally, a new phosphine ligand such as 2-dicyclohexyl-phosphino-2′,6′-dimethoxybiphenyl (S-Phos)[42] might be more reactive than $PPh_3$ in the case of highly steric substrates like cavitands and 3,4,5-trimethoxyphenyl boronic acid.
3. To prevent the side reaction which may come from the presence of $O_2$ in water or alcohol (such as methanol or ethanol), a one solvent system (DMF or toluene) could be a better alternative strategy for this coupling reaction.
4. The formation of homocoupling product from a boronic acid indicates that the reaction vessel was contaminated with oxygen. To solve this problem, the reaction mixture may be purged with inert gas at room temperature for a significant period of time to make certain that all oxygen is completely evacuated from the reaction vessel. Moreover, the freeze-pump-thaw process should be repeated more than three times to ensure oxygen-free conditions.

### 3.5.2 Extension of macrocycles using the condensation reaction between aromatic aldehyde and primary amine.

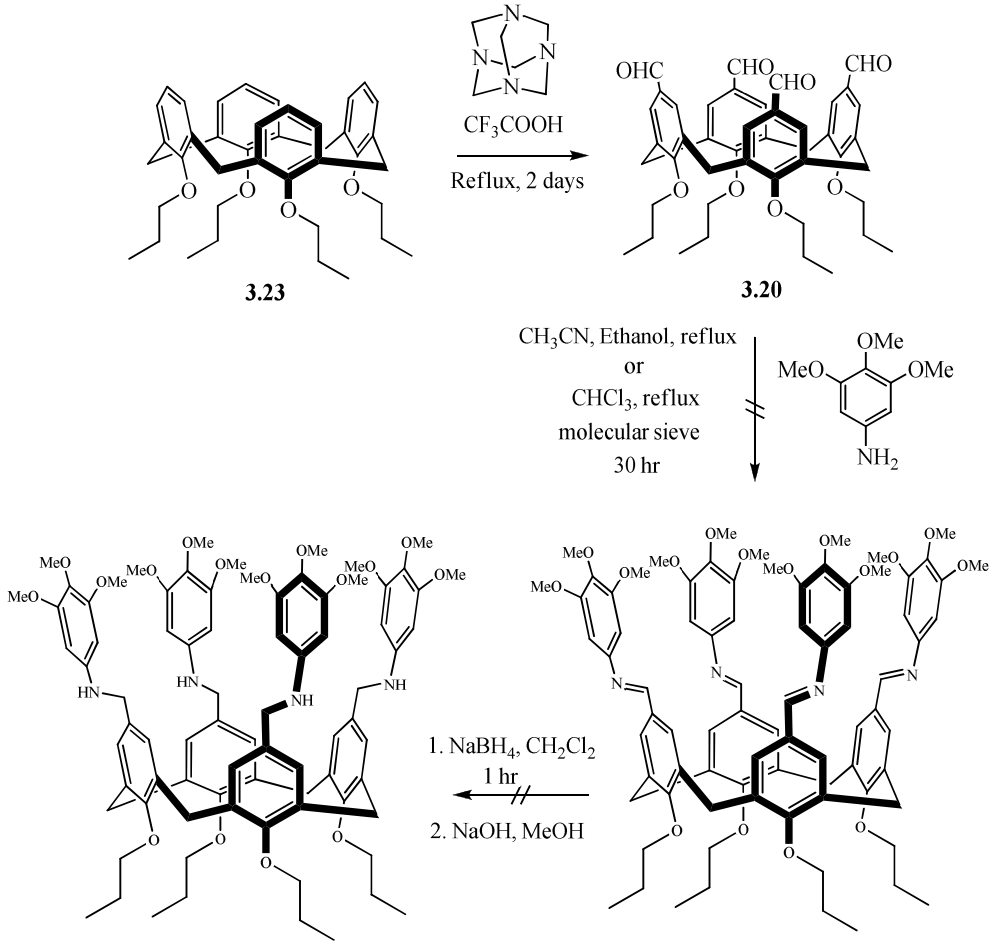
The other approach to enlarge the cavity of a relevant macrocycle is to employ the condensation reaction between aldehyde and primary amine. To explore this strategy, other three calix[4]arene derivatives: 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxy-calix[4]arene (**3.20**), 5,11,17,23-tetraamino-25,26,27,28-tetrahydroxycalix[4]arene (**3.21**) and 5,11,17,23-tetraamino-25,26,27,28-tetrapropoxycalix[4]arene (**3.22**), were synthesized. The 3,4,5-trimethoxyphenyl moiety which will be attached to the calix[4]arene structure came from 3,4,5-trimethoxyaniline or 3,4,5-trimethoxy-benzaldehyde.

#### 3.5.2.1 Synthesis of tetraformyl-calix[4]arene and its condensation reaction with 3,4,5-trimethoxyaniline

Tetraformyl tetrapropoxycalix[4]arene **3.20** was synthesized from the reaction of calix[4]arene **3.23** with hexamethylenetetramine (HMTA) in refluxed trifluoroacetic acid.[43] Pure **3.20** was obtained as a white solid in 58% yield. The $^{1}$H-NMR spectrum of **3.20** showed a –C*H*O signal at 9.56 ppm. The aromatic protons' signal appears as a singlet ($\delta$ = 7.13 ppm). Moreover, the chemical shifts of the methylene bridge's protons are at 4.48 and 3.32 as a pair of doublets with $^{2}J$ = 13.5 Hz. This indicates that the calix[4]arene molecule adopts a cone conformation. The $^{13}$C-NMR spectrum of **3.23** revealed a signal of –*C*HO at 191.3 ppm. Four aromatic carbon signals appear in the range of 161.9-130.2 ppm. Only one set of methylene bridge carbons emerges as a singlet

at 30.9 ppm. The mass spectrum and elemental analysis results are also consistent with the expected chemical formula of compound **3.20**.

The proposed synthetic route of tetraformyl calix[4]arene **3.20**[44] and its products from the condensation reaction with 3,4,5-trimethoxyaniline is shown in Scheme 3.4.




**Scheme 3.4** The proposed synthetic procedure of tetraformyl tetrapropoxycalix[4]arene and its product from the condensation reaction with 3,4,5-trimethoxyaniline.

The reaction between **3.20** and 3,4,5-trimethoxyaniline afforded a mixture of products. The $^{1}$H-NMR spectrum of the crude product is shown in Figure 3.12.

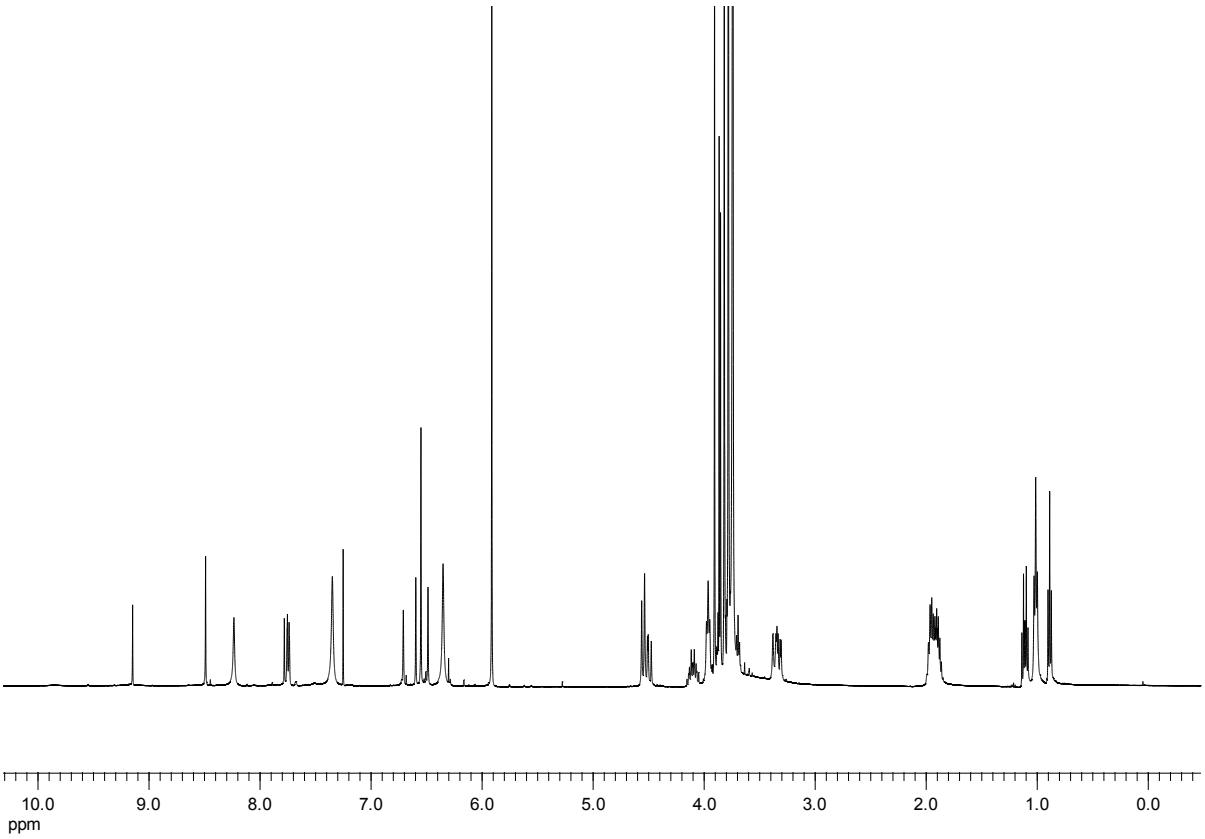



**Figure 3.12** $^{1}$H-NMR spectrum (500 MHz) of the crude product from the reaction between calix[4]arene **3.20** and 3,4,5-trimethoxyaniline.

The $^{1}$H-NMR spectrum showed three sets of the $CH_3$ protons suggesting the presence of a mixture in the crude product. The –CHO and –CH=N- signals also appear at 9.13, 8.48 and 8.22 ppm. This also reveals that not all formyl groups reacted with 3,4,5-trimethoxy-aniline. Several aromatic protons of a trimethoxyphenyl group emerge in the range of 6.69-6.34 ppm. Moreover, the signals of the methylene bridges' protons appear as more than one set, indicating the magnetic inequivalence of these protons.

Incompletion of the condensation reaction between **3.20** and 3,4,5-trimethoxyaniline may come from the fact that aromatic primary amines are weaker nucleophiles and bases than aliphatic primary amines because the lone pair electrons on a

nitrogen atom participate in the delocalization of electrons in an aromatic ring. Therefore, nucleophilic attack at the formyl groups of compound **3.20** may be slower leading to the partial condensation product.

Moreover, most condensation reactions between primary amines and aldehydes use polar solvents such as acetonitrile, ethanol and methanol. The major reason is most imines are less soluble in these solvents, so the products tend to precipitate from the reaction mixture. This characteristic feature drives the reaction forward and prevents the hydrolysis of imine back to the corresponding aldehyde and amine. However, the difficulty with compound **3.20** is its solubility in polar solvents is extremely poor. The evidence is that a considerable amount of unreacted calix[4]arene **3.20** was recovered from the reaction. Changing the solvent system to an apolar solvent such as $CHCl_3$ facilitates the solubility of calix[4]arene **3.20** but does not drive the reaction forward. Even in the presence of a molecular sieve 4 Å, a mixture of products was still observed.

The attempts to drive the reaction forward by adding a catalytic amount of glacial acetic acid or trifluroacetic acid failed to produce a fully condensed calix[4]arene derivative. However, it does not mean that *tetrakis*[(3,4,5-trimethoxyphenyl)imido]-tetrapropoxycalix[4]arene could not be obtained. An alternative strategy is reductive amination by reducing the imine bonds formed during the condensation reaction immediately with $NaBH_3CN$. Sodium cyanoborohydride can reduce an imine functional group selectively without interfering with a secondary amine or a formyl group.

### 3.5.2.2 Synthesis of tetraamino calix[4]arene and its condensation reaction with 3,4,5-trimethoxybenzaldehyde

A similar strategy on utilizing the condensation reaction to produce the extended-cavity macrocycles was performed by switching the aldehyde and primary amine. In this approach, amino groups were introduced into the calix[4]arene scaffold first and then the corresponding tetraamino calix[4]arenes were reacted with 3,4,5-trimethoxybenzaldehyde to afford the tetraimino calix[4]arenes. Finally, the reduction reaction of tetraimino calix[4]arenes with sodium borohydride could produce the desired calix[4]arene tetraamines.

Tetraamino calix[4]arene **3.21** was synthesized in two steps from calix[4]arene **3.24**.[45-47] First, macrocycle **3.24** was reacted with 4-aminobenzoic acid in the presence of $NaNO_2$ to give tetraazo calix[4]arene **3.25** in quantitative yield. After that, compound **3.25** was reduced by $Na_2S_2O_4$ in the presence of sodium hydroxide to afford tetraamino calix[4]arene **3.21**. Unfortunately, compound **3.21** is easily oxidized at room temperature so the crude product from the reduction reaction was subjected to the condensation reaction without any weighing or purification. The reaction of calix[4]arene **3.21** with benzaldehyde in dry acetonitrile afforded *tetrakis*[(3,4,5-trimethoxyphenyl)imido] calix[4]arene **3.26** in moderate yield (65%).

The $^1$H-NMR spectrum of tetraimino calix[4]arene **3.26** (see Figure 3.13) showed the broad peak of –OH around 10.14 ppm. The imine and aromatic protons appear as a singlet at $\delta$ = 8.27, 7.11, and 7.07 ppm, respectively. The integration for the proton ratio is approximately 4:8:8, indicating the fully substituted calix[4]arene. The methylene bridge's protons were detected around 4.32 and 3.59 ppm as two broad peaks. This

suggests that there is somewhat the conformational flexibility in this calix[4]arene derivative. This is reasonable since the lower rim of calix[4]arene **3.26** is not functionalized with any chemical group. Therefore, the fluctuation of the methylene bridge protons is observed because the calix[4]arene **3.26** adopts not only a cone but also other conformations as well.[48] The other possible conformers might be a pinched cone orientation in which two opposite aromatic rings of calix[4]arene move close to each other, whereas the other two rings are repelled from their original positions as the result of the former feature.

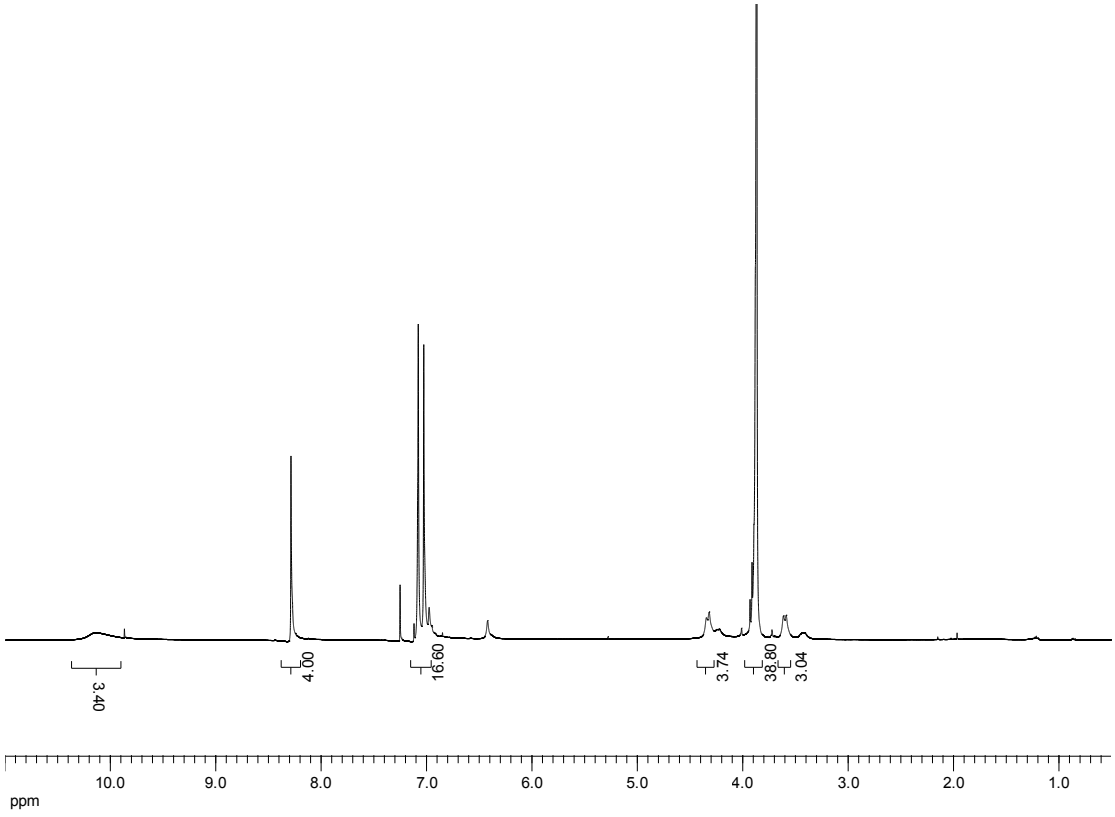
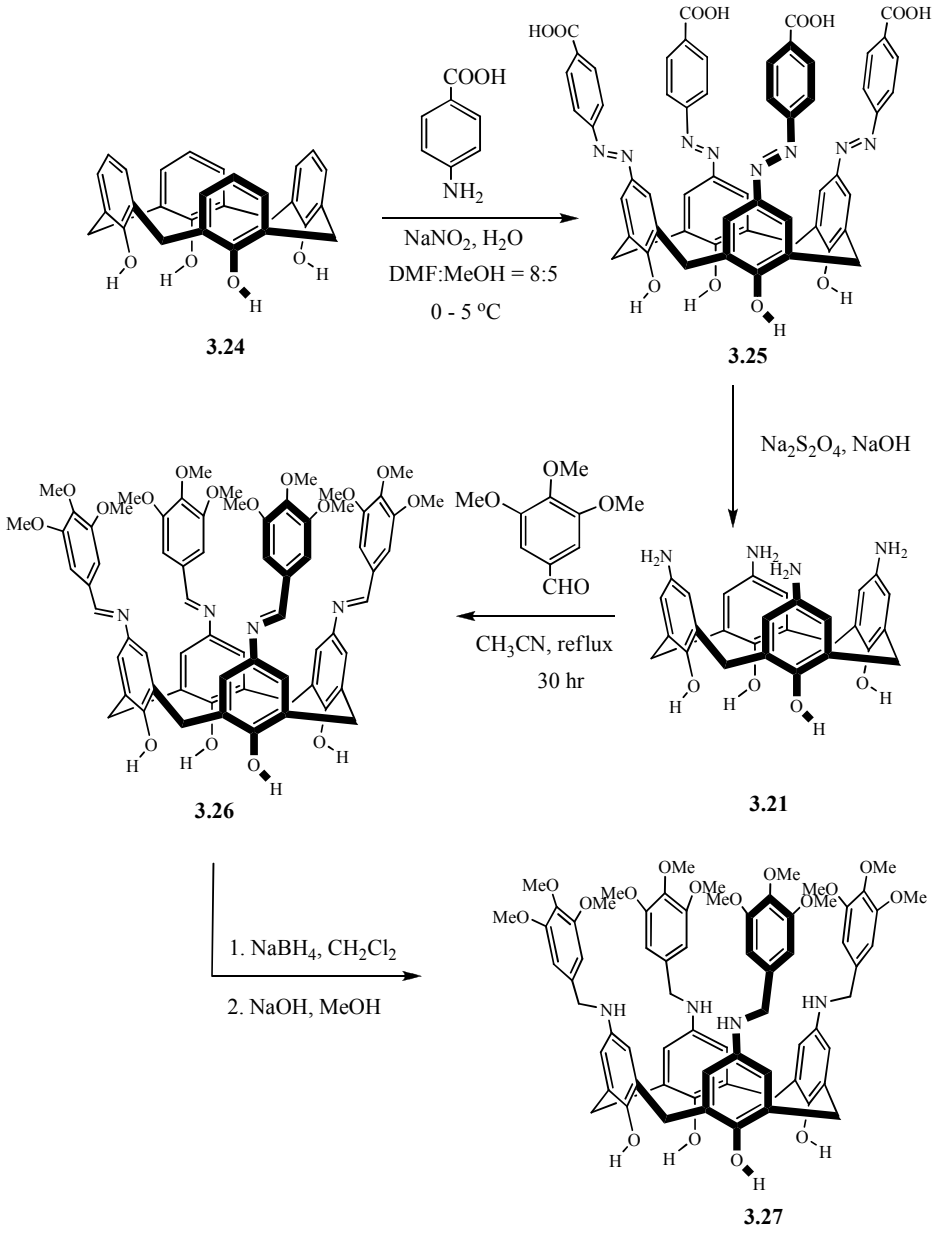



**Figure 3.13** $^{1}$H-NMR spectrum (500 MHz) of tetraimino calix[4]arene **3.26** in $CDCl_3$**.**

The proposed synthetic procedure of tetraamino calix[4]arene **3.20** and its products from the condensation reaction with 3,4,5-trimethoxybenzaldehyde is depicted in Scheme 3.5.




**Scheme 3.5** The proposed synthetic procedure of tetraamino calix[4]arene and its product (**3.26** and **3.27**) from the condensation reaction with 3,4,5-trimethoxy-benzaldehyde.

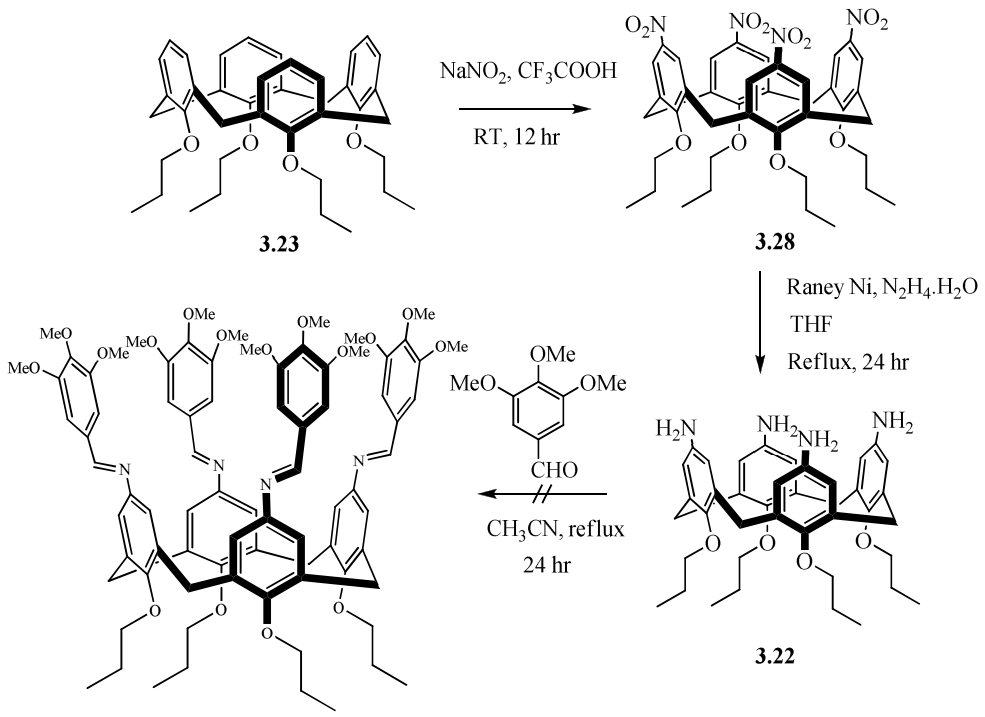
The $^{13}$C-NMR spectrum of compound **3.26** exhibited only one peak for the imine carbons at δ = 158.5 ppm, indicating the formation of a tetraimino product. The signals of the aromatic carbons appear in the range of 153.5-106.7 ppm. Two signals for $-OCH_3$ groups were found at 60.9 and 56.2 ppm. The results from mass spectrometry and elemental analysis are also consistent with the calculated exact mass and elemental composition of tetraimino calix[4]arene **3.26**.

The reduction of calix[4]arene **3.26** with $NaBH_4$ did not proceed smoothly as anticipated. The recrystallization of calix[4]arene **3.27** from $CH_2Cl_2$-methanol solution afforded a dark brown powder, which was expected to be calix[4]arene **3.27**. However, the $^1$H-NMR spectrum of the solid product revealed numerous peaks and a reasonable structure could not be deduced. It is possible that the reduction of imine to amine was not complete due to the short reaction time (30 minutes). Further attempts to produce pure compound **3.26** are in progress but will not be discussed in this dissertation.

#### 3.5.2.3 Synthesis of tetraamino tetrapropoxycalix[4]arene and its condensation reaction with 3,4,5-trimethoxybenzaldehyde

The proposed synthetic pathway of calix[4]arene **3.22** and its Schiff base derivative is depicted in Scheme 3.6.

Nitration of tetrapropoxycalix[4]arene **3.23** with $NaNO_2$ in trifluoroacetic acid afforded tetranitro tetrapropoxycalix[4]arene **3.28** in moderate yield (57%) as a light yellow solid. Reduction of calix[4]arene **3.28** with hydrazine monohydrate in the presence of Raney nickel produced a quantitative yield of tetraamino tetrapropoxycalix[4]arene **3.22**.[49]




**Scheme 3.6** The proposed synthetic procedure of tetraamino tetrapropoxycalix[4]arene **3.22** and its derivative from the condensation reaction with 3,4,5-trimethoxybenzaldehyde.

The $^{1}$H NMR spectra of calix[4]arenes **3.22** and **3.28** showed a similar pattern of peaks. However, the aromatic proton signal of tetranitro calix[4]arene is found at $\delta$ = 7.54 ppm while that of tetraamino calix[4]arene appears at 6.06 ppm. The ArC*H*$_2$Ar protons of calix[4]arenes **3.22** and **3.28** appear as a pair of doublets ($\delta$ = 4.27 and 2.88 ppm with $^{2}J$ = 13.0 Hz for compound **3.22**; $\delta$ = 4.50 and 3.38 ppm with $^{2}J$ = 14.0 Hz for compound **3.28**). Therefore, it is obvious that both calix[4]arenes adopt a cone conformation. Moreover, the protons of the –$NH_2$ groups also appear as a broad singlet around 3.51 ppm.

The $^{13}$C-NMR spectrum of **3.22** showed 4 peaks for the aromatic carbons in the range of 150.4-116.2 ppm and a peak for Ar*C*$H_2$Ar at 77.3 ppm, indicating a symmetrical tetraamino-calix[4]arene. The $^{13}$C-NMR spectrum of **3.28** exhibited a similar peak pattern but with different chemical shifts for the aromatic carbons (161.7-124.0 ppm).

The reaction between calix[4]arene **3.22** and 3,4,5-trimethoxybenzaldehyde afforded a mixture of products similar to the reaction of tetraformyl tetrapropoxy-calix[4]arene and 3,4,5-trimethoxyaniline. A possible explanation for this incomplete reaction is that calix[4]arene **3.22** has a poor solubility in dry acetonitrile so the condensation reaction could not proceed forward at a satisfactory rate. This may lead to the hydrolysis of tetraimino calix[4]arene to give the corresponding starting material. The presence of a catalytic amount of glacial acetic acid or trifluroacetic acid did not improve the overall reaction. A mixture of products was still obtained from the condensation reaction.

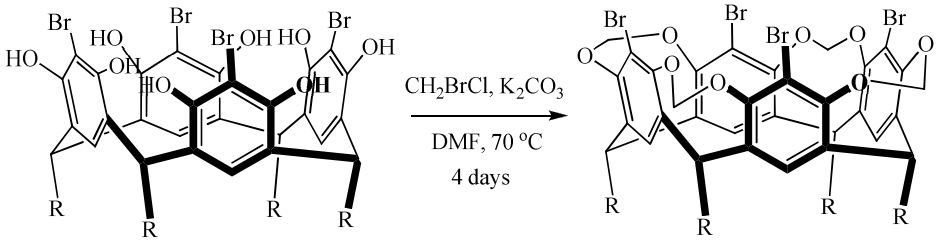
The rising question is why calix[4]arene **3.21** reacted with 3,4,5-trimethoxy-benzaldehyde a lot better than its analog, calix[4]arene **3.22**, even though both of them are the tetraamino derivatives. A possible rationalization is that calix[4]arene **3.21** is more soluble in acetonitrile than macrocycle **3.22**. Therefore, upon the condensation reaction with 3,4,5-trimethoxybenzaldehyde, compound **3.21** was consumed faster than its analogue **3.22**. This feature may lead to a better formation of the corresponding imino calix[4]arene.

## 3.6 Experimental section

### 3.6.1 General procedure

In addition to the general procedure described in section 2.8, 3,4,5-trimethoxy-phenyl boronic acid was purchased from Frontier Scientific Inc. and used without any further purification. Both 3,4,5-trimethoxyaniline and 3,4,5-trimethoxybenzaldehyde were obtained from Sigma-Aldrich and used as received without any purification. Two calix[4]arene derivatives: *p-tert*-butylcalix[4]arene[50-52] and 25,26,27,28-tetrahydroxy-calix[4]arene (**3.24**)[53] were synthesized according to the literature. Both 5,11,17,23-tetrabromo *C*-methyl- and *C*-hexylresorcin[4]arenes were synthesized according to the procedure in section 2.8.7.

### 3.6.2 Synthesis of 5,11,17,23-tetrabromo *C*-alkylcavitands




A mixture of appropriate tetrabromo *C*-alkylresorcin[4]arene (20.0 mmol), and anhydrous potassium carbonate (34.17 g, 0.247 mol) was charged with dry DMF (200 mL) under nitrogen and the reaction mixture was stirred at room temperature for an hour. Then bromochloromethane (41.45 g, 20.8 mL, 0.320 mol) was added dropwise *via* an

adding funnel. After the addition was completed, the reaction mixture was heated to 65-70ºC under nitrogen atmosphere for 4 days. Every 24 hours, additional bromochloroethane (6.47 g, 3.25 mL, 50.0 mmol) was added. After cooling down to room temperature, DMF was removed under vacuum to give a dark brown solid. Dichloromethane (150 mL) was added to the reaction mixture along with 2M HCl (50 mL). The aqueous phase was separated and extracted with more $CH_2Cl_2$ (3 x 50 mL). The combined organic phase was then washed with water (3 x 100 mL), brine (100 mL) and dired over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a brown residue which was subjected to silica gel column chromatography with a mixture of hexane:$CH_2Cl_2$ (40:60) as the eluent. Tetrabromo *C*-alkylcavitand was isolated as a white solid.

5,11,17,23-Tetrabromo *C*-methylcavitand **3.16** 11.91 g (64% yield)

$^1$H-NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.17 (s, 4H, -Ar*H meta* to –OCH-), 5.97 and 4.38 (two sets of d, 8H, $^2J$ = 7.5 Hz, O-C$H_2$-O), 5.08 (q, 4H, $^3J$ = 7.5 Hz, ArC*H*Ar), 1.77 (d, 12H, $^3J$ = 7.5 Hz , -C$H_3$); $^{13}$C-NMR (75.1 MHz, $CDCl_3$): δ = 151.7 ($C_q$-$OCH_2$-), 140.1 ($C_q$ *ortho* to $COCH_2$-), 118.5 ($C_H$ *meta* to $COCH_2$-), 113.4 ($C_q$ *ipso* to Br), 98.4 (-O*C*$H_2$O-), 32.0 (Ar*C*HAr), 15.9 (-*C*$H_3$) ppm.

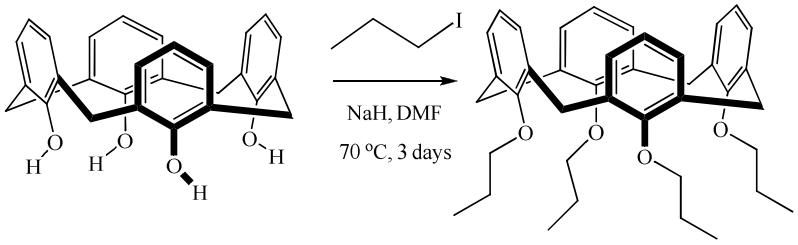
(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{36}H_{28}Br_4O_8$·2$CH_3OH$ + $H^+$] m/z = 969.93, Found m/z = 969.70 (100%). Analytical calculated for $C_{36}H_{36}Br_4O_{12}$·4$H_2O$: C, 44.11; H, 3.70. Found: C, 44.33; H, 3.20.

5,11,17,23-Tetrabromo *C*-hexylcavitand **3.17** 17.52 g (74% yield)

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.08 (s, 4H, -Ar*H meta* to –$OCH_2$-), 5.97 and 4.40 (two set of d, 8H, $^{2}J$ = 7.5 Hz, -OC$H_2$O-), 4.86 (t, 4H, $^{3}J$ = 7.6 Hz, ArC*H*Ar), 2.18-2.24 (m, 8H, ArCH-C$H_2$-), 1.43-1.33 (m, 32H, -C$H_2$-), 0.87 (t, 12H, $^{3}J$ = 7.8 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 151.8 ($C_q$-$OCH_2$-), 139.3 ($C_q$ *ortho* to $COCH_2$), 119.0 (CH *meta* to $COCH_2$), 113.5 ($C_q$ *ipso* to Br), 98.4 (-O*C*$H_2$O), 37.7 (Ar*C*HAr), 33.7, 31.8, 29.8, 28.6, 23.3 (-*C*$H_2$-), 14.3 (-*C*$H_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{56}H_{68}Br_4O_8$·2$CH_3OH$ + $H^+$] m/z = 1249.22, Found m/z = 1248.79 (100%). Analytical calculated for $C_{56}H_{68}Br_4O_8$: C, 56.58; H, 5.77. Found: C, 56.29; H, 5.49.

## 3.6.3 Synthesis of 25,26,27,28-tetrapropoxycalix[4]arene



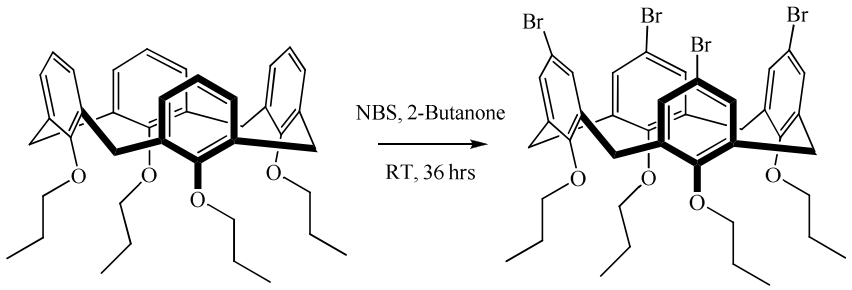

To a mixture of 25,26,27,28-tetrahydroxycalix[4]arene (21.42 g, 50.4 mmol) and 95% NaH (8.38 g, 0.349 mol) in a 1L three-necked round bottom flask under nitrogen was added dry DMF (500 mL). The reaction mixture was stirred at room temperature for 1-2 hr. Then, 1-iodopropane (74.86 g, 43.00 mL, 0.440 mol) was added dropwise *via* an adding funnel. The reaction mixture was heated at 70ºC for 3 days. After cooling to room

temperature, DMF was removed under vacuum. The residue was dissolved in $CH_2Cl_2$ (250 mL) and deionized water (200 mL) was added. The biphasic solution was stirred for an hour and the organic layer was separated, washed with water (3 x 50 mL), and dried over anhydrous $Na_2SO_4$. The organic phase was concentrated on a rotary evaporator to give a white solid. The crude product was purified by a silica gel column using hexane:$CH_2Cl_2$ (1:1) as the eluent. The combined organic solvent was evaporated to dryness under reduced pressure. Recrystallization from methanol afforded calix[4]arene 3.23 as a white powder (21.70 g, 73% yield).

$^1$H-NMR (500 MHz, CDCl3, 300 K): $\delta$ = 6.66 (s, 8H, -Ar*H*), 4.52 and 3.21 (tow sets of d, 8H, $^2J$ = 13.5 Hz, ArC*H*$_2$Ar), 3.91 (t, 8H, $^3J$ = 7.5 Hz, OC*H*$_2$CH$_2$), 2.00 (tq, 8H, $^3J$ = 7.5 MHz, -CHC*H*$_2$CH$_3$), 1.06 (t, 12H, $^3J$ = 7.5 Hz, -C*H*$_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ = 156.5 (-*C*$_q$-OCH$_2$-), 135.1, 128.1, 121.8, 77.2 (O-*C*H$_2$CH$_2$-), 30.9 (Ar*C*H$_2$Ar), 23.2 (-*C*H$_2$CH$_3$), 10.3 (-*C*H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{40}H_{48}O_4$ + $Na^+$] m/z = 615.38, Found m/z = 615.58 (100%). Analytical calculated for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 81.03; H, 8.20.

### 3.6.4 Synthesis of 5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxy-calix[4]arene

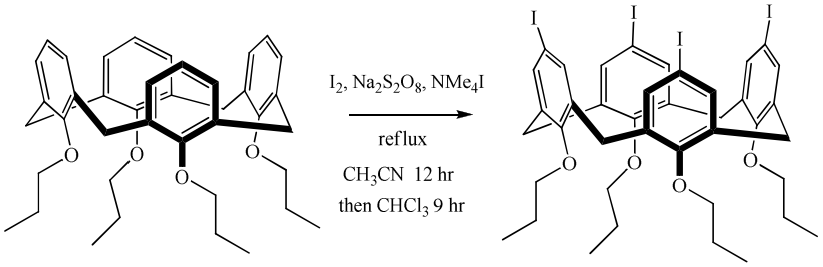



To a solution of calix[4]arene **3.23** (6.02 g, 10.2 mmol) in 2-butanone (200 mL) was added NBS (18.38 g, 0.103 mol) at room temperature under nitrogen. The reaction mixture was stirred for 24 hours. The mixture was then added with 150 mL of 10% $Na_2S_2O_3$ and stirred for 15 minutes. The organic layer was then separated, washed with water (2 x 100 mL), and dried over anhydrous $Na_2SO_4$. The solvent was then evaporated to dryness. The yellow residue was recrystallized from $CHCl_3$-methanol to give compound **3.19** as a white solid (7.29 g, 80% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.78 (s, 8H, -Ar*H*), 4.33 and 3.06 (tow sets of d, 8H, $^2J$ = 13.5 Hz, ArC$H_2$Ar), 3.79 (t, 8H, $^3J$ = 7.5 Hz, OC$H_2$CH$_2$), 1.86 (tq, 8H, $^3J$ = 7.5 MHz, -CHC$H_2$CH$_3$), 0.95 (t, 12H, $^3J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 155.5 (-$C_q$-OCH$_2$-), 136.4 ($C_{ar}$H *ortho* to Br), 131.0, 115.1, 77.2 (O-*C*H$_2$CH$_2$-), 30.7 (Ar*C*H$_2$Ar), 23.0 (-*C*H$_2$CH$_3$), 10.2 (-*C*H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{40}H_{44}Br_4O_4 + Na^+$] m/z = 926.99, Found m/z = 928.98 (100%). Analytical calculated for $C_{43}H_{50}Br_4O_5 \cdot CH_3COCH_3$: C, 53.44; H, 5.21. Found: C, 53.52; H, 5.04.

### 3.6.5 Synthesis of 5,11,17,23-tetraiodo-25,26,27,28-tetrapropoxy-calix[4]arene



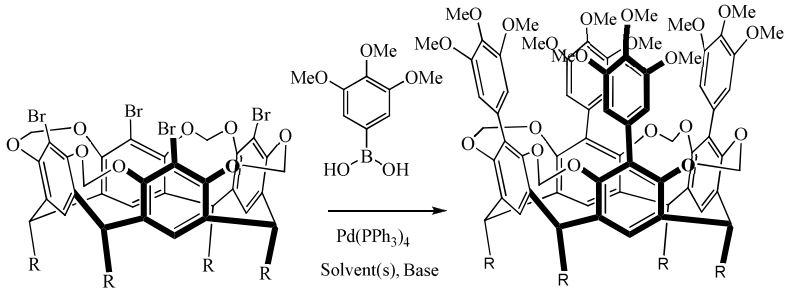

To a suspension of 25,26,27,28-tetrapropoxycalix[4]arene (5.93 g, 10.0 mmol) in dry acetonitrile (200 mL) was added $I_2$ (11.73 g, 46.2 mmol), sodium peroxodisulfate (11.79 g, 47.0 mmol), and tetramethylammonium bromide (2.47 g, 12.3 mmol). The reaction mixture turned deep purple immediately after the addition of all reagents was completed. The solution was heated to 80ºC after 12 hours. Then dry $CHCl_3$ (40 mL) was added via syringe and the reaction was continued at the same temperature for another 9 hours. After cooling to room temperature, the reaction mixture was poured into aqueous 40% sodium bisulfite (20.15 g in 50 mL of water) solution and stirred for 1 hr or until the color of the solution turned to light yellow. The mixture was extracted with 25% vol/vol $CH_2Cl_2$ in diethyl ether (3 x 100 mL). The combined organic layer was washed with water (3 x 50 mL), brine (50 mL), and dried over $MgSO_4$. Solvents were then removed

on a rotary evaporator to afford a light yellow solid. The crude product was recrystallized from a mixture of $CH_2Cl_2$-MeOH to give tetraiodo tetrapropoxycalix[4]arene as white crystals. The product was dried under high vacuum for 24 hr.

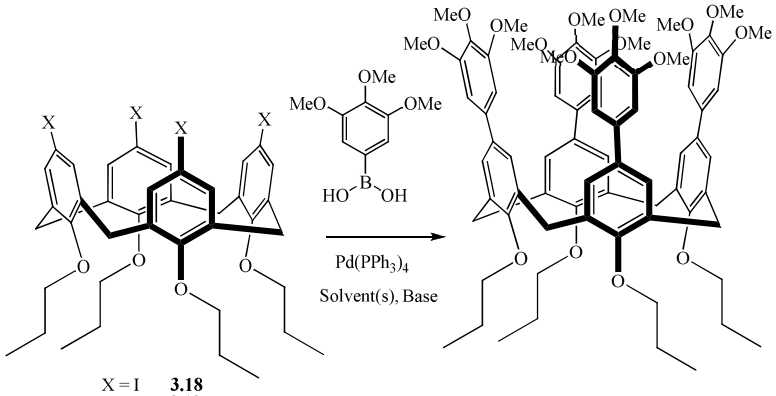
$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): $\delta$ = 6.98 (s, 8H, -Ar*H*), 4.27 and 3.03 (tow sets of d, 8H, $^2J$ = 13.5 Hz, ArC*H*$_2$Ar), 3.79 (t, 8H, $^3J$ = 7.5 Hz, OC*H*$_2$CH$_2$), 1.86 (tq, 8H, $^3J$ = 7.5 MHz, -CHC*H*$_2$CH$_3$), 0.94 (t, 12H, $^3J$ = 7.5 Hz, -C*H*$_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ = 156.3 (-*C*$_q$-OCH$_2$-), 137.0 (*C*$_{ar}$H *ortho* to I), 136.8, 86.0, 77.1 (O-*C*H$_2$CH$_2$-), 30.3 (Ar*C*H$_2$Ar), 23.0 (-*C*H$_2$CH$_3$), 10.2 (-*C*H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{40}H_{44}I_4O_4$ + $Na^+$] m/z = 1118.93, Found m/z = 118.24 (85%). Analytical calculated for $C_{40}H_{44}I_4O_4$: C, 43.81; H, 4.05. Found: C, 43.62; H, 4.01.

### 3.6.6 Attempts of the Suzuki-Miyaura cross coupling between tetrahalo macrocycles and 3,4,5-trimethoxy boronic acid




R = $CH_3$ **3.16**
R = $(CH_2)_5CH_3$ **3.17**




X = I **3.18**
X = Br **3.19**

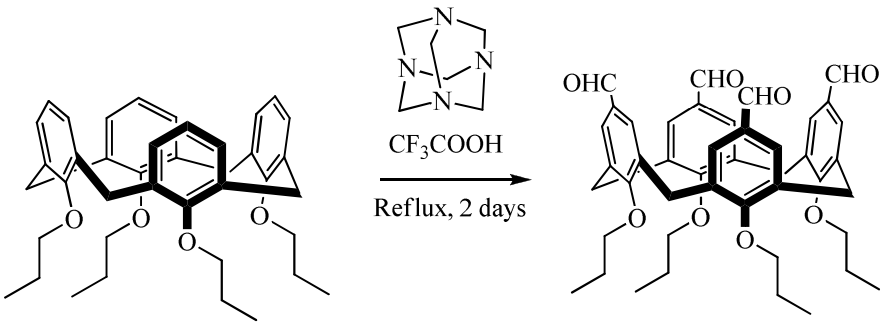
To a mixture of the appropriate tetrabromo *C*-alkylcavitand or tetrahalo tetrapropoxycalix[4]arene (3.00 mmol), and $Pd(PPh_3)_4$ (0.89 g, 0.722 mmol, 20 mol% ) in an oven-dried three-necked round bottom flask or a pressure tube was evacuated and flushed with nitrogen in a cycle three times. Degassed appropriate solvent (30-40 mL) was added *via* syringe and the reaction mixture was stirred for 10 minutes. 3,4,5-Trimethoxyphenylboronic acid (6.21 g, 29.3 mmol) in degassed appropriate solvent (20-30 mL) was added slowly. After the addition was completed, the reaction vessel was subjected to a freeze-pump-thaw cycle three times. Then, the reaction mixture was heated

to reflux for a considerable period of time (72 hours to 5 days). After cooling to room temperature, $Pd(PPh_3)_4$ and the decomposed palladium compounds were filtered over Celite. The filtrate was concentrated on a rotary evaporator. $CH_2Cl_2$ or $CHCl_3$ (100 mL) was added to the residue and deionized water (100 mL) was subsequently added. The resulting solution was stirred for an hour and the organic phase was separated, washed with water (2 x 50 mL), brine (50 mL), and dried over $MgSO_4$. The organic phase was evaporated to dryness under vacuum to afford a dark oily residue.

If applicable, the residue was purified by a silica gel chromatographic column using the mixture of appropriate solvents. The collected fractions of the mobile phase were evaporated under reduced pressure to obtain to the mixture of compounds or a pure 3,3′,4,4′,5,5′-hexamethoxybiphenyl.

The alternative procedure regarding the base used in the attempts could be carried on if the base did not require water to dissolve. The appropriate base was introduced into the reaction vessel directly with the aryl halide and $Pd(PPh_3)_4$ and the same consequent steps were applied. If a pressure tube was used, it is important to flush nitrogen into the tube when a septum was removed to ensure the least amount of $O_2$ as much as possible.

### 3.6.7 Synthesis of 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxycalix[4]arene

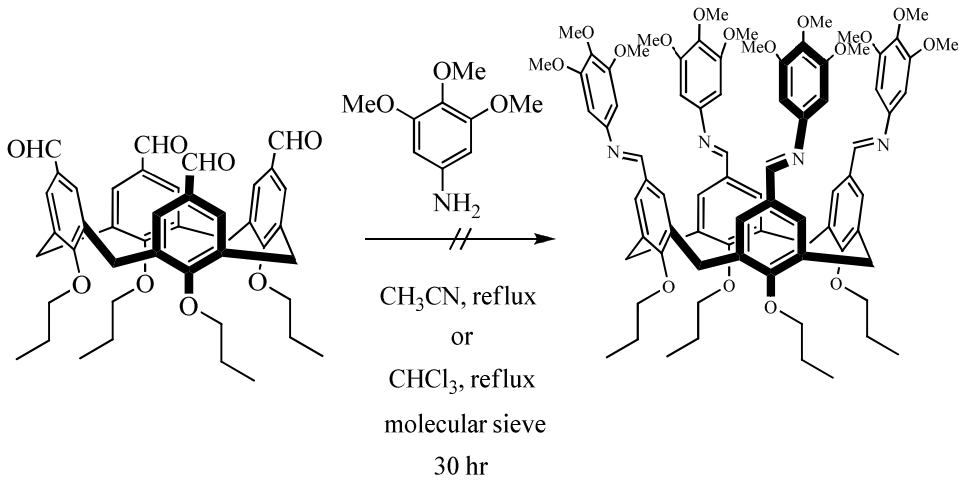



To a solution of 25,26,27,28-tetrapropoxycalix[4]arene (8.47 g, 14.3 mmol) in trifluoroacetic acid (160 mL) was added hexamethylenetetramine (66.34 g, 0.473 mol) in portions under the stream of nitrogen. After all solids dissolved completely, the light orange solution was refluxed for 2 days. After the solution was cooled to room temperature, 1M HCl (150 mL) and $CH_2Cl_2$ (150 mL) was added slowly to avoid the excessive heat and the resulting mixture was stirred for an hour at room temperature. The organic layer was then separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 50 mL). The combined organic layer was concentrated to *ca* 150 mL on a rotary evaporator, washed with saturated aqueous $Na_2CO_3$ solution (75 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give an oily residue which was recrystallized from $CH_2Cl_2$-methanol to afford tetraformyl calix[4]arene as a white solid (5.86 g, 58% yield)

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 9.56 (s, 4H, C*H*O), 7.13 (s, 8H, -Ar*H*), 4.27 and 3.03 (two sets of d, 8H, $^{2}J$ = 13.5 Hz, ArC$H_2$Ar), 3.79 (t, 8H, $^{3}J$ = 7.5 Hz, OC$H_2$CH$_2$), 1.86 (tq, 8H, $^{3}J$ = 7.5 MHz, -CHC$H_2$CH$_3$), 0.94 (t, 12H, $^{3}J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 191.3 (*C*HO), 161.9 (-$C_q$-OCH$_2$-), 135.6, 131.4, 30.2, 77.2, 30.3 (Ar*C*H$_2$Ar), 23.3 (-*C*H$_2$CH$_3$), 10.2 (-*C*H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{44}H_{48}O_8$ + $Na^+$] m/z = 727.32, Found m/z = 726.78 (100%). Analytical calculated for $C_{44}H_{48}O_8$: C, 74.96; H, 6.86. Found: C, 74.47; H, 6.80.

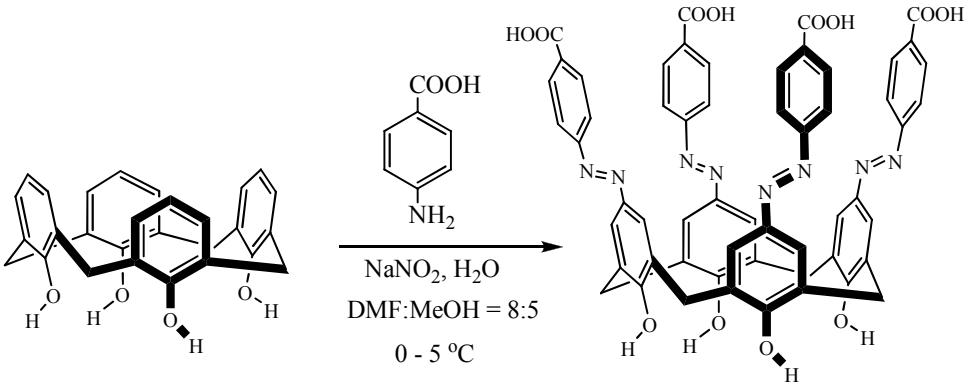
### 3.6.8 Synthetic attempts of 5,11,17,23-*tetrakis*[(3,4,5-trimethoxy-phenyl)imido]-25,26,27,28-tetrapropoxycalix[4]arene




To a suspension of calix[4]arene **3.20** (4.96 g, 7.05 mmol) in 100 mL of dry acetonitrile (or dry $CHCl_3$ with molecular sieve 4 Å), a solution of 3,4,5-trimethoxyaniline (5.85 g, 31.9 mmol) in dry acetonitrile (or dry $CHCl_3$) (60 mL) was

added slowly at room temperature. After stirring for one hour, the reaction mixture was heated to 60ºC for 30 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The solid residue was triturated with absolute ethanol to give a pale yellow solid.

### 3.6.9 Synthesis of 5,11,17,23-*tetrakis*[(4-carboxyphenyl)azo]-25,26,27,28-tetrahydroxycalix[4]arene



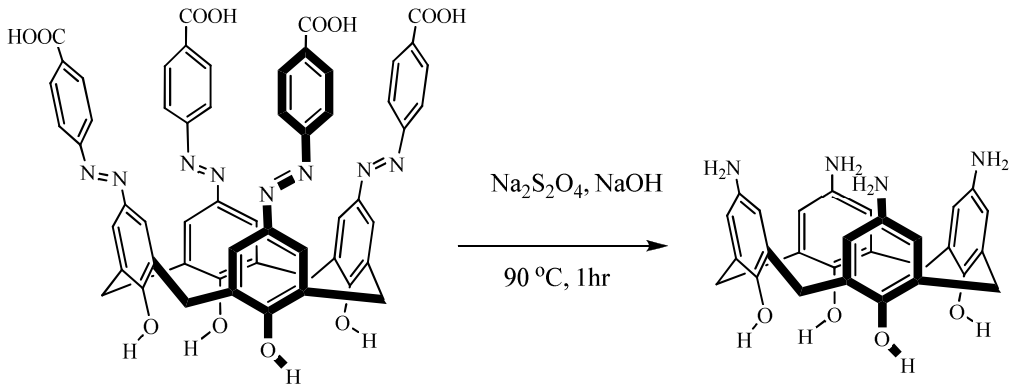

A cold solution of 4-carboxybenzenediazonium chloride, which was prepared from 4-aminobenzoic acid (6.94 g, 50.6 mmol), sodium nitrite (4.10 g, 59.4 mmol), and conc. HCl (9.0 mL) in HPLC grade water (125 mL), was added slowly into a cold (0-5ºC) solution of 25,26,27,28-tetrahydroxycalix[4]arene **3.24** (4.25 g, 10.02 mmol) and sodium acetate (12.47 g, 0.152 mol) in DMF:MeOH (8:5 v/v) (130 mL) to give a deep red suspension. After being allowed to stand at 0-5 ºC for 2 hours, the suspension was acidified with 0.25% HCl. The mixture was warmed to 60ºC for 30 minutes to produce calix[4]arene **3.25** in quantitative yield (9.98 g, 98% yield) as a reddish solid. The

precipitate was filtered and washed with water and methanol. The analytical sample was obtained by the following method: 2.00 g of calix[4]arene was dissolved in 100 mL of hot $NaHCO_3$ (4.20 g) solution. To the solution was added activated charcoal (1.00 g). After the charcoal was filtered off, the filtrate was cooled in an ice bath and acidified with 1-2 mL of conc. HCl. The solution with a red precipitate was heated again for 30 minutes and cooled to room temperature. A bright red solid was filtered, washed with water until the filtrate was neutral to pH paper, and dried in *vacuo*.

$^1$H-NMR (500 MHz, DMSO-$d_6$, 300 K): δ = 8.04-8.02 (m, 8H, -Ar*H* of calix[4]arene), 7.84-7.81 (m, 16H, -Ar*H* of 4-carboxyphenyl), 4.23 and 3.95 (br, 8H, ArC$H_2$Ar); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 166.8, 159.2, 154.5, 144.8, 131.4, 130.5, 130.4, 124.5, 121.9, 31.4 (Ar*C*$H_2$Ar) ppm.

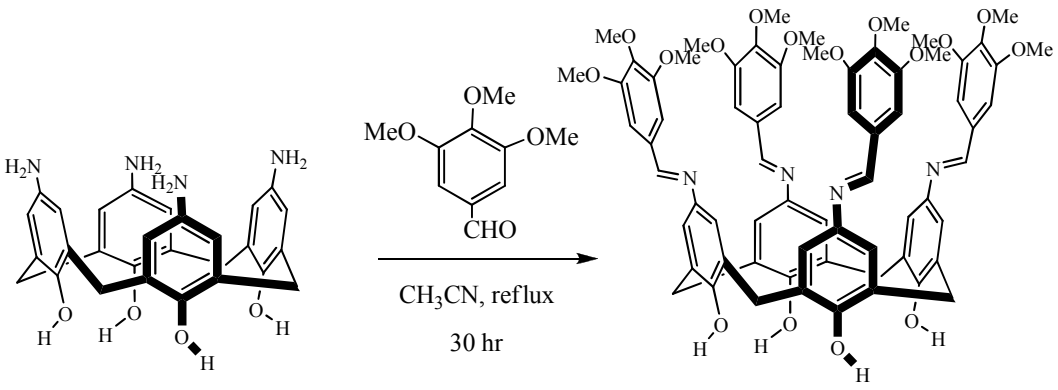
Analytical calculated for $C_{56}H_{40}N_8O_{12}\cdot H_2O$: C, 64.99; H, 4.09; N, 10.83. Found: C, 64.60; H, 4.14; N, 10.72. No satisfied mass spectrometry result was obtained.

### 3.6.10 Synthesis of 5,11,17,23-tetraamino-25,26,27,28-tetrahydroxycalix[4]arene




The resulting moist paste of tetraazo calix[4]arene (6.17 g, 6.07 mmol) was dissolved in 200 mL of an aqueous NaOH (2.81 g, 70.4 mmol) solution and reduced with sodium hydrosulfite (19.17 g, 0.110 mol) at 90ºC for 1 hr to give a white suspension. The reaction mixture was cooled rapidly to 20ºC in an water bath mixed with ice, filtered, and washed with water to give tetraamino calix[4]arene as white crystals. Compound was dried quickly at room temperature under vacuum and was then used on the condensation reaction with 3,4,5-trimethoxybenzaldehyde immediately to avoid the decomposition of tetraamino calix[4]arene.

### 3.6.11 Synthesis of 5,11,17,23-*tetrakis*[(3,4,5-trimethoxyphenyl) -imido]-25,26,27,28-tetrahydroxycalix[4]arene

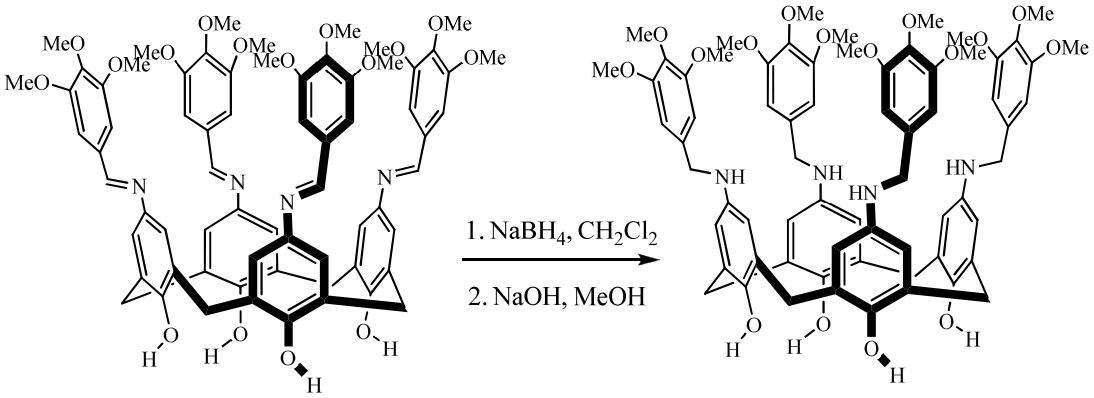



To a solution of tetraamino calix[4]arene from section 3.6.8 in dry acetonitrile (150 mL) was purged with nitrogen for 20 minutes. 3,4,5-Trimethoxyphenyl-benzaldehyde (6.38 g, 32.5 mmol) in dry acetonitrile (40 mL) was added dropwise to the former solution. After the addition was completed, the reaction mixture was refluxed for 30 hours under nitrogen. After cooling to room temperature, the light brown precipitate was filtered and washed with cold methanol. The product was then further dried under reduce pressure at room temperature for 24 hours to afford Schiff base calix[4]arene **3.26** as a light brown solid (4.73 g, 65% yield).

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 10.14 (s (broad), 4H, -OH), 7.11 (s, 8H, -Ar*H*), 7.02 (s, 8H, -Ar*H*), 4.32 and 3.59 (br, 8H, Ar$CH_2$Ar), 3.86 (s, 36H, -O$CH_3$);$^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 158.6, 153.5, 147.4, 145.8, 140.8, 131.7, 128.5, 121.7, 105.6, 60.9, 56.2, 32.0 (Ar$CH_2$Ar) ppm.

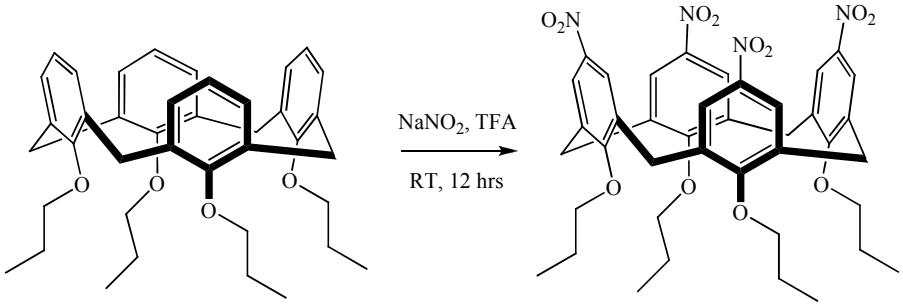
(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{68}H_{68}N_4O_{16}$] m/z = 1196.46, Found m/z = 1197.30 (100%). Analytical calculated for $C_{68}H_{68}N_4O_{16}\cdot CH_3OH$: C, 67.41; H, 5.90; N, 4.56. Found: C, 67.10; H, 5.61; N, 5.14.

### 3.6.12 Synthesis of 5,11,17,23-*tetrakis*[(3,4,5-trimethoxybenzyl)-amino]-25,26,27,28-tetrahydroxycalix[4]arene




Sodium borohydride (5.00 g, 0.132 mol) was added to the solution of 5,11,17,23-*tetrakis*[(3,4,5-trimethoxyphenyl)imido]-25,26,27,28-tetrahydroxycalix[4]arene (2.99 g, 2.50 mmol) in dry dichloromethane (130 mL). The reaction mixture was stirred at room temperature overnight. The organic layer was separated and adjusted the pH with 1M HCl and 1M NaOH (both as the solutions in methanol) until the pH reached 8. The dichloromethane solution was then washed with water (2 x 50 mL), brine (50 mL), and dried over $MgSO_4$. Organic solvent was evaporated on a rotary evaporator to give a dark brown solid. Recrystallization from $CH_2Cl_2$/methanol gave a light brown powder.

### 3.6.13 Synthesis of 5,11,17,23-tetranitro-25,26,27,28-tetrapropoxy-calix[4]arene

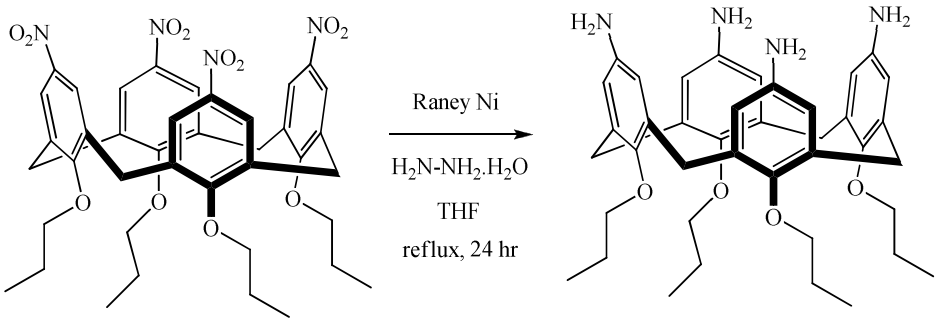



An 80 mL trifluoroacetic acid solution containing 25,26,27,28-tetrapropoxy calix[4]arene **3.23** (5.96 g, 10.1 mmol) was treated with $NaNO_2$ (10.62 g, 0.154 mol). The solution was stirred at room temperature for 12 hours and was poured in deionized water (300 mL). The resulting suspension was extracted twice with $CH_2Cl_2$ (300 mL). The organic phase was washed with an aqueous saturated $Na_2CO_3$ solution (2 x 50 mL) and then with water (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting orange product was washed twice with methanol. The pure tetranitro calix[4]arene **3.28** was recrystallized from $CH_2Cl_2/CH_3OH$ to afford a light yellow solid (4.42 g, 57%).

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.54 (s, 8H, -Ar*H*), 4.50 and 3.38 (two sets of d, 8H, $^{2}J$ = 14.0 Hz, ArC$H_2$Ar), 3.94 (t, 8H, $^{3}J$ = 7.5 Hz, OC$H_2$CH$_2$), 1.88 (tq, 8H, $^{3}J$ = 7.5 MHz, -CHC$H_2$CH$_3$), 1.00 (t, 12H, $^{3}J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 161.7 (-$C_q$-OCH$_2$-), 142.8 ($C_q$ *ipso* to $NO_2$), 135.4 ($C_q$ *meta* to $NO_2$), 124.0 ($C_{ar}$H *ortho* to $NO_2$), 77.7 (O-$C$H$_2$CH$_2$-), 31.1 (Ar$C$H$_2$Ar), 23.2 (-$C$H$_2$CH$_3$), 10.1 (-$C$H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{40}H_{44}N_4O_{12}$ + $Na^+$] m/z = 795.29, Found m/z = 794.87 (100%). Analytical calculated for $C_{40}H_{44}N_4O_{12}\cdot H_2O$: C, 60.75; H, 5.86; N, 7.08. Found: C, 60.93; H, 5.63; N, 7.06.

### 3.6.14 Synthesis of 5,11,17,23-tetraamino-25,26,27,28-tetrapropoxy-calix[4]arene



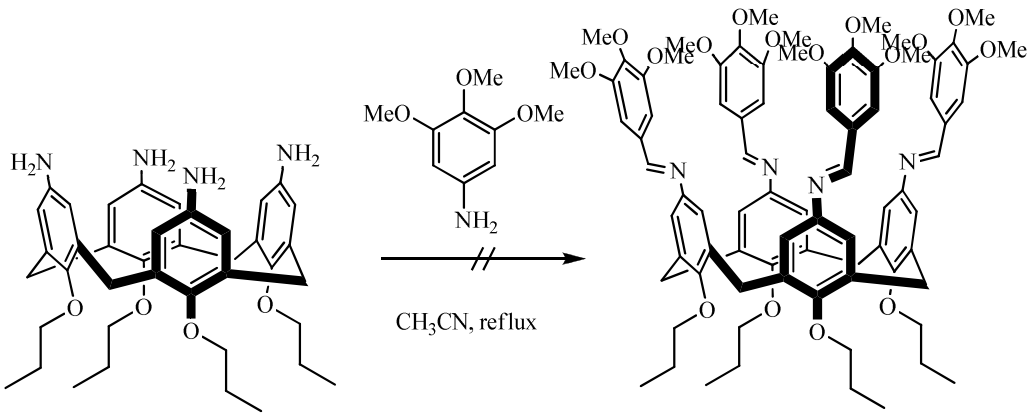

To a solution of calix[4]arene **3.28** (2.92 g, 3.78 mmol) in dry THF (150 mL) was added Raney Nickel (50% suspension in water) and the reaction mixture was purged with nitrogen for 30 minutes. Hydrazine monohydrate (12.38 g, 20.0 mL, 0.247 mol) was added slowly *via* syringe. The reaction turned colorless after the addition of hydrazine was completed. The reaction mixture was refluxed for 24 hours. After cooling to room

temperature, Raney Ni was filtered off over Celite and the filtrate was evaporated to dryness. A white solid of compound **3.22** was obtained in quantitative yield (2.42 g, 98% yield).

$^{1}$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.09 (s, 8H, -Ar*H*), 4.29 and 2.90 (two sets of d, 8H, $^{2}J$ = 13.0 Hz, ArC$H_2$Ar), 3.70 (t, 8H, $^{3}J$ = 7.5 Hz, OC$H_2$CH$_2$), 3.57 (s(broad), 8H, -N$H_2$), 1.84 (tq, 8H, $^{3}J$ = 7.0 MHz, -CHC$H_2$CH$_3$), 1.00 (t, 12H, $^{3}J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 150.1 (-$C_q$-OCH$_2$-), 140.2 ($C_q$ *ipso* to $NH_2$), 135.7 ($C_q$ meta to $NH_2$), 115.9 ($C_{ar}$H *ortho* to $NH_2$), 76.6 (O-$C$H$_2$CH$_2$-), 31.1 (Ar$C$H$_2$Ar), 23.2 (-$C$H$_2$CH$_3$), 10.4 (-$C$H$_3$) ppm.

(+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{40}H_{44}N_4O_{12}$ + $Na^+$] m/z = 795.29, Found m/z = 794.87 (100%). Analytical calculated for $C_{40}H_{44}N_4O_{12}\cdot H_2O$: C, 73.59; H, 8.03; N, 8.58. Found: C, 66.49; H, 7.64; N, 7.63. The elemental analysis result was unsatisfactory.

### 3.6.15 Synthetic attempts of 5,11,17,23-*tetrakis*[(3,4,5-trimethoxy-phenyl)imido]-25,26,27,28-tetrapropoxycalix[4]arene



A solution of tetraamino tetrapropoxycalix[4]arene **3.22** (1.00 g, 1.53 mmol) in dry acetonitrile (50 mL) was purged with nitrogen for 20 minutes. 3,4,5-Trimethoxyphenylbenzaldehyde (3.74 g, 19.1 mmol) in dry acetonitrile (30 mL) was added dropwise to the former solution. After the addition was completed, the reaction mixture was refluxed for 24 hours under nitrogen. After cooling to room temperature, $CH_3CN$ was evaporated to dryness. The residue was dissolved in $CH_2Cl_2$ and triturated with absolute ethanol to afford a yellow solid.

## 3.7 Conclusions

This chapter discusses the preparation of new macrocycles with an extended-cavity which are structurally similar to *C*-alkylpyrogallol[4]arenes by using two different synthetic approaches: Suzuki-Miyaura cross coupling and aldehyde-amine condensation reaction.

Attempts to synthesize such macrocycles through the Suzuki reaction afforded a mixture of compounds which could not be totally separated by column chromatography. The major setback is the contamination of $O_2$ in the reaction system. The clear evidence is the formation of homocoupling product from the starting boronic acid, 3,3′,4,4′,5,5′-hexamethoxybiphenyl. Moreover, it is possible that another side reaction such as dehalogenation occurs when alcohols were used in the coupling reaction.

Condensation reactions between tetraformyl tetrapropoxycalix[4]arene with 3,4,5-trimethoxyaniline afforded a mixture of products, likely the partially condensed macrocycles. The attempts to accelerate the reaction forward by adding a catalytic amount of acid did not provide any significant improvement. The same problem was

observed in the reaction between tetraamino tetrapropoxycalix[4]arene and 3,4,5-trimethoxybenzaldehyde. The poor solubility of calix[4]arene derivatives in acetonitrile or ethanol may be a great factor in the lack of success of these condensation reactions.

Only the reaction between tetraamino calix[4]arene and 3,4,5-trimethoxy-benzaldehyde gave the desired Schiff base derivative in 65% yield. In solution, the tetraimino calix[4]arene exhibits conformational fluctuation between a stabilized cone conformer and the others. Unfortunately, the reduction of tetraimino calix[4]arene by $NaBH_4$ gave unexpected products with impurities. Further efforts to obtain the pure macrocycle are underway.

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# CHAPTER 4

# DIAMINO-TRIAZINE FUNCTIONALIZED MACROCYCLES

## 4.1 Introduction

Numerous 1,3,5-triazine ($C_3N_3H_3$) derivatives have received a lot of interest in the field of supramolecular chemistry because of their ability to participate in π-π interactions and their aptitude to be involved in elaborate hydrogen-bonded networks.[1,2] A 1,3,5-triazine ring is a particular aromatic moiety which resembles a benzene ring in term of its aromaticity.[3] However, the 1,3,5-triazine ring is more electron-deficient than a benzene ring since the presence of the more-electronegative nitrogen atoms contribute to an uneven-delocalization of the π electrons in the ring. With this specific character, 1,3,5-triazine can behave as both a σ-donor (through the lone pair electrons on a nitrogen atom) and a π-acceptor (*via* unoccupied π* orbitals).[1] The comparison between a triazine moiety and a benzene ring in terms of polarization and interacting sites is presented in Figure 4.1.

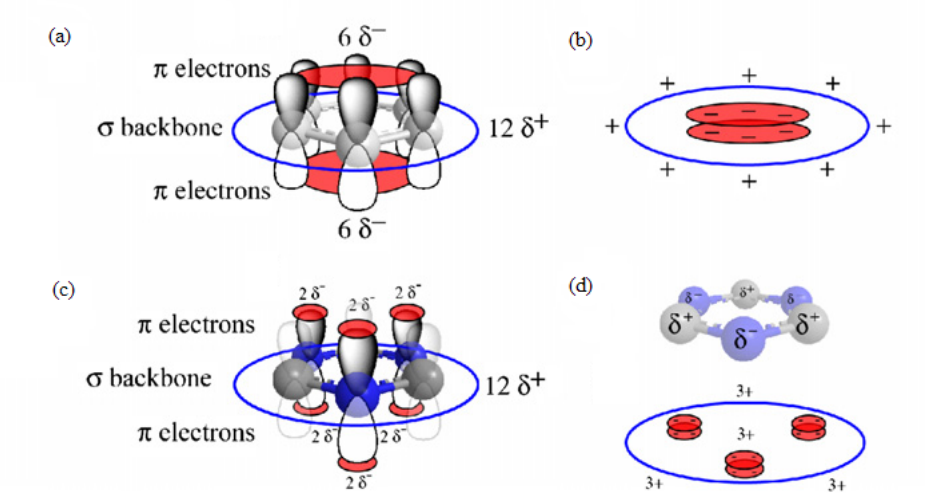



**Figure 4.1** Schematic representation of the bonding interactions and polarization of benzene (a and b respectively) and of 1,3,5-triazine (c and d, respectively).[2]

Consequently, the usage of a 1,3,5-triazine ring as a ligand for transition metal ions provides the great stabilization of their coordination complexes because of the ability of a triazine ring to form π bond by overlap of the metal d-orbitals with its empty π* orbitals. For example, Rheingold and coworkers[4] demonstrated that a triazine forms the complex with CuCl in the presence of triphenylphosphite. 1,3,5-Triazine molecules act as bridging ligands connecting the Cu(I) centers in the complex.(complex **4.1**, Figure 4.2)

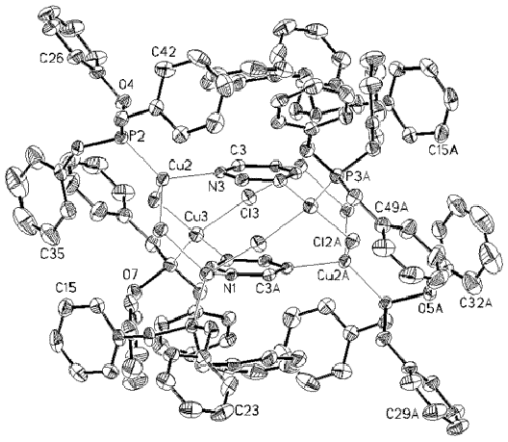



**Figure 4.2** X-ray crystal structure of $[(CuCl)_6(POPh_3)_6(triazine)_2]$ **4.1**. All hydrogen atoms are omitted for clarity.[4]

Melamine or 2,4,6-triamino-1,3,5-triazine is one of the 1,3,5-triazine derivatives that has become very popular in the field of crystal engineering because of its great ability to form hydrogen-bonded superstructures.[1,5,6] The amino groups of melamine act as hydrogen bond donors whereas the nitrogen atoms in the 1,3,5-triazine ring can serve as hydrogen bond acceptors (see Figure 4.3). Several hydrogen-bonded self assemblies based on melamine have been prepared.[7] Some of these systems were already discussed in section 1.4.3 of this dissertation.

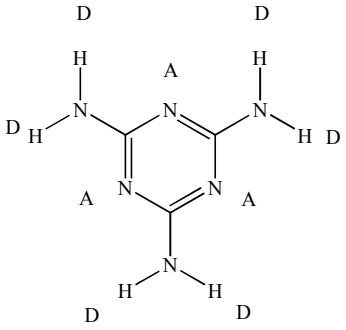



**Figure 4.3** Schematic representation of the hydrogen bond donors and acceptors of melamine. (D = hydrogen bond donor and A = hydrogen bond acceptor)

## 4.2 Macrocyclic compounds possessing 1,3,5-triazine moieties

Reinhoudt and coworkers[8] developed the interesting strategy to generate the hydrogen-bonded superstructures by embedding a 1,3,5-triazine ring on the calix[4]arene scaffold. Dimelamine calix[4]arene **4.2** was synthesized and its ability to form hydrogen-bonded self-assembly with diethylbarbituric acid was examined by $^1$H-NMR spectroscopy.

$^1$H-NMR titration of calix[4]arene **4.2** with diethylbarbituric acid in $CDCl_3$ showed significant downfield shifts of the protons of $–NH_2$ and $–NH(C_4H_9)$. Moreover, the –NH protons of diethylbarbituric acid appear at $\delta$ = 14.10 and 13.32 ppm. When the ratio of ligand to guest reached 1:2, the proton signals of $–NH_2$ and $–NH(C_4H_9)$ in the free ligand disappears and two new sharp peaks were found at $\delta$ = 8.37 and 7.43 ppm. This ratio indicates that the hydrogen-bonded system is in a double-rosette structure.

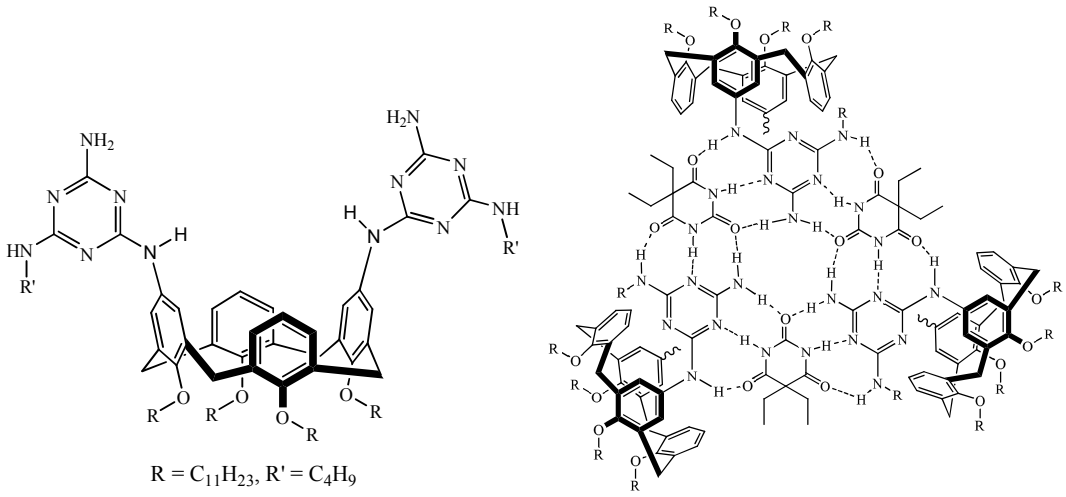



**Figure 4.4** Chemical structures of (a) *bis*(triaminotriazine) calix[4]arene **4.2** and (b) its hydrogen-bonded self-assembly with diethylbarbituric acid. The other side of a box is omitted for clarity.

The X-ray crystal structure of the [calix[4]arene **4.2**-diethybarbituric acid] complex revealed that a cage-like structure is formed by combining three molecules of compound **4.2** and 6 molecules of diethylbarbituric acid. The hydrogen-bond pattern between the triazine moieties of calix[4]arene **4.2** and diethylbarbituric acid resembles a wall of a molecular box.[9]

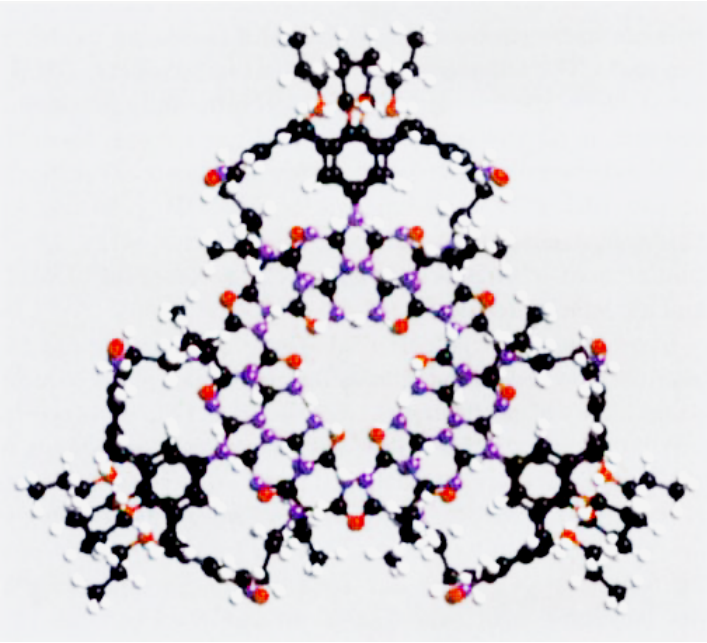


**Figure 4.5** X-ray crystal structure of the molecular box assembled from 3 molecules of calix[4]arene **4.2** and 6 molecules of diethylbarbituric acid.[9]

Several derivatives of calix[4]arene **4.2** were prepared. The complexation studies of these macrocycles with various derivatives of barbituric acid suggested that all of them exhibit the same type of hydrogen-bonded morphology.[9,10] Later in 2000, circular dichroism studies of these calix[4]arenes with chiral barbiturates[11] indicated that the molecular boxes are actually enantiomers based on the arrangement of the hydrogen bond pattern between the triazine moieties and the barbituric acid core structure. Therefore,

these superstructures become chiral systems controlled by the stereochemistry of barbiturates.

Double-rosette self-assemblies based on dimelamine calix[4]arene can serve as a host to complex some transition metal ions. In 1998, Reinhoudt *et al*. [12]studied the self-assembly of *bis*(triaminotriazine) calix[4]arene **4.3** with diethylbarbituric acid in the presence of $Ag^+$ ion. The MALDI-TOF mass spectrometric result revealed that the $Ag^+$ ion is stabilized in the structure of a double-rosette between the aromatic ring of a calix[4]arene structure and the benzyl group of a –NH-substituent.(see Figure 4.6)

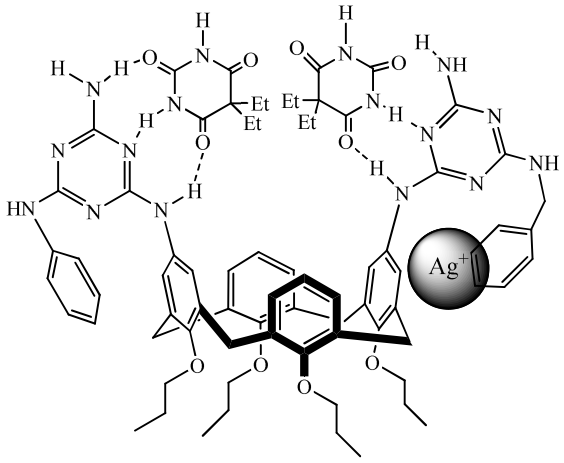



**Figure 4.6** The proposed complexation of $Ag^+$ ion by a hydrogen-bonded self-assembly of calix[4]arene **4.3** and diethylbarbituric acid.

The 1,3,5-triazine moiety can be functionalized directly on the core structure of macrocycles such as calix[4]arene. Reinhoudt and coworkers[13] synthesized two *bis*(2,4-diaminotriazine) calix[4]arenes **4.4** and **4.5** from the reaction of their dicyano derivatives with dicyandiamide. Derivatization of compound **4.4** with hexanoyl chloride afforded the tetraamide *bis*(2,4-diaminotriazine) calix[4]arene **4.6** (Figure 4.7).

Complexation studies of compound **4.6** with *bis*uracil calix[4]arene **4.7** by $^1$H-NMR spectroscopy in $CDCl_3$ showed an unexpected result. No self-assembly entity was found between compounds **4.6** and **4.7**. A variable-temperature NMR study of compound **4.6** showed that the proton signal of the amido group changes from one broad peak into two separate sharp signals when the temperature was decreased from 30ºC to -55ºC. This result suggests that the amido protons participate in intramolecular hydrogen bonding. Therefore, the complex between calix[4]arenes **4.6** and **4.7** could not be obtained because all amido protons participate in these hydrogen bonds.

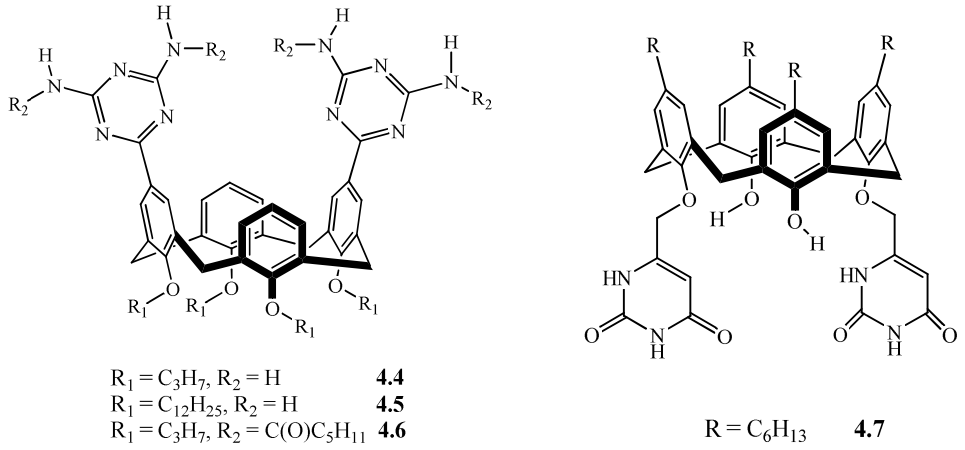
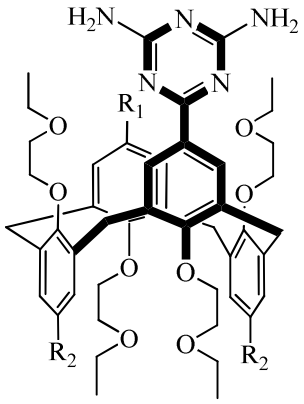



**Figure 4.7** Chemical structures of *bis*(2,4-diaminotriazine) calix[4]arenes **4.4-4.6** and biuracil calix[4]arene **4.7**

Calix[4]arenes functionalized with 2,4-diaminotriazine functional groups can exhibit intermolecular hydrogen bonds among themselves. In 2004, Mattey and coworkers[14] reported the formation of hydrogen-bonded self-assemblies of two calix[4]arene derivatives **4.8** and **4.9**. Both macrocycles are in a 1,3-alternate conformation (see Figure 4.8). The X-ray crystal structure of *bis*(2,4-diamino-triazine)

calix[4]arene **4.8** showed hydrogen bond-directed infinite bands of molecules **4.8**. In contrast, calix[4]arene **4.9** which possesses four diaminotriazine moieties favors face-to-face self-assembly resulting in infinite polymer-like strands.




$R_1$ = diaminotriazine, $R_2$ = H **4.8**
$R_1 = R_2$ = diaminotriazine **4.9**

**Figure 4.8** Chemical structures of diaminotriazine calix[4]arenes **4.8** and **4.9** in a 1,3-alternate conformation.

## 4.3 Hypothesis and objectives

As previously discussed in the last section, many research groups have shown a lot of interest in a diaminotriazine moiety since this aromatic group can exhibit promising properties as a ligand for transition metal complexes and a building block for self-assembled superstructures (both metal-directed and hydrogen-bonded types). Moreover, several diaminotriazine derivatives are considered excellent molecular tectonics[15-19] for crystal engineering research. Therefore, it was decided to synthesize novel macrocycles which are functionalized by diaminotriazine moieties. The starting materials for these attempts are 5,11,17,23-tetracyano-25,26,27,28-tetrapropoxycalix[4]arene, and 4,6,10,12,16,18,22,24-octamethoxy-5,11,17,23-tetracyano *C*-hexylresorcin[4]arene **2.41**.

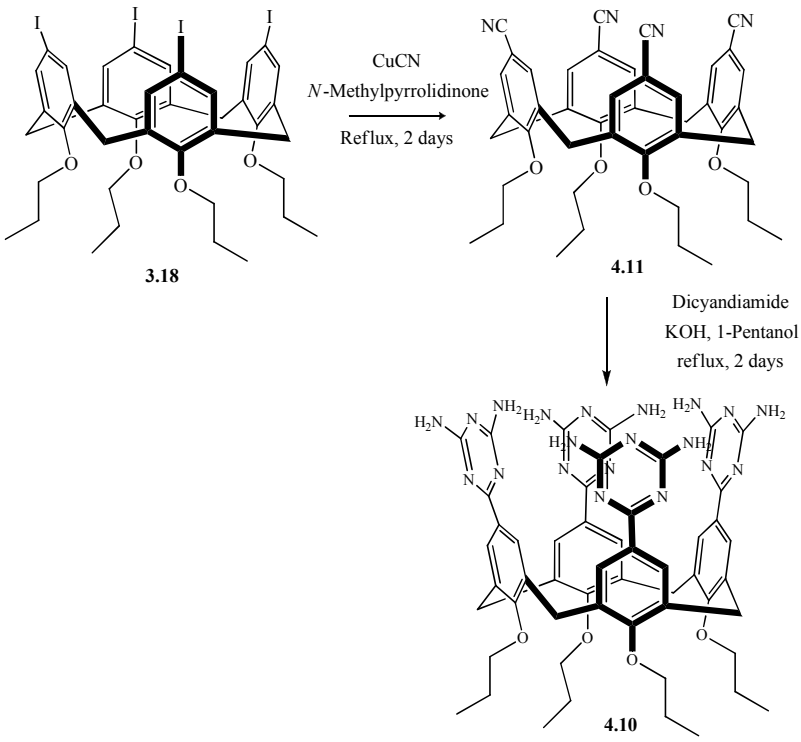
These new compounds may exhibit some interesting self-assembly patterns *via* hydrogen bonding and metal coordination. Preliminary complexation studies of the new macrocycles with $Zn(CF_3SO_3)_2$ and barbituric acid will also be discussed.

## 4.4 Results and discussion

### 4.4.1 Synthesis of new diaminotriazine-functionalized macrocycles

#### 4.4.1.1 Preparation of *tetrakis*(2,4-diamino-1,3,5-triazine) tetrapropoxy-calix[4]arene

New diaminotriazine calix[4]arene **4.10** was prepared from reaction of tetracyano tetrapropoxycalix[4]arene **4.11** with dicyandiamide (or cyanoguanidine) in the presence of base. Formation of a diaminotriazine ring requires a very large excess of dicyandiamide to prevent side-reactions such as the hydrolysis of the cyano group.[20] The synthetic route for the new diaminotriazine calix[4]arene is depicted in Scheme 4.1.




**Scheme 4.1** The synthetic procedure for tetracyano tetrapropoxycalix[4]arene **4.11** and its *tetrakis*(diaminotriazine) derivative **4.10**.

A Rosemund-von Braun reaction of tetraiodocalix[4]arene **3.18** with CuCN in refluxed NMP afforded tetracyano tetrapropoxycalix[4]arene **4.11** in good yield (83%). Calix[4]arene **4.11** was characterized by $^{1}$H- and $^{13}$C-NMR spectroscopy, mass spectrometry and elemental analysis. The $^{1}$H-NMR spectrum of **4.11** showed one peak of aromatic protons at $\delta$ = 7.02 ppm. The signal of the methylene bridge protons appears as a pair of doublets at 4.47 and 3.27 ppm ($^{2}J$ = 14.0 Hz). This indicates that calix[4]arene **4.11** adopts a cone conformation. In the $^{13}$C-NMR spectrum of **4.11**, the peak belonging to the cyano carbon appears at $\delta$ = 118.2 ppm. The methylene bridge carbons show one set of chemical shifts at 30.5 ppm, confirming that this calix[4]arene has $C_4$-symmetry.

Reaction of calix[4]arene **4.11** with excess dicyandiamide in the presence of KOH yields a very light white powder of *tetrakis*(2,4-diamino-1,3,5-triazine) tetrapropoxy calix[4]arene in 92% yield after drying under high vacuum for 24 hours. The $^{1}$H-NMR spectrum of diaminotriazine calix[4]arene **4.10** in DMSO-$d_6$ showed one set of aromatic protons at 7.72 ppm. The protons of the $-NH_2$ groups appears as a broad singlet at 6.58 ppm. Surprisingly, even in the presence of a bulky diaminotriazine moiety, this calix[4]arene still adopts a cone conformation which can be deduced from the appearance of the methylene bridge protons at 4.47 and 3.36 ppm ($^{2}J$ = 12.5 Hz). For the $^{13}$C-NMR result, it showed 6 different aromatic carbons (170.2-128.2 ppm) which is in agreement with the expected chemical structure. However, in the region of the methylene bridge carbons and alkyl groups, there are several peaks instead of one set of signals for those carbon atoms. This feature suggests that this molecule might actually exhibit other different conformations.

The solubility of compound **4.10** is extremely poor in most organic solvents except DMSO, which can dissolve this compound. This indicates that a molecule of calix[4]arene **4.10** might form intermolecular hydrogen bonds with other arene molecules in proximity (similar to *p-tert*-butylcalix[4]arene which dissolves in only hot toluene). DMSO is a very good hydrogen bond acceptor, so the addition of DMSO could interrupt the hydrogen bonding network of calix[4]arene **4.10**.

#### 4.4.1.2 Synthetic attempts of *tetrakis*(2,4-diamino-1,3,5-triazine) octamethoxy *C*-hexyl-resorcin[4]arene

With the success in the preparation of new calix[4]arene **4.10**, tetracyano octamethoxy *C*-hexylresorcin[4]arene was subjected to the same reaction with dicyandiamide to produce its corresponding diaminotriazine *C*-hexylresorcin[4]arene. However, the reaction between resorcin[4]arene **2.43** and dicyandiamide afforded only melamine as a product. Actually, a substantial amount of melamine is normally obtained with these reaction conditions.[13] However, this by-product can be removed from the diaminotriazine derivative by washing with a copious amount of hot water. Other attempts to change the solvent from 1-pentanol to 2-methoxyethanol gave the same disappointing result. There is a possibility that under these synthetic conditions, hydrolysis of the cyano group occurs resulting in resorcin[4]arene tetracarboxylic acid instead of the desired diaminotriazine-functionalized resorcin[4]arene. When the crude product was treated with hot water, tetracarboxy resorcin[4]arene was flushed away with the filtrate.

### 4.4.2 The solid state structure of tetracyano tetrapropoxy calix[4]arene

Single crystals of tetracyano tetrapropoxycalix[4]arene **4.11** which are suitable for X-ray crystallography were obtained from slow evaporation of the solution of calix[4]arene **4.11** in chloroform-methanol or DMSO. The X-ray crystal structure revealed that the asymmetric unit is composed of one macrocycle without inclusion of solvent molecule(s) in the aromatic cavity of compound **4.11**. The molecule of

calix[4]arene is in a pinched cone conformation in which two aromatic rings at the opposite side of a molecule move close together whereas the other two rings are pushed away from the center of a molecule.

Compound **4.11** recrystallized in a point group $P2_1/n$ which belongs to the monoclinic crystal system. The asymmetric unit of calix[4]arene **4.11** with labeled heteroatoms is shown in Figure 4.9.

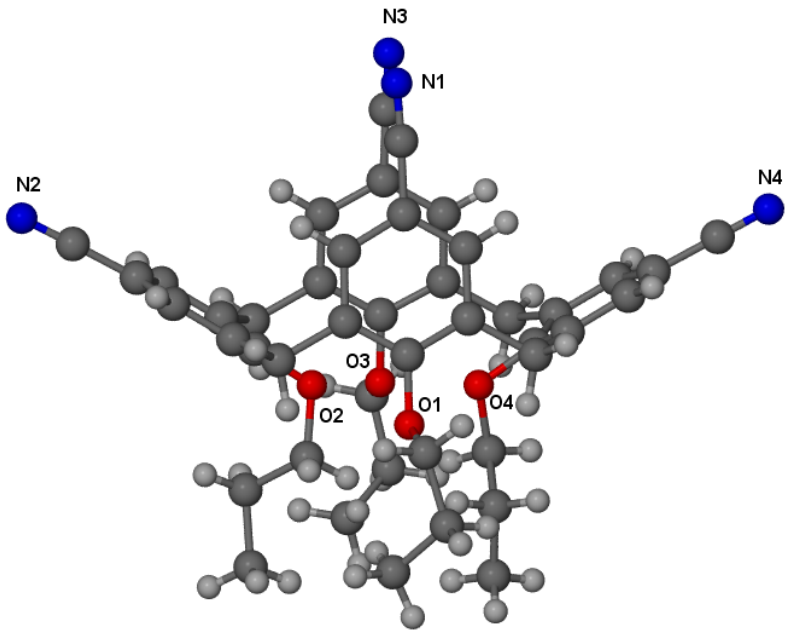



**Figure 4.9** The asymmetric unit of tetracyano tetrapropoxycalix[4]arene **4.11**.

The crystal packing of tetracyano tetrapropoxycalix[4]arene shows two arrays of macrocycles which are anti-parallel to each other. There is no insertion of a cyano group into the alkyl side region like the crystal structure of tetracyano *C*-hexylresorcin[4]arene. Bond distances for the C-N triple bond (1.139-1.144 Å) are in the expected range. The angles between $C_{ar}$ and the CN group are almost 180º (176.55º–179.77º). Moreover, there

is no evidence of π-π interaction between two adjacent molecules (centroid-centroid = 5.384 Å). The crystal packing of compound **4.11** is depicted in Figure 4.10.

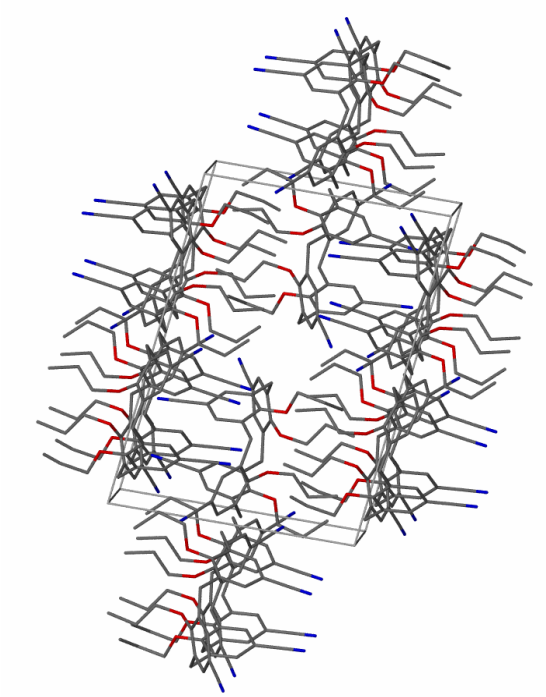


**Figure 4.10** Packing arrangement of compound **4.11** as the view along the *c* axis.

The X-ray crystal data and refinement methods of compound **4.11** are shown in Table 4.1. Its selected bond angles and bond distances are presented in Table 4.2.

**Table 4.1** X-ray crystal data and refinement methods of compound **4.11**.

| | |
|---|---|
| Chemical Formula | $C_{44}H_{44}N_4O_4$ |
| Formula Weight (g· $mol^{-1}$) | 692.83 |
| Crystal System | monoclinic |
| Space Group | $P2_1/n$ |
| Temperature (K) | 173(2) |
| $a$ (Å) | 12.866(3) |
| $b$ (Å) | 16.701(4) |
| $c$ (Å) | 17.598(5) |
| $\alpha, \beta, \gamma$ (°) | 90.00, 96.767(3),90.00 |
| $V$ ($Å^3$) | 3754.8(17) |
| $Z$ | 4 |
| $\rho_{calc}$ (g·$cm^{-3}$) | 1.226 |
| Mo-Kα radiation wavelength(Å) | 0.71073 |
| Absorption coefficient ($mm^{-1}$) | 0.079 |
| $F_{000}$ | 1472 |
| $2\theta_{max}$ (°) | 55.14 |
| Crystal size | 0.60 x 0.30 x 0.30 $mm^3$ |
| Index ranges | -16<=$h$<=16, -21<=$k$<=21, -22<=$l$<=22 |
| Reflection collected | 43320 |
| Independent reflections to θ = 27.57º | 8644 ($R_{int}$ = 0.0334) |
| Data/restraints/parameters | 8644/0/473 |
| Goodness-of-fit on $F^2$ | 1.127 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0499, ω$R_2$ = 0.1309 |
| R indices (all data) | $R_1$ = 0.0595, ω$R_2$ = 0.1360 |

**Table 4.2** Selected bond distance (Å) and bon angles (º) of calix[4]arene **4.11**

| | |
|---|---|
| N(1)-C(41) | 1.140(3) |
| N(2)-C(42) | 1.139(3). |
| N(3)-C(43) | 1.139(3) |
| N(4)-C(44) | 1.144(3) |
| N(1)-C(41)-C(4) | 176.5(2) |
| N(2)-C(42)-C(11) | 178.7(2) |
| N(3)-C(43)-C(18) | 177.8(2) |
| N(4)-C(44)-C(25) | 179.8(2) |

### 4.4.3 X-ray crystal structure of *tetrakis*[(2,4-diamino-1,3,5-triazine)-6-yl]-tetrapropoxycalix[4]arene hydrochloride

All attempts to recrystallize the basic form of diaminotriazine calix[4]arene **4.10** from the solution of this compound in DMSO were not successful. However, when excess conc. HCl was added to a suspension of calix[4]arene **4.10** in the mixture of methanol:water = 8:1, the white cloudy solution turned clear. This indicates that compound **4.10** was protonated and became a hydrochloride salt. Good quality crystals which are suitable for X-ray analysis were obtained from slow evaporation of the aforementioned solution. The X-ray crystal structure determination showed that the asymmetric unit comprises one macrocycle, 6 molecules of methanol (one of them could not be totally refined), 4 chloride ions and an unidentified oxygen atom. The asymmetric unit of diaminotriazine calix[4]arene **4.10** (as a hydrochloride salt) with labeled nitrogen, oxygen and chloride atoms (or ions) is depicted in Figure 4.11.

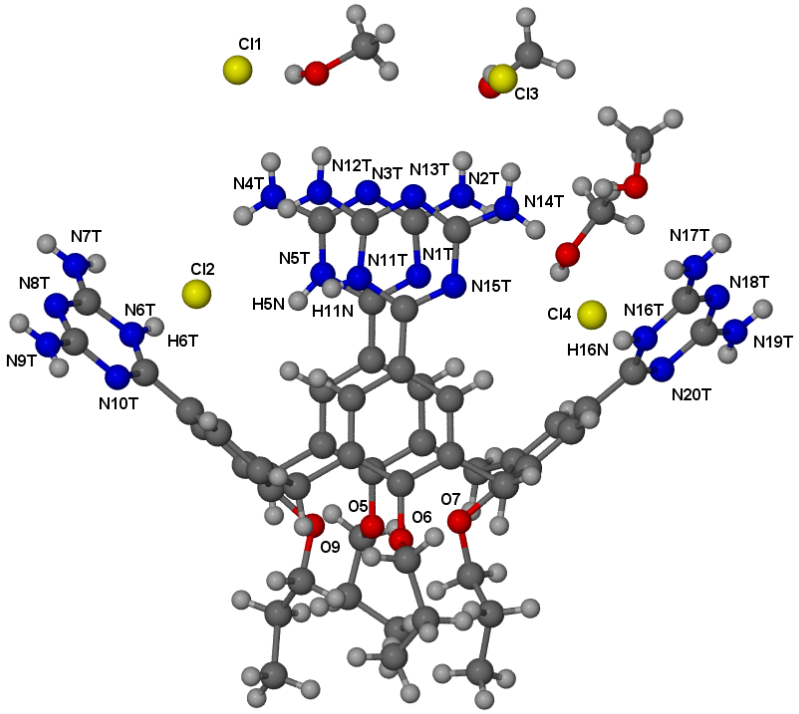


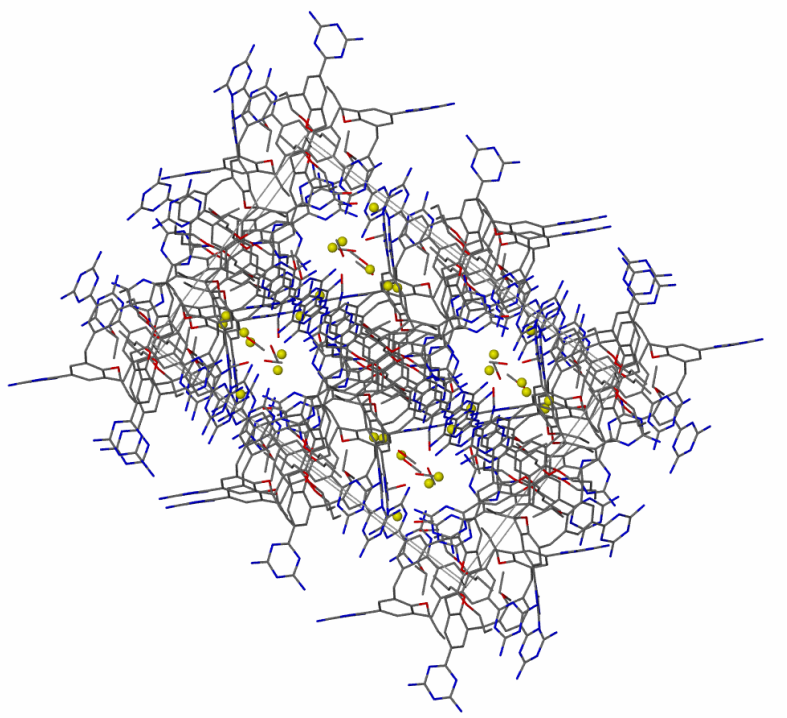

**Figure 4.11** The asymmetric unit of *tetrakis*(diaminotriazine) tetrapropoxycalix[4]arene **4.10** as a hydrochloride salt with labeled heteroatoms.

The molecule of *tetrakis*(2,4-diamino-1,3,5-triazine)tetrapropoxycalix[4]arene hydrochloride adopts a pinched cone conformation like compound **4.11**. Four 1,3,5-triazine rings are protonated at the nitrogen atoms located at the bottom part of a triazine ring. Therefore, this hydrochloride salt of calix[4]arene **4.10** is actually a partially protonated compound. The $-NH_2$ groups are not protonated. This observation helps to confirm that the nitrogen atoms of a triazine ring are more basic than those of the $-NH_2$ group. This is because the lone pair electrons of a triazine ring's nitrogen atom do not participate in the delocalization of π-electrons like those of an amino group. Therefore, when hydrochloric acid was added, the nitrogen atom of a triazine ring would be the first one to get protonated.

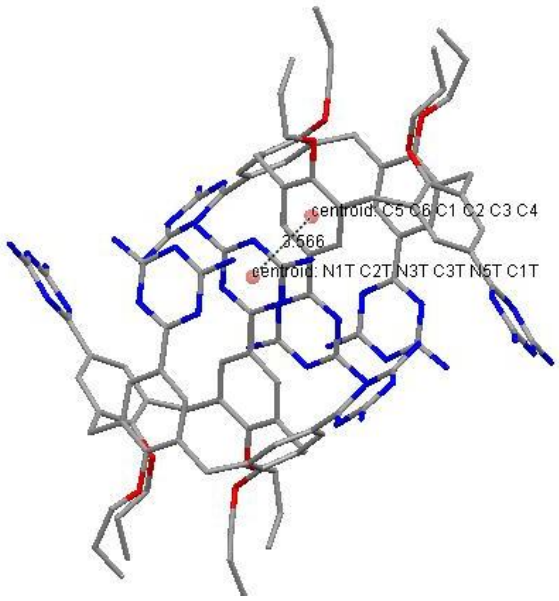
After one nitrogen atom is protonated, the triazine ring may become more electron- deficient and does not allow any further protonation to prevent an excessive repulsion of positive charges. It is possible that this partially protonated calix[4]arene may not undergo more protonation even when excess hydrochloric acid is added. Four chloride ions in the asymmetric unit are not located near the protonated nitrogen atoms but rather distribute into the space between triazine moieties.

Bond distances for the C-N bonds in a triazine ring are in the range of 1.30-1.38 Å whereas the C-$NH_2$ bond length is about 1.32 Å. The bond angles of a triazine ring are close to 120º (116.1º-125.6º). The bond lengths between the protonated nitrogen atoms and chloride ions are too distant to have any significant ion-ion interaction.

The crystal packing of compound **4.10** shows a similar pattern to that of tetracyano calix[4]arene **4.11**. The molecules of triazine calix[4]arene arrange into two arrays which are anti-parallel to each other. There is no existence of any hydrogen bond between the triazine rings suggesting that the hydrochloric salt of calix[4]arene **4.10** does not form intermolecular hydrogen bonds between molecules in close proximity. Nevertheless, there is evidence of π-π interaction between a molecule of calix[4]arene in each array. A protonated triazine ring forms a face-to-face π-stacking with one of the benzene rings which belongs to a calix[4]arene scaffold. The nitrogen atom which is located between two amino groups (N(3T) lays in the center of a benzene ring of the adjacent calix[4]arene. The calculated distance between the centroid of a triazine ring and the centroid of a benzene ring (calix[4]arene core structure) is close to 3.57 Å. The packing arrangement of calix[4]arene **4.10**·HCl and the representation of π-π interaction between two molecules of compound **4.10**·HCl is shown in Figure 4.12.



(a)




(b)

**Figure 4.12** (a) Crystal packing of diaminotriazine calix[4]arene **4.10** hydrochloride. (b) Structural representation of π-π interaction between a triazine ring and a benzene ring. The centroid of each aromatic moiety is colored as a red spot.

Crystal data and refinement methods of compound **4.10** HCl are shown in Table 4.3 while its selected bond angles and bond distances are presented in Table 4.4.

**Table 4.3** Crystal data and refinement methods of compound **4.10** HCl.

| | |
|---|---|
| Chemical Formula | $C_{57}H_{86}Cl_{3.50}N_{20}O_{10}$ |
| Formula Weight (g· $mol^{-1}$) | 1335.53 |
| Crystal System | monoclinic |
| Space Group | C 2/c |
| Temperature (K) | 173(2) |
| *a* (Å) | 26.390(7) |
| *b* (Å) | 28.402(8) |
| *c* (Å) | 20.183(6) |
| $\alpha, \beta, \gamma$ (°) | 90.00, 112.065(3), 90.00 |
| *V* ($Å^3$) | 14019(7) |
| *Z* | 8 |
| $\rho_{calc}$ (g·$cm^{-3}$) | 1.266 |
| Mo-Kα radiation wavelength (Å) | 0.71073 |
| Absorption coefficient ($mm^{-1}$) | 0.217 |
| $F_{000}$ | 5660 |
| $2\theta_{max}$ (°) | 55.12 |
| Crystal size | 0.25 x 0.25 x 0.25 $mm^3$ |
| Index ranges | -34<=*h*<=34, -36<=*k*<=36, -25<=*l*<=26 |
| Reflection collected | 82634 |
| Independent reflections to θ = 27.56º | 16058 ($R_{int}$ = 0.0477) |
| Data/restraints/parameters | 16058/14/911 |
| Goodness-of-fit on $F^2$ | 1.035 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0653, ω$R_2$ = 0.1829 |
| R indices (all data) | $R_1$ = 0.0971, ω$R_2$ = 0.2094 |

**Table 4.4** Selected bond distance (Å) and bond angles (º) of compound **4.10** HCl.

| | |
|---|---|
| N(5T)-C(1T) | 1.368(3) |
| N(5T)-C(3T) | 1.372(3) |
| N(1T)-C(1T) | 1.302(3) |
| N(1T)-C(2T) | 1.376(4) |
| N(4T)-C(3T) | 1.323(4) |
| N(3T)-C(3T) | 1.322(4) |
| N(3T)-C(2T) | 1.348(4) |
| C(2T)-N(2T) | 1.314(4) |
| C(1T)-N(5T)-C(3T) | 119.8(2) |
| C(1T)-N(1T)-C(2T) | 116.1(2) |
| C(4T)-N(6T)-C(5T) | 118.9(2) |
| C(3T)-N(3T)-C(2T) | 115.9(2) |
| C(5T)-N(8T)-C(6T) | 115.8(2) |
| N(1T)-C(1T)-N(5T) | 121.4(3) |
| N(1T)-C(1T)-C(4) | 120.3(2) |
| N(5T)-C(1T)-C(4) | 118.3(2) |
| N(2T)-C(2T)-N(3T) | 119.1(3) |
| N(2T)-C(2T)-N(1T) | 115.2(3) |
| N(3T)-C(2T)-N(1T) | 125.6(3) |
| N(3T)-C(3T)-N(4T) | 121.6(3) |
| N(3T)-C(3T)-N(5T) | 121.1(3) |
| N(4T)-C(3T)-N(5T) | 117.3(3) |

### 4.4.4 Complexation studies of diaminotriazine tetrapropoxy-calix[4]arene with barbituric acid and $Zn^{2+}$ ion

To investigate the properties of the new macrocycle **4.10** as a ligand for transition metal ions and a building block for hydrogen-bonded self-assemblies, it was decided to study the complexation of diaminotriazine calix[4]arene with barbituric acid and $Zn(CF_3SOO)_2$. As previously described in section 4.2, many barbiturate derivatives induce the formation of hydrogen-bonded self-assemblies with diaminotriazine–functionalized calix[4]arenes. Therefore, it was hypothesized that the new compound **4.10** may form a self-assembly entity with barbituric acid *via* hydrogen bonds. $Zn(CF_3SOO)_2$ was utilized as the example of a transition metal ion to investigate the ability of compound **4.10** as a ligand in coordination complexes. $Zn^{2+}$ is a diamagnetic metal ion ($d^{10}$) and the study of its complexes by $^1$H-NMR spectroscopy is accessible. Additionally, trifluoromethanesulfonate ion is a bad coordinating ligand so the proposed metal complex between $Zn^{2+}$ and compound **4.10** would not be interfered within the presence of the coordinating anion.

A 1.0 x $10^{-3}$ M solution of calix[4]arene **4.10** in DMSO-$d_6$ (0.3 mL) was added 10-fold amount (30 mmol) of barbituric acid ( or $Zn(CF_3SOO)_2$) directly into the NMR tube. The resulting solution was sonicated for 30 minutes and allowed to stand at room temperature for at least 2 hours. The $^1$H-NMR spectrum of the solution was recorded every 24 hours to ensure the equilibrium between the ligand and the complex.

The $^1$H-NMR spectra of compound **4.10** with barbituric acid and $Zn(OTf)_2$ showed no significant chemical shifts (see Figure 4.13 and Figure 4.14). All proton signals of free ligand **4.10** are intact even after 5 days. This implies that no complexation

between ligand **4.10** and barbituric acid (and $Zn^{2+}$) occurs. These unexpected results were stunning at the beginning because there are so many examples of self-assembled systems using hydrogen bonding between barbituric acid and diaminotriazine derivatives. However, this lack of success in the complexation of ligand **4.10** may come from its unappreciable solubility. Most $^{1}$H-NMR titration experiments for the hydrogen-bonded systems are performed in apolar solvents such as $CDCl_3$ to avoid competition from solvent molecules. However, calix[4]arene **4.10** does not dissolve in any other common organic solvents except DMSO. Since DMSO is a good hydrogen bond acceptor, so it is likely that DMSO disrupts the hydrogen bonding between diaminotriazine moieties of compound **4.10** and barbituric acid resulting in the absence of any complex. Hydrogen bonds between calix[4]arene **4.10** and DMSO might be strong enough to prevent the nitrogen atoms of a triazine ring from donating lone pair electrons to a metal center.

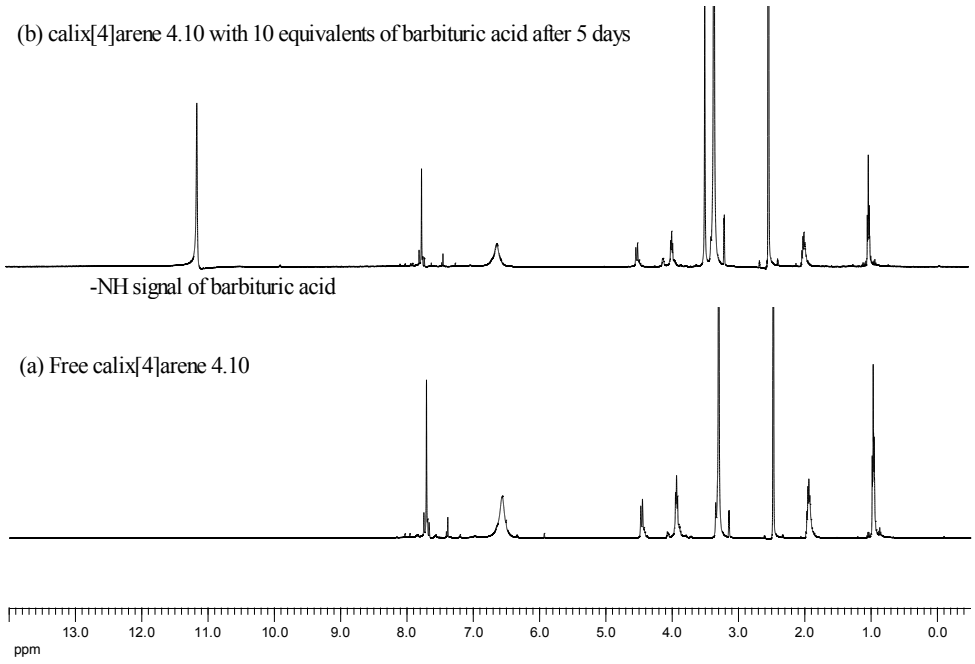



**Figure 4.13** $^{1}$H-NMR spectra of (a) a free calix[4]arene **4.10** (10 mmol), and (b) calix[4]arene **4.10** with 10 equivalents of barbituric acid after 5 days.

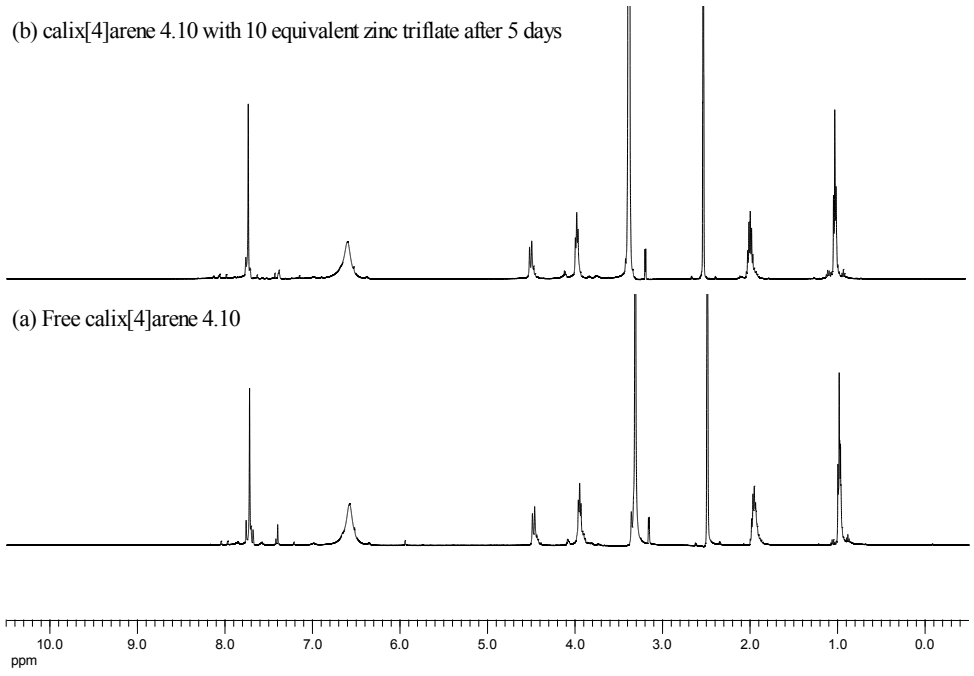
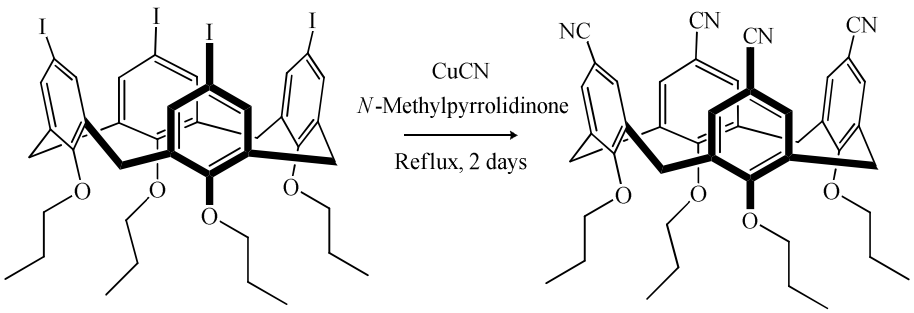



**Figure 4.14** $^{1}$H-NMR spectra of (a) a free calix[4]arene **4.10** (10 mmol), and (b) calix[4]arene **4.10** with 10 equivalents of zinc trifluoromethanesulfonate after 5 days.

## 4.5 Experimental section

### 4.5.1 Synthesis of 5,11,17,23-tetracyano-25,26,27,28-tetrapropoxy-calix[4]arene

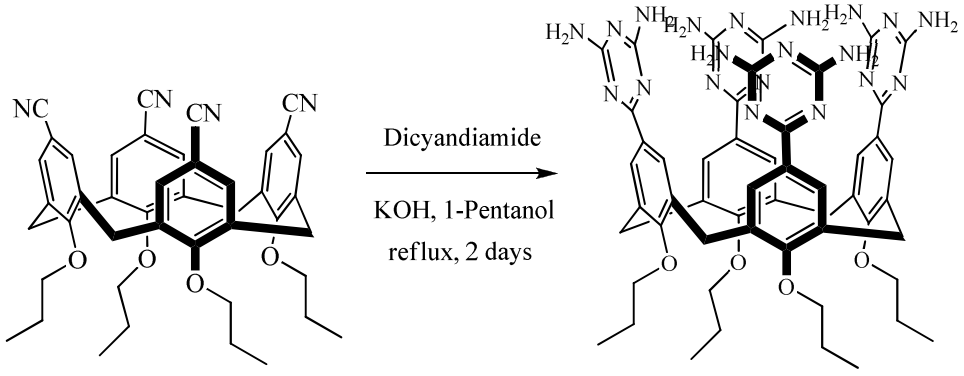



To a mixture of compound **3.18** (5.50 g, 5.02 mmmol) and CuCN (2.89 g, 32.3 mol) in a 500 mL three-necked round bottom flask was added dry 1-methyl-2-pyrollidinone (60 mL) under nitrogen. The reaction mixture was refluxed for 2 days. After reducing the heat to 100 ºC, a solution of $FeCl_3$ (10.00 g, 64.3 mmol) in 2M HCl (150 mL) was added slowly and the resulting solution was vigorously stirred at this temperature for 2 hours. The solution mixture was filtered and washed with hot water until the filtrate was neutral to pH paper. The dark brown crude product was purified by silica gel column chromatography eluting with $CH_2Cl_2$ and then $CH_2Cl_2$: EtOAc (from 99:1 to 97:3). Combined organic solvent was evaporated to dryness to give a white semi-solid. Recrystallization from $CH_2Cl_2$-methanol afforded compound 4.11 as a white solid (2.89 g, 83% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.02 (s, 8H, -Ar*H*), 4.47 and 3.27 (two sets of d, 8H, $^2J$ = 14.0 Hz, ArC$H_2$Ar), 3.93 (t, 8H, $^3J$ = 7.5 Hz, OC$H_2$CH$_2$), 1.95 (tq, 8H, $^3J$ = 7.5

MHz, -CHC$H_2$CH$_3$), 1.02 (t, 12H, $^3J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 160.0 (-*C*q-OCH$_2$-), 135.6 ($C_q$ *ipso* to CN), 132.4 ($C_{ar}$H *ortho* to CN), 118.2 (*C*N), 106.8 ($C_q$ *meta* to CN), 77.1 (O-*C*H$_2$CH$_2$-), 30.5 (Ar*C*H$_2$Ar), 23.2 (-*C*H$_2$CH$_3$), 10.1 (-*C*H$_3$) ppm. (+)-MALDI-TOF MS ($CH_2Cl_2$): calculated for [$C_{44}H_{44}N_4O_4$ + $Na^+$] m/z = 947.49, Found m/z = 946.72 (100%). Analytical calculated for $C_{44}H_{44}N_4O_4$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.01; H, 6.23; N, 8.01.

### 4.5.2 Synthesis of 5,11,17,23-*tetrakis*[(2,4-diamino-1,3,5-triazine)-6-yl]-25,26,27,28-tetrapropoxycalix[4]arene




A mixture of tetracyano tetrapropoxycalix[4]arene (2.29 g, 3.30 mmol), dicyandiamide (17.21, 205 mmol) and potassium hydroxide (3.06 g, 54.5 mmol) in1-pentanol (140 mL) was refluxed for 2 days. After cooling to room temperature, the precipitate was filtered off and rinsed with water. The residue was stirred in water (300 mL) at 100ºC for 3 hours, whereupon the suspension was filtered while still hot. The residue was rinsed thoroughly with hot water and dried under high vacuum for 24 hours. The diaminotriazine calix[4]arene 4.10 was obtained as a white solid (3.13 g, 92% yield)

$^1$H-NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.72 (s, 8H, -Ar*H*), 6.58 (broad s, 8H, -N$H_2$), 4.47 and 3.35 (two sets of d, 8H, $^2J$ = 12.5 Hz, ArC$H_2$Ar), 3.95 (t, 8H, $^3J$ = 7.5 Hz, OC$H_2$CH$_2$), 1.96 (tq, 8H, $^3J$ = 7.5 MHz, -CHC$H_2$CH$_3$), 0.99 (t, 12H, $^3J$ = 7.5 Hz, -C$H_3$); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 170.2 (*C*$NH_2$), 167.4, 167.2, 158.7, 133.9, 131.3, 128.2, 76.0 (O-*C*$H_2$CH$_2$-), 60.7, 32.2 (Ar*C*$H_2$Ar), 27.7, 22.7 (-*C*$H_2$CH$_3$), 14.0, 10.1 (-*C*$H_3$) ppm.

(+)-ESI MS (DMSO): calculated for [$C_{52}H_{60}N_{20}O_4$ + $Na^+$] m/z = 1051.50, Found m/z = 1050.81 (100%). Analytical calculated for $C_{52}H_{66}N_{20}O_4 \cdot 2H_2O \cdot CH_3OH$: C, 58.02; H, 6.25; N, 25.53. Found: C, 58.28; H, 5.92; N, 24.93.

## 4.6 Conclusions

To explore the chemistry of the 2,4-diamino-1,3,5-triazine moiety as a ligand for transition metal ions and a building block for hydrogen-bonded self-aggregates, *tetrakis*(2,4-diamino-1,3,5-triazine) tetrapropoxycalix[4]arene was synthesized from the reaction of tetracyano tetrapropoxycalix[4]arene with excess dicyandiamide in 92% yield. No X-ray quality crystals of the new calix[4]arene derivative were obtained. However, the crystal structure of the hydrochloride salt of the new calix[4]arene derivative shows that there is no hydrogen bond between diaminotriazine moieties. Calix[4]arene **4.10** adopts a pinched cone conformation. There is evidence of π-π interaction between a protonated triazine ring and a benzene ring of the calix[4]arene scaffold.

Preliminary complexation studies of calix[4]arene **4.10** with barbituric acid and zinc trifluoromethane sulfonate by $^1$H-NMR spectroscopy suggest that no complexes of calix[4]arene **4.10** are formed. It is possible that DMSO forms hydrogen bonds with a

free ligand and prohibits the interaction between diaminotriazine groups and guest species.

## 4.7 References for Chapter 4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# VITA

Praput Thavornyutikarn was born on May 18th, 1976 at The Maharaj Chiang Mai Municipal Hospital in Chiang Mai, Thailand. He is a second son of Mrs. Primprow and Assoc. Prof. Dr. Prasak Thavornyutikarn. After two years in the kindergarten level at Anuban Chiangmai School, he attended The Prince Royals' College in Chiang Mai for 12 years until graduated with a high school degree with the second honors award in the excellent academic performance in 1994. From 1994-1998, he attended the Department of Chemistry at Chulalongkorn University in Bangkok, Thailand where he received a Bachelor of Science with the second class honors in Chemistry. After that he attended graduate school in the same institution, conducting a master degree research in calixarene chemistry under the supervision of Prof. Thawatchai Tuntulani. He earned his Master of Science degree in Inorganic Chemistry at the end of October 2001. During January 2002 to May 2003, he worked as an inorganic chemistry instructor in the Department of Chemistry at Chiang Mai University. Since August 2003, he attended graduate school in the Department of Chemistry at the University of Missouri-Columbia, receiving his Doctor of Philosophy degree in May 2010 under the supervision of Prof. Jerry L. Atwood. After graduation, he plans to return back to his home country to continue his career as an instructor in the Department of Chemistry at Chiang Mai University.