SYNTHESIS AND COMPLEXATION STUDY OF THE CONFORMATIONAL ISOMER OF CYCLOTETRACHROMOTROPYLENE

by

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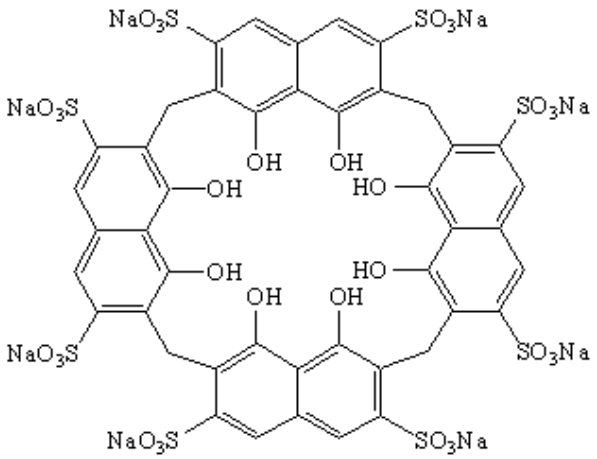
SINTESIS DAN KAJIAN PENGKOMPLEKSAN ISOMER KONFORMASI SIKLOTETRAKROMOTROPILENA

ABSTRAK

Dalam keadaan tindakbalas yang berbeza, asid kromotropik bertindakbalas dengan formaldehid untuk menghasilkan konformer perahu (**25a**) dan konformer kerusi (**25b**) siklotetrakromotropilena, **25**. Konformer **25b** telah dihasilkan pada suhu bilik dan apabila dipanaskan, ia boleh ditukarkan kepada konformer yang lebih stabil iaitu **25a**. Konformer **25a** boleh dihasilkan secara refluks dengan hasil yang tinggi (~ 90 %) sementara **25b** boleh disintesiskan pada suhu bilik dengan hasil 20-25 % sahaja.



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Kedua-dua konformer **25a** dan **25b** mempunyai spektrum UV-Visible yang berbeza tetapi mempunyai spektrum ^{I}H dan ^{13}C NMR yang serupa.

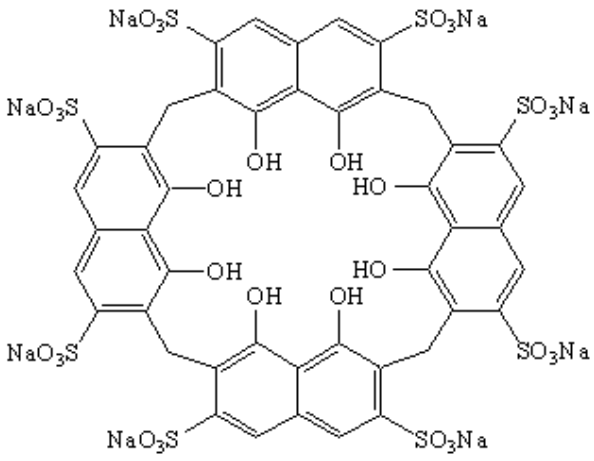
Pengecaman kedua-dua konformer telah dilakukan melalui kajian pengkompleksan dengan tetamu alkohol. Ini berdasarkan jangkaan yang konformer perahu akan bertindak sebagai perumah yang lebih baik seterusnya akan memberi nilai pemalar penyekutuan yang lebih tinggi daripada nilai yang diberi oleh konformer kerusi. Selain itu, pengecaman konformer adalah konsisten berdasarkan laporan kajian ke atas makrosiklik tetramer yang berkaitan.

Bagi pengkompleksan dengan tetamu besar seperti siklodekstrin dan garam tetraalkilammonia, kedua-dua konformer bertindak sebagai perumah yang sama baik.

SYNTHESIS AND COMPLEXATION STUDY OF THE CONFORMATIONAL ISOMER OF CYCLOTETRACHROMOTROPYLENE

ABSTRACT

Chromotropic acid reacts with formaldehyde to give the boat and chair conformers (**25a** and **25b** respectively) of cyclotetrachromotropylene, **25**, under different reaction conditions. At room temperature, **25b** was isolated in which upon heating can convert to the thermodynamically more stable **25a**. Conformer **25a** is best synthesized via reflux in high yield (~ 90 %). In contrast, **25b** can only be synthesized at room temperature giving a moderate yield of 20-25 %.



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Both **25a** and **25b** have different UV-Visible spectra but identical ^{1}H and ^{13}C NMR spectra.

Via complexation studies with alcohols, the conformational assignment of **25a** and **25b** is done. The assignment is based on the expectation that the boat conformer is a better host and will give relatively higher association constant, K values than those of the chair conformer. In addition, the assignment is consistent with the reported analogous macrocyclic tetramers.

In the case of bulky guests such as cyclodextrins and the tetraalkylammonium salts, both conformers are equally good as hosts.

1. INTRODUCTION

1.1 Background

The remarkable abilities of enzymes to catalyze organic reactions and regulate their occurrence, challenge chemists to devise simpler organic compounds that will perform similar functions. It was after the structures of the active sites of enzymes are well understood that chemists are able to provide models for the synthesis of nonpeptide organic systems that may stimulate enzymatic behaviour (Cram & Cram, 1974).

Enzyme is a protein that acts as a catalyst to increase the rate of reaction in the human body. The active site of an enzyme is located at its cavity. Enzyme chooses its specific substrate according to the substrate shape, size and interaction on its active site. This enzyme-substrate interaction involves hydrogen bonding as well as hydrophobic, ionic and polar interactions (Mundy et al., 1993). Thus, enzyme is acting as a host that includes guest (substrate) into its cavity. Most of the enzymes contain a hydrophobic phase in its cavity whereas the outer part hydrophilic thus making them water-soluble. Although the enzyme is water-soluble and attracts its substrate in aqueous medium, it is in its hydrophobic active site cavity the catalytic process actually happens (Pretagard & Chan, 1970).

In 1967, Pedersen (1967a) accidentally discovered a cyclic polyether, dibenzo(18)crown-6 (DB18C6), **1**, or simply called as crown ether. This white crystalline solid was reported to be able to form a highly structural complex by

including both alkaline earth and alkaline ionic metal into its cavity (Pedersen, 1967b).

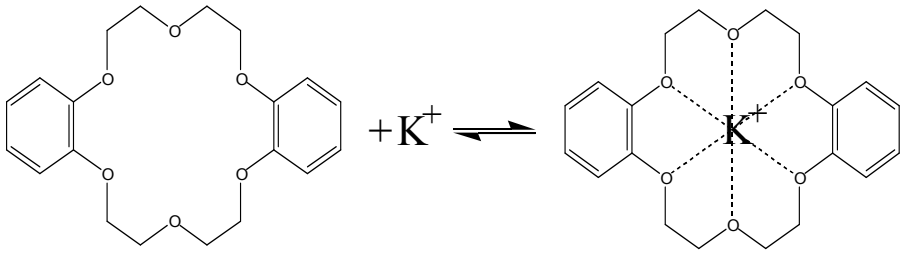

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Figure 1.1: DB18C6 and K^+ complexation.

It was from here that triggers the race and development for efficient synthetic hosts and the vast increase in the study and knowledge of selective complexations with either organic or inorganic guests. This work of Pedersen was continued by Lehn in 1969 followed by Cram in 1974. They eventually were awarded the Nobel Prize in 1987 for their contribution towards the development of supramolecular complexation, chiral recognition and catalysis in chemistry.

1.2 Supramolecular Chemistry

Supramolecular chemistry is defined as chemistry beyond the molecule, referring to organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. (Vogtle, 1993). Host-guest chemistry together with some other related fields have begun evolving into supramolecular chemistry.

1.2.1 Host-Guest Interaction

In host-guest relationships, a complementary stereoelectronic arrangement of the binding sites in the host and guest is involved. Only complete match or specific binding between host and guest produces a strong complex.

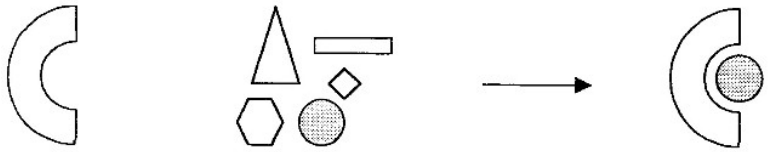


Figure 1.2: Selective complexation between host and guest.

Host is normally larger of the two and is defined as an organic molecule or ion whose binding sites converged in the complex whereas guest is smaller and defined as any molecule or ion whose binding sites diverge in the complex (Kyba et al., 1976). Although simple guests are easy to obtain due to its abundance, hosts are rare in nature and therefore they need to be synthesized or designed to fulfill the host-guest interactions needs.

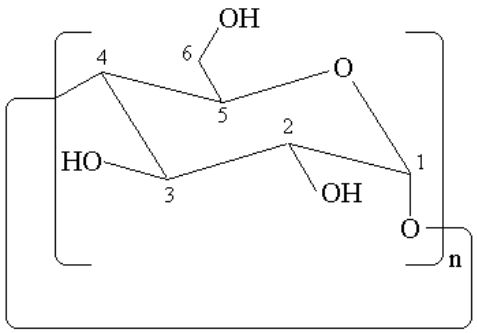
The first study on host-guest chemistry was aimed at designing a compound acting as enzyme as well as understanding its biological behaviour. This is because structural molecular complex plays an important role in the regulation and catalysis of biological processes and phenomenon. For example, most of the important biochemical processes such as enzymic catalysis and inhibition, immunological response, storage and retrieval of genetic information, biological regulatory function, drug action and ion transfer all involve molecular recognition and selective complexation (Cram & Trueblood, 1981).

1.3 Naturally Occurring Macrocyclic Host

Only a few hosts occur in nature. They are namely;

1.3.1 Cyclodextrins

They are among the most well-known naturally occurring hosts. They are cyclic oligomers composed of 6 to 8 glucopyranoside units, better known as α-, β- and γ- cyclodextrins respectively.



n = 6 (α-cyclodextrin) , 7 (β-cyclodextrin), 8 (γ-cyclodextrin)

Figure 1.3: Structures of cyclodextrins.

They are water-soluble and able to complex with molecules which contain either one or two benzene rings or even larger molecules carrying a side chain of comparable size to form crystalline inclusion complexes (Szejtli, 1982). Cyclodextrins have become very useful hosts in aqueous solution because they show strong recognition towards hydrophobic guests. They are widely used in food and pharmaceutical industry nowadays as well as for the protection of large number of sensitive molecules against oxidation by molecular encapsulation (Hingerty & Saenger, 1976).

1.3.2 Antibiotics

Nonactin, **2**, is a macrocyclic antibiotic which regulates metabolic behaviour due to its ability to selectively enhance the transport of sodium and potassium ions across cell membranes (Pretagard & Chan, 1970).

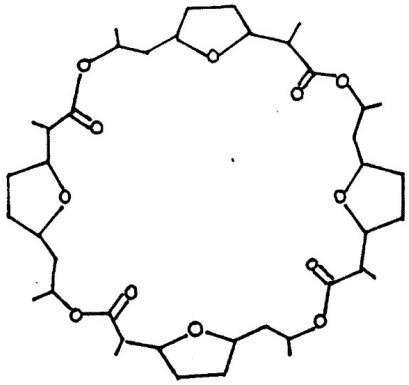


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Figure 1.4 : Nonactin structure.

Valinomycin, **3**, is another antibiotic which shows an extreme affinity towards potassium than sodium ion in the transport into lipophilic phases across neutral membranes (Hilgenfield & Saenger, 1982).

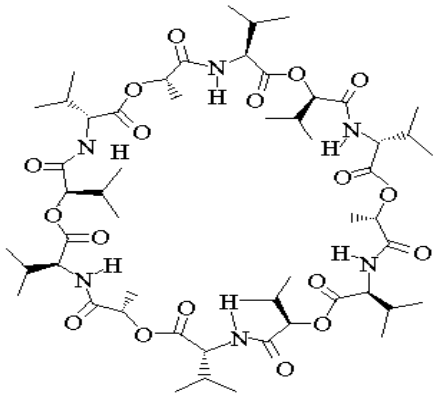

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Figure 1.5 : Valinomycin structure.

1.4 Synthetic Macrocyclic Host

The discovery of crown ether has led to the production of more macrocyclic hosts. Some of them are as stated below (Cram & Trueblood, 1981);

1.4.1 Cryptand

A monocyclic crown ether but attached with additional oligoether chain resulting in a bicyclic ligand formation. An example is **4**.

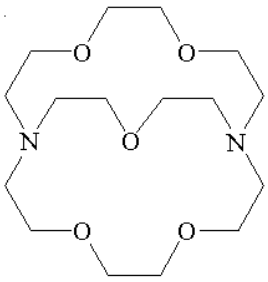

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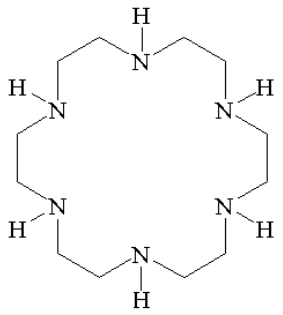
Figure 1.6 : A cryptand.

1.4.2 Coronands

They are multidentate monocyclic ligands with oxygen atoms or any other type of donor atoms (Cram & Trueblood, 1981). Examples are coronand amine, **5** and (18)crown-6, **6**.



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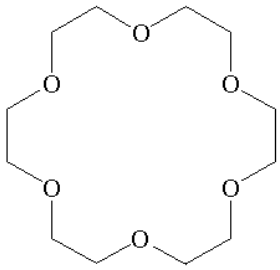

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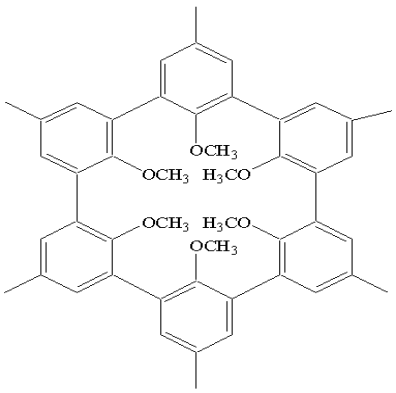
Figure 1.7 : Different types of coronands.

1.4.3 Spherands and hemispherand

Spherands, **7**, are macrocyclic or macropolycyclic systems that contain enforced cavities that are fully preorganized for complexation during synthetic process. They often possess a spherical complex arrangement with the donor sites arranged rigidly around the cavity. Hemispherand, **8**, on the other hand has half its structure rigidly fixed in position so as to dominate the general shape of the host molecule while leaving the other half of the polyether chain freely mobile.



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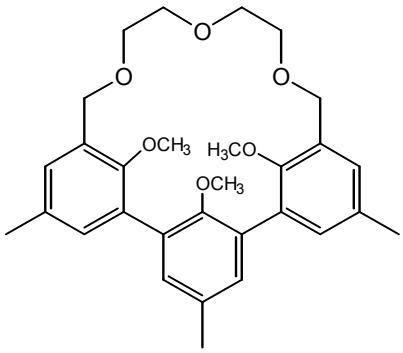

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Figure 1.8 : Spherand and hemispherand.

1.5 Water-soluble Synthetic Macrocyclic Host

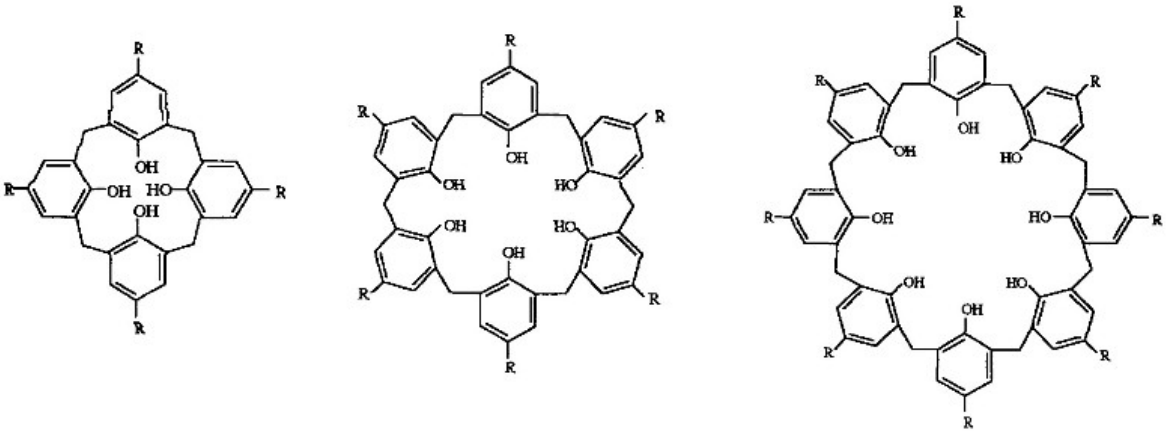
The existence of water-soluble macrocyclic hosts in nature is of much interest to chemists because their hydrophobic cavity is an excellent model for the pocket hydrophobic enzyme. Some of the interesting ones are;

1.5.1 Calixarenes

In 1870s, Adolph von Baeyer accidentally discovered cyclic oligomer consisting of benzene units during his phenol-fomaldehyde resin preparation. However, the products he obtained remained uncharacterized. Later, in 1940s, Zinke and Ziegler have assigned a cyclic tetrameric structures which was formed by the condensation of *p*-t-butylphenol and fomaldehyde (Vicens & Bohmer, 1991; Bohmer, 1995). This class of product is now known as calixarenes.

The study on calixarenes was abandoned for some time until Gutsche started to continue the work in 1970s. This is due to the fact that calixarenes are expected to be useful in designing enzyme mimics in totally synthetic systems owing to their similar cylindrical architecture to cyclodextrins (Gutsche & Bauer, 1985).

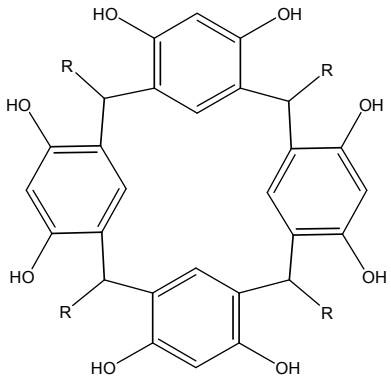
This macrocyclic from the class of metacyclophane can be synthesized via the condensation of fomaldehyde with the *para*-substituted phenol in basic condition (Gutsche, 1991). Some of the products produced are the tetrameric, **9**, hexameric, **10**, and octameric, **11**, calixarenes (Gutsche et al., 1981).



9 **10** **11**

Figure 1.9 : Calixarenes (n= 4, 6, 8).

The reaction between aliphatic and aromatic aldehyde with resorcinol by using acid as catalyst produced a cyclic tetramer of resorc[4]arene, **12**, (Abis, et al., 1988; Weinelt & Schneider, 1991).



12

R = Me, Ph, $(CH_2)_{10}Me$

Figure 1.10 : Resorc[4]arene

Calixarenes can be modified via functionalization at the phenolic hydroxy groups (lower rim) and at the *para*-position of the phenols (upper rim) (Gutsche, 1991; Takeshita & Shinkai, 1995).

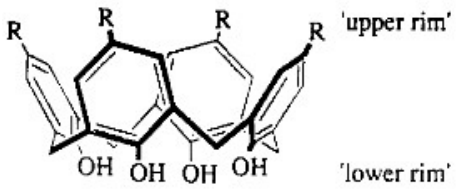
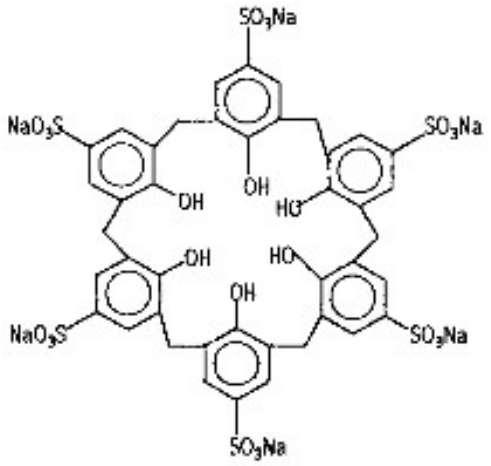


Figure 1.11 : Two different zones of calixarene

Parent calixarenes have poor solubility because they are sparingly soluble in several organic solvents but insoluble in aqueous solutions. They have to be functionalized with polar groups to make them water-soluble. Thus, efforts were done toward improving the solubility of calixarenes that would eventually lead to the exploitation of calixarene-based host molecules and enzyme mimics. It was only until 1984, Arduni and coworkers succeeded in synthesizing a water-soluble calixarene by introducing four carboxylate groups at the lower rim of calix[4]arene. However, no inclusion of neutral molecules was observed with the compound in water.

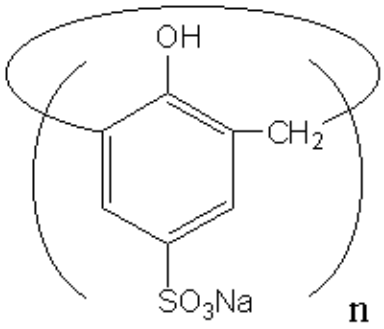
Later, a more successful water-soluble calixarene was designed by Shinkai and coworkers (1986) through the sulfonation of the non water-soluble calix[6]arene into a water soluble hexasulfonated calix[6]arene, **13**. Compound **13** can serve as a new class of catalyst, surfactant and host molecule.



13

Figure 1.12 : A water-soluble calixarene.

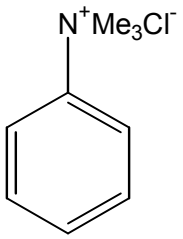
Several other sulfonated calixarenes which are highly soluble in water that were synthesized by Shinkai are **14** and **15**.



n = 4 (**14**); n = 8 (**15**)

Figure 1.13 : Water-soluble calixarenes by Shinkai and coworkers.

Compound **14** is able to form inclusion complexes with several organic molecules and cations (Shinkai et al., 1989). It forms a 1:1 complex with trimethylanilinium cation **16** and adamantyltrimethylammonium cation **17** at pH 7.3 in which the driving force for the inclusion is considered to be the electrostatic interaction between the ammonium cation and the negatively charged aromatic cavity of the host.



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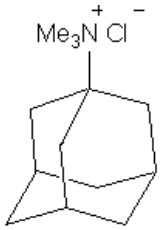


17

Figure 1.14 : Trimethylanilinium and adamantyltrimethylammonium cations.

At pH 0.4, where all phenolic hydroxy groups are not ionized, the aromatic nucleus of the guest is preferentially complexed into the apolar cavity of calixarene due to hydrophobic effects (Shinkai et al., 1990).

Compounds **16** and **17** form 1:1 complexes with hexasulfonated calix[6]arene, **13** (Shinkai et al., 1986) and form 1:1 as well as 1:2 complex with octasulfonated calix[8]arene, **15** (Shinkai et al., 1988). However, the association constants for both complexes were found to be lower compared to the complexes formed with **14**.

One of the most important features of calixarenes in supramolecular chemistry is their ability to recognize organic molecules on the basis of their shapes and sizes. Calixarenes are not completely rigid molecules and their shapes and flexibilities can be varied by changing solvents, temperatures and by further functionalization.

Although both cyclodextrins and calixarenes have similar cylindrical architecture, there exists an essential difference - the cyclodextrin cavity is conformationally fixed, whereas the calixarene cavity is not (Gutsche et al., 1988; Gutsche, 1983).

It was reported that calix[4]arene can exist in four discrete forms which are referred to “cone”, “partial cone”, “1,2-alternate” and “1,3-alternate” conformations (figure 1.15). (Gutsche, 1983; Gutsche, 1987).

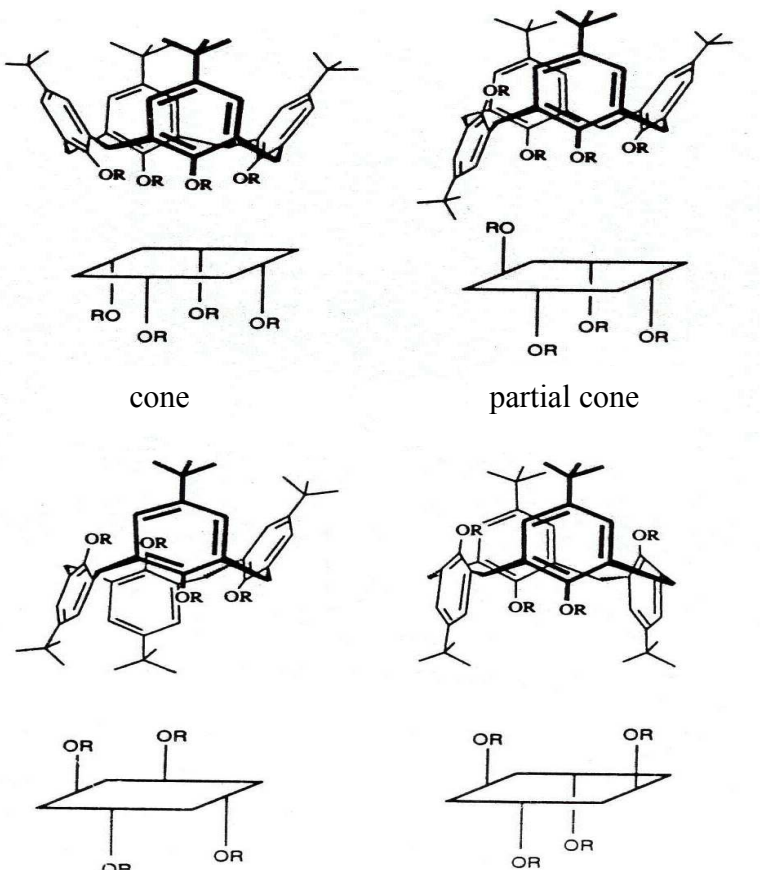


Figure 1.15 : Conformations of calixarenes.

Parent calix[4]arenes are conformationally mobile in solution. Via interpretation of their ^{1}H NMR spectra at low and high temperature experiments for their methylene bridges, it was discovered that an interconversion (Figure 1.16) between two mirror-image cone conformations occur (Kammerer et al., 1981).

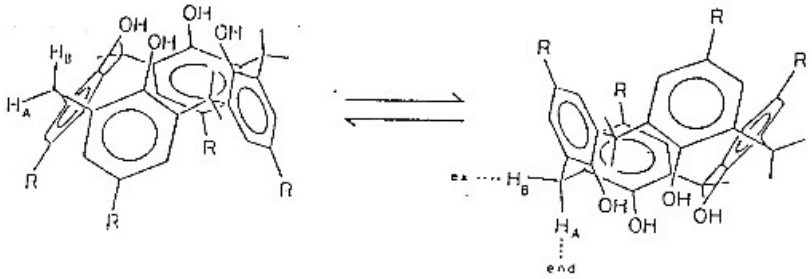


Figure 1.16 : Ring inversion between mirror image cone-cone conformations.

The ring inversion process is mostly governed by enthalpy term (Araki et al., 1989b). When the cavity of water-soluble calix[4]arenes includes guest molecules, the rate of ring inversion is significantly reduced (Shinkai, et al.,1989). The cone conformation in calix[4]arene is stabilized by intramolecular hydrogen-bonds.

All native calix[4]arenes known have a cone conformation in the solid state (Andreetti, et al., 1991). An example is the first reported (Andreetti, et al., 1979) 1:1 complex between *p*-t-butylcalix[4]arene and toluene (Figure 1.17).

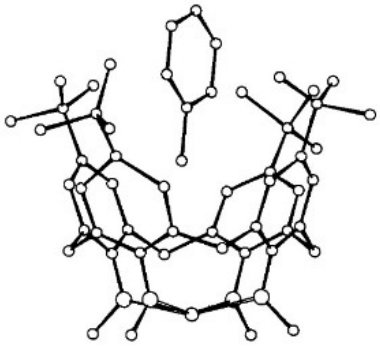
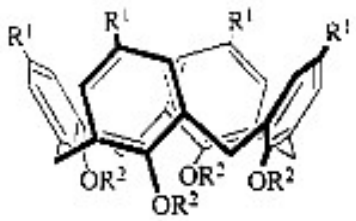


Figure 1.17 : X-ray crystal structure of toluene and *p*-t-butylcalix[4]arene of a 1:1 complex.

The cone conformation adopted in *p*-t-butylcalix[4]arene is due to the strong hydrogen-bonding interactions among the OH groups. Introduction of alkyl or acyl substituents into the OH groups suppresses the conformational freedom owing to steric hindrance (i.e., inhibition of the oxygen-through-the-annulus rotation) (Iwamoto et al., 1991).

On the contrary, in some cases, the cone conformation is not favoured. Tetra-O-alkylation of the *p*-t-butylcalix[4]arenes with alkyl halogens (Araki, et al., 1989a; Iwamoto, et al., 1991) resulted in the formation of **18** (Harada, et al., 1992) and **19** (Araki, et al., 1989a) which are of partial-cone conformations. The alkylation also resulted in the formation of **20** and **21** that adopt a cone and partial-cone conformation of approximately 1:1 ratio.

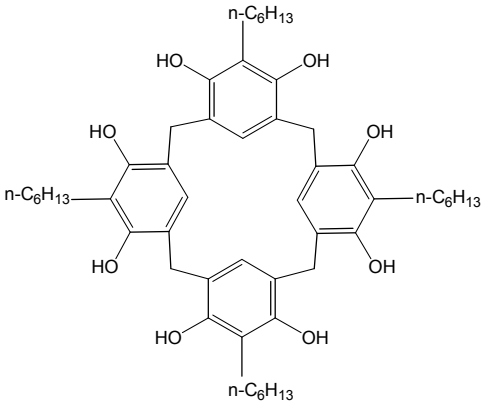


R^1 = *tert*-butyl

R^2 = Me (**18**), Et (**19**), n-Pr (**20**), n-Bu (**21**)

Figure 1.18 : Tetra-O-alkylated *p*-t-butylcalix[4]arenes.

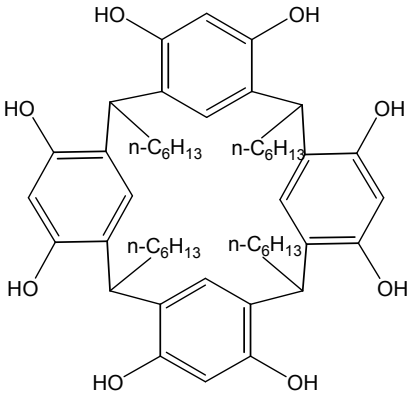
The conformational properties of resorc[4]arene, **12**, are affected by the nature of the R group present on the bridge between adjacent aromatics. It was not long ago that unsubstituted methylene bridges have been synthesized (Konishi et al., 1989; Konishi & Morikawa, 1993). However, due to solubility problem, only compound from 2-hexylresorcinol, **22**, could be studied.



22

Figure 1.19 : 2-hexylresorcinol

In all cis isomers of resorc[4]arenes, **23**, via interpretation of their ^{1}H NMR spectra, a C_4 symmetry was revealed. The symmetry resulted from time averaging of two flattened cone conformations rapidly interconverting through the symmetric cone conformation (Abis et al., 1990).



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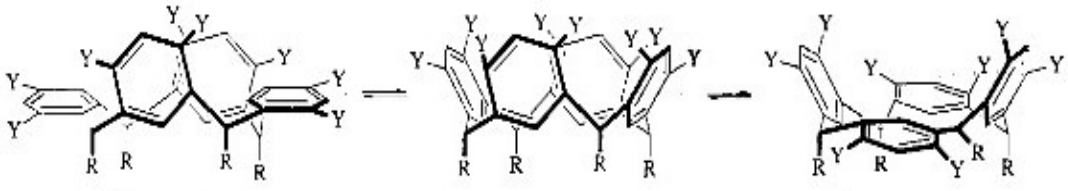
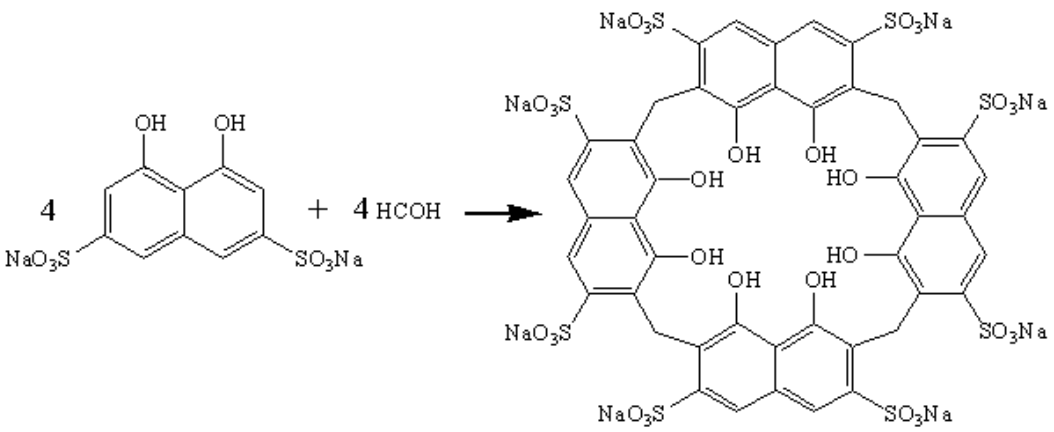


flattened cone cone flattened cone

Figure 1.20 : Conformers of all-cis resorc[4]arenes, **23**.

1.5.2 Cyclotetrachromotropylene

In 1989, Poh and coworkers succeeded in synthesizing a water-soluble cyclic tetramer that was named cyclotetrachromotropylene, **25**. The purple in colour macrocycle was obtained by the reaction of chromotropic acid, **24** with formaldehyde in neutral condition (Poh et al., 1989; Tan, 1994). Similar to calixarenes, it has a hydrophobic cavity and hydrophilic sulfonate groups which allows it to be soluble in water.



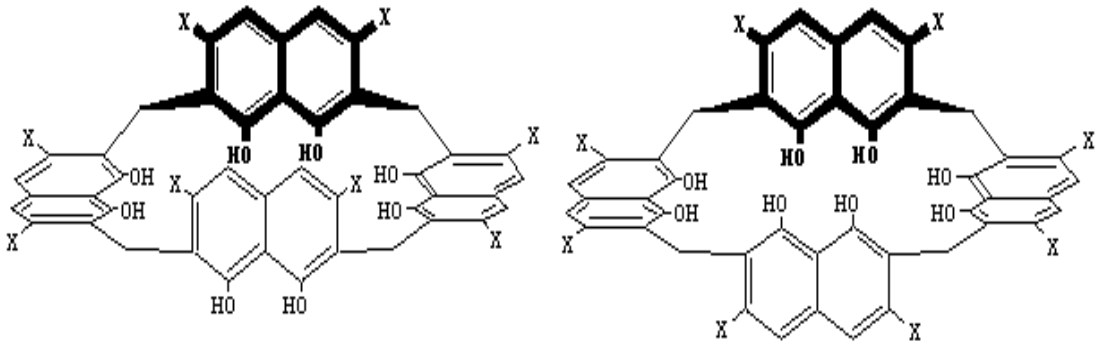
24 **25**

Figure 1.21 : Synthetic reaction of cyclotetrachromotropylene.

Cyclotetrachromotropylene has successfully been used to form complexes with various guests such as several divalent metal cations (Poh et al., 1990a; Poh et al., 1993a), polyaromatic hydrocarbons (Poh et al., 1990b; Poh & Koay ,1990), phenols (Poh et al., 1993b), amino acids (Poh & Tan, 1994a), alcohols and sugars (Poh & Tan, 1993). In addition, **25** is able to include cyclodextrins, a naturally occurring host, in its cavity, making cyclodextrins acting as guests (Poh & Tan, 1994b).

Complexations that were formed with the mentioned organic molecules were due to the hydrophobic interactions between the aliphatic or aromatic hydrocarbon chains of the guests (CH- or π-) and the naphthalene wall (π-) of the host.

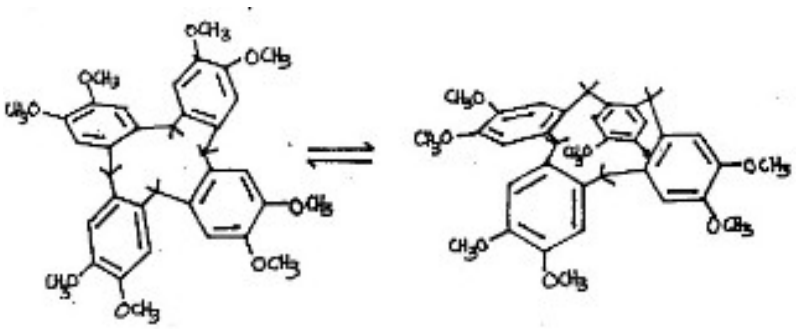
The role of **25** as host in various complexation studies is of much interest to Poh and coworkers. However, little is known about the conformation of **25**. Via CPK molecular models examination, **25** can exist in two conformations namely 'boat' (**25a**) and 'chair' (**25b)**.



25a **25b**

Figure 1.22 : Boat and chair conformations of cyclotetrachromotropylene.

The two possible conformations of **25** are also supported by reference to a structurally-related macrocyclic tetramer such as cyclotetraveratrylene, **26**. Low temperature ^{1}H NMR spectrum analysis of **26** shows strong evidence of flexible chair and boat conformations (White, 1968).

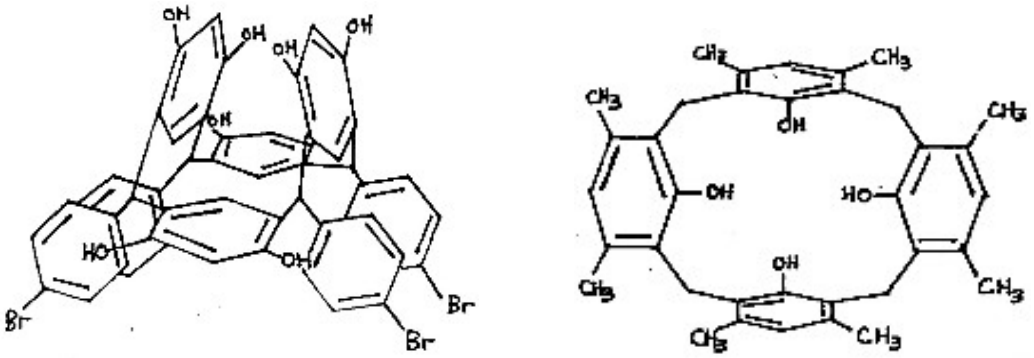


chair boat

26 **26**

Figure 1.23 : Flexible chair and boat conformations of cyclotetraveratrylene.

In addition, the condensation product, **27**, of resorcinol and p-bromobenzaldehyde in presence of hydrochloric acid (Erdtman et al., 1968) and also octamethylcalix[4]arene, **28**, (Dahan & Biali, 1989) revealed a boat conformation.



27 **28**

Figure 1.24 : Boat conformations of **27** and **28**.

The aims of this thesis are

(i) to synthesize the second conformer of cyclotetrachromotropylene

(ii) to assign their conformations

(iii) to study the complexation of alcohols, cyclodextrins and the tetraalkylammonium salts with the second conformer.

2. EXPERIMENTAL

Chemicals used

1. Chromotropic Acid, disodium salt from Merck, Germany.
2. α-Cyclodextrin from Aldrich Chemical, UK.
3. β-Cyclodextrin from Sigma, USA.
4. γ-Cyclodextrin from Sigma, USA.
5. Deuterium Oxide (99 % D) from Merck, Germany.
6. Diethyl ether (AR) from Fischer Chemicals, USA.
7. Ethanol (99.5 %) from Systerm, Malaysia.
8. Ethanol (99.7 %) from James Burrough (F.A.D) Ltd, UK.
9. Formaldehyde (37 %) from Merck, Germany.
10. n-Butanol from Merck, Germany.
11. n-Propanol from Fisher Scientific, UK.
12. s-Butanol / 2-Butanol from BDH Chemicals, England.
13. Sephadex LH-20 (bead size: 25-100 μm) from Sigma, USA. Used for lipophilic (polar organic solvent) and hydrophilic. Deviation limit: 2000-10000 g /mol.
14. Tetrabutylammonium iodide 98 % from Aldrich Chemical, UK.
15. Tetraethylammonium chloride monohydrate from Merck, Germany.
16. Tetramethylammonium chloride 97 % from Aldrich Chemical, UK.
17. Tetrapropylammonium bromide 98 % from Aldrich Chemical, UK.

Instruments used

1. ^{1}H NMR 300 MHz and ^{13}C NMR 75 MHz spectra were recorded in D_2O with a Bruker AC300 Superconducting NMR (nuclear Magnetic Resonance) spectrometer.
2. ^{1}H NMR 400 MHz and 2Ds spectra were recorded in D_2O with a Bruker AV400 Superconducting NMR spectrometer.
3. CHN analysis were carried out with a Perkin Elmer PE 2400 CHN Elemental Analyzer.
4. FAB Nominal Mass Analysis spectra were analyzed using Finnigan MAT95XL-T Mass Spectrometer using thioglycerol as the matrix and solvent methanol and water by the Department of Chemistry, National University of Singapore.
5. Sodium content was carried out with AAS Perkin Elmer 3100 Spectrometer.
6. Ultraviolet and Visible Spectra were recorded with a Hitachi U-2000 Spectrophotometer.