UNEXPECTED CYCLIZATION OF DIPYRIDYL-GLYCOLURIL IN THE PRESENCE OF FORMALDEHYDE AND STRONG ACID: A NEW SCAFFOLD WITH A POTENTIAL AS A RECEPTOR AND SYNTHESIS OF VARIOUS CALIXARENE PRECURSORS

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FOR
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IN
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Approval of the Graduate School of Natural and Applied Sciences.

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ABSTRACT

Unexpected Cyclization of Dipyridyl-glycoluril in the Presence of Formaldehyde and Strong Acid: A New Scaffold with a Potential as a Receptor

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August 2005, 80 pages

This thesis covers combination of two independent works accomplished throughout the study. One part research is about the unexpected cyclization of Dipyridyl-glycoluril, and the other part is about synthesis of precursor calix[4]arene derivatives.

In an attempted synthesis of peripherally pyridine substituted cucurbituril, an unexpected cyclized product was obtained. A careful NMR analysis followed by mass spectrometry and preliminary crystallographic analyses, helped us in resolving the structure. The structure has two quaternized pyridine functionalities and a groove suitable as a potential receptor site. In addition, just like the parent glycoluril structure, two remaining urea-derived nitrogens can be alkylated by alkyl halides. Thus, we believe this high yielding reaction may become an entry point to a new class of anion receptors.

Keywords: glycolurils, cucurbituril, cucurbituril derivatives, molecular scaffolds

In the second work, certain important calix[4]arene derivatives were synthesized. They are the building blocks of important potential molecular, anion and cation sensing, and enzyme mimics. For these precursor molecules, functionalizations both on lower and upper rim have been studied. A careful study on NMR data has been performed and detailed investigation on the NMR data was discussed herein. Applying further one or two step procedures produces important target molecules having potential as sensors or artificial enzymes.

Keywords: supramolecular chemistry, calixarenes, calix[4]arene, upper – lower rim functionalization

ÖZ

Bipiridil-Glikolüril'in Formaldehit ve Güçlü Asit Birlikteliğinde Beklenmedik Halkalaşması: Potansiyel Algılayıcı Olan Yeni Bir Yapı

Cevheroğlu, Orkun
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Engin U. Akkaya

Ağustos 2005, 80 sayfa

Bu tez, master çalışmaları süresince tamamlanmış, birbirinden bağımsız iki çalışmayı içermektedir. Araştırmanın bir kısmı Bipiridil-Glikolüril'in formaldehit ve güçlü asit birlikteliğinde beklenmedik halkalaşmasını ve diğer kısım da öncü Kaliksaren türevlerinin sentezi hakkındadır.

Periferik Piridin yerleştirilmiş kükürbitüril sentezi girişiminde, beklenmemiş halkalaşmış bir ürün elde edildi. Dikkatli NMR analizleri onu takip eden kütle spektrometresi ve ön kristalografik araştırmalar, bize yapıyı aydınlatmada yardımcı oldu. Yapıda iki tane kuarterner piridin fonksiyonları ve potansiyel bir algılayıcı için uygun oluk vardır. Bunlara ek olarak, aynı ana Glikolüril yapısında olduğu gibi, geriye kalan iki üre türevi azot alkil halojenürlerle alkillenebilmektedir. Sonuç olarak, inanıyoruz ki bu yüksek verimli reaksiyon yeni grup anyon algılayıcıları için yeni bir giriş olabilir.

Anahtar sözcükler: Glikolüril, Kükürbitüril, Kükürbitüril türevleri, Eşik moleküller

Yapılan ikinci çalışmada, belirli önemli Kaliks[4]aren türevleri sentezlendi. Bu moleküller önemli moleküler, anyon ve katyon algılayıcıları ve enzim taklitçileri için potansiyel yapıtaşlarıdır. Bu öncü moleküllerde, alt ve üst çemberde fonksiyonlandırma çalışılmıştır. NMR çıktısı üzerine dikkatli bir çalışma yapılmıştır ve bu tezde, NMR verisi ayrıntılı bir şekilde incelenmiştir. Fazladan bir veya 2 adım sentez prosedürleriyle potansiyel algılayıcı ve enzim taklitçisi olan önemli hedef moleküller üretilebilir.

Anahtar sözcükler: Supramoleküler kimya, Kaliksarenler, Kaliks[4]aren, Üst – Alt çember fonksiyonlandırılması.

"*To the three women in my life*"

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Thanks to my family; I love you all; for their limitless support, generosity and believing in me. Just one more sentence to my mother, “mom, from now on I promise not to let the things in my life to stand till the very last moments and then try to finish them in a different way or hurry.”

It would be the most unacceptable thing not to mention about you- Burcu- here since you have been in every second in my life for 6 years and since that I love you so much.

I believe so so so few people are lucky like me in the case of friendships. I even cannot accept the names, I am mentioning here as just friends, they are my brothers. Emin, Erdem, Hüseyin, Kemal, Kerem and Umut, (guys, don’t be offended from the order of the names in the list, it is just alphabetical, not sentimental) I know you’ll be always there for me whenever I need.

Finally, I would like to thank to my lab mates, it has always been a fun to work in such an atmosphere we created in the laboratory. Special thanks go to Neslihan, Funda and Tarık, for you two being so good and of course many other details I am observing for years.

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CHAPTER I

INTRODUCTION

1.1. Supramolecular Chemistry

"Just as there is a field of molecular chemistry based on the covalent bond, there is a field of supramolecular chemistry, the chemistry of molecular assemblies and of the intermolecular bond" (Lehn, 1995). This is the definition according to the one of the leading proponents Jean-Marie Lehn, who shared the Nobel Prize with Cram and Pedersen in 1987, for giving birth to a one of the most active areas of contemporary chemical research.

This field of chemistry can be called as the "chemistry beyond the molecule", which can be further explained as the "chemistry of non-covalent bond".

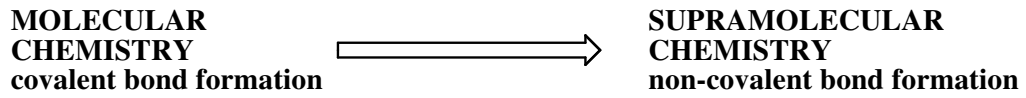


Figure 1.1. Molecular Chemistry vs. Supramolecular Chemistry.

The term intermolecular or non-covalent refers to the weak interactions such as, electrostatic interactions, hydrogen bonding, π-π stacking interactions, van der Waals forces and hydrophobic or solvatophobic effects. All these weak

interactions are the basics of molecular design, and the strength of supramolecular chemistry lies beneath all these weak interactions.

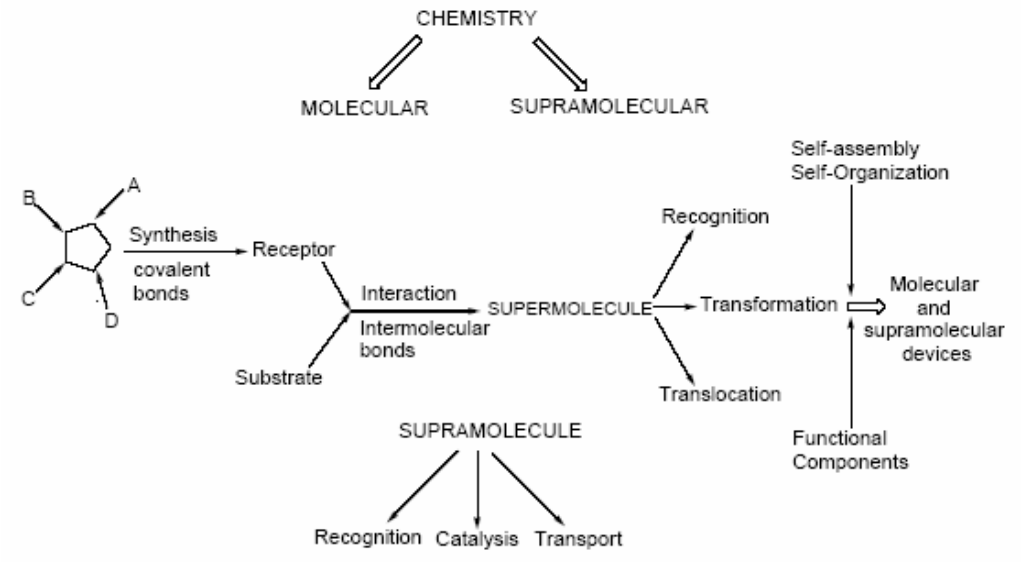


Figure 1.2. From molecular to supramolecular chemistry

Electrostatic interactions are based on the Coulombic attraction between opposite charges, ion-ion, ion-dipole and dipole-dipole interactions are that kind of interactions. Ion-ion interactions are non-directional, whereas for the case of ion-dipole interactions, the dipole must be suitably aligned for the optimal binding efficiency. Hydrogen bonding can be seen as a particular kind of dipole-dipole interaction in which a hydrogen atom attached to an electronegative center is attracted to a neighboring dipole or a molecular or functional group. Because of its comparably stronger interaction and highly directional nature, hydrogen bonding is accepted as a "masterkey interaction in supramolecular chemistry". π-π stacking interactions are among all one of the weakest interaction. This weak interaction occurs between aromatic rings, often in situations where one is relatively electron rich and one is electron poor.

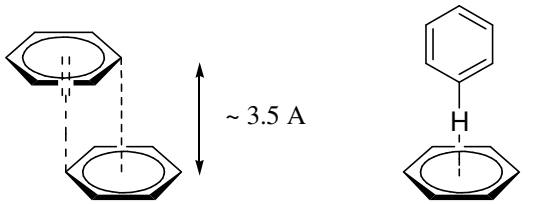


Figure 1.3. Types of π-π stacking interactions.

π stacking interactions between aryl rings of nucleobase pairs also help to stabilize the DNA double helix. Edge to face type of π-π stacking interaction can be regarded as a weak kind of hydrogen bonding between an electronically poor hydrogen atom of an aromatic ring interacting with an electronically rich aromatic π-cloud of another. Van der Waals interactions results from the polarization of the electron cloud by the proximity of the adjacent molecules. In supramolecular chemistry, this kind of weak interaction is important for the formation of inclusion compounds, as in the case of inclusion of toluene within the molecular cavity of the *p*-tert-butylcalix[4]arene. Hydrophobic effect is related to the association of nonpolar binding patterns in aqueous solution. Hydrophobic effects are in vital importance in binding of organic guest molecules by cyclodextrin and cyclophane hosts in water.

All these interactions are the foundation for highly specific biological processes. The supramolecular hosts are the receptor sites of enzymes, genes, antibodies of the immune system and ionophores and the guests are substrates of enzymes, cofactors, drugs or antigens. All of these biological components display supramolecular properties and use of non-covalent interactions.

1.2. Supramolecular Design

In order to design a host that will selectively bind a particular guest, we make use of the chelate and macrocyclic effects as well as the concept of complementarity (matching of host and guest steric and electronic requirements), and crucially, host preorganisation, (Steed and Atwood, 2000).

The exact knowledge of the energetic and stereochemical characteristics of these non-covalent, multiple intermolecular interactions within defined structural areas should allow the design of artificial receptor molecules, which bind the substrate strongly and selectively by forming supramolecular structures, (Vögtle, 1991).

The guest parameters such as required host size, charge, character of the donor atoms etc., must be very well defined before starting the molecular architecture. It requires the design of receptors possessing steric and electronic features complementary to those of the substrate to be bound and a balance between rigidity and flexibility suitable for the function to be performed, (Lehn, 1988). One of the most crucial concepts is the organization. Host-guest interaction occurs through their binding sites therefore the organization of binding sites must be arranged in a fashion that on the organic scaffold or framework must be suitable in size to accommodate the guest and with a well-matching geometry. The use of hydrogen bonding with its modest directionality and easily recognized patterns has been quite successful in this regard, (Rebek et al., 1992).

Chelate and macrocyclic effects are related to organization of a host molecule. In particular chelating or macrocyclic ligands are frequently employed due to the high thermodynamic stability of their complexes. The chelate effect refers to the enhanced stability of a complex containing chelate rings as compared to a similar system containing fewer rings. From five membered chelate rings upwards, the chelate effect decreases in magnitude

with increasing the ring size. The macrocyclic effect is related to the chelate effect and refers to the increased thermodynamic stability of macrocyclic systems compared to their cyclic analogues.

1.3. Host-Guest Chemistry

A molecular entity comparably being larger and having convergent binding sites, "the host", binds to another molecule, smaller and having divergent binding sites, "the guest", therefore forming a "host-guest" complex or a supramolecule is produced.

The host-guest chemistry is based upon three historical concepts:

1. The recognition by Paul Ehrlich in 1906 that molecules do not act if they do not bind; in this way Ehrlich introduced the concept of a biological receptor.
2. The recognition in 1894 by Emil Fischer that the binding must be selective, as part of the study of receptor-substrate binding by enzymes. He described this by a "lock and key" image of steric fit in which the guest has a geometric size or shape complementarity to the receptor or host. This concept laid the basis for molecular recognition, the discrimination by a host between a numbers of different guests.

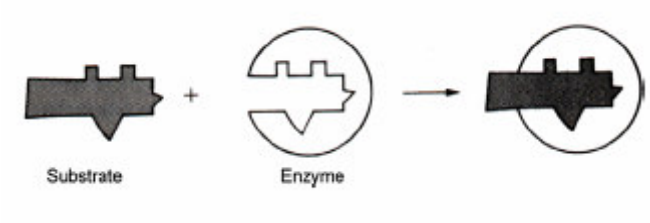
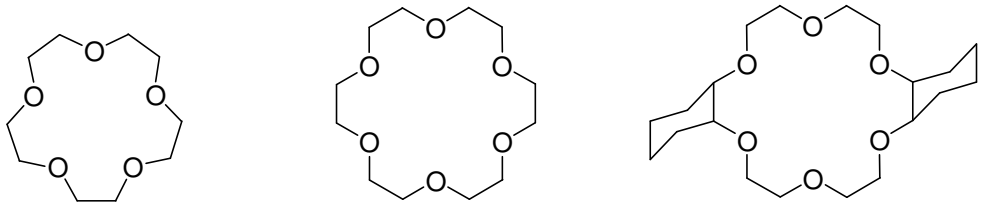


Figure 1.4. Fischer' "lock and key" hypothesis

3. The fact that selective binding must involve attraction or mutual affinity between host and guest. This is, in effect, a generalization of Alfred Werner's 1893 theory of coordination chemistry, in which metal ions are coordinated by a sphere of ligands. (Steed and Atwood, 2000)

The first host molecules are the crown ethers (**1.1**), they consist simply of a cyclic array of ether oxygen atoms linked by organic spacers and typically $–CH_2CH_2-$ units. The first applications of crown ethers as supramolecules was, as cation binding hosts and later on published in the literature as neutral guest binding hosts. Although hydrogen bonds between neutral molecules are generally weaker than charge/dipole attraction and polar hydrogen bonds, several recent reports indicate that networks of hydrogen bonds may be used to form neutral complexes that are stable in solution, (Bell & Liu, 1988).



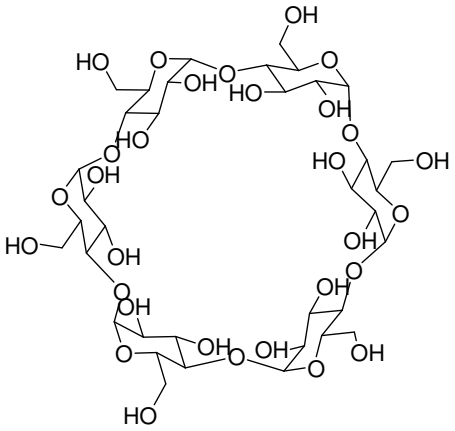
[15]crown-5 [18]crown-6 Dicyclohexyl[18]crown-6

1.1 **1.2** **1.3**

Figure 1.5. Some common crown ethers

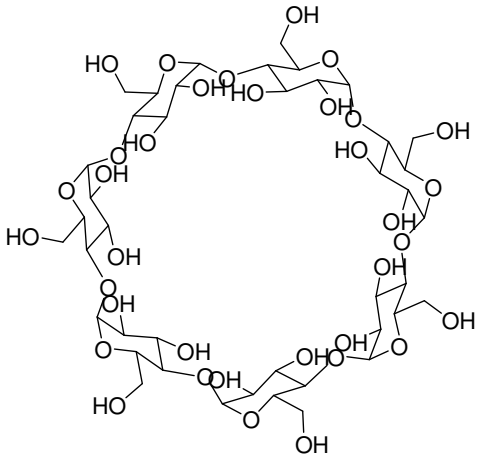
A second important group of host molecule known for a long time is cyclodextrins (**1.2**), they are among the most common, most studied and the cheapest commercially available host. Cylclodextrins are fully saturated and rely upon a combination of intramolecular hydrogen bonding and a sharp radius of curvature in order to introduce rigidity. They have enormously huge industrial uses in food, cosmetics and pharmaceutical sectors, generally as

slow-release and compound-delivery agents, as well with a significance importance as enzyme mimics.



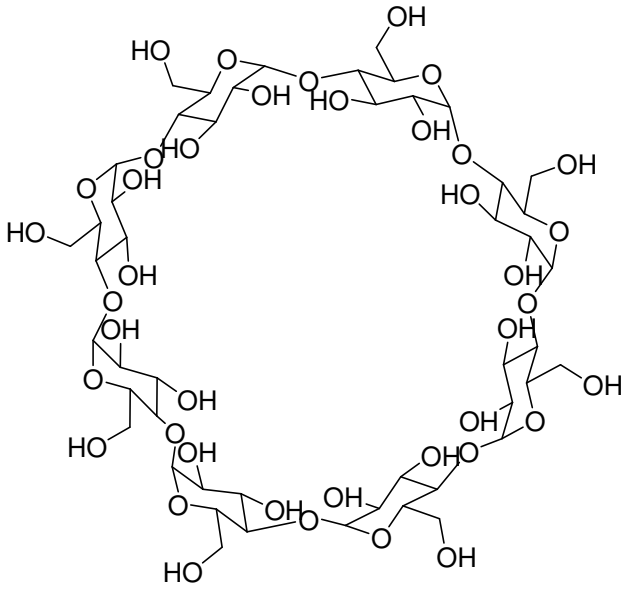
α-Cycylodextrin

1.4



β-Cyclodextrin

1.5



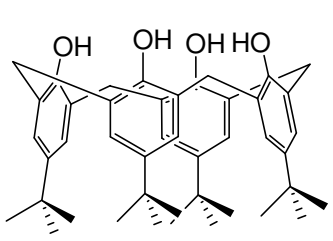
γ-Cyclodextrin

1.6

Figure 1.6. Cyclodextrin homologues

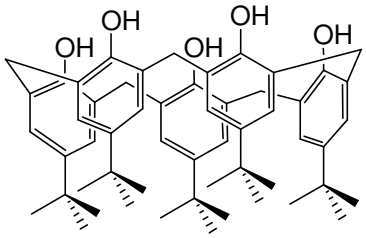
The calixarenes (**1.3**) are a popular and versatile class of macrocycle formed from the condensation of a *p*- substituted phenol (e.g. *p*-tert-butylphenol) with formaldehyde and due to the bridged aromatic units in their

structure, calixarenes are accepted as a part of cyclophane family. An in depth theory on calixarenes are given in the following chapters.



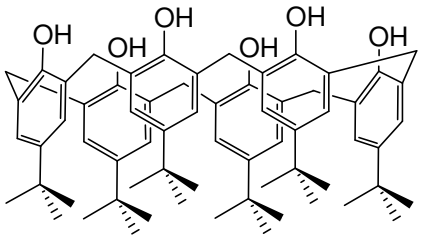
Calix[4]arene

1.7



Calix[5]arene

1.8



Calix[6]arene

1.9

Figure 1.7. Calixarene homologues

Lastly, again as a part of the study in this thesis, glycoluril-based host molecules; cucurbiturils (**1.4**) are explained again in the following chapters. Cucurbiturils are the most well-known type of glycoluril-based hosts and formed from the condensation reaction between glycoluril and formaldehyde.

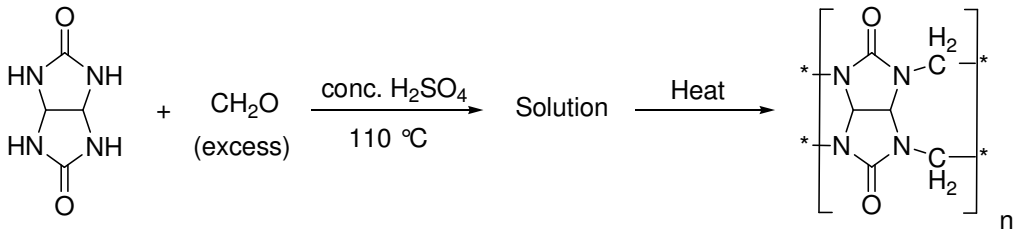


Figure 1.8. Synthesis of cucurbituril

1.4. Calixarenes

Because of the resemblance between the shapes of calixarenes, these cyclic tetramers and a type of Greek vase known as crater, Gustche suggested that they be called "calixarenes" (Greek, calix, chalice; arene, indicating the incorporation of aromatic rings), specifying the size of the macrocycle by a bracketed number inserted between calix and arene and specifying the nature and position of substitution in the aromatic rings by appropriate prefixes. It is obvious that, this nomenclature is far more easy when compared to Zinke's "mehrkernmethylenephenolverbindungen", or 1:8:15:22-tetrahydroxy-4:11:18:25-tetra-m-benzylenes by Conforth, or even [1_n]metacyclophanes by Cram and Steinberg .Thus, a cyclic tetramer derived from p-tert-butylphenolic and methylene units is most simply designated as a p-tert-butylcalix[4]arene. The name was first chosen to apply in particular for the phenol-derived cyclic oligomers, but it has subsequently taken on a more generic aspect and is now applied to a wide variety of structurally related types of compounds.

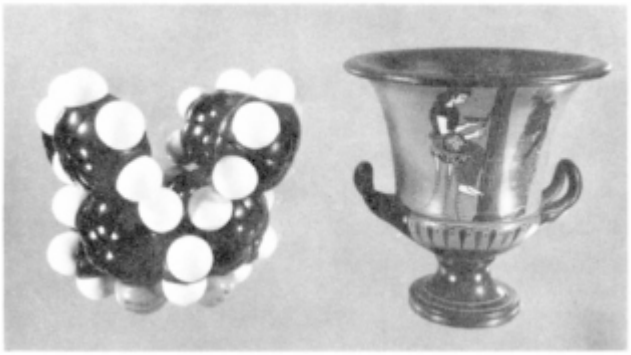
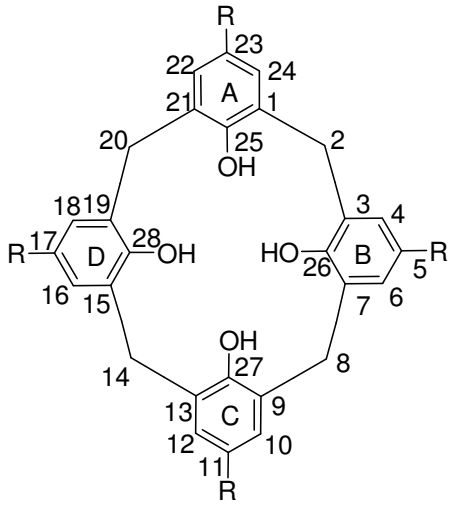


Figure 1.9. Resemblance of calixarenes to the Greek vase calyx crater

Calixarenes are divided into two major sub-groups: the *p*-alkylphenol derived cyclooligomers and the resorcinol derived cyclooligomers as shown in figure 1.10. (Timmerman, 1996). Zinke and Ziegler in 1941 were synthesized calixarenes by base induced condensation of a *p*-alkylphenol and

formaldehyde, later, Cornforth and co-workers investigated that more than one product can be formed.



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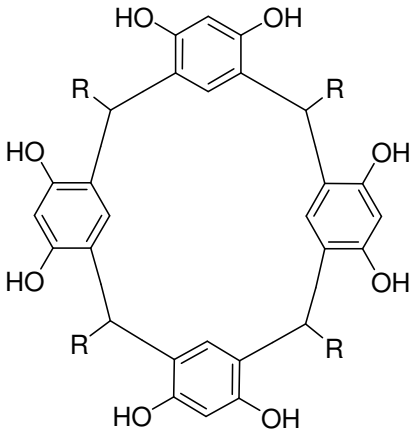


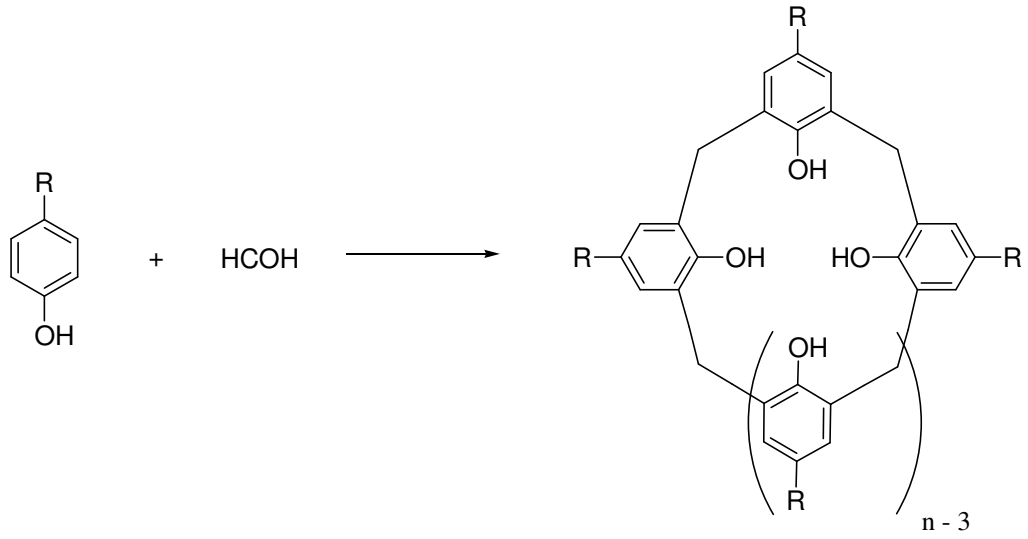
1.12

Figure 1.10. The *p*-alkylphenol-derived cyclooligomers (**1.11**), and the resorcinol derived cyclooligomers (**1.12**)

1.5. History of Calixarene Chemistry

In 1872 Adolph von Baeyer heated aqueous formaldehyde with phenol and observed a reaction that yielded a hard, resinous, noncrystalline product. However, the chemistry of the day was not sufficiently advanced to allow characterization of such materials, and the structure remained unprobed. Three decades later during the years 1905-1909, Leo Baekeland devised a process for using the phenol-formaldehyde reaction to make a tough, resilient resin (called a phenoplast), which he marketed under the name "Bakelite" with tremendous commercial success. As a result, much attention was directed both in industrial and academic research laboratories to a study of the chemistry of the phenol-formaldehyde process, and a significant literature arose dealing with phenoplasts. Among these investigations were ones carried out in the 1940s

and 1950s by Alois Zinke's group at the University of Graz in Austria. To simplify the reaction, they treated various p-alkylphenols with aqueous formaldehyde and sodium hydroxide, first at 50-55 °C for 45 h, then at 110-120 °C for 2 h and, finally, in a suspension of linseed oil at 200 °C for several hours. The products of this treatment are very high melting, insoluble materials to which Zinke assigned cyclic tetrameric structures, calling them "mehrkernmethylenephenolverbindungen". Zinke's products were actually mixtures, David C. Gutsche, the father of modern calixarene chemistry, and his co-workers in 1970s turned their attention to this group of compounds, as potential interesting prospects for enzyme mimic building. In the mid 1970s, they established the identity of three of the components of the mixture as cyclic tetramer, cyclic hexamer, and cyclic octamer and during 1980s simple and easily reproduced procedures for synthesizing *p*-tert-butylcalix[4]arene, *p*-tert-butylcalix[6]arene, *p*-tert-butylcalix[8]arene in good or excellent yield on any scale from a gram or less to many kilograms. In recent studies, Gutsche and co-workers reported that the reaction conditions are very important in the synthesis of calixarenes. Base, reactant ratio and reaction temperature affect the stnthesis of *p*-tert-butylcalix[4]arene in terms of yield. The amount of base is very important in determining the nature of the product. Lower amount of base produces cyclic tetramer, whereas higher concentrations give increasingly larger amounts of cyclic hexamer (Gutsche et al., 1986). Zinke and all subsequent workers with the calixarenes have noted their propensity to form molecular complexes with smaller molecules, a direct consequence of the presence of cavities in the calixarenes. The enzymes are known to possess cavitated active sites, where complex formation with substrate occurs as the first step in the catalytic process. Thus, the calixarenes are particularly attractive compounds for attempting to construct in vitro systems that mimic the in vivo catalytic activity of the enzymes.



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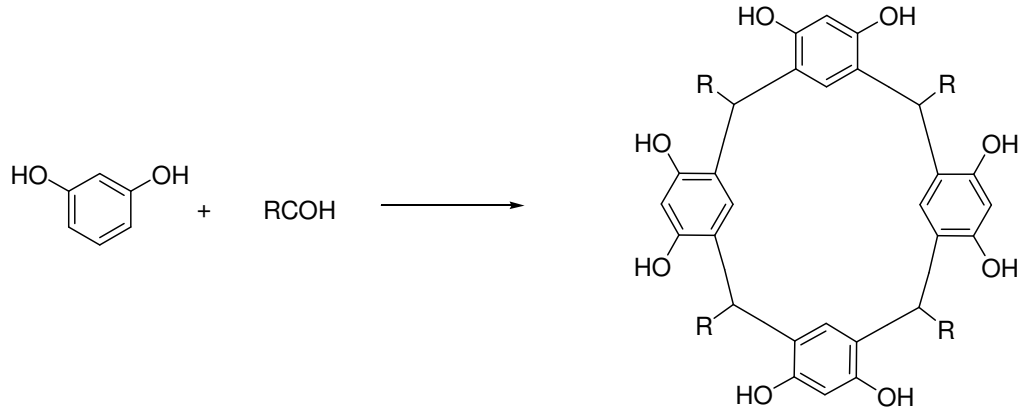


1.14

Figure 1.11. Phenol derived calixarenes (**1.13**), resorcinol derived calixarenes (**1.14**).

1.6. Conformations of Calixarenes

Calixarenes are highly flexible molecules, capable not only of minor flexingbut also possessing the ability to undergo complete ring conversions. The conformations of calix[4]arene were designated as "cone" (u,u,u,u), "partial cone" (u,u,u,d), "1-2-alternate" (u,u,d,d), and "1,3-alternate" (u,d,u,d), (Gutsche and Bauer, 1985), (Figure **1.12**). Metal cations such as Na^+, Ba^{2+}, Li^+, Cs^+ in base play a vital role as templates in the conformation distribution

(Iwamoto et al., 1990). Not only calix[4]arene has conformers, but also the other homologues have them, calix[5]arenes can have four true up/down conformers, calix[6]arenes have 8 and calix[8]arenes have sixteen conformations.

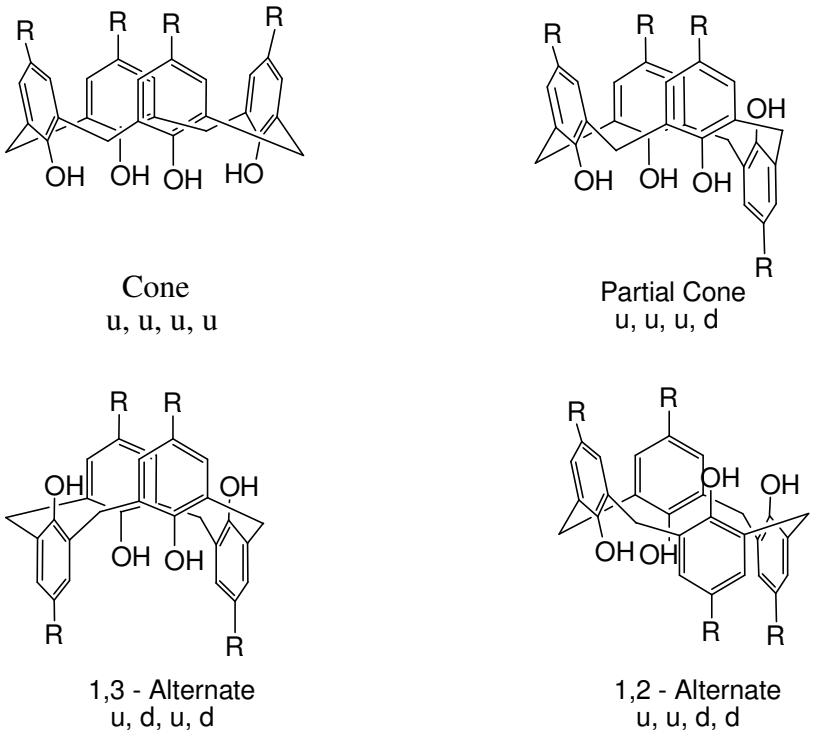


Figure 1.12. Conformations of calix[4]arene

Cone conformation is the lowest energy structure in calix[4]arene and calix[5]arenes, in number of calix[4]arenes having the cone conformation, two of the aryl groups are parallel and the other two are splayed outward to give pinched cone conformation. The double pinched conformers are the lowest energy structures in calix[6]arenes and calix[7]arenes (Gutsche, 1998).

Calix[4]arenes containing four *endo*-OH groups exist in the cone conformation in the solid state. The first X-ray structure of a calix[4]arene to show this was that of *p*-tert-butylcalix[4]arene and this observation has since been confirmed with a number of other calix[4]arenes (Gutsche, 1998). *p*-tert-

butylcalix[4]arene (as its 1:1 toluene complex) is a cone with almost perfect C_4 symmetry (u,u,u,u), this is mostly because of the hydrogen bonding interactions between –OH groups. The conformations of flexible calix[4]arenes largely depends on the ring size and the substituents on the lower rim.

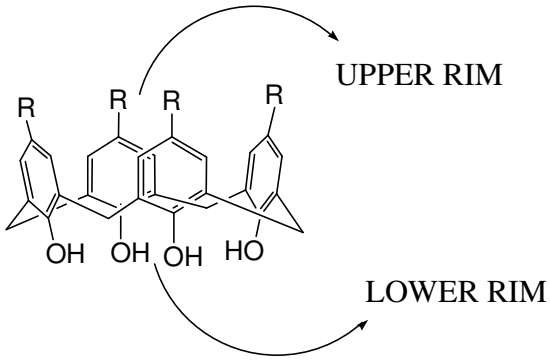


Figure 1.13. Upper and lower rim on calixarenes

Calix[4]arenes in which one or more of the hydrogens of the OH groups on the lower rim are replaced by other groups also frequently exists in the cone conformation in solid state. Any group larger than OH restrain this mobility, when any larger groups are attached to the lower rim of calix[4]arene which is modified at the upper rim providing the molecule in a fixed cone conformation (Casnati et al., 1993). The attachment of bulky substituents at the lower rim of the calixarenes prevents the interconversion among the four possible stereoisomers (cone, partial-cone, 1,2-alternate, 1,3-alternate) (Chang and Cho, 1986; Casnati et al., 1993; Iwamoto et. Al., 1990, Arduini et al., 1995, Groenen et al., 1991). Four ethoxyethyl groups at the lower rim prevent the inversion of the aromatic units, hence bringing the calix[4]arene skeleton in a rapid equilibrium between flattened (diverged) or pinched conformations (Molenveld et al., 2000). N-propyl and n-butyl groups are bulky enough to inhibit the oxygen-through-the-annulus rotation. Alkylation by propyl or any larger groups have showed conformations of cone and partial cone. Tetramethylation exists as a stable partial cone conformer, and tetraethylation mostly exists as a partial cone conformer (Iwamoto et al., 1991).

According to the investigations by Gutsche and Bauer (1985), the calix[4]arenes and calix[8]arenes showed almost same flexibility in nonpolar solvents, whereas, calix[6]arenes and calix[7]arenes are more flexible when compared and the size of the macrocyclic ring ,which as well, influences the nature of hydrogen intramolecular bonding determines the conformational flexibility of calixarenes. As the size of the ring increases throughout the homologues, the preferred conformation of calixarenes starts becoming increasingly planar.

1.7. Modifying the Calixarenes

The development of supramolecular chemistry has led to a growing research in the design, synthesis and functionalization of macrocyclic molecules containing intramolecular cavities. Considerable attention was devoted in the 1980s and 1990s to functionalizing the upper and lower rims of calixarenes, and the research is still continuing unabated. The utility of calixarenes for the majority of potential applications depends upon suitable modification of the parent compounds. Organic synthesis in its many guises remains essential for a large fraction of chemical research. Calixarenes have been used as building blocks for the synthesis as host molecules with different supramolecular functions since they are readily available, there has been much work on modification on both upper and lower rim in the literature, and can serve as both for small guests (lower rim), and for large guests (upper rim). Calix[4]arene homologue ,when compared with the other, is among the most studied one since, it can act as a host towards anions, cations and neutral molecules as well. While lower rim can be used for cation binding and transport, upper rim contains hydrophobic cavity complexing neutral substances. In the absence of structural modifications, calixarenes showed weak affinity toward alkali metal cations (Danil de Namor et al., 1998).

1.8. Modifying the Lower Rim of Calixarenes

The esters were the earliest of the lower rim modified calixarenes to be prepared. With acid halides and NaH, acid halides and $AlCl_3$, or acid anhydrides and H_2SO_4 the acylation or aroylation generally involves all of the OH groups if the derivitizing agent is used in excess. Esterification studies carried out in the 1990s have focused primarily on partial substitution because of the potential utility of the products for selective upper rim functionalization. By using acid halides, in the presence of bases weaker than NaH, by using limiting amounts esterifying reagent, and/or by using bulky esterifying reagents it is often possible to obtain partially substituted calixarenes in quite selective fashion.

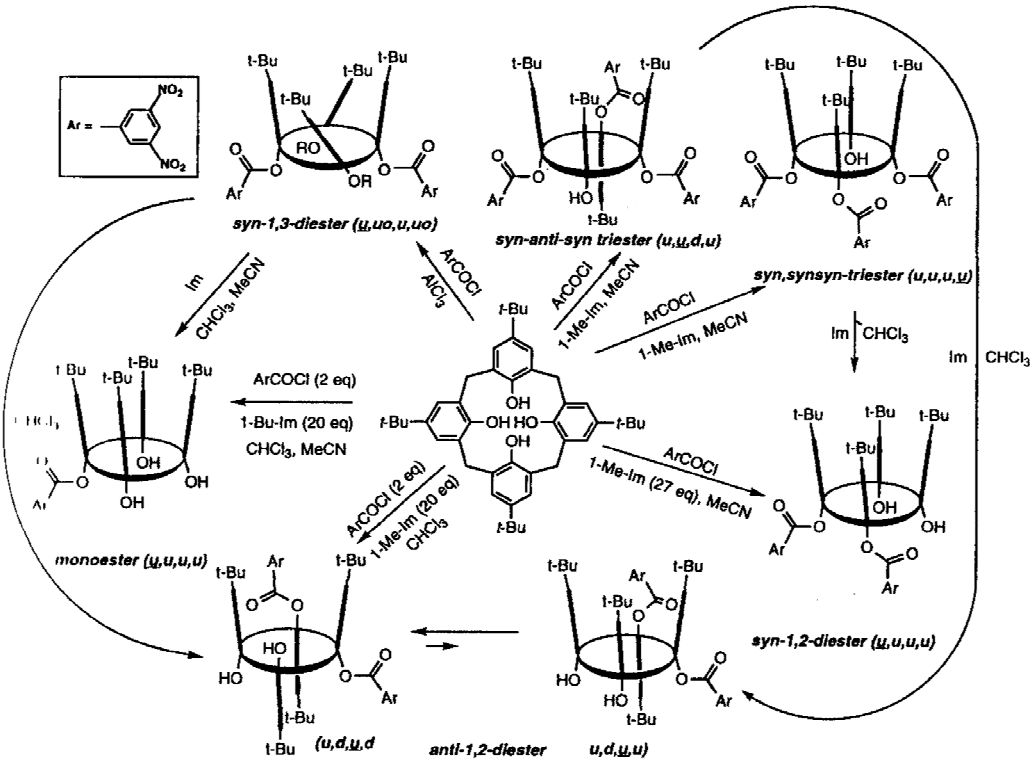


Figure 1.14. Esterification of p-tert-butylcalix[4]arene with 3,5-dinitrobenzoyl chloride.

The reactions of calix[4]arenes with acyl or aroyl halides in the presence of $AlCl_3$ yields either tetraester or the A,C-diester, the difference being attributable either to the *p*-substituent and/or the solvent (CH_2Cl_2 in the first case; CH_2Cl_2/DMF in the second case) (Gutsche et. al., 1986). In the calix[5]arenes, the only reported partial ester is tetrapivaloate prepared from *p*-tert-butylcalix[5]arene and pivaloyl chloride/NaH. In calix[6]arenes A,B,D,E-tetraesters can be obtained in good yield with aroyl chlorides and 1-methyimidazole or NaH (Gutsche et. al., 1992). A number of other types of calixarene esters are known, including the aryl sulfonates, phosphates (often used as intermediates in the replacement of the OH groups with H), and with phosphonates (Floriani et. al., 1989).

Alkylation has been studied in considerable detail in calix[4]arene series, and methods have been devised for preparing the mono-, A,B-di-, A,C-di-, -tri- and tetraethers. Monoethers can be prepared in moderate to good yields by direct alkylation using:

i. An alkylating agent with NaH as the base in toluene solution
ii. $Ba(OH)_2$ as the base in DMF solution (Iwamoto et. al., 1991)
iii. 1.2 equiv of a weak base (i.e. K_2CO_3, in MeCN or CsF in DMF) and an excess of alkylating agent RX, where R includes, methyl, ethyl, allyl, or ethoxycarbonylmethyl (Groenen, et. al., 1991).

An alternative to direct alkylation for generating partially alkylated calixarenes involves selective dealkylation of the readily available A,C-diethers or tetraethers by means of stoichiometric amounts of Me_3SiI.

Distal dialkylation leading to A,C-diethers is generally much more easily achieved than proximal dialkylation leading to A,B-diethers. Under conditions similar to those leading to monoethers, but with an excess of alkylating agent, A,C-diethers are produced, often in very high yields (Dijkstra et. al, 1989). Proximal dialkylation leading to A,B-diethers can be carried out by direct alkylation or by selective dealkylation. In the former case, a strong

base is used with a limiting amount of alkylating agent and for the latter case, treatment of tetramethyether with $TiBr_4$ in $CHCl_3$ gives the A,B-dimethyl ether in good yield. Trimethylation of *p*-tert-butylcalix[4]arene can be accomplished in fair yield with Me_2SO_4 in DMF in the presence of $BaO.Ba(OH)_2$. Higher yields of triether can be obtained when the starting material is already partially alkylated. In general, tetraalkylation of calix[4]arenes is carried out with a excess of the alkylating agent in the presence of the strong base NaH, and in some cases, a much weaker base K_2CO_3 or CsF suffices (Groenen et al., 1991; Sanyoto et al., 2000). Tetraalkylation of calix[4]arenes has at least two different dialkylated intermediates, depending on the reaction conditions (Groenen et al., 1991). Tetraesters can also be prepared by alkylation using alkylating agent with K_2CO_3 as a base in acetone or again K_2CO_3 again as a base in acetonitrile (Abidi et al., 2001). A wide variety of alkyl and aralkyl groups have been introduced in this fashion, ranging in size from Me to naphtylmethyl.

Alkylating agents of the structure XCH_2Y (X is the leaving group, generally Br or tosyl; Y is a functional group) have frequently been used for introducing functionality onto the lower rim of the calixarenes.

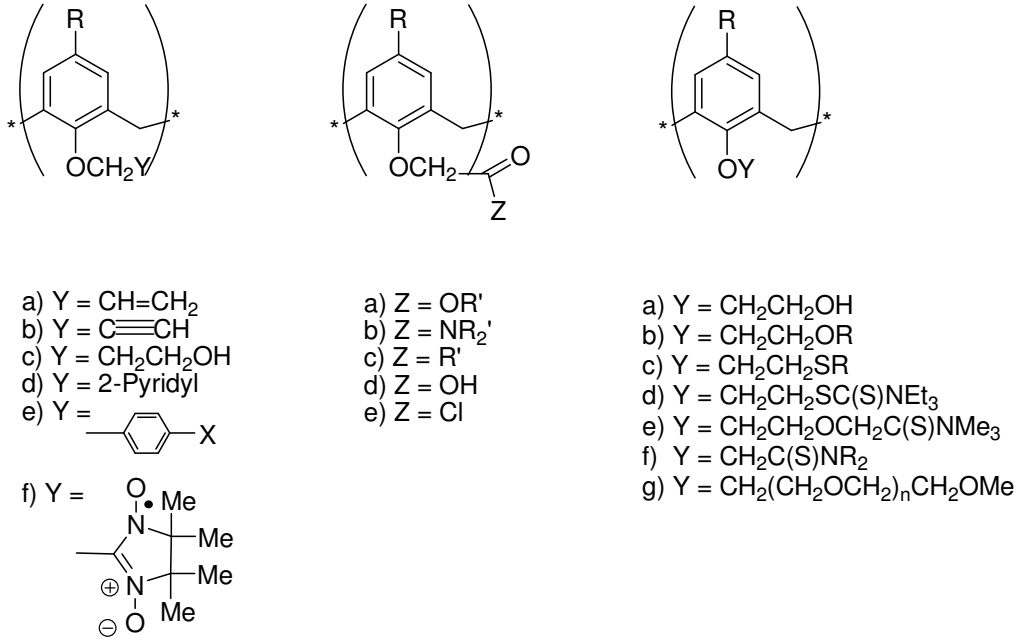


Figure 1.15. With functionalized alkylating agents

1.9. Modifying the Upper Rim of Calixarenes

Functionalization of the upper rim is more appropriate when we take into account of the fact of preorganisation and the steric requirements of the substrates. The selective Functionalization of upper rim of calixarenes is also very well investigated. Functionalization of upper rim of calixarenes has a great importance for further functionalizations, with de-tert butylation of *p*-positions of the calixarenes, a wide variety of *p*-functionalization procedures have been explored. De-tert butylation of *p*-tert-butylcalix[n]arenes are obtained from a reverse Friedel-Crafts reaction, which is obtained by a Lewis base; $AlCl_3$; catalyzed transfer of tert-butyl group to toluene, which is as well the solvent of the reaction, and small amounts of phenol are also added to reaction mixture to increase the rate of reaction, possibly because phenol is a good acceptor molecule but also because, for steric reasons, it may be more

efficient than the calixarene in generating the H^+ necessary to initiate the reaction.

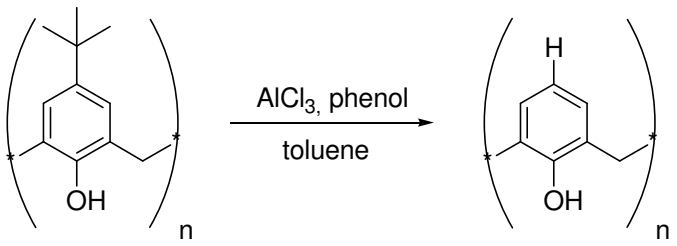


Figure 1.16. De-tert-butylation of calix[n]arenes

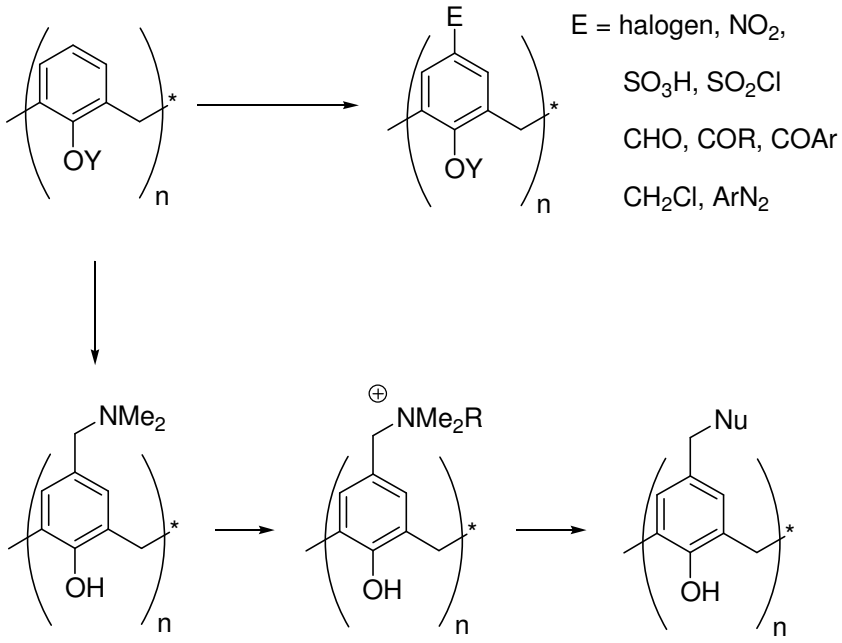
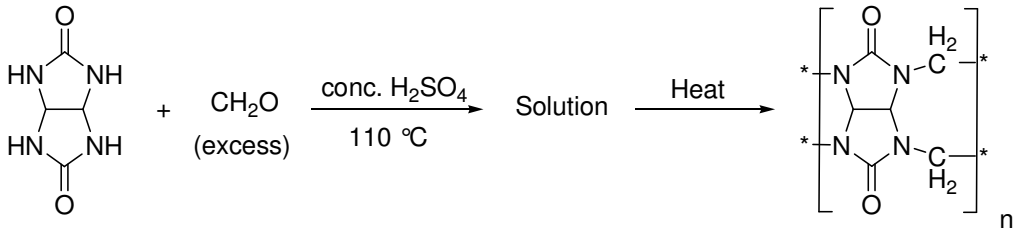


Figure 1.17. Upper rim Functionalization of calixarenes

By using the lower and upper rim functionalization of calixarenes, the supramolecular chemistry of these very special types of molecules starts.

1.10. Cucurbiturils

Cucurbituril, CB[6], is a hexameric macrocyclic compound self-assembled from an acid catalyzed condensation reaction of glycoluril and formaldehyde. Although, first synthesis of cucurbit[6]uril first appeared in the literature in 1905, but the structure or the chemical nature was not known until 1981. It was Mock and co-workers, who first reported the full characterization of the molecule.



1.15 **1.16**

Figure 1.18. Acid catalyzed condensation of cucurbiturils from glycoluril and formaldehyde

Cucurbit[6]uril was the first homologue of the cucurbituril family. It has a cavity diameter of ~ 5.5 Å, and it is accessible from the exterior by symmetrical two carbonyl laced portals having the diameter of ~4 Å. Cucurbit[6]uril resembles α-cyclodextrin in means of cavity size, but the highly symmetrical structure and its identical carbonyl portals distinguishes it from α-CD. One more resembles of cucurbiturils with cyclodextrins is in term of their hydrophobic cavity which provides a potential site for inclusion of hydrocarbon molecules, but unlike cyclodextrins cucurbiturils can form stable inclusion complexes with various protonated aryl and alkyamines, again because of the carbonyl portals (Kim et. al., 2003).

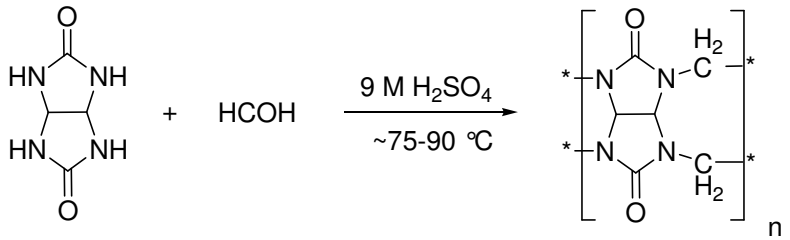
The rigid structure of cucurbiturils and their capability of forming stable complexes with molecules and ions make cucurbiturils attractive

building blocks for the construction of supramolecular architectures. So far, cucurbit[6]uril were used in variety of supramolecular systems, such as host molecules, rotaxanes, rotaxane dendrimers, polyrotaxanes, molecular necklaces, rotaxane based molecular switches, as gene carriers, as catalysts for certain cycloaddition reactions, charge transfer complexes.

Cucurbiturils are in fact as useful as cyclodextrins, crown ethers or calixarenes in many applications, but they suffer from several shortcomings and that may explain why their chemistry developed so slowly. The limitations of chemistry of cucurbiturils are as follows.

i. Solubility at common solvents except for strong acidic or concentrated alkaline metal solution is extremely low,
ii. Homologues, bearing greater of fever glycoluril units than CB[6] were not available,
iii. There were no methods to introduce any functional groups to the molecules was known up to 1990s and still introduction of functional groups is difficult and limited (Kim et. al., 2003).

The poor solubility of cucurbiturils in common solvents poses serious problems in expanding its applications. In fact, the other two limitations can be overcome by synthesizing the other homologues or mainly by functionalization. But not until 2003 the synthesis of first functionalized cucurbit[6]uril was reported (Kim et. al, 2003). Before, the only exception was decamethylcucurbit[5]uril as the only cyclization product from dimethylglycoluril (Stoddart et al., 1992). The first breakthrough in cucurbituril chemistry was the synthesis of new cucurbituril homologues bearing 5, 7 and 8 glycoluril units, the synthetic protocol of CB homologues is similar to the conventional CB[6] synthesis, reaction of glycoluril with formaldehyde in 9 M sulfuric acid at ~75-90 °C for 24 h yields a mixture of cucurbituril family (Kim et al., 2000).



1.15 CB[n]: n = 5 - 11

Figure 1.19. Synthesis of cucurbituril homologues

The key is to lower the reaction temperature than that employed in the conventional CB[6] synthesis (>110 °C). NMR and ESI mass studies confirmed that the reaction mixture contains a family of CB homologues, mostly from pentamer to octamer with typically contents being ~10-15% CB[5], ~50-60% CB[6], ~20-25% CB[7], 10-15% CB[8]. Trace amounts of higher homologues (CB[n], n = 9-11) were also detected by mass spectrometry. The separation of CB homologues in pure form was done by fractional crystallization and dissolution. On standing the reaction mixture first yields crystals of CB[8]. CB[6] was then separated by fractional dissolution of other cucurbituril homologues with acetone/water. From the soluble portion, CB[5] and CB[7] homologues were isolated and separated by fractional crystallization (Kim et al., 2000). All the cucurbituril homologues, CB[5], CB[7] and CB[8] have been fully characterized by various spectroscopic techniques and X-Ray crystallography.

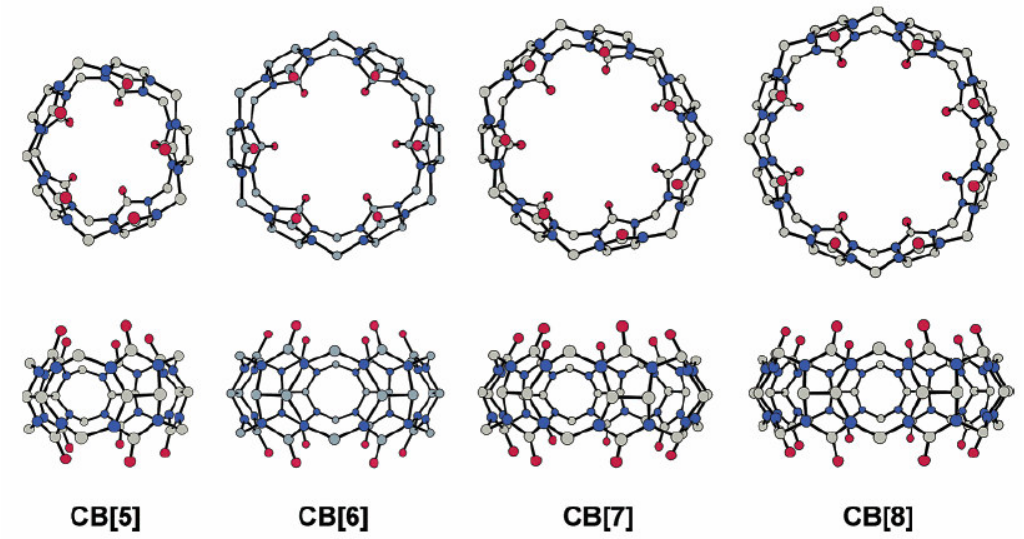
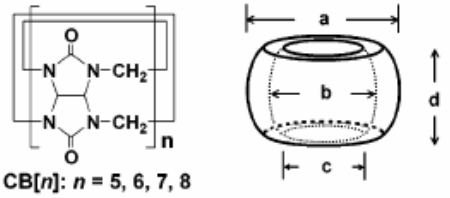


Figure 1.20. X-ray crystal structures of CB[n] (n = 5-8). Color codes: carbon, gray; nitrogen, blue; oxygen, red.

On going from CB[5] to CB[8], the mean diameter of internal cavity increases progressively from ~4.4 to 8.8 Å, and the mean diameter of the portals increases from ~ 2.4 to 6.9 Å.



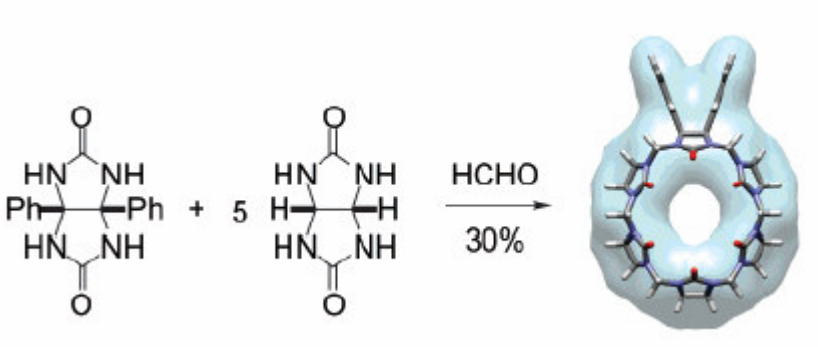
		CB[5]	CB[6]	CB[7]	CB[8]
outer diameter (Å)	a	13.1	14.4	16.0	17.5
cavity (Å)	b	4.4	5.8	7.3	8.8
	c	2.4	3.9	5.4	6.9
height (Å)	d	9.1	9.1	9.1	9.1
cavity volume (Å^3)	-	82	164	279	479

Figure 1.21. Cavity and portal diameter of cucurbituril

In terms of cavity size, CB[6], CB[7] and CB[8] are analogous to α-, β-, γ-cyclodextrins respectively. Solubility of cucurbituril homologues in common solvents is also low (< 10^{-5} M), except that CB[5] and CB[7] have a moderate solubility in water (2-3 x 10^{-2} M), which is comparable to that of β-cyclodextrin (1.6 x 10^{-2} M). All cucurbituril homologues are soluble in acidic water as well as in strong alkali metal ion solutions. All the homologues have high thermal stability, no decomposition is observed up to 420 °C for the homologues bearing 5, 6 and 8 glycoluril units, CB[7] starts decomposing a lower temperature (370 °C).

1.11. Cucurbituril Derivatives in the Literature

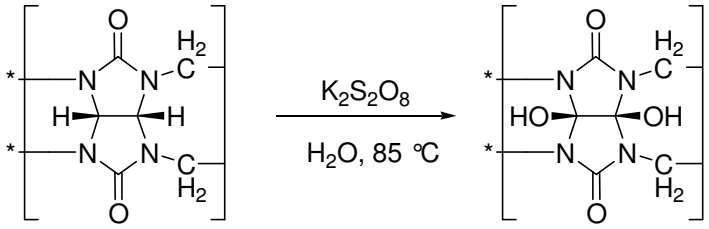
The first cucurbituril derivativereported in the literature was the decamethylcucurbit[5]uril (Me_{10}CB[5]). The isolation and first characterization of this compound was first reported by Stoddart et al, in 1992. X-ray crystal structure of Me_{10}CB[5] is nearly identical to that of CB[5], with a cavity diameter 4 Å and portals of diameter ~2.5 Å. Me_{10}CB[5] binds most of the metal ions in 1:1 formic acid/water mixture. Interestingly, Me_{10}CB[5] shows exceptionally high affinity for Pb^{2+} ion (log K > 9), which may be due to the size match between Pb^{2+} and Me_{10}CB[5] portals (Bradshaw, Izatt and co-workers, 2000). Me_{10}CB[5] also encapsulates small guest molecules such as N_2, O_2, methanol or acetonitrile and these molecules are trapped by the ammonium ions at the portals (Dearden et. al., 2001). The synthesis of first unsymmetrical and disubstituted cucurbituril was reported by Nakamura et al., in 2002. Synthesis of diphenyl cucurbit[6]uril was performed by co-oligomerization of stoichiometric amounts of diphenyldiphenyl glycoluril and unsubstituted glycoluril and later again in this article they reported the further conversion of Ph_2CB[6] to a rotaxane incorporating bis(dinitorophenyl)spermine (Nakamura et. al., 2002).



1.16

Figure 1.22. Synthesis of diphenyl cucurbit[6]uril

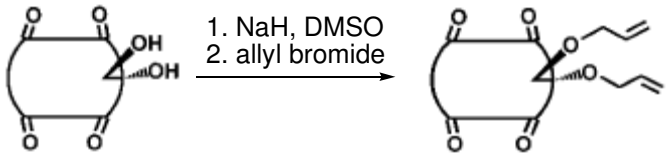
Reaction of CB[6] with $K_2S_2O_8$ in water at 85 °C for 6h allowed by crystallization produces perhydroxycucurbit[6]uril. The X-ray crystallography showed that the hydroxyl groups are at the periphery of the CB[6]. The portal and cavity sizes of $(OH)_{12}$CB[6] are essentially same as CB[6] with a mean cavity and portal diameters of 5.5 and 3.9 Å, respectively. In a similar fashion, $(OH)_{2n}$CB[n] (n = 5, 7 and 8) are also produced from the corresponding CB homologues. The mechanism is believed to follow a radicalic path. The new cucurbituril derivative is soluble in DMSO and moderately soluble in DMF.



1.15 **1.17**

Figure 1.23. Synthesis of perhydroxycucurbit[6]uril

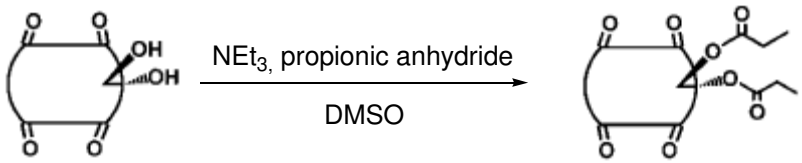
Most importantly, $(OH)_{12}$CB[6] allows further functionalization by conventional methods. Alkyl ethers from $(OH)_{12}$CB[6] can be prepared by treatment with NaH in DMSO followed by reaction with alkyl bromides.



1.17 **1.18**

Figure 1.24. Alkyl ether functionalization from $(OH)_{12}$CB[6]

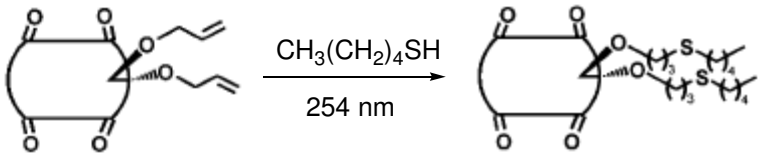
Similarly, esters of $(OH)_{12}$CB[6] can be prepared in moderate yields by reaction with acid anhydrides in the presence of triethylamine. In most cases, the products are isolated by addition of water followed by washing with ether or hexane to remove unreacted alkyl bromides of anhydrides.



1.17 **1.19**

Figure 1.25. Synthesis of esters of $(OH)_{12}$CB[6].

Further functionalization of **1.18** by photoinitiated reaction with alkyl thiol producesthioether-substituted CB[6].



1.18 **1.20**

Figure 1.26. Synthesis of thioether substituted CB[6].

A long-standing problem in cucurbituril chemistry was answered by, these procedures through the first direct functionalization of CB[n] leading to perhydroxy CB[n] which can be further modified to provide tailored CB[n] derivatives with desired functional groups and desired solubility in common solvents (Kim et. al., in 2003).

1.12 Host Guest Chemistry of Cucurbituril

CB homologues share the characteristic features of CB[6], hydrophobic cavity, and polar carbonyl groups surrounding the portals. But, since they have remarkable different portal and cavity sizes, the recognition properties differs as well. CB[6] forms very stable complexes with protonated diaminoalkanes, and moderately stable complexes with protonated aromatic amines. CB[6] can also encapsulate neutral molecules like tetrahydrofuran and benzene in aqueous solution.

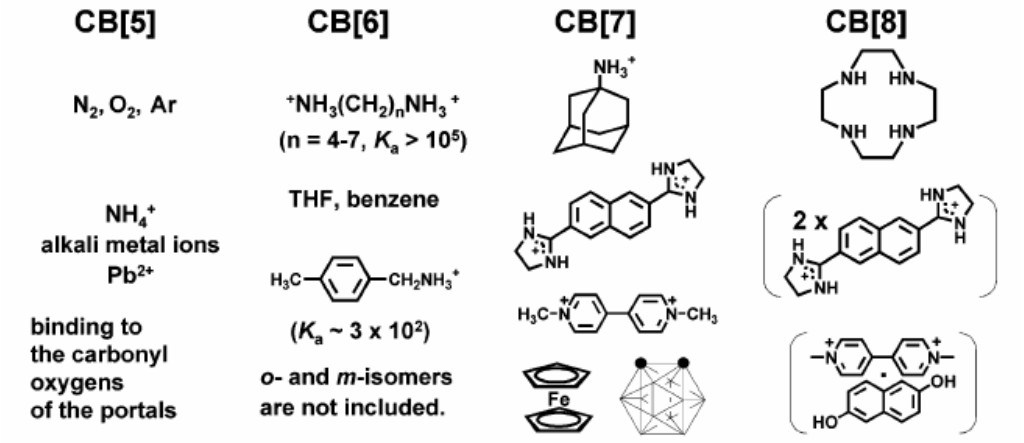


Figure 1.27. Cucurbiturils as host molecules

CB[5] being the smallest homologue can encapsulate small molecules like such as N_2, O_2 in its cavity and can bind to NH_4^+ and Pb^{2+} strongly through its portals forming 1:2 complexes.

CB[7] can form 1:1 complexes with 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene (**BDIN**), protonated adamantylamine, and *N-N'*-dimethyl-4,4'-bipyridinium ($\mathbf{MV^{2+}}$). Neutral molecules like ferrocene and carborane can also be encapsulated with CB[7]. CB[8] being the largest homologue of the series can form 1:2 complex with **BDIN** with its large cavity. It can also bind to two different molecules at the same time, forming 1:1:1 complex with *N-N'*-dimethyl-4,4'-bipyridinium ($\mathbf{MV^{2+}}$) and 2,6-dihydroxynaphthalene (**HN**)(Kim et. al., 2002, Ong et. al., 2002).

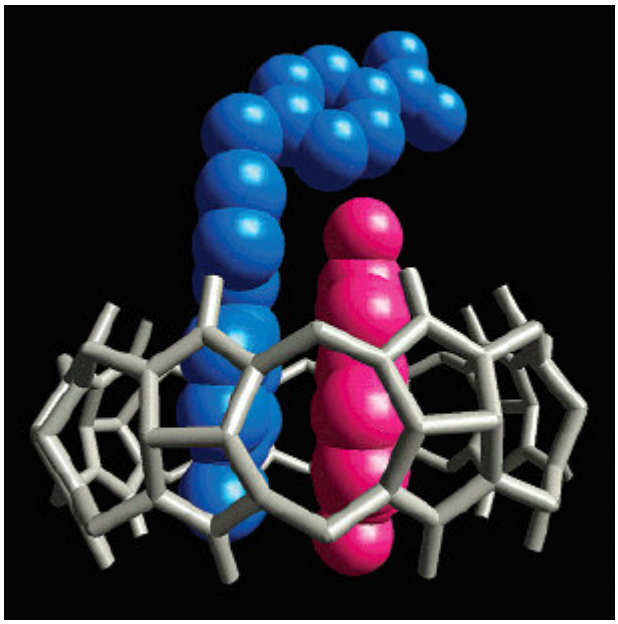


Figure 1.28. 1:1:1 complex formed from CB[8], $\mathbf{MV^{2+}}$and **HN**

By encapsulating these two molecules, CB[8] takes these two molecules into close contact resulting an efficient charge transfer of about 120 nm red shift in the spectrum, whereas without CB[8] the interaction is very weak (Kim et. al., 2002). One other interesting example of CB[8] chemistry is a macrocycle within a macrocycle, or in other words, encapsulating a macrocycle guest into a macrocycle host.

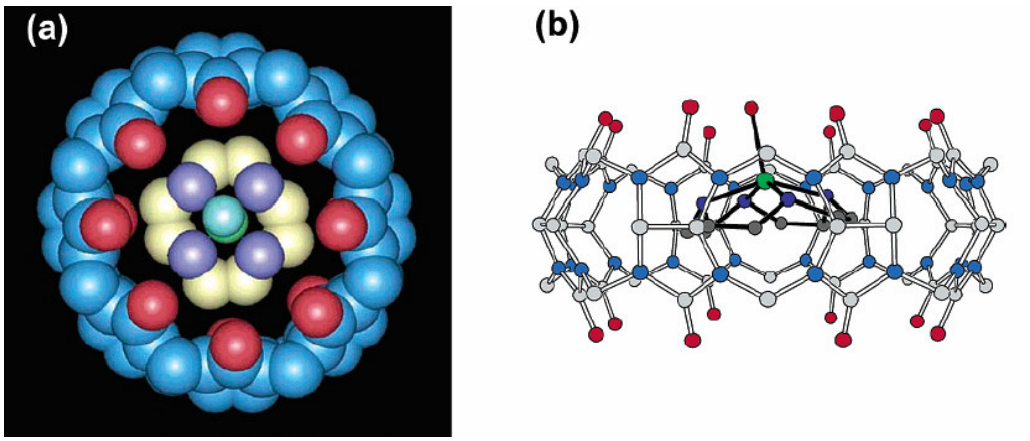


Figure 1.29. X-Ray crystal structure of [Cu(cyclen)H_2O] encapsulated in CB[8], a) space filling model, b) ball and stick model. Color code: copper, green; oxygen, red; nitrogen, blue; carbon, gray.

One other interesting macrocycle within a macrocycle, has been repoted by Day and co-workers which is CB[5] is located inside the CB[10]. Free motion of CB[5] within CB[10], reminiscent of a gyroscope, suggested the name gyroscane.

The cavity of CB[n] can be used as a reaction chamber to mediate chemical reactions. A highly stereoselective [2 + 2] photoreaction of *trans*-diaminostilbene dihydrochloride (DAS) in the cavity of CB[8] solution. UV irradiation of an aqueous solution containing CB[8] and *trans*-DAS in a 1:2 ratio followed by a base treatment affords α,α,β,β-tetrakis-(4-aminophenyl)cyclobutane almost exclusively with a small amount of αβαβ isomer. One other important thing is that, in the absence of CB[8] in the solution, upon irradiation the *trans*-DAS isomerizes back to the *cis*- isomer (Kim et. al., 2001).

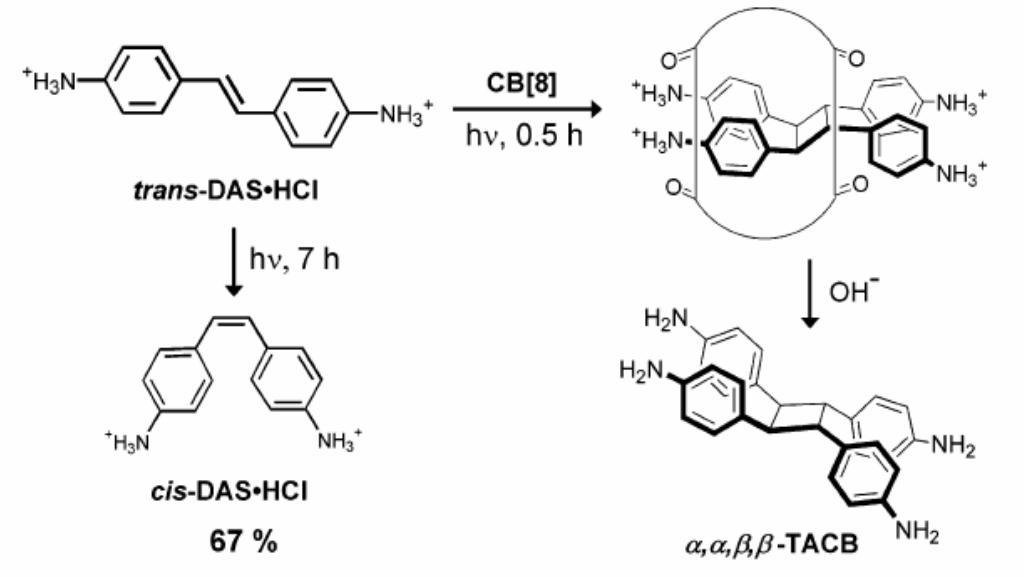


Figure 1.30. CB[8] mediated cycloaddition of *trans*-DAS

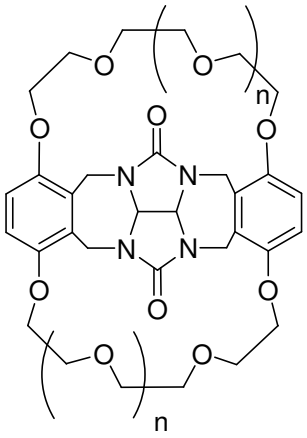
Although these very special molecules were discovered about a century ago, the cucurbituril chemistry has revived in past 20 years and the research is still undergoing with an increasing speed, the homologues bearing 5, 7 and 8 glycoluril units has been synthesized, isolated and fully characterized, and the first functionalization was performed just few years ago, which means the real potential of cucurbituril chemistry is only beginning to be defined.

1.13. Supramolecular Chemistry of Glycoluril

Starting from 1980s a new class of synthetic receptors called as molecular tweezers are became known. Their ability is to bind aromatic guests sandwiching between its more or less parallel aromatic surfaces. Since then, there has been a rapid development on these kinds of molecular hosts in the literature and vast magnitude of host molecules with different kind of molecular recognition patterns has been synthesized.

Host molecules derived from glycoluril were shown to be excellent receptors for neutral aromatic guests, particularly phenols, and dihydroxybenzenes (Nolte et. al., 1991) with their very well organized clefts. The binding strength of these types of guests (K = 0-10^5 M^{-1}) can even be strengthened with simple modifications either on guest of the host molecule. The binding is a result of hydrogen bonding and π-π stacking. Upon binging a suitable guest, simultaneously carbonyl group π-orbitals forms two hydrogen bonds. The strength of the hydrogen bonding can be modified by altering the type of donor or acceptor group, or changing the acidity of OH groups on guest has dramatic effect on binding.

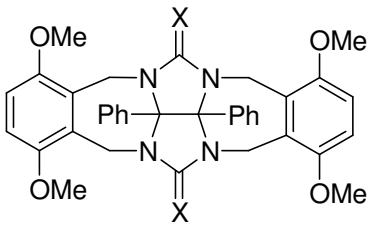
To extend the binding interactions in glycoluril based hosts, they can be further functionalized with crown ether moieties. The resulting compounds are known as molecular baskets due to their bow like shape (Nolte et. al., 1995).



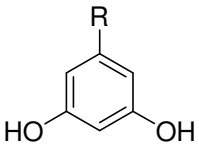
1.22

Figure 1.31. Crown ether modified glycoluril host, "molecular basket".

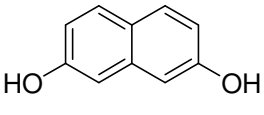
1.22 hosts are excellent binders of alkali metal ions (having n=2, and K^+, K = 4.2 x 10^8 M^{-1}), and organic diammonium salts of type $^+H_3N(CH_2)_nNH_3^+$ (having n=2, and guest having n=6, K = 6.1 x 10^9 M^{-1}) (Nolte et. al., 1990)



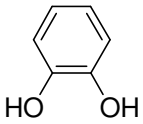
1.21a X=O, Y=O
1.21b X=S, Y=O
1.21c X=S, Y=S



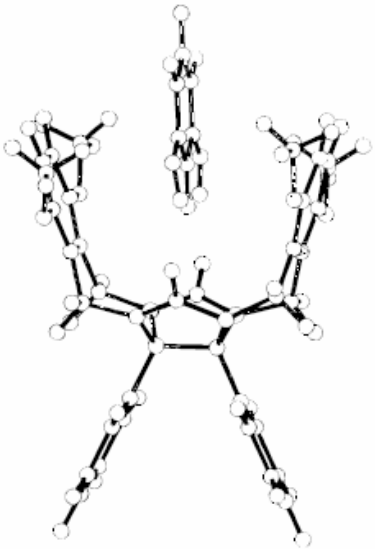
G1 R=CH_3
G2 R=H
G3 R=OCH_3
G4 R=$C(O)OCH_3$
G5 R=Cl
G6 R=CN



G7



G8

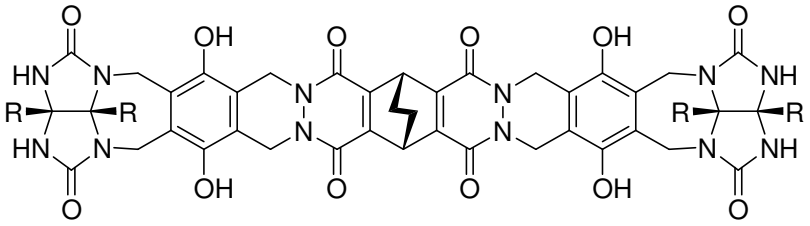


	Host		
Guest	**1.21a**	**1.21b**	**1.21c**
G1	1900	450	56
G2	2600	750	51
G3	4400	1300	82
G4	16500	2500	177
G5	16000	3500	225
G6	1×10^5	-	772
G7	7100	-	-
G8	60	-	-

Figure 1.32. Association constants (M^{-1}) of Glycoluril based host with different guests

It is also reported in the literature that basket based hosts can also be further functionalized with aza-crown and naphthalene side walls (Nolte et. al., 1992).

One other interesting topic under glycoluril based host molecules is chiral softballs, which is introduced in the literature by Rebek and his co-workers. Enantioselection has always been a motive of molecular recognition, and so far in the literature it is seen that so many different groups of host molecules has been studied, cyclodextrins, crown-ethers, cryptophanes, cyclophanes, carcerands and even some structures that are not macrocyclic. The use of weak intermolecular forces instead of covalent bonds for assembly of the receptor imparts reversibly to the guest exchange process, a process that is called encapsulation (Whitesides et. al., 1991). The first examples of chiral capsules formed through self-assembly were used to study the dynamics of assembly and guest exchange in the "tennis ball".



R = 4-n-heptylphenyl

1.23

Figure 1.33. Rebek's glycoluril building block which dimerizes to for am tennis ball shaped self assembly.

The "tennis ball" assembles through self-complementary hydrogen bonding between the subunits and it exists as highly symmetrical, pseudo spherical dimmer in noncompetitive organic solvents (Rebek et. al., 1996).

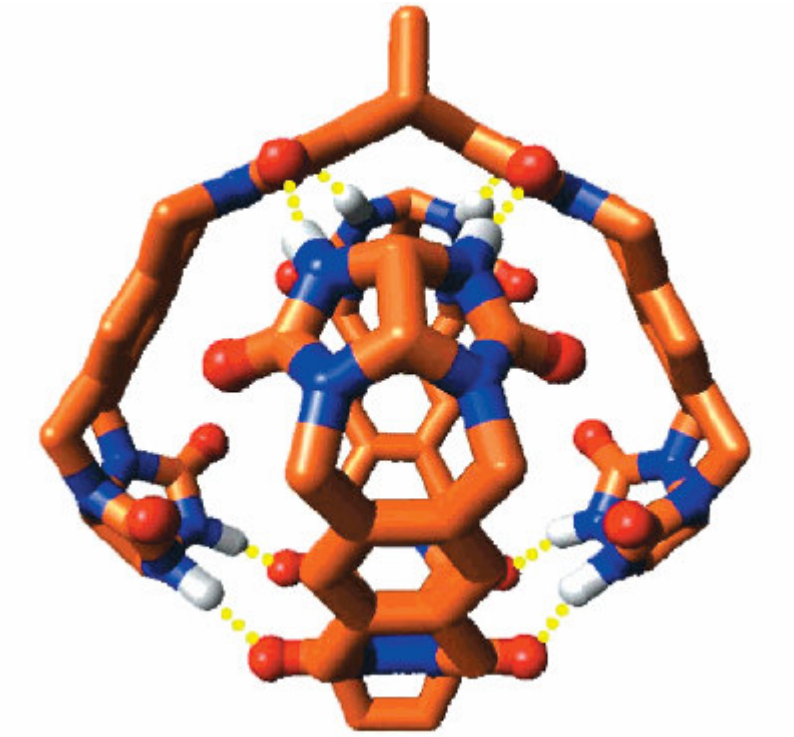


Figure 1.34. Molecular model of dimmer; color codes: red, oxygen; blue, nitrogen; orange, carbon.

The supramolecular chemistry of the glycoluril based molecules is versatile and rich. Further modifications on these groups of molecules have been demonstrated. So far, host-guest chemistry, enzymatic catalysis, substrate selectivity and allosteric binding have been shown.

CHAPTER 2

EXPERIMENTAL

2.1. Instrumentation

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded on, METU Chemistry Department NMR Laboratory with a 400 MHz Brucker Instruments Avance Series-Spectrospin DPX-400 Ultra Shield High Performance Digital FT-NMR spectrometer. During the interpretation of spectra, all chemical shifts are referenced to TMS (tetramethylsilane) solvent and the splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

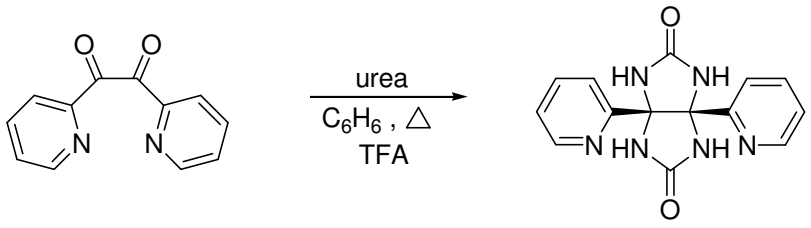
Chemicals and solvents used during the experiments were supplied from Aldrich and used without further purification. Reactions were monitored by using Merck Silica Gel 60 Kieselgel F_{254} Aluminum Sheets 20x20 cm TLC (Thin Layer Chromatography) plates. During the purification, where column chromatography were performed, Merck Silica Gel 60 having particle size of 0.040-0.063 mm, 230-400 mesh ASTM were used.

Mass spectrometry was performed at Colorado State University Macromolecular Resources Facility and University of Alberta Mass Spectrometry Laboratory, Canada.

2.2. Synthesis of Di(2-pyridyl)glycoluril (2.2)

To a suspension of 2,2'-Pyridil (3.18 g, 15 mmol), urea (1.8 g, 30 mmol) in benzene (50 mL) was added TFA (3 mL, 39 mmol). The resulting dark brown sticky mixture was refluxed under Dean Stark apparatus overnight. Onto the reaction mixture, 30 mL of EtOH was added the solid was collected by suction filtration and further washed with 50 mL of EtOH. After washing di(2-pyridyl)glycoluril (**2.2**) was obtained as a brown powder. Yield 1.69 g (38%).

^{1}H NMR (400 MHz, DMSO-d_6), δ 2.5 (s, 4H, -NH), 7.08 – 7.02 (m, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.49 – 7.44 (m, 2H), 8.32 (d, J = 4.6 Hz, 2H).



2.1 **2.2**

Scheme 2.1. Syenthesis of Di(2-pyridyl)glycoluril (**2.2**).

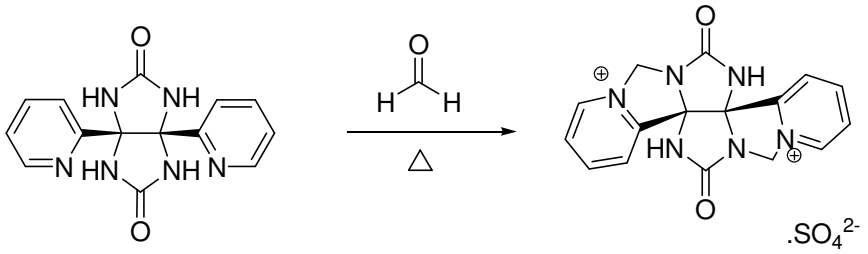
2.3. Synthesis of Cyclization product (2.3)

To a heterogeneous solution of "Glycoluryl" (1.4 g, 4.7 mmol), 37% formaldehyde (1.4 mL) in 7.1 mL water, 0.7 mL concentrated sulfuric acid was added. The mixture was heated to 120 °C (during heating homogeneous solution was obtained) and kept at this temperature for 3 h. Then the temperature of the oil bath was increased to 150-160 °C and kept at this temperature for 1 h. To counteract the evaporation of water, 5 mL portions of water was added a few times. Then, the reaction mixture was cooled down

room temperature and 30 mL of acetone was added, the precipitated solid was collected by suction filtration, and further washed with 50 mL of acetone. The "cyclization product" (**2.3**) was obtained as a dark white powder. Yield 1.33 g (88%).

^{1}H NMR (400 MHz, D_2O), δ 6.01 (d, *J* = 11.8 Hz, 2H), 6.60 (d, *J* = 11.8 Hz, 2H), 7.82 (d, *J* = 8.07, 2H), 8.30 (t, *J* = 7.0 Hz, 2H), 8.60 (t, *J* = 7.92 Hz, 2H), 9.22 (d, *J* = 6.04Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 70.6 (-CH_2), 88.2 (q.C), 126.3 (Py.), 130.8 (Py.), 141.8 (Py.),145.3 (Py.), 148.9 (Py.), 159.7 (C=O).



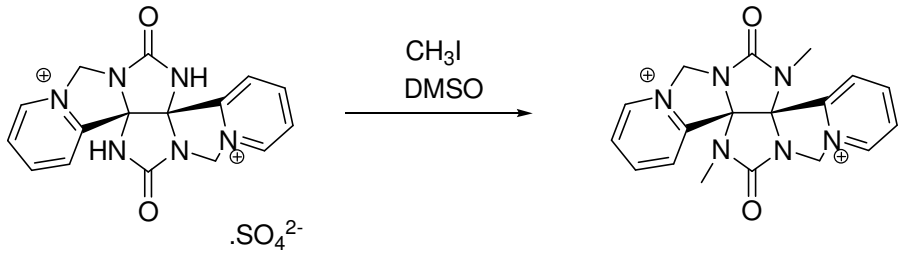
2.2 **2.3**

Scheme 2.2. Synthesis of Cyclization product (**2.3**).

2.4. Methylation of compound (2.3)

Into a mixture of compound (**2.3**) (1.0 g, 2.4 mmol), Na_2CO_3 (1.2 g, 11.3 mmol) in 10 mL DMSO was added CH_3I (1.0 mL, 16.1 mmol). The mixture was stirred at room temperature for overnight. After the reaction was completed, isopropyl alcohol was added onto the reaction mixture, and the desired product (**2.4**) was collected by suction filtration as brownish solid. Yield 0.76 g (71%).

^{1}H NMR (400 MHz, DMSO-d6) δ: 2.62 (s, 6H), 6.21 (d, *J* = 11.8 Hz, 2H), 6.45 (d, *J* = 11.8 Hz, 2H), 8.06 (d, *J* = 7.84 Hz, 2H), 8.42 (t, *J* = 6.24 Hz, 2H), 8.71 (t, *J* = 7.84 Hz, 2H), 9.49 (d, *J* = 6.24 Hz, 2H).



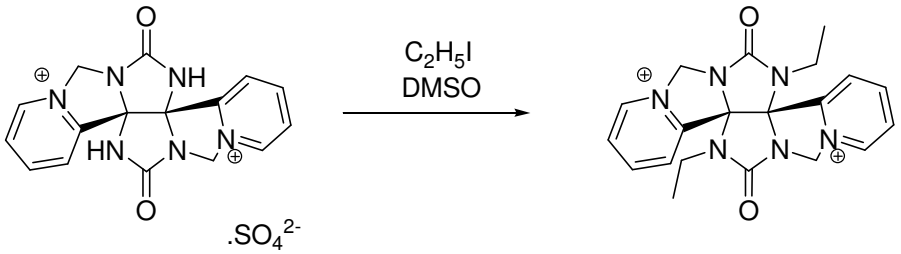
2.3 **2.4**

Scheme 2.3. Methylation of Compound (**2.3**).

2.5. Ethylation of compound (2.3)

Into a mixture of compound (**2.3**) (1,0 g, 2.4 mmol), Na_2CO_3 (1.2 g, 11.3 mmol) in 10 mL DMSO was added C_2H_5I (0.8 mL, 9,6 mmol). The mixture was stirred at room temperature for overnight. After the reaction was completed, isopropyl alcohol was added onto the reaction mixture, and the desired product (**2.5**) was collected by suction filtration as brownish solid. Yield 0.91 g (79%).

^{1}H NMR (400 MHz, DMSO-d6) δ 0.97 (t, *J* = 7.04 Hz, 6H), 3.01 (m, 2H), 3.30 (m, 2H), 6.21 (d, *J* = 11.8 Hz, 2H), 6.51 (d, *J* = 11.8 Hz, 2H), 8.12 (d, *J* = 7.90 Hz, 2H), 8.48 (t, *J* = 6.40 Hz, 2H), 8.73 (t, *J* = 7.90 Hz, 2H), 9.57 (d, *J* = 6.40 Hz, 2H).



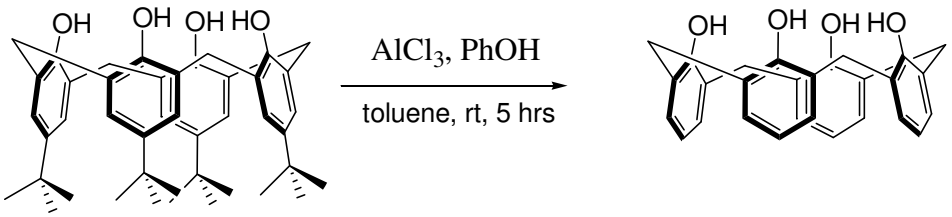
2.3 **2.5**

Scheme 2.4. Ethylation of Compound (**2.3**).

2.6. Synthesis of Calix[4]arene from *p*-tert-butylcalix[4]arene (2.7)

Calix[4]arene can be obtained from the detert-butylation of commmercially available *p*-tert-butylcalix[4]arene. This reaction is simply reverse Friedel-Crafts alkylation. To a solution of *p*-tert-butylcalix[4]arene (**2.6**), (5g, 7.7 mmol) in toluene (50mL), was added phenol (0.875 g, 9.3 mmol) and the mixture was let to mix by using a mechanical stirrer. After 30 mins. of mixing $AlCl_3$ (5g, 37.5 mmol) was added, and the reaction was mixed for further 3h. The solutions with gel like, gummy material on the walls of reaction flask was poured onto the crushed ice (100 g), the reaction vessel was further washed with 50 mL of chloroform and 50 mL of water. The yellow solution was transferred into a separatory funnel and 200 mL of chloroform was added. The organic phase was washed with 1 M HCl (3x50 mL) and with water (3x50 mL). After extraction, the organic phase was collected and dried under sodium sulfate, the solution was filtered off and the solvent was removed under reduced pressure. Onto the remaining yellow oily residue 25 mL of diethyl ether was added and kept at -15 °C for overnight. The solution was filtered by Buchner Filtration to obtain pure calix[4]arene crystals (**2.7**). Yield 2,48 g (76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50-3.63 (4H, br, -CH_2-), 4.20-4.40 (4H, br, -CH_2-), 6.77 (4H, t, Ar-H), 7.10 (8H, d, Ar-H), 10.24 (4H, s, -OH). Yield 2.8 g (85%).



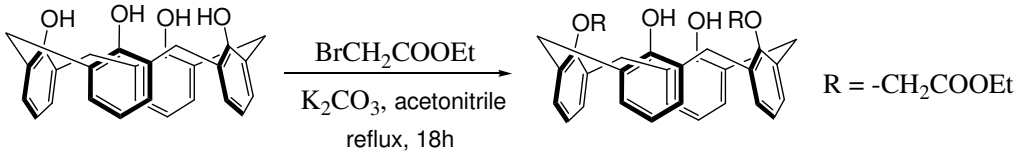
2.6 **2.7**

Scheme 2.5. Detert-butylation of calix[4]arene (**2.7**)

2.7. Synthesis of Bis[(ethoxycarbonyl)methoxy]-calix[4]arene (2.8)

Into a heterogeneous mixture of calix[4]arene (2.01g, 4.8 mmol), and K_2CO_3 (0.72g, 5.02 mmol), in 80 mL of acetonitrile, bromoethyl acetate (1.05 mL, 9.5 mmol) was added. The reaction mixture was refluxed for 18 h. After the reaction is completed, the reaction mixture was filtered bu Büchner Filtration and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (3x50 mL). The organic layer, then is dried under sodium sulfate, filtered by Büchner Filtration, and removed under reduced pressure. After the evaporation of CH_2Cl_2, the crude product was dissolved in the minimum amount of CH_2Cl_2, onto this solution MeOH was drop wise added till further addition leads to turbidity and the obtained solution was let in -15 °C for overnight. The obtained pure diestercalix[4]arene crystals was filtered by Büchner Filtration. Yield 2.6g (89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, *J* = 7.1 Hz, 6H), 3.3 (d, *J* = 13.2 Hz, 4H), 4.25 (q, *J* = 7.1 Hz, 4H), 4.4 (d, *J* = 13.2 Hz, 4H), 4.65 (s, 4H), 6.58 (t, *j* = 7.45 Hz, 2H), 6.66 (t, *J* = 7.55 Hz, 2H), 6.81 (d, *J* = 7.6 Hz, 4H), 6.97 (d, *J* = 8.2, 4H).



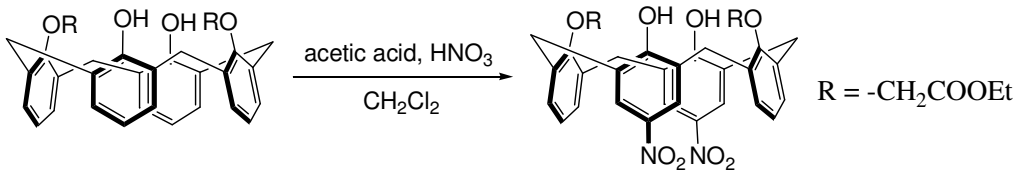
2.7 **2.8**

Scheme 2.6. Synthesis of 25,27-Bis[(ethoxycarbonyl)methoxy]-26,27-dihydroxy-calix[4]arene (**2.8**).

2.8. Synthesis of Bis[(ethoxycarbonyl)methoxy]-dinitro-calix[4]arene (2.9)

Into a solution of diestercalix[4]arene (**2.8**) (2 g, 3.3 mmol), and acetic acid (6.8 mL, 118 mmol) in 60 mL CH_2Cl_2 was added 65% HNO_3 (11.7 mL, 168 mmol) at 0 °C in ice bath. After the addition the reaction vessel was taken out of the ice bath and further stirred for about half an hour, and then water (50 mL) was added. The organic layer was separated and washed with water (3x50 mL), dried under sodium sulfate, filtered and evaporated under reduced pressure. The residue is then dissolved in the minimum amount of CH_2Cl_2, onto this solution MeOH was drop wise added till further addition leads to turbidity and the obtained solution was let in -15 °C for overnight. The obtained pure diester-dinitro-calix[4]arene crystals was filtered by Büchner Filtration. Yield 1.36g (60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.2 (t, *J* = 7.14 Hz, 6H), 3.4 (d, *J* = 13.4 Hz, 4H), 4.29 (q, *J* = 7.14 Hz, 4H), 4.39 (d, *J* = 13.34 Hz, 4H), 4.66 (s, 4H), 6.75 (t, *J* = 7.84 Hz), 6.9 (d, *J* = 7.58 Hz, d), 7.95 (s, $4H_{ar}$), 8.8 (s, 2H, phenolic).



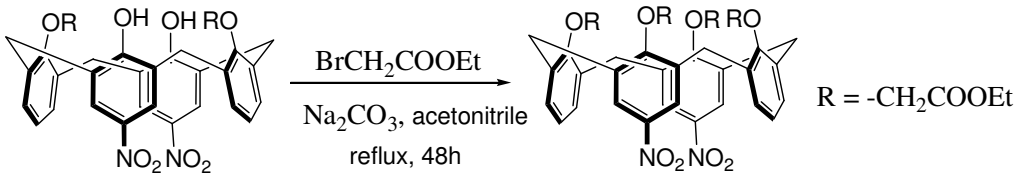
2.8 **2.9**

Scheme 2.7. Synthesis of 25,27-Bis[(ethoxycarbonyl)methoxy]-26,27-dihydroxy-5,17-dinitorocalix[4]arene (**2.9**).

2.9. Synthesis of Tetrakis[(ethoxycarbonyl)methoxy]-dinitro-calix[4]arene (2.10)

Into a mixture of diester-dinitro-calix[4]arene (**2.9**) (1 g, 1.46 mmol), Na_2CO_3 (1.6 g, 15 mmol), in 60 mL acetonitrile was added bromoethyl acetate (1.63 mL, 14.6 mmol). The reaction mixture was refluxed for 48 h. After the reaction was completed the reaction mixture was filtered and the solvent was removed under reduced pressure, the residue was then dissolved in CH_2Cl_2 (50 mL) and vigorously stirred with water for 15 h. The organic layer was separated, dried under sodium sulfate and removed under reduced pressure. The residue is then dissolved in the minimum amount of CH_2Cl_2, onto this solution MeOH was drop wise added till further addition leads to turbidity and the obtained solution was let in -15 °C for overnight. The obtained pure tetraester-dinitro-calix[4]arene crystals was filtered by Büchner Filtration. Yield 1.05g (83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, *J* = 7.1, 12H), 3.4 (d, *J* = 13.95, 4H), 4.19 - 4.28 (m, 8H), 4.88 (s, 8H), 4.95 (d, *J* = 13.95 Hz, 4H), 6.71 – 6.81 (m, 6H_{ar}), 7.64 (s, 4H_{ar})



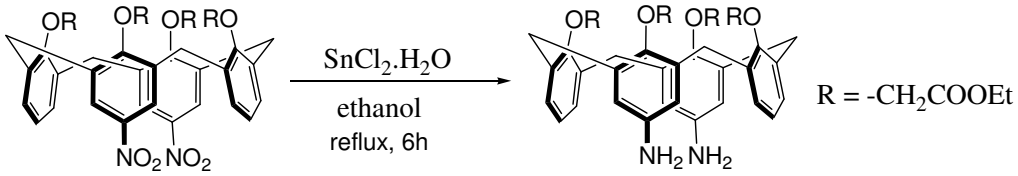
2.9 **2.10**

Scheme 2.8. Synthesis of 25,26,27,28-Tetrakis[(ethoxycarbonyl)methoxy]-26,27-dihydroxy-5,17-dinitrocalix[4]arene (**2.10**).

2.10. Synthesis of Tetrakis[(ethoxycarbonyl)methoxy]-diamino-calix[4]arene (2.11)

A heterogeneous solution of tetraester-dinitrocalix[4]arene (**2.10**) (1 g, 1.17 mmol), and $SnCl_2.2H_2O$ (2,62 g, 11,76 mmol), in ethanol (40 mL) was refluxed for 6 h. The obtained yellowish homogeneous solution after 6 hours of reflux was then poured onto 40 g of ice, and the pH was adjusted to 8 by addition of saturated NaOH solution and let the mixture stir for further 5 h. The organic layer was separated, washed with water (3x50 mL), dried under sodium sulfate, filtered and removed under reduced pressure. The tetrakis[(ethoxycarbonyl)methoxy]-diamino-calix[4]arene was obtained as yellowish-orange oily residue. Yield 0.4 g (43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 – 1.25 (m, 12 H), 3 (d, *J* = 14.15, 4H), 4.09 – 4.16 (m, 8H), 4.55 (s, 4H), 4.65 (s, 4H), 4.72 (d, *J* = 14.15, 4H), 5.9 (s, $4H_{ar}$), 6.56 (t, *J* = 7.13, $2H_{ar}$), 6.63 (d, *J* = 7.13, $4H_{ar}$).



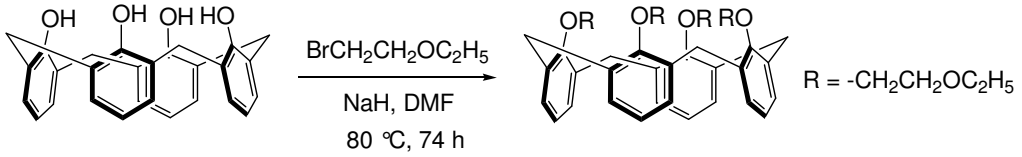
2.10 **2.11**

Scheme 2.9. Synthesis of 25,26,27,28-Tetrakis[(ethoxycarbonyl)methoxy]-5,17-diaminocalix[4]arene (**2.11**).

2.11. Synthesis of Tetrakis(2-ethoxyethoxy)calix[4]arene (2.12)

Calix[4]arene (**2.7**) (2 g, 4.8 mmol) was suspended in dry DMF (60 mL) in a flask in ice bath, onto the suspension slowly addition of NaH (3.44 g, 143 mmol) was done by controlling the temperature. After complition of addition of NaH, 2-Bromoethyl ethyl ether (11,9 mL, 103,8 mmol) was added (Groenen et. al., 1991) and the mixture was stirred at 80 °C for 74 h. The solvent was evaporated under reduced pressure, onto the residue, $CHCl_3$ (100 mL) was added and the organic layer was washed with water (3x100 mL) and with hexane to get rid of mineral oil coming from NaH which is suspended on it, and dried with sodium sulfate. After the evaporation of organic solvent under reduced pressure, the residue was let to crystallize in hot ethanol. Yield 0.71 g (30%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, *J* = 6.5 Hz, 12H), 3.06 (d, *J* = 13.39 Hz, 4H), 3.48 (q, *J* = 6.5 Hz, 8H), 3.78 (t, *J* = 5.78 Hz, 8H), 4.05 (t, *J* = 5.78 Hz, 8H), 4.42 (d, *J* = 13.39 Hz, 4H), 6.59 (t, *J* = 6.6 Hz, $4H_{ar}$), 6.7 (d, *J* = 6.6, $8H_{ar}$).



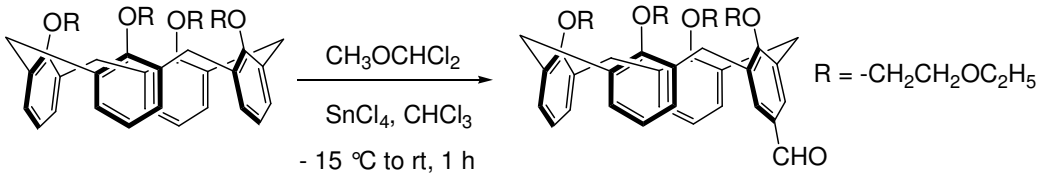
2.7 **2.12**

Scheme 2.10. Synthesis of 25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.12**)

2.12 Synthesis of 5-Formyl Tetrakis(2-ethoxyethoxy)calix[4]arene (2.13)

Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.12**) (1 g, 1,35 mmol), and 1-1-dicholoro methylmethyl ether (1.8 mL, 19.9 mmol) were dissolved in $CHCl_3$ (75 mL), and cooled to -15 °C, onto the solution tin tetrachloride (2.4 mL, 20.44 mmol) was added, and the reaction mixture was stirred for 1 h, and then treated with water (150 mL). The organic layer was washed with water (3x100 mL), dried under sodium sulfate, and evaporated under reduced pressure. The further purification of product (**2.13**) was carried out by silica gel column chromatograpy (ethyl acetate/hexane:4/1). Yield 0,43 g (60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, *J* = 7 Hz, 12H), 3.25 (d, *J* = 13.48 Hz, 2H), 3.30 (d, *J* = 13.64 Hz, 2H), 3.6 (q, *J* = 7 Hz, 8H), 3.87 – 3.96 (m, 8H), 4.34 (t, *J* = 5.14 Hz, 8H), 4.6 (d, *J* = 13.48 Hz, 2H), 4.65 (d, *J* = 13.64 Hz, 2H), 6.52 (t, *J* = 4.18, $1H_{ar}$), 6.62 (d, J = 14.4 Hz, $2H_{ar}$), 6.66 – 6.78 (m, $6H_{ar}$), 7.2 (s, $2H_{ar}$), 9.7 (s, 1H, -CHO).



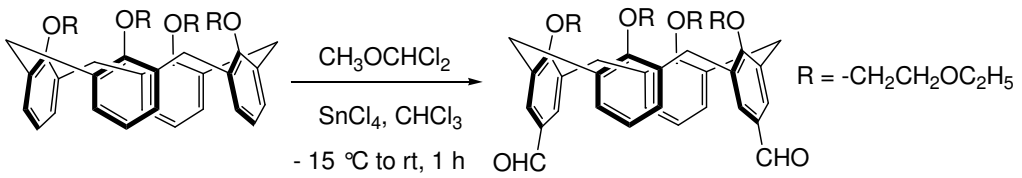
2.12 **2.13**

Scheme 2.11. Synthesis of 5-Formyl-25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.13**)

2.12 Synthesis of 5,17-Bisformyl Tetrakis(2-ethoxyethoxy)calix[4]arene (2.14)

Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.12**) (0.5 g, 0.7 mmol), and 1-1-dicholoro methylmethyl ether (1.15 mL, 12.78 mmol) were dissolved in $CHCl_3$ (35 mL), and cooled to -15 °C, onto the solution tin tetrachloride (1.52 mL, 12.71 mmol) was added, and the reaction mixture was stirred for 30 min in – 15 °C, and 1 h at room temperature, then treated with water (100 mL). The organic layer was washed with water (3x100 mL), dried under sodium sulfate, and evaporated under reduced pressure. The further purification of product (**2.13**) was carried out by silica gel column chromatograpy (ethyl acetate/hexane:4/1). Yield 0,3 g (56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 – 1.13 (m, 6H), 1.2 (t, *J* = 7.14 Hz, 6H), 3.17 (d, *J* = 13.65 Hz, 4H), 3.40 – 3.50 (m, 8H), 3.53 – 3.61 (m, 8H), 4.03 (t, *J* = 7.29 Hz, 8H), 4.5 (d, *J* = 13.65 Hz, 4H), 6.5 (s, $6H_{ar}$), 7.1 (s, $4H_{ar}$), 9.1 (s, 2H, -CHO).



2.12 **2.14**

Scheme 2.12 Synthesis of 5,17-Bisformyl Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.14**)

CHAPTER 3

RESULTS AND DISCUSSIONS

Following the detailed procedure in the experimental section compound **3** was obtained as a highly water soluble sulfate salt. In the ^{1}H NMR spectrum in D_2O, in addition to other peaks the spectrum shows an AB - system very much reminiscent of cucurbituril exo and endo methylene hydrogens, a doublet at 6.01 and another doublet at 6.60 both with coupling constants of 11.8 Hz. This result was confusing at best, and misleading at worst. However, another ^{1}H NMR spectrum in DMSO-d_6 alerted us about the possibility of an unexpected product (this NMR spectrum had one more peak at 7.32 ppm. with an integral corresponding to two hydrogens). The others signals are in the aromatic region corresponding to pyridil rings. In the ^{1}H NMR spectrum the four signals at the aromatic region are a doublet at 7.82, followed by two triplets at 8.30 and 8.60 and a doublet at 9.02 ppm. The Highly downfield shift when compared to a benzene ring is because of the electron donating ability of the nitrogen atom on the ring. The AB – systems are easily seen between these aromatic protons. The doublet at 7.82 ppm couples with the triplet at 8.60 and the doublet at 9.02 couples with the triplet signal at 8.30 both forming AB – systems on the spectrum. The unexpectedly cyclized product has two –NH protons, whereas due to the fast exchange with deuterium these protons cannot be catched as NMR signals. In all the spectra we have taken a very small, negligible signal is observed around 2.1 ppm, this signal may be related with these two protons but cannot be integrated and cannot be taken as a data. The ^{13}C NMR data is well matching the structure, at peak at 70.6 ppm corresponding to $–CH_2$-s on the molecule. At 88.2 ppm another peak is

observed and for the quarternary carbon. The other peaks at 126.3, 130.8, 141.8, 145.3, and 148.9 correspond to pyridine carbon, and the peak at 159.7 ppm corresponds to the carbonyl carbon. Two other derivatives (**4, 5**) obtained by alkylation using alkyl iodides had expected NMR spectra in DMSO-d_6 but in D_2O methylene peaks disappeared as a result of solvent exchange. This was also unexpected for a cucurbituril structure but not for structures for **4** and **5**. In the NMR spectrum of the methylated compound, the 6H coming from the –CH_3 groups resonates at 2.62 ppm as expected. The rest of the NMR spectrum is very much similar with the unexpected cyclized product (**3**), doublets at 6.21 and 6.45 corresponding to –CH_2- protons and forming an AB – system, and the pyridine protons coming at 8.06 ppm, doublet coupling with the triplet at 8.71 ppm and forming an AB – system, and the second doublet at 9.49 ppm, coupling with the triplet at 8.42 ppm and again forming an AB – system. The NMR spectrum of the Ethylation product just differs in a triplet for 6H at 0.97 ppm and two sets of multiplets corresponding to 2H each at 3.01 and 3.30 ppm. The aromatic protons resonate as the other two derivatives, a doublet at 8.12 and corresponding triplet at 7.90, a doublet 9.57 and its corresponding triplet at 8.48, both forming AB – systems each. Electrospray ionization and MALDI are two soft ionization mass spectrometry techniques. For this reason, we preferred mass spectrometry studies with these techniques. The results were conclusive largest molecular ion peaks corresponded to mono sulfate salt of **3** and with the alkylated compounds diiodides of **4** and **5**. Preliminary crystallographic studies (details to be published elsewhere) also confirm the structure assignment. Energy minimized structure of compound **3** is shown in Figure 2 The structure shows a very well defined binding groove with full positive charges on both ends. Thus, this molecule could be a very good receptor for negatively charged and electron rich aromatic guests. The possibility of further functionalization as we demonstrated by methylation and ethylation increases the scope of this, and structurally related glycoluril derivatives even further. Our work along these lines is in progress.

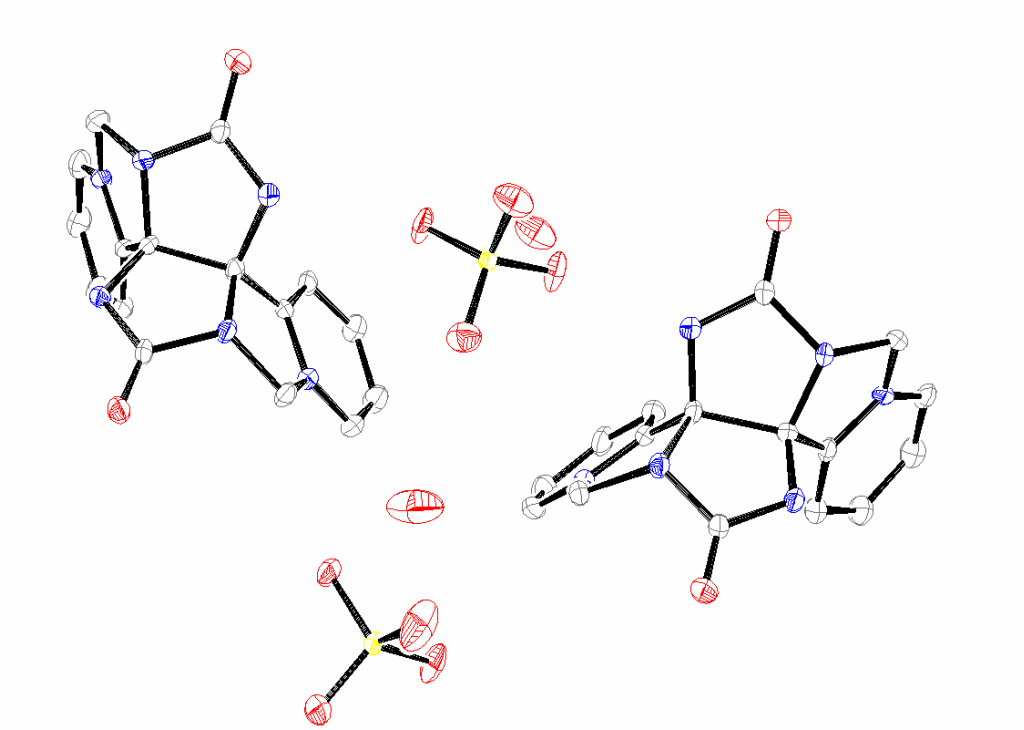


Figure 3.1. Preliminary crystallographic study of **3**, color codes: red, oxygen; blue, nitrogen, yellow, sulfur, gray, carbon.

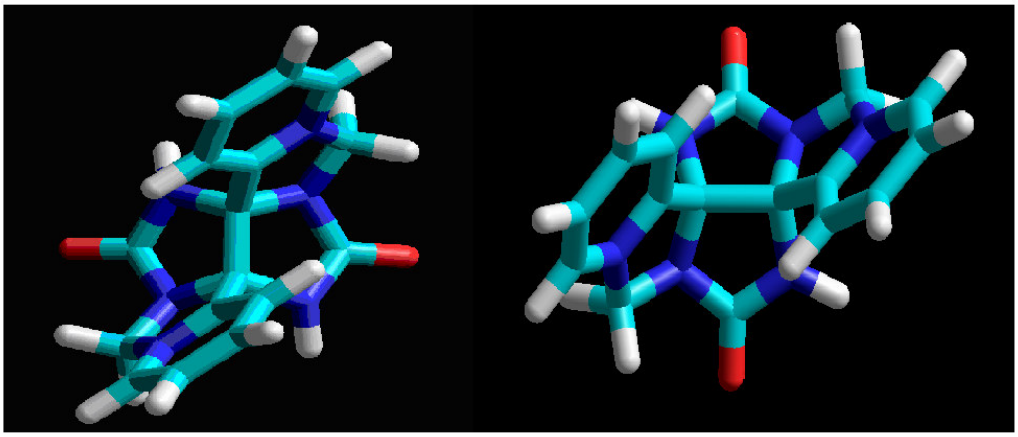


Figure 3.2. Two views of the energy minimized structure of compound **3.** Preliminary X-ray diffraction studies also in full accordance with this structure.

The importance of calixarenes in supramolecular chemistry is because of its well-defined cavity in use as a host molecule and possessing two possible sites for binding. One other vital importance is the ease of functionalizing the both sites of these special molecules. Both lower and upper rim can be further functionalized. The lower rim is simply a phenolic proton and most of the literature about functionalizing the phenolic proton is applicable also to the calixarenes. But one difference it that, if we only take into account calix[4]arene, there is 4 acidic hydrogens, and it can be accepted as a polyprotic acid, therefore the pK_a values of increases for each abstraction. It is calculated in the literature by Shinkai and co-workers for sulfonated calixarenes, since they are soluble in water. For a sulfonated calix[4]arene pK_1 is around 3, pK_2 is around 9, pK_3 is around 12 and the last one pK_4 is greater than 14. The abstraction of first proton is very easy, and the reason beneath this fact is related with stabilization of the formed monoanion. The formed monoanion is strongly bonded to its flanking OH groups by a hydrogen bonding, therefore stabilizing the anion. This fact can be useful in partial functionalization of the lower rim, and one can obtain monosubstitution, or 1,3 alternate functionalization is common in the literature and some examples are also shown in this thesis.

The most common and feasible commercially available form of calix[4]arene is the tert-butycalix[4]arene, so it was our starting point. For the functionalization of the upper rim, one has to get rid of these tert-butyl groups, and this can be easily performed by a reverse Friedel-Crafts alkylation. The functionalization at the upper rim can be seen as the *para-* position of phenols, even for this case one further advantage is that methylene bridge blocks *ortho-* positions. It is known that OH on the aromatic ring is an *ortho- para-* directing group. The detailed procedure for the detert-butylation of tert-butylcalix[4]arene is explained in the experimental chapter. In the reaction toluene is also the solvent and a reactant, it captures the tert-butyl groups freed from tert-butylcalix[4]arene, and the phenol is used to speed up the reaction. The reason is attributed to two factors first one is phenol being a good acceptor

and the second is related with steric effects, it speeds up the reaction by generation of H^+ more efficiently compared to calixarene and H^+ is necessary for initiating the reaction. The reaction is completed in 3 hours and can be easily monitored with TLC. The removal of all four bulky tert-butyl groups is expected to have a pronounced effect on the polarity of the molecule, and simply for the case of NMR, the disappearance of a huge singlet coming from 32 hydrogens. For the calix[4]arene, we observe two broad peaks at 3.50-3.63 and 4.20-4.40, corresponding to 4Hs each. These are in fact very characteristic peaks for calixarenes. These broad peaks arise from the methylenic protons bridging the phenols. When to visualize, one proton faces inwards the cavity of lower rim and the other facing outward, therefore being in two different environments, but because of the free rotation of the aromatic rings around methylene groups, and since the time scale of NMR instrument is not that fast, the two characteristic signals are obtained as broadened peaks in the NMR spectrum. The aromatic region of the spectrum is very clear having two sets of signals at 6.77 and 7.10, 4 and 8Hs respectively corresponding to the *meta-* and *para-* protons. One other characteristic signal is arising from the OH groups of calixarene which is highly downfield shifted and coming at 10.24 ppm. This paramagnetic shift is related to the strong hydrogen bonding between the OH protons. The removal of tert-butyl groups can be accepted as the very first step for the further functionalization of lower and upper rim. In our strategy the second part is the functionalization of the lower rim. The first compound starting from detert-butylated calixarene is Bis[(ethoxycarbonyl)methoxy]-calix[4]arene, a 1,3-alternate product. At first glance it seem to be interesting to obtain 1,3-alternate product in high yield with recrystallization, but the important factor here is the p*K* values of the phenolic protons. By using a milder base, which lacks the ability to abstract the third and forth proton, K_2CO_3 in our case, and controlling the stoichiometry of the calixarene and the ethylbromoacetate as 1 to 2, it is possible to obtain a 1,3- diester product. The improvement in the procedure from the one in the literature is at the purification step. In the literature, it is given that, to obtain pure product, recrystallization in hot methanol should be employed, whereas we obtained

higher yields. First of all, during recrystallization in hot ethanol, since our product is nearly insoluble, too many solvent is required for recrystallization which lowers the yield. Whereas, in our case, the impure product just after removal of solvent under reduced pressure, the residue is dissolved in minimum amount of CH_2Cl_2, and onto the clear solution dropwise addition of MeOH is performed until the solution becomes turbid. In few seconds after the turbidity the crystallization begins and seems like precipitation rather than crystallization. Upon waiting for overnight in the freezer, then the crystals can be collected by filtration and must further be washed with cold methanol. About the NMR spectrum, Ethyl group of the bromoethylacetate is clearly seen, having a triplet at 1.3 ppm integration for 6H as expected, 0.4 ppm chemical shift coming from the oxygen as expected, and a quartet at 4.25, furthermore as expected coupling for both sets of protons is same which is 7.1 Hz. For the other 4Hs on the ester group, a singlet at 4.65 as expected. The integration is important for determining the structure for this kind of partially functionalized calixarenes, by this way you can determine the number of groups attached. For this case, 1,3- substitution, the symmetry of the molecule changes, so the splitting pattern of aromatic protons change. The methylenic protons in symmetrical calixarenes, bearing C_4 and C_2 symmetry is divided into two groups as in the case of detert-butylated calix[4]arene. In the case of calix diester, the two sets of protons come at 3.3 and 4.4 as doublets for 4Hs each as an AB system, which also shows us the two sets of doublets are related. The coupling $^2J_{HH}$ = 13.6 when compared this is a large for the case of geminal coupling and can be explained by the increase of the angle between the methylenic protons due to the strain on calix[4]arene. Since the symmetry is axis is changed from C_4 to C_2 the signals coming from aromatic rings are expected to divide into two groups, and it is exactly seen in the NMR spectrum. A highfield shift for the aromatic protons attached to the ester functionalized phenol ring is expected to be lower compared to the ones attached to phenol ring. The triplet at 6.58 ppm and the doublet at 6.81 ppm are correspondent to the protons on the phenol ring, whereas, the triplet at 6.66 ppm, and the doublet at 6.97 ppm are coming from the protons attached to the ester modified ring.

The third synthesis is the nitration of calixdiester. The 1,3-diester product is necessary for the selective and high yield nitration. The left 1,3-OH groups are good para directing groups, therefore nitration follows the route of selective nitration at positions 5 and 17 by control of temperature. The dinitro-diester product can be obtained in high yield. The nitro group as known in the literature makes the compound much more prone to crystallization, by the same method explained above, 25,27-Bis[(ethoxycarbonyl)methoxy]-26,27-dihydroxy-5,17-dinitorocalix[4]arene was obtained as yellow crystal. The difference in NMR spectrum is mainly in aromatic protons. Again a triplet at 1.2 ppm and a corresponding quartet at 4.29 having the same couplings are observed. A singlet at 4.66 ppm for 4Hs, which is just between the phenolic oxygen and the ester carbonyl, the characteristic methylenic protons are obtained as clear doublets at 3.4 and 4.39 having nearly the same coupling as the diester derivative $^{2}J_{HH}$ = 13.4 Hz again forming an AB – system on spectrum. In the aromatic region, a triplet at 6.75 and a corresponding doublet at 6.9 ppm having exactly same coupling constants are observed for the protons which are attached to the ester modified phenol ring. The two hydrogens at the *ortho-* positions of the nitro groups are seen as a singlet in the spectrum at 7.95 ppm. The downfield shift is as expected because of the electron-drawing nitro group. The Δδ for the *ortho-* position coming from the nitro group is 0.93 ppm theoretically, and here it is seen that this theoretic data well-matches the experimental one. At 8.8 ppm as a broad singlet, integration for 2H is observed for the phenolic –OH protons. The forth synthesis is the esterification of the left two phenol groups, hence the synthesis of 25,26,27,28-Tetrakis[(ethoxycarbonyl)methoxy]-26,27-dihydroxy-5,17-
dinitrocalix[4]arene. The left two OH groups can be esterified by using stronger bases, Na_2CO_3 in our case, and longer reflux times, 48 hours for our case, and use of excess alkylbromide, therefore after completion of the reaction a further 15 hours of vigorously washing is necessary to get rid of salts formed. The integrations in the NMR spectrum well-matches the exact structure, a triplet at 1.3 ppm for 12H and a corresponding multiplet between 4.19 – 4.28 ppm for 8H, a singlet for 8H at 4.88 for the methylene group between the

phenol oxygen and carbonyl carbon, two sets of doublets at 3.4 and 4.95 ppm, which also indicates the molecule is in cone conformation. The coupling constants for these two sets of methylenic doublets are $^2J_{HH}$ = 13.95 Hz, which is an increase of about 0.6 Hz. This fact can be attributed to the increase in angle between methylenic protons or in other words, upon introduction of two more ester functions on the lower rim, the bulky 4 ester groups are repelling each other and the strain in molecule increases therefore reflecting to the increase in coupling constants. The 4 protons *ortho-* to nitro group is at 7.64 ppm, again because of the downfield shift due to -NO_2, the other set of aromatic protons is seen as a multiplet between 6.71 – 6.81 ppm and the integration is correspondent to 6H. Conversion of dinitro-diester-calixarene to diamino derivative was the most challenging procedure. For this case, the reflux time is very important, and the reaction must be monitored regularly, since aromatic amines are not stable and upon standing on air oxides are formed, this can even be analyzed on the TLC plate, after applying and waiting for few hours, the spot corresponding to diamino compound darkens, which shows us the air oxidation products. One other factor we believe is the exact adjustment of pH to 8, and the base should be a saturated NaOH solution, in our attempts where, the bases are Na_2CO_3 are K_2CO_3 the isolation of diamino compound failed. The reduction is performed by $SnCl_2.2H_2O$ in ethanol. After careful work-up, diamino compound was obtained as a pure orange oily substance. The NMR data corresponding to ester functionality remains nearly same, but one difference is the further splitting of the -CH_3 protons. In fact these signals are expected to come in two sets, because of the C_2 symmetry axis on the molecule, or in other words, two ester groups have amine functionality at *para-* position whereas the other two have hydrogens, whereas the distance between two groups is so far that, neither the methylene protons, nor the –CH_3 protons are affected from this fact. The –CH_3 protons are seen like two triplets but rather can be identified as a multiplet around 1.16 – 1.25 ppm, the corresponding methylene protons again observed as multiplet around 4.09 – 4.16 ppm, one other difference that the dinitro compound is, again the methylenic protons, between the phenol oxygen and carbonyl carbon are seen

as two different sets of singlets at 4.55 ppm for 4H and at 4.65 ppm for 4H. The characteristic signals in calixarenes for bridging methylene protons are again observed at 3 and 4.72 ppm for 4H each as doublets having $^{2}J_{HH}$ = 14.15. This also shows the conformation is clearly cone conformation. The difference, which is as expected in aromatic region, is from the *ortho-* protons at 5.9 ppm. As explained above for nitro it was 7.64 ppm, the electron donating amine functionality is responsible for this diamagnetic shift on the NMR spectrum. The other signals are in a well-defined splitting a triplet at 6.56 ppm corresponding to 2H, and a doublet at 6.63 for 4H, and both having the coupling ^{3}J = 7.13 Hz, which is a acceptable coupling for aromatic protons *ortho-* to each other. The $-NH_2$ protons are observed in the spectrum as a broad signal between 2.5 – 3 ppm and overlapping with the signal coming from bridging methylenic proton at 3 ppm.

One other parallel work starting from detert-butylated calixarene is etherification of lower rim. The first target product was 25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene. The procedure is similar to esterification, but for this special case, since our target molecule must bear four ether units, or in other words tetraalkylation must be performed, thus a strong base must be employed and reaction time must be kept longer. As a base, NaH was used, and the solvent, DMF, must therefore be dried freshly before the reaction. One other important point is to add 2-Bromoethyl ethyl ether in excess, after finishing addition of NaH, and the reaction later was kept for 74h at 80°C. This time, our crystallization procedure failed, therefore by classical means, the compound was recrystallized in hot ethanol. The NMR spectrum is very clear for this molecule, at 1.12 ppm a triplet is observed matching to 12H coming from $-CH_3$, and the corresponding quartet for 8H, comes 3.48 ppm. $-CH_2CH_2-$ protons come at 3.78 and 4.05 ppm, and as expected having exactly the same coupling constant, ^{3}J = 5.78 Hz, both have integrations for 8H each. The characteristic calixarene bridging methylene protons are at 3.06 and 4.42 ppm for 4H each forming an AB - system, when we think on the coupling constants, $^{2}J_{HH}$ = 13.39 Hz, it implies that the molecule has some small strain

due to the ethers on the lower rim. The molecule has C_4 symmetry axis, therefore it is expected to have two sets of aromatic protons, one set arises from the ones at *para-* position, at 6.59 ppm, and the integration shows that signal is coming from 4 protons, and the left 8 protons signals at 6.59 ppm as a triplet as expected, and these two sets of doublets also show the conformation is simply cone. Ether groups at lower rim, blocks the free rotation of the aromatic rings. The formylation of tetraether was performed by 1-1-dicholoro methylmethyl ether dissolved in $CHCl_3$ and adding tin tetrachloride; this is a known procedure in literature for the formylation of benzene ring. The temperature is kept at around -15°C to prevent further formylation. By control of temperature and stoichiometry, two derivatives were synthesized, -Formyl-25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene and 5,17-Bisformyl Tetrakis(2-ethoxyethoxy)calix[4]arene. In bisformylation the reaction temperature should be kept around -15°C and stoichiometry must be carefully adjusted. Even though under these careful conditions, monoformylation, bisformylation and even triformylation can be monitored on TLC plate. After the reaction is completed, the purification is performed by silica gel column chromatography, and the solvent system is 4 to 1 mixture of ethyl acetate, hexane. The symmetry of molecule is destructed by bisformylation so different signals are expected from two sets of ether groups and for aromatic rings. Different than the dinitro-tetraester derivative, as expected, the $-CH_3$ protons resonates as two different signals, one is a multiplet between 1.07 – 1.13 ppm for 6H and the second one is a triplet at 1.2 ppm for 6H, this splitting is because of the disturbed symmetry and therefore the change in the electronical environment of the protons. The corresponding expected quartet is seen as a multiplet again between 3.40 – 3.50 ppm for 8H. The $-CH_2CH_2-$ groups resonates as two sets, one is a multiplet between 3.53 – 3.61 and the other one is a well-defined triplet at 4.03 ppm, this fine splitting may be attributed to the distance of this group from the formyl part of the molecule. The characteristic signals coming from methylenic bridges resonates as two sets of doublets at 3.17 ppm and 4.5 ppm, having the same coupling $^2J_{HH}$ = 13.65 Hz. The integration and splitting pattern in the aromatic region of the NMR spectrum

clearly shows the di-substitution by a singlet signal coming at 6.5 ppm and integration corresponding to 4H. One unexpected thing for this case is the singlet signal at 6.5 ppm corresponding to 6H. The expected splitting is a triplet for 2H and a corresponding doublet for 4H. In the spectrum a broadening in the unexpected singlet can be observed and the small peaks can be attributed to an overlap between two sets of signals, and this can explain the broadened unexpected singlet. One more signal is observed in the 9.1 ppm, integration giving two protons, clearly showing two aldehyde functionalities on the molecule. The procedure for monoformylation resembles to the bisformylation procedure, but for this case, the stoichiometry is adjusted to give mono substitution and the stirring at room temperature is skipped. For this case, the ether part of the molecule seems to be unaffected from the formly group at position 5. In some cases since the molecule is large enough to tolerate the change in electronic environment at this specific part, it can be said that, the rest of the molecule stays mostly unaware of addition of a group the aromatic rings therefore, triplet is observed at 1.3 ppm for 12H, exactly as expected, but further splittings can also be seen and this signal cannot be defined as a perfect triplet. The reason is simple, distortion in symmetry results from different signals for all -CH_3 protons and these all four signals resonates so close that we observe a distorted triplet. The corresponding quartet for this triplet is at 3.6 ppm. The coupling constants are calculated to be different, which for this case can be attributed to the possible long range couplings. For the two neighboring methylene groups, -CH_2CH_2- again two sets are observed as expected, one being a broad distorted multiplet around 3.87 – 3.96 ppm, and the second set being a broad triplet like signal at 4.34 ppm. It is obvious that because of the formyl group at position 5, all four different -CH_2- protons resonate so closely that an overlap is seen on the spectrum. For the second signal, the triplet, these methylene proton stay a bit far away compared to the ones resonating as multiplet and the overlap is seen as a broadening in the triplet in the spectrum. In fact the best answer on the spectrum about distortion of the geometry arises from the bridging methylene protons, rather than resonating in two sets, they are also further splitted into two hence resonating

as four sets of doublets. First set resonating at 3.25 ppm and 4.6 ppm for 2H each, forming an AB – system and having the coupling constant $^{2}J_{HH}$ =13.56 Hz each, and the second set again forming an AB – system resonates as doublets at 3.3 and 4.65 ppm for 2H each, having the coupling constants $^{2}J_{HH}$ = 13.64 Hz. In the aromatic region the most important signal comes from the neighboring protons to formyl group, resonating as singlets at 7.2 ppm corresponding to 2H. Other signals in aromatic region are, triplet at 6.52 ppm for 1H, doublet at 6.62 ppm for 2H, and a multiplet between 6.66 – 6.78 ppm for 6H. At 9.7 ppm, a singlet for the formyl proton is observed.

These last 3 compounds, diamino-tetraester-calix[4]arene, monoformyl-tetraether-calixarene and the diformyl derivative are important precursor molecules for enzyme mimics, molecular sensors, and cation, anion recognition. Our primal future work is a BODIPY based energy transfer device. BODIPY dyes are fluorophores having high quantum yields, and there has been quite a heavy research on this special fluorophores in our laboratory. Many energy transfer devices have been synthesized so for, but in this special design we are expecting a better energy-transfer. Calix[4]arene body is a sort of spacer in this design, but the aim of such choice is because of its rigid structure and well-defined geometry. After the synthesis of dibodipy tetraester-calix[4]arene, one of the conjugation on one of the BODIPY dye will be elongated, hence obtaining two different fluorophores facing each other. The expected energy transfer mechanism is irradiation of the first fluorophore, transfer of energy to the second fluorophore, named as blue BODIPY in the literature and obtaining the emission from Blue BODIPY (Figure 3.4).

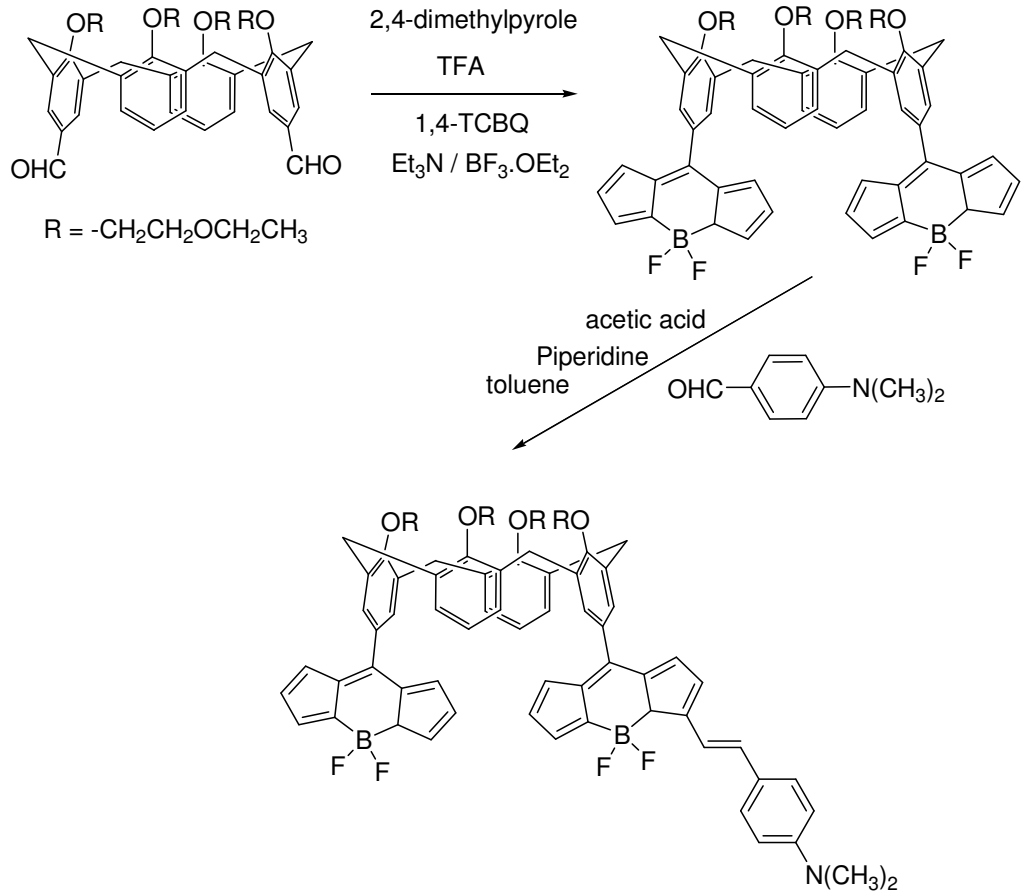


Figure 3.3. Synthesis of BODIPY modified energy transfer device based on calix[4]arene.

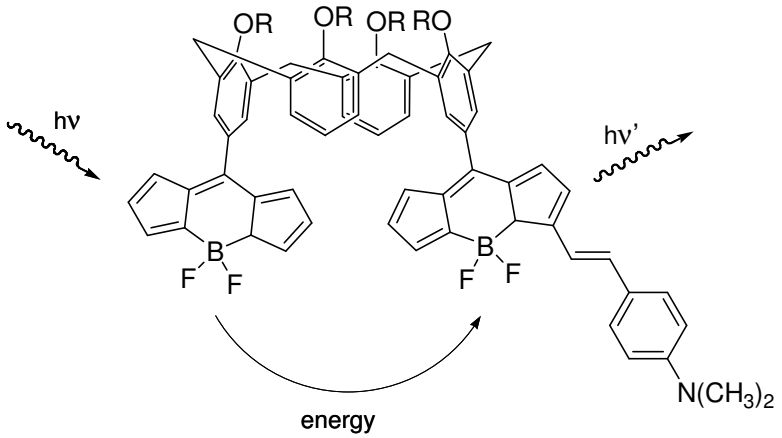


Figure 3.4. Energy transfer mechanism

From diamino-tetraester-calix[4]arene, synthesis of an allosteric sensor is possible, by reacting it with a fluorophore bearing isothiocyanate group, for example, 4-isothiocyanatopyrene.

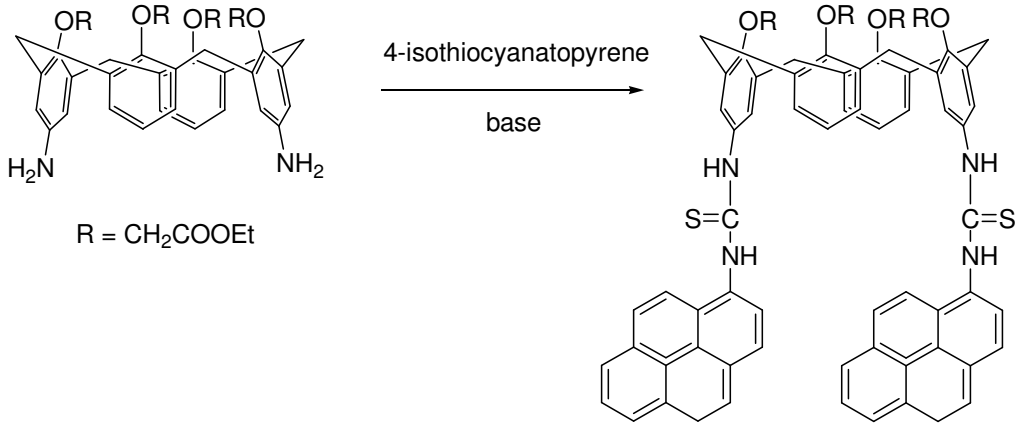


Figure 3.5. Allosteric sensor based on calix[4]arene

The sensor to be synthesized has two possible binding sites, the lower rim, bearing ester groups, is known to have affinity towards certain alkali and alkali earth metals having certain selectivity on Na^{+}, and even cations as Eu^{3+}. The upper rim is both a fluorophore and the thiourea has affinity towards anions and selective for fluoride, therefore forming an allosteric sensor. Many other fluorophores can be employed instead of pyrene as well.

CHAPTER 4

CONCLUSION

At the first part of our study, starting by the aim of synthesizing a new cucurbituril derivative with peripheral pyridine units, but we obtained an unexpectedly cyclized product, a new glycoluril derivative.. Cucurbiturils are important host molecules, because of the well-defined cavity and rigid structure and have already been used successfully in catalytic processes in construction of polyrotaxanes and supramolecular switches.

Glycolurils are considered highly interesting molecular scaffolds due to their rigid concave structure. In addition, many derivatives have found applications as biotin analogs, bleaching activators, radioiodination agents for biomolecules, psychotropic agents, and catalysts. Our study covers the synthesis and full characterization of a new cyclized glycoluril derivative, **2.3**. Two other derivatives have also been synthesized, **2.4** and **2.5**, methylation and ethylation products respectively.

The characterization has been performed by detailed NMR studies, mass spectrometry and preliminary crystallographic analyses. At first glance the ^{1}H NMR data taken in D_2O is very much similar to the one we were expecting from the pyridyl-modified cucurbituril, because of the symmetry on both molecules. They both have two sets of doublets coupling with each other coming from methylenic protons. But further mass spectroscopic analysis and preliminary crystallographic analysis alerted us of the exact structure.

As a conclusion for the first part, we have synthesized and fully characterized a new compound having very well defined binding groove with

full positive charges on both end. This new molecule could be a very good receptor for negatively charged and electron rich aromatic guests and the possibility of further functionalization as we demonstrated by methylation and ethylation increases the scope of this, and structurally related glycoluril derivatives even further.

During the second part of the study, certain calixarene derivatives were synthesized as important precursors to, molecular sensors and artificial enzymes. An extensive study on lower and upper rim functionalization of calixarenes have been performed.

Calixarenes are important host molecules in supramolecular chemistry, and so far in the literature have been reported as catalysts, used in molecular separations (chromatographic columns and crystallizations), widely used as chromogenic and fluorescent chemical sensors, and as host molecules for anions, cations and neutral molecules as well.

Our precursor molecules open to further functionalizations are, Tetrakis [(ethoxycarbonyl)methoxy] -diamino-calix[4]arene (**2.11**). **5-**Formyl Tetrakis (2-ethoxyethoxy)calix[4]arene (**2.13**), 5,17-Bisformyl Tetrakis(2-ethoxyethoxy)calix[4]arene (**2.14**), Herein, a detailed ^{1}H NMR discussion on all the derivatives synthesized throughout the study has been done.

As a result, important precursor calix[4]arene derivatives were synthesized and fully characterized, the future work with this molecules were planned and further discussed and the research for further applications of these precursor molecules and the target molecules is in progress.

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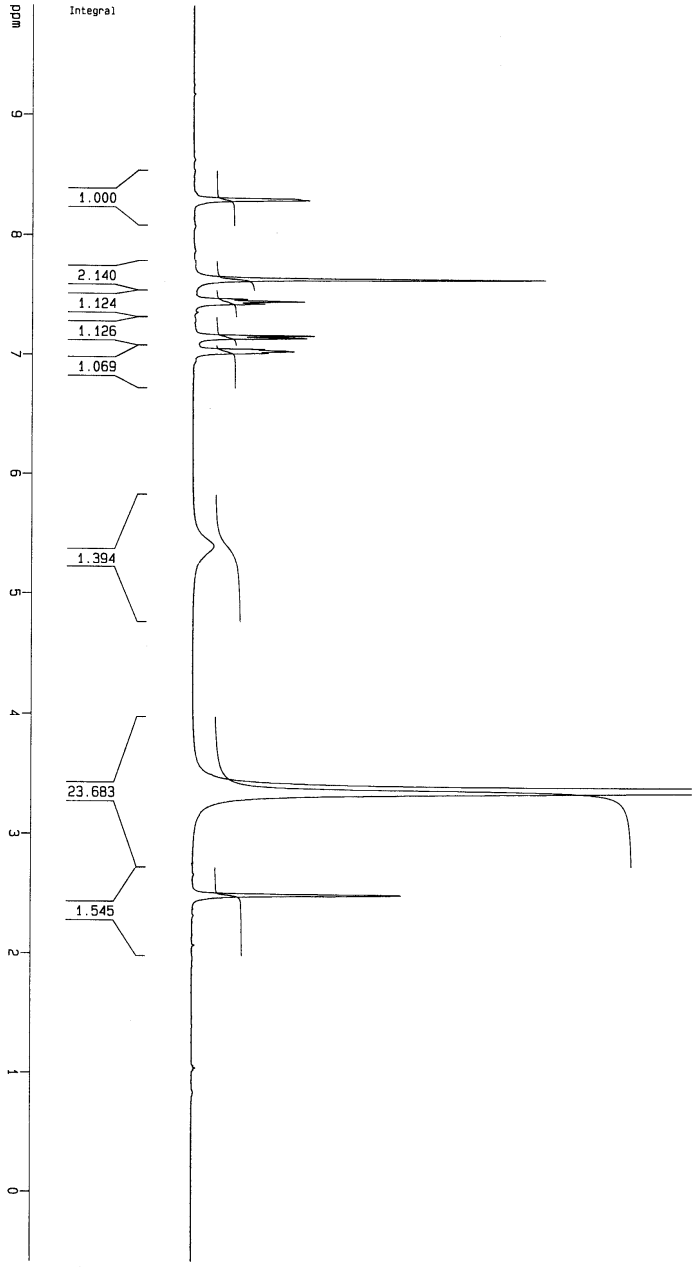
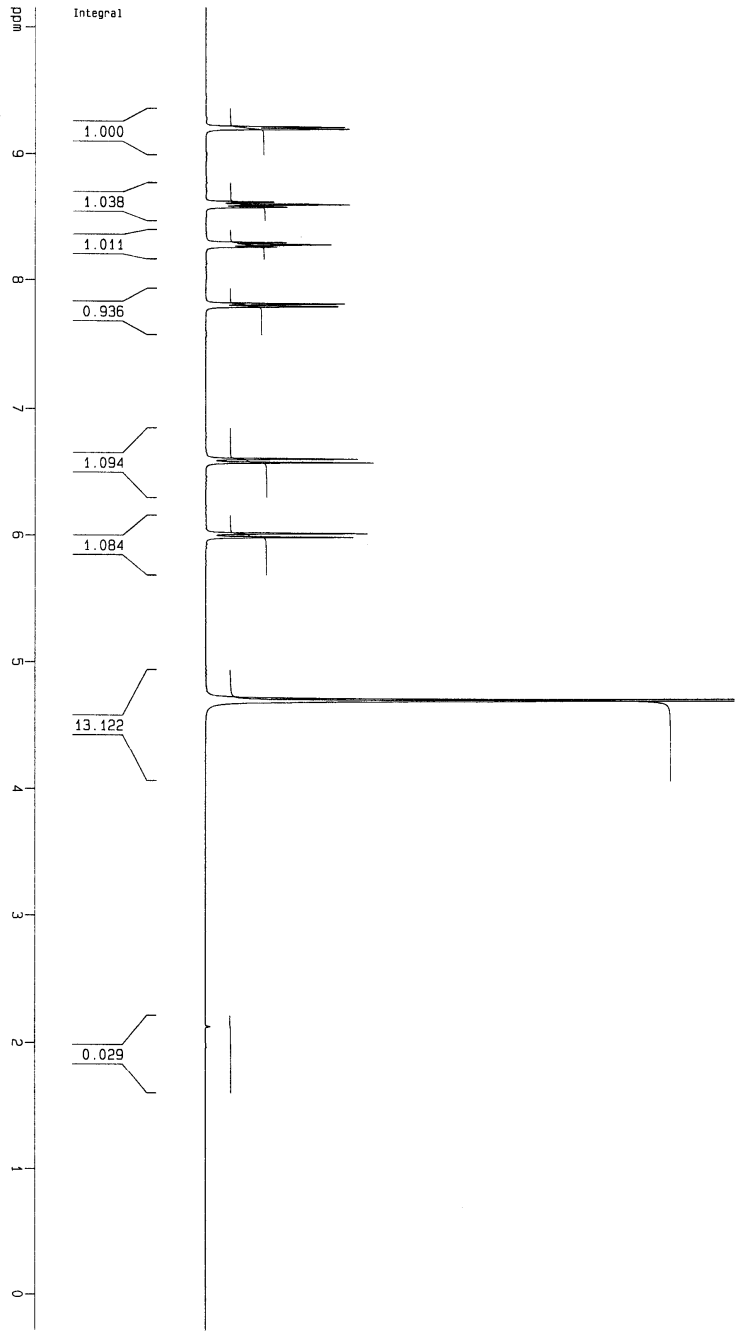
APPENDIX

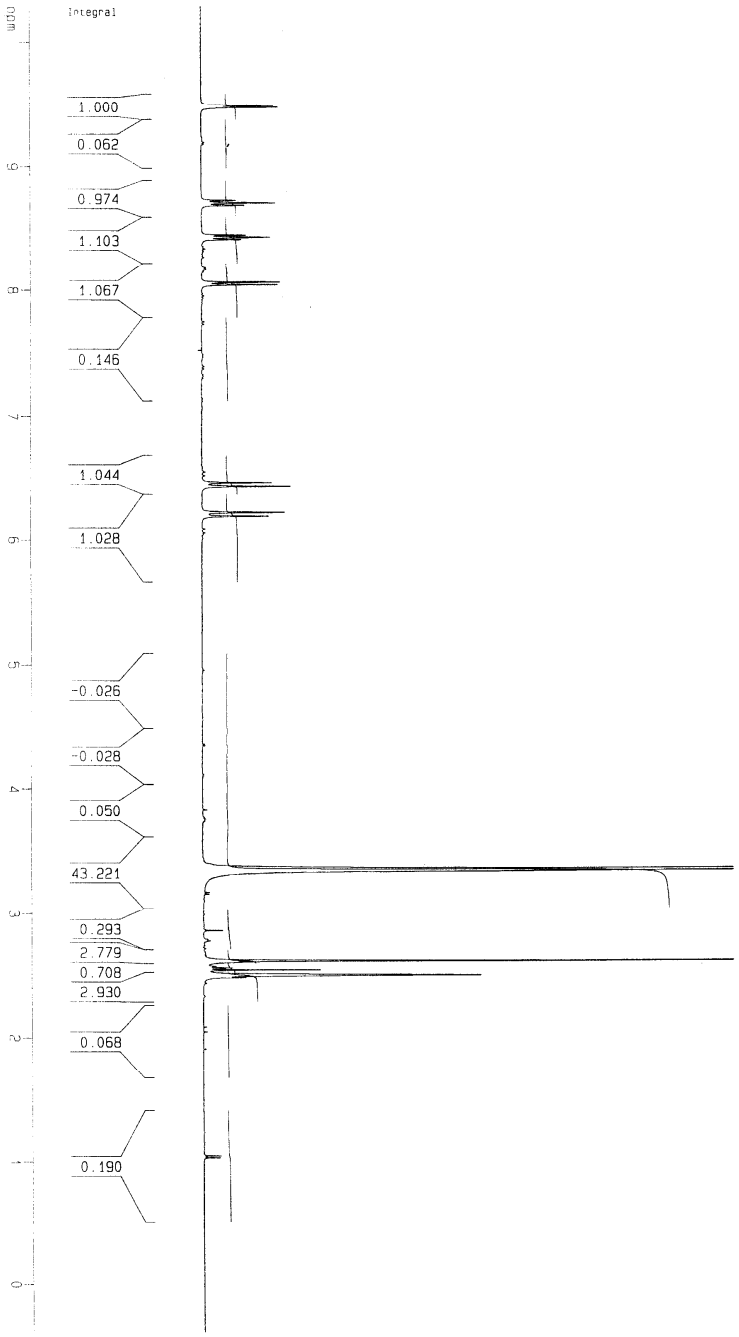
^{1}H NMR of Di(2-pyridyl)glycoluril (2.2)



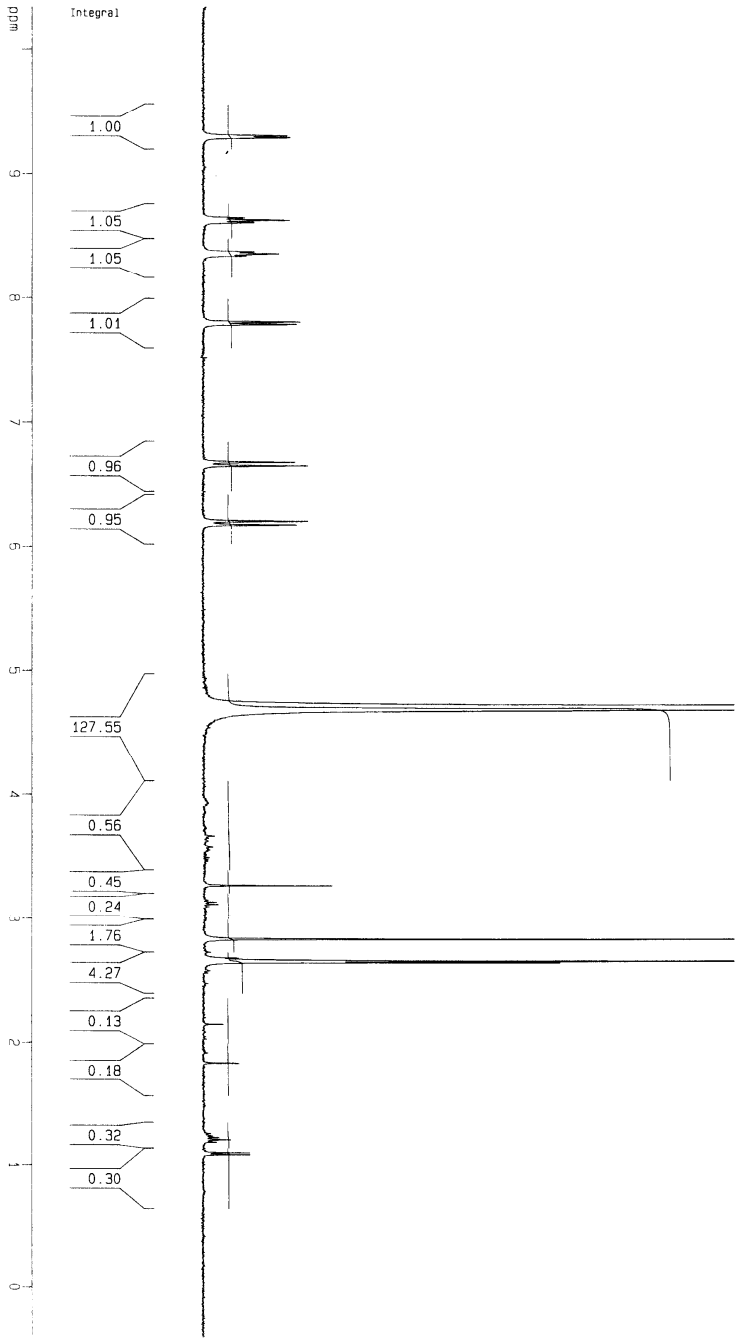
^{1}H NMR of Cyclization product (2.3)



^{1}H NMR of Methylation of compound (2.3) in DMSO



^{1}H NMR of Methylation of compound (2.3) in D_2O



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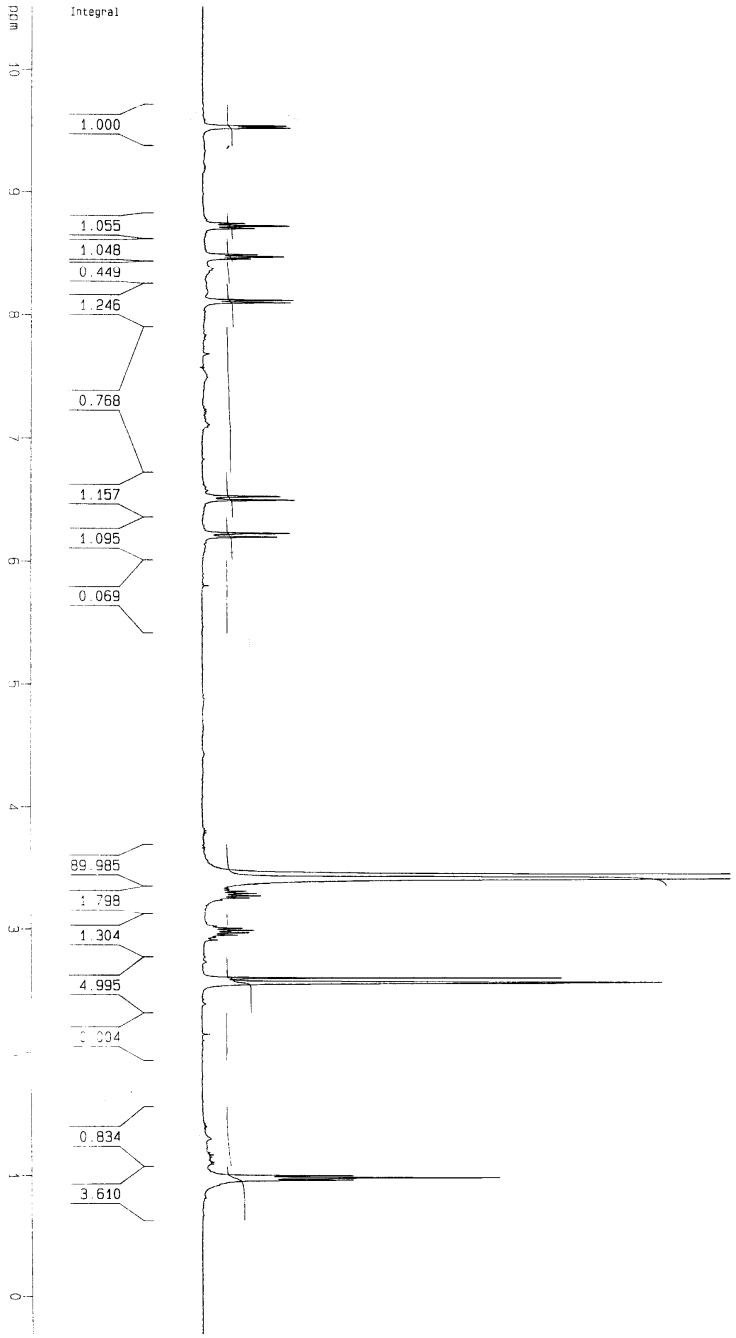

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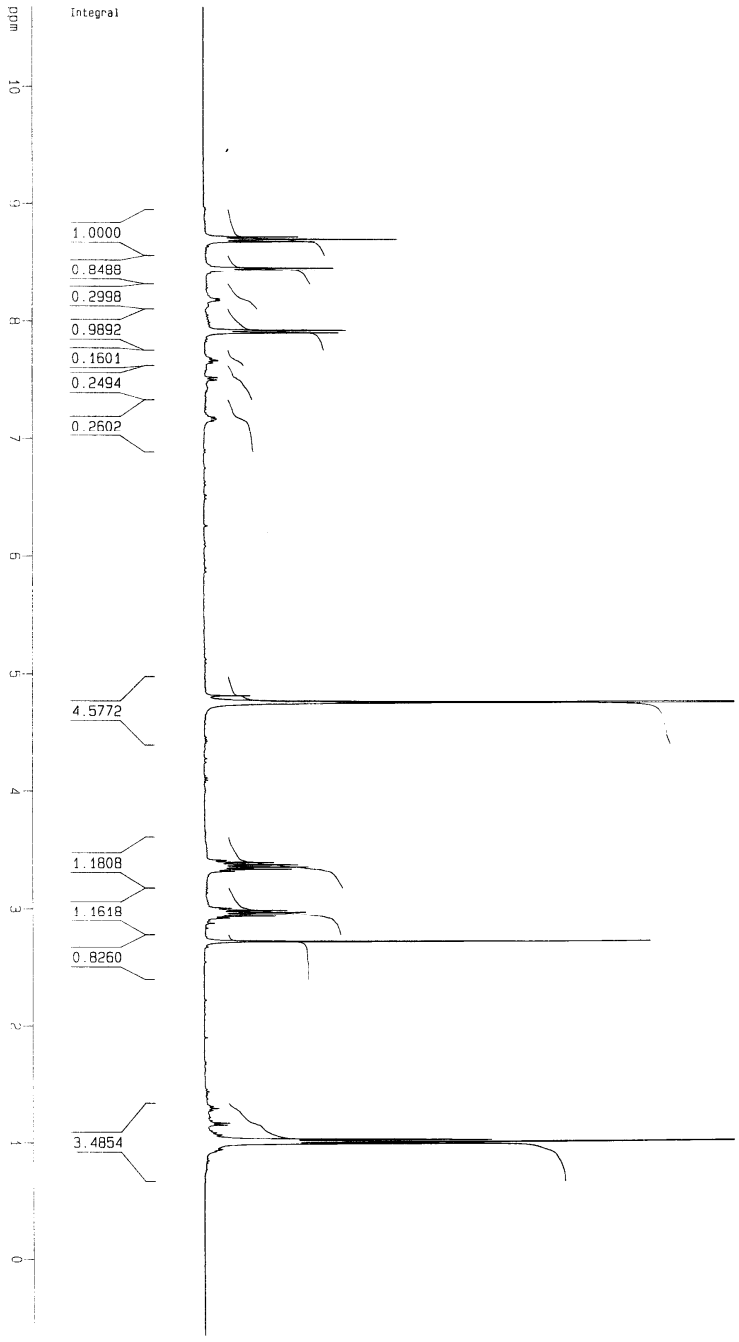
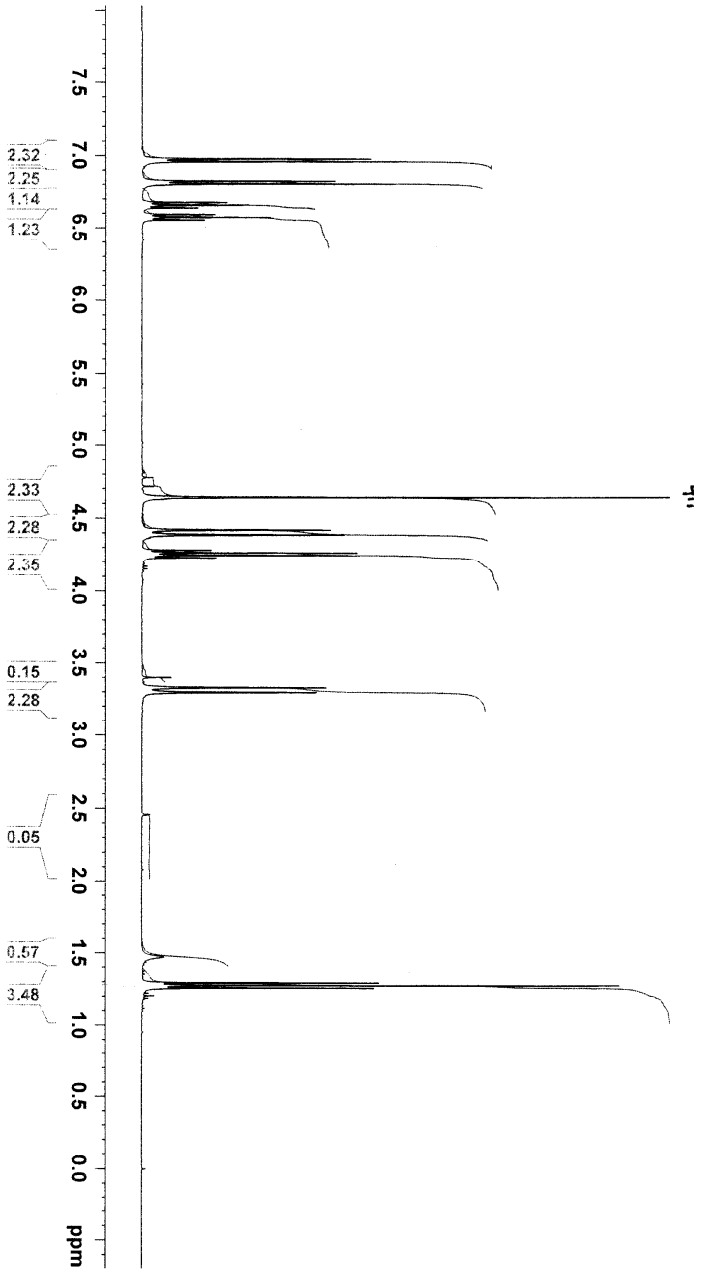
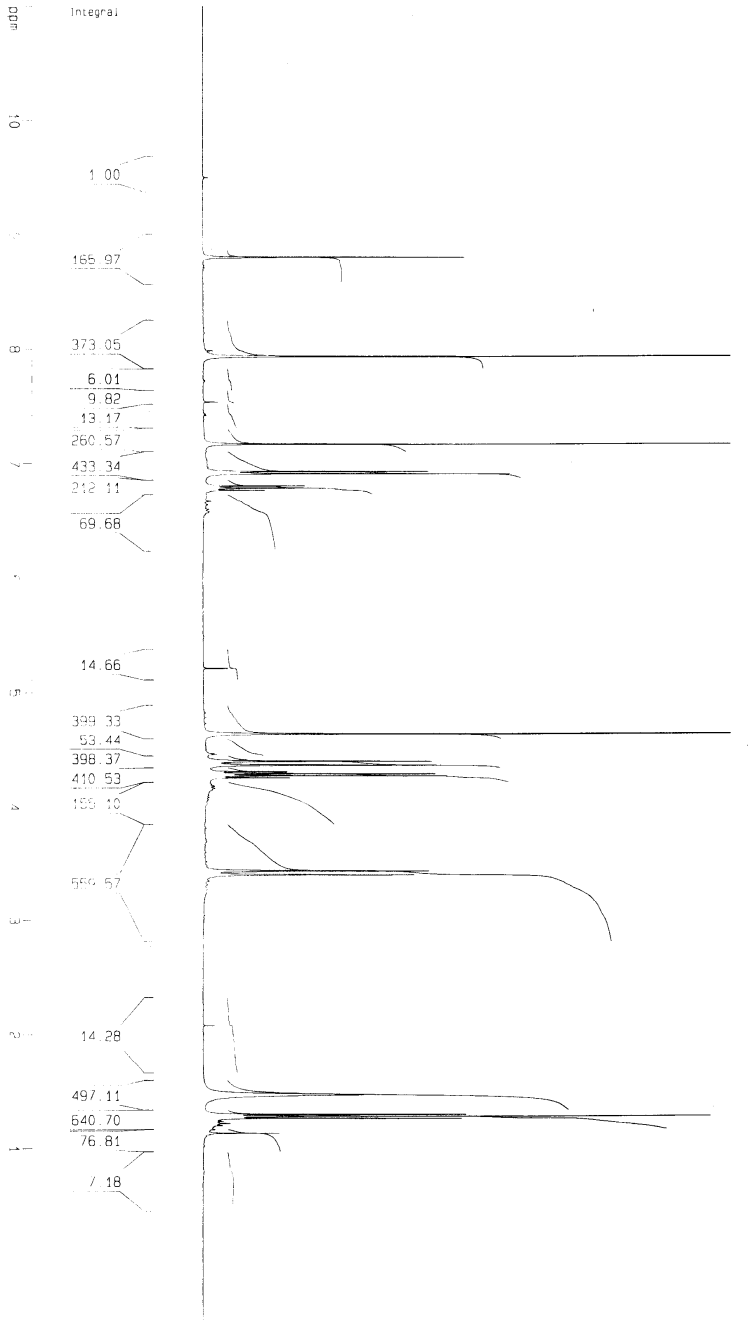


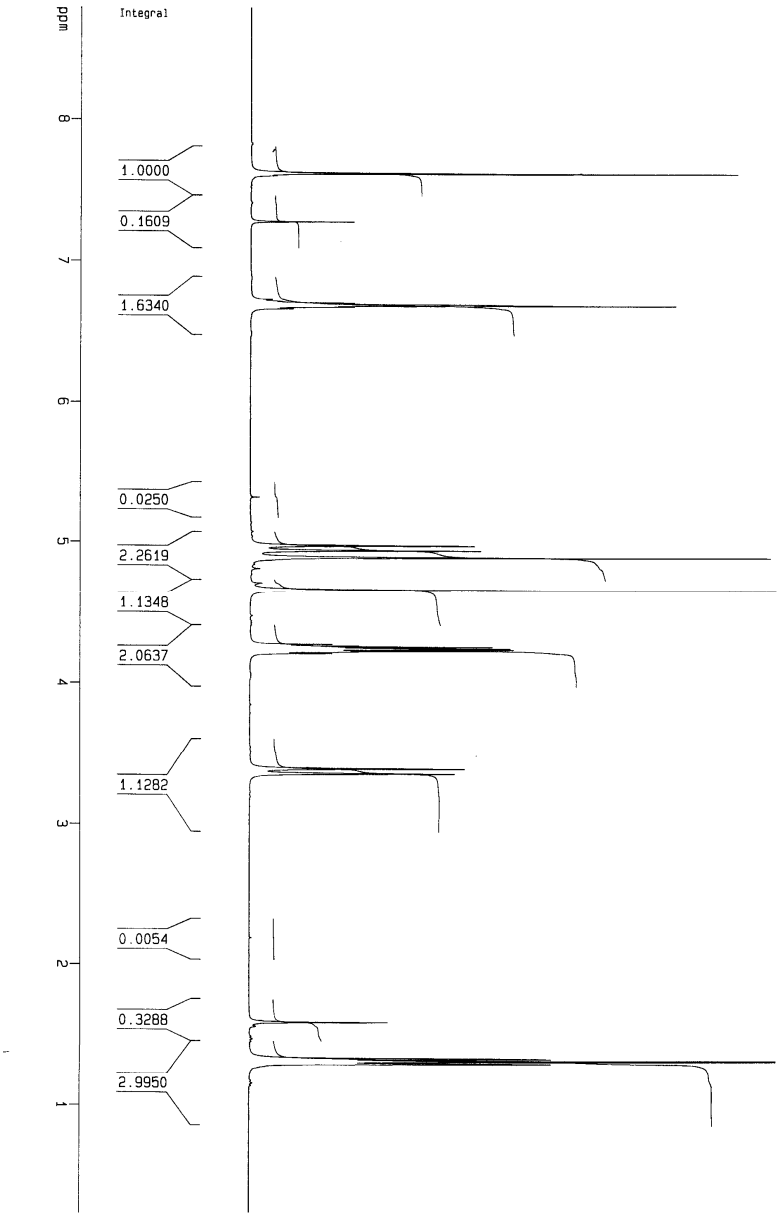
^{1}H NMR Bis[(ethoxycarbonyl)methoxy]-calix[4]arene (2.8)



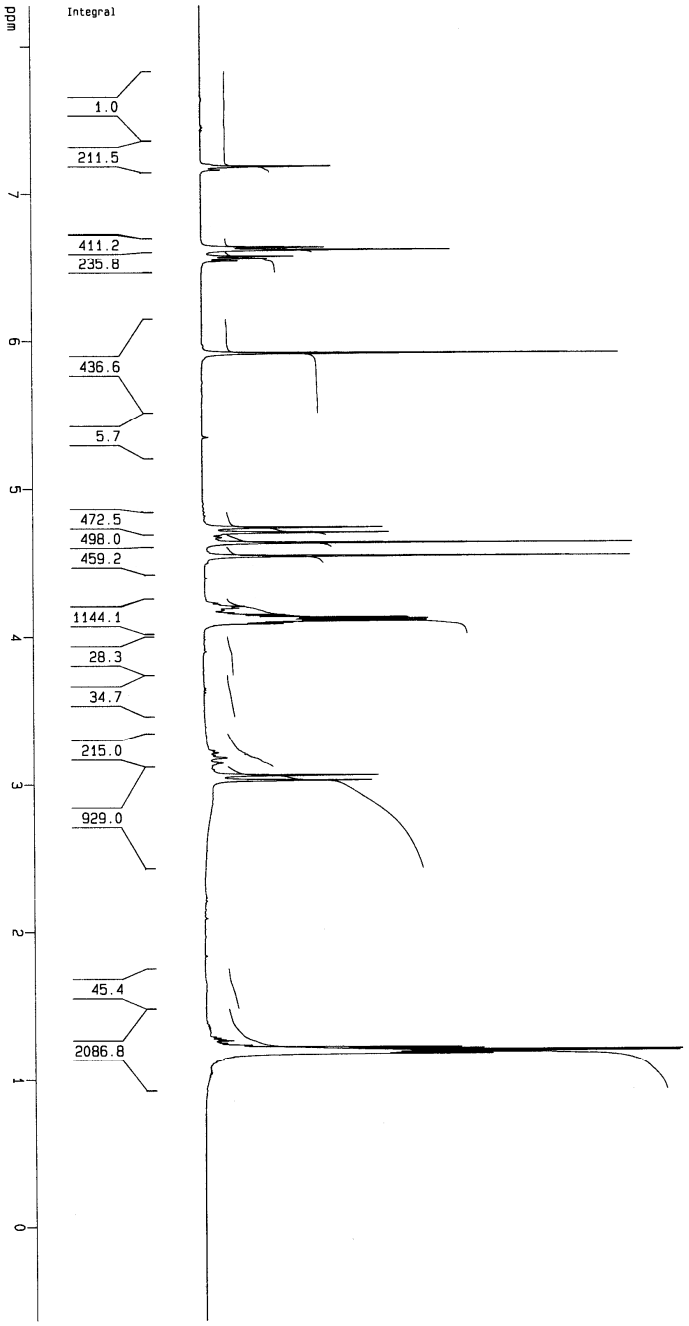
^{1}H NMR Bis[(ethoxycarbonyl)methoxy]-dinitro-calix[4]arene (2.9)



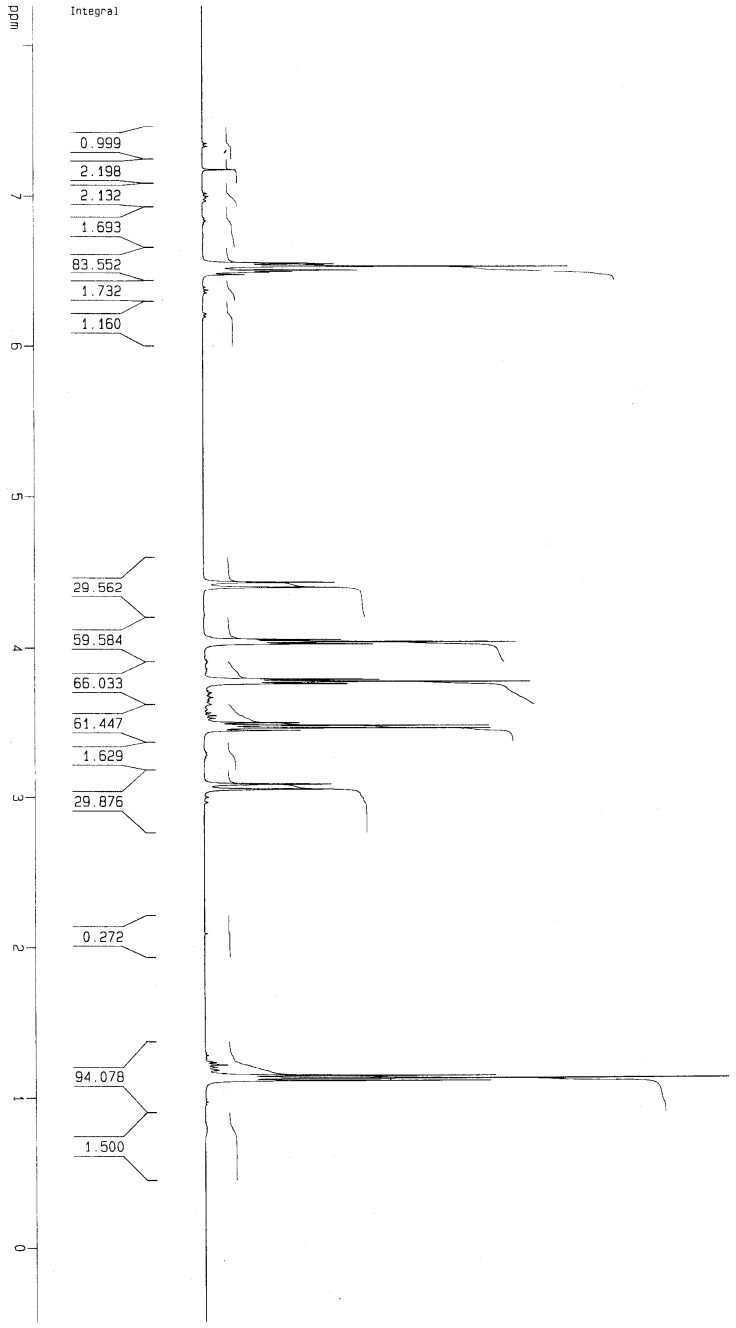
^{1}H NMR Tetrakis[(ethoxycarbonyl)methoxy]-dinitro-calix[4]arene (2.10)



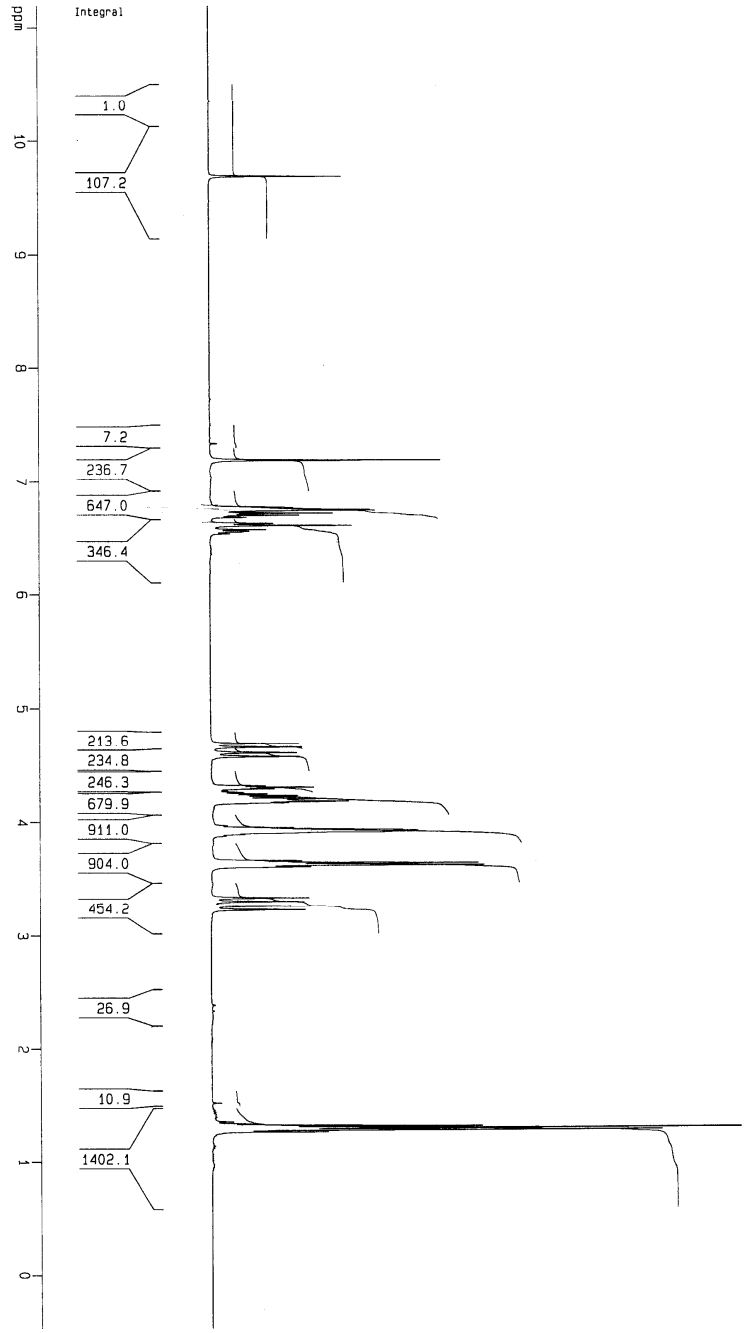
^{1}H NMR Tetrakis[(ethoxycarbonyl)methoxy]-diamino-calix[4]arene (2.11)



^{1}H NMR Tetrakis(2-ethoxyethoxy)calix[4]arene (2.12)



^{1}H NMR 5-Formyl Tetrakis(2-ethoxyethoxy)calix[4]arene (2.13)



^{1}H NMR 5,17-Bisformyl Tetrakis(2-ethoxyethoxy)calix[4]arene (2.14)