Cyclotriveratrylene Based Molecular Capsules: Synthesis, Characterization and Guest Entrapment

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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

PARDHASARADHI SATHA

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1. # First synthesis of a triazole bridged Cryptophane and guest entrapment studies **Pardhasaradhi Satha**, Giriteja Illa, Chandra Shekhar Purohit

= pertaining into this thesis

Conferences attended

1. Participated and presented Oral presentation in JNOST-2015 organized by NISER-Bhubaneswar from 14-17th December- 2015
2. Participated and presented a poster in IGCBIC-2014 organized by IISC-Banglore from 10-12th September 2014.
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4. Indo-European symposium on Frontiers of Chemistry, November 10-12, 2011, conducted at School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhubaneswar, India.
5. Participated in Chemical Research Scholar Meeting (CRSM-2011) organized by IGCAR from 14-15th July-2011.
6. National Seminar on Frontiers in Chemistry, November 11-14, 2010, conducted at School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhubaneswar, India

PARDHASARADHI SATHA

Dedicated to

My Amma , Nanna

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CONTENTS

SYNOPSIS

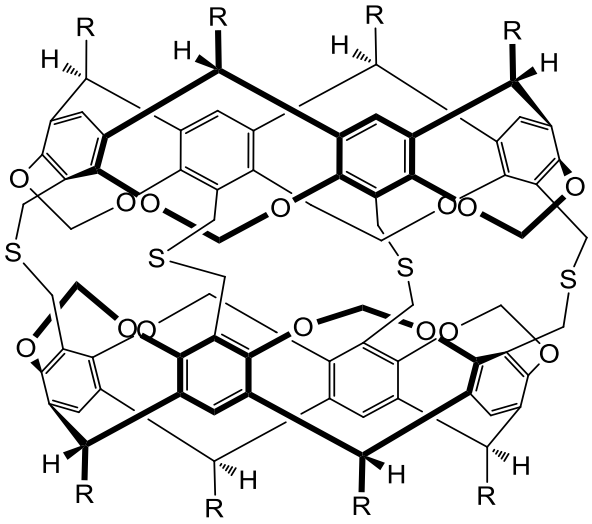
Molecular capsules are the molecules or supramolecules, which have space inside to accommodate foreign molecules. The accommodated guests are of different types, ranging from simple solvent molecules, drug molecules or unstable reaction intermediates.[1] Molecular capsules are a matter of intense study because of its possible interdisciplinary applications during last few decades.[2] Bowl shaped, or cone shaped molecules may assembled in to capsular structure with aid of different binding forces. The concept of molecular capsules has been started from Cram's molecular cavitands and Lehn's Cryptands which are connected via covalent bonds.[3-5] Besides covalently connected cavitands, cryptands different non-covalent forces have been used to prepare capsules.[6]

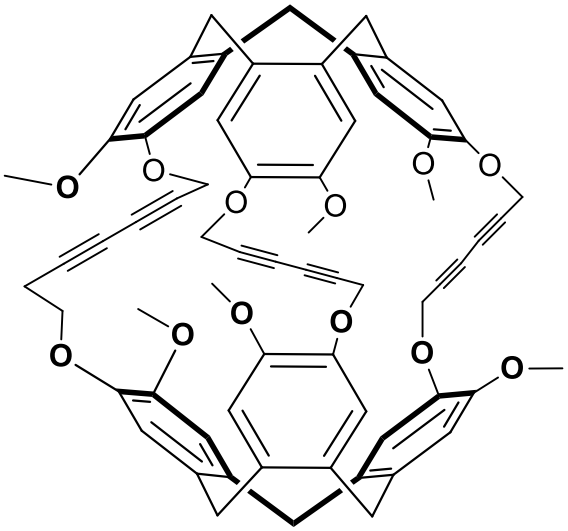
This area of research is relatively new and therefore most reports are based on synthesis and different guest binding properties and only a few applications is currently studied. Cyclotriveratrylene(CTV)and its derivatives which are stable in the bowl shape were shown to form cryptophanes, connected by covalent bond and metal mediated cages. CTV and its derivatives based molecular capsules has not been explored thoroughly.[7,8] Hence, the main objective of this thesis is to investigate CTV based non- covalently linked molecular capsules. The thesis is organized into the following five chapters.

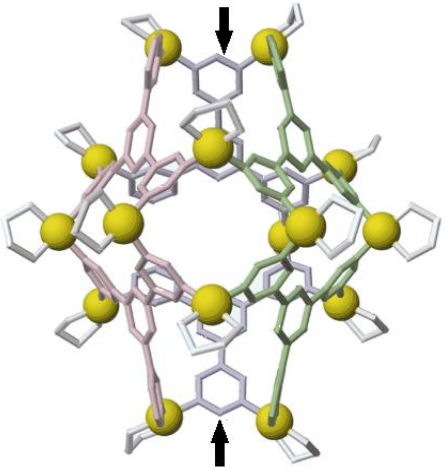
Chapter 1: Introduction (Molecular Capsules – An Evolution)

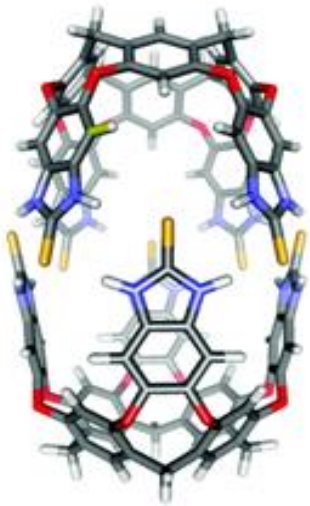
A general introduction about molecular capsules which includes various strategies,such as covalently linkage, non-covalent interactions, metal mediated formation etc. are discussd. The idea of using non covalent interactions in supra molecular chemistry for creating variety of molecules is learned from nature's self assembly and molecular recognition. Variety of molecules used to prepare molecular capsules viz. Resorcinol[n]arenes, Calix[n]arenes, Pyrogallol[n]arenes, cyclotriveratrylene and its

derivatives, Rebek's Tennis Ball and softball has been discussed.[9-11] Fujita's novel concept called molecular panelling, which provides a way to convert planner molecule in to 3-D molecular cages with aid of metal binding along with synthetic strategies applied by Fujita to synthesize variety of cages has been reviewed in this chapter.[12-16]Also, applications, functional properties of molecular capsules are explained, including storage of unstable molecules and using them as reaction chambers, catalysing the reactions has been discussed. Finally, the chapter ends with discussing the scope of the present thesis.









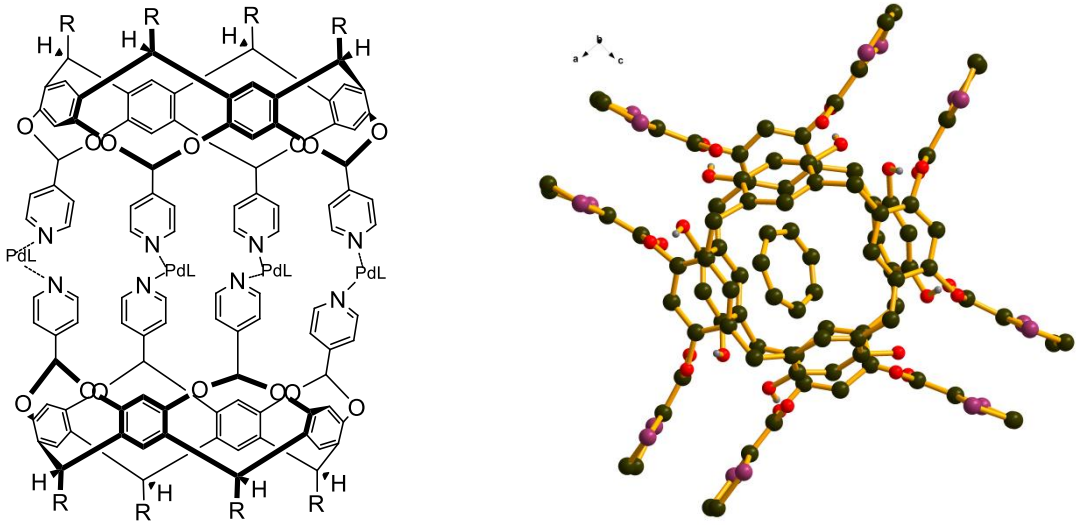


Figure.1: different molecular capsules discussed in chapter-1: a) cram's carcerand b) cram's Cryptophane c) Fujita's metal cage d) Rebek's capsule based on self assembly e) Resorcarene's cavitand based Metalo capsule f) A guest induced molecular capsule

Chapter 2: Propeller shaped self-sssembled molecular capsules: synthesis and guest entrapment

This chapterdescribes hydrogen bonded molecular capsules based on Cyclotricatechylene (CTC), and its guest entrapment. Cyclotricatechylene (CTC), is a bowl shaped molecule with six phenolic groups as potential hydrogen bond donors. In this work, we utilize this hydrogen bonding capability of CTC to generate the supramolecular complexes with hydrogen bond acceptors such as 4,4'-bipyridine, pyrazine, 2,2'-bipyridine and phenanthroline. These supramolecular entities were studied in solid state by X-ray crystallography and scanning electron microscopy. They are not soluble in low polar solvents. Therefore, hydrogen bonding behaviour in solution could not be studied by NMR. Except in case of pyrazine, capsular supramolecular assemblies were formed in all the cases. One of these capsules was studied for guest entrapment.[17] Planar molecules like naphthalene and pyrene, phenantrene were trapped inside its cavity with a little reorganization of the capsular assembly. We further studied the effect of changing

phenanthroline to 9,10-phenanthraquinone where the two more oxygen atoms have been imported capable of forming hydrogen bonds with phenolic hydrogen atoms besides nitrogen atoms of phenanthroline.[18]

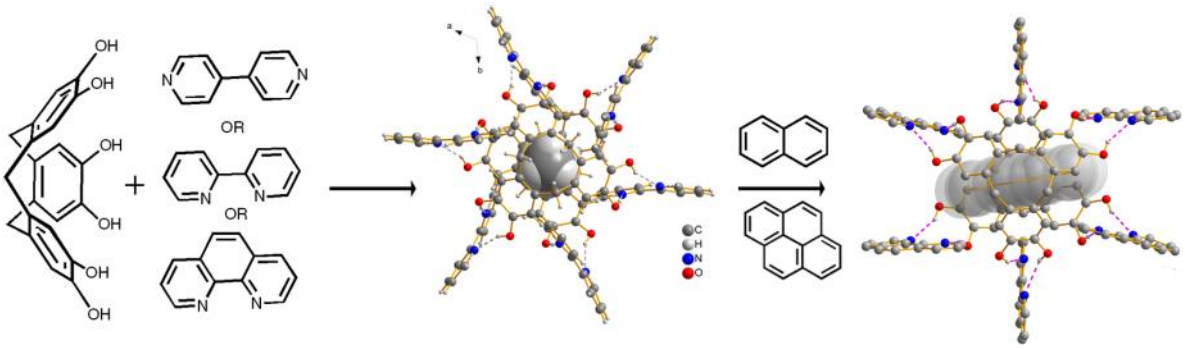


Figure.2: Over all essence of the chapter-2

Chapter 3: Bio-inspired self-assembled molecular capsule

This chapter reports a molecular capsule synthesized from biologically relevance molecules. Continuing our previous work on CTV and its modified based capsules we further synthesized hydrogen bonding based capsule which is a mimic of A-T base pairing of DNA. Bowl shaped molecules are useful for making molecular capsules with suitable non-covalent bond. Bowl shaped Cyclotriguaiacylene can be suitably modified at its phenolic groups for attaching suitable functionality to construct molecular capsule.

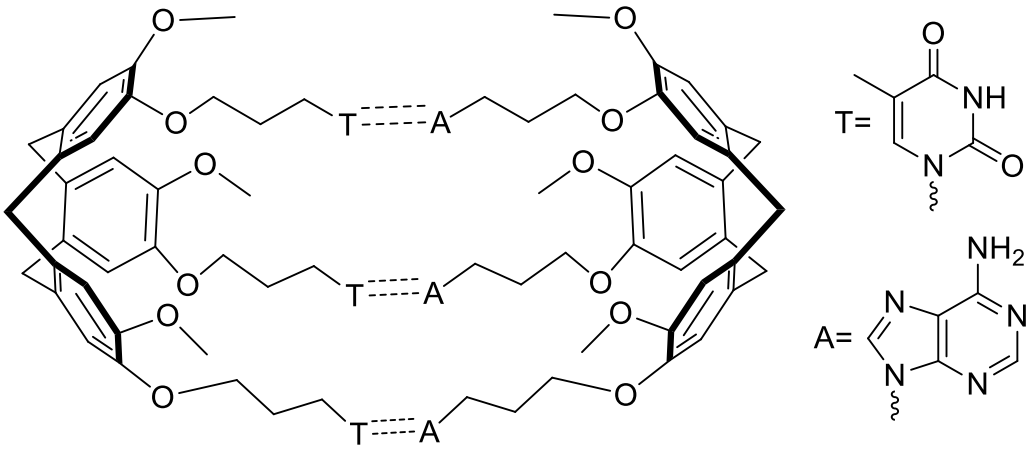


Figure.3: The summary of chapter-3

In this work, a molecular capsule has been prepared by appending adenine and thymine to Cyclotriguaiacylene.[19] These blocks when mixed in mixture of solvents give a molecular capsule as ascertained by mass and NMR spectroscopy.

Chapter 4: Guest induced, self assembled molecular capsule

Molecular capsules form due to various interactions between molecules. Cyclotricatechylene (CTC) due to its poly phenolic nature shown to form capsule under highly basic conditions. We successfully synthesized a molecular capsule under ambient conditions, from CTC by addition of a guest molecule. The capsule formation most probably is through pure electrostatic interaction between the guest and CTC. Confirmation of the capsule formation has been obtained, using solution studies, such as NMR and Mass spectroscopy. The solid state structure obtained by single crystal X-ray diffraction, corroborates well with these findings. Also, through other studied we proved, anions do not contribute to the capsule formation. By increasing size of the guest molecule the capsular structure has been disrupted and resulted in supramolecular assemblies. Cyclotricatachylene(CTC) is forming hydrogen bonding with halide anions Cl-, Br-, which are characterized by single crystal X ray-diffraction

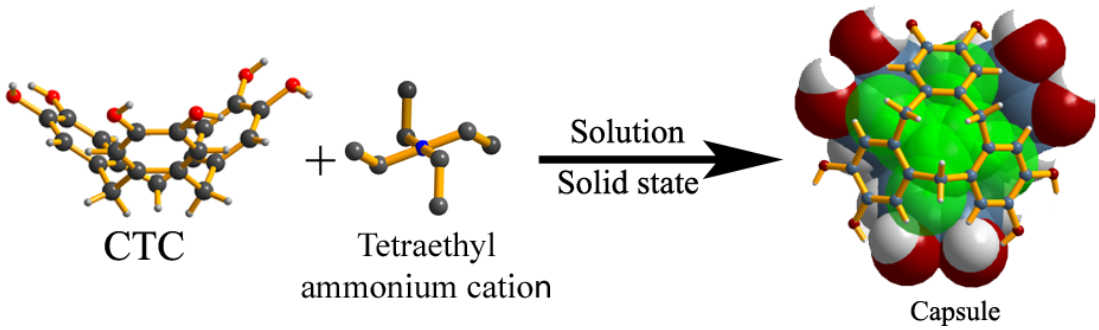


Figure.4a: Formation of molecular capsule induced by guest (tetraethyl ammonium cation)

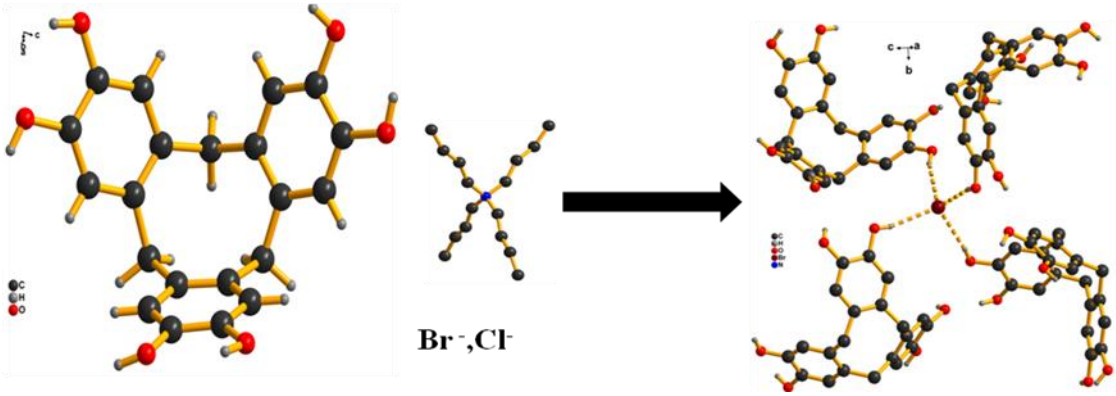


Figure.4b: Breaking of the capsular structure after increasing the guest size (tetrabutyl ammonium cation)

Chapter 5: A novel triazole bridged extended cryptophane

Cyclotriguaiacylene(CTG) a derivative of CTV has three methoxy and three phenolic oxygen atoms, the phenol groups can be easily modified for preparing molecular cryptophanes. Cyclotriguaiacylene(CTG) is known to form cryptophanes, a variety of cryptophanes were synthesized by imposing suitable ether spacers between two (CTG) units. Cryptophanes were used for different applications entrapping small organic, inorganic molecules as guests. The ability of crpytophanes to bind noble gas Xe as guest leads a special place due to its important role in biomedical applications.[20] Two different methodologies were proposed to synthesize cryptophanes direct method and template method. We used the later strategy by joining vanillyl alcohol azide to Propargyl-CTG unit which leads to, three triazole bridged rings between CTG and vanillyl alcohol (a pre cryptophane). The pre cryptophane cyclised using a lewis acid $BF_3.(OEt)_2$ which leads formation of two diastereomeric cryptophanes. This chapter will emphasize on the methods used to synthesize covalent capsule constructed by bridging triazole moieties with aid of click reaction,

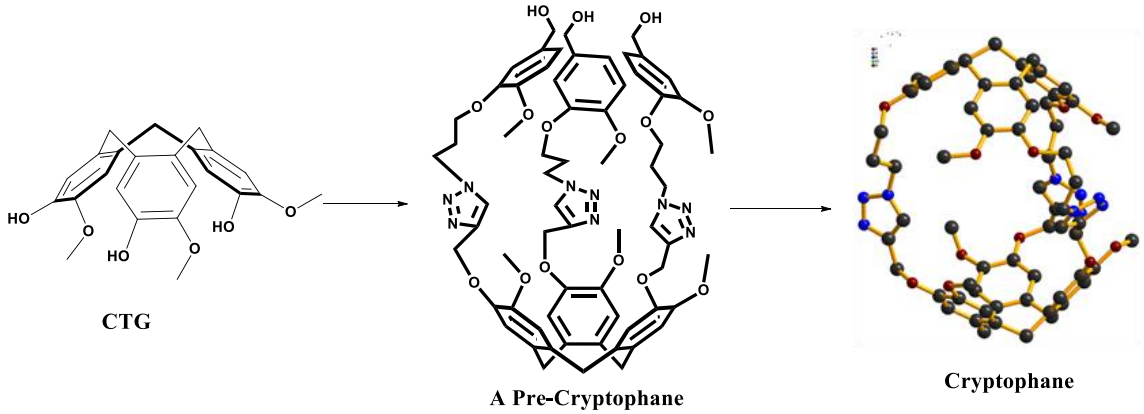


Figure.5: Schematic represntation of triazole bridged cryptophane

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List of Abbreviations

CH_3CN	Acetonitrile
AD	Adenine
$BF_3.OEt_2$	Borontrifluoridediethyletherate
BBr_3	Borontribromide
Br^-	Bromide ion
BF_4^-	Tetrafluoroborate ion
Cl^-	Chloride ion
CCDC	Cambridge crystallographic data centre
$CHCl_3$	Chloroform
CD_3OCD_3	Deutriated acetone
CD_3OD	Deutriated methanol
$CDCl_3$	Deutriated chloroform
CD_3CN	Deutriated acetonitrile
CTV	Cyclotriveratrylene
CTC	Cyclotricatechylene
CTG	Cyclotriguaiacylene
DCM	Dichloromethane
DMDAP	Dimethyl diazo pyrenium
DOSY	Diffusion ordered spectroscopy
BPBD	4, 4’-biphenylbisdiazonium
DMF	Dimethylformamide
DMA	Dimethyl acetamide
DFT	Density functional theory

DNA	Deoxyribonucleic acid
DMSO	Dimethylsulphoxide
FT-IR	Fourier transformation infra red
EtOAc	Ethyl acetate
ESI	Electron spray ionization
equiv.	Equivalents
RT	Room temperature
KBr	Potassium bromide
K_2CO_3	Potassium Carbonate
SEM	Scanning electron microscopy
h	hours
min	minutes
PEG	Poly Ethylene Glycol
NMR	Nuclear magnetic resonance
H_2SO_4	Sulfuric acid
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
UV	Ultraviolet
TLC	Thin layer chromatography
TMS	Tetramethylsilane
p-TSA	*para*-toluene sulphonic acid
PAQ	9,10-phenanthraquinone
PF_6^-	Hexafluorophosphate ion
2,2’Bpy	2,2'-bipyridine
4,4’Bpy	4,4'-bipyridine

Phe	1,10-Phenanthroline
Ty	Thymine
Na_2SO_4	Sodium Sulphate
$^{+}NEt_4$, TEA	Tetra ethyl ammonium cation
$^{+}NMe_4$, TMA	Tetra methyl ammonium cation
$^{+}NBu_4$,TBA	Tetra butyl ammonium
$HClO_4$	Perchloric acid
DIPEA	N,N-Diisopropylethylamine

CHAPTER 1

Molecular Capsules – An Evolution

1.1 Introduction: Molecules are of different shape and sizes ranging from simple linear molecules such as hydrogen to naturally occurring complex proteins, carbohydrates and nucleic acids. Proteins, for example has 1D to 3D shape depending upon its function in cell, whereas DNA remains mostly in double helical structure. Out of this vast kingdom of molecules, there are molecules, those are having space inside, large enough to engulf other atoms or molecules. In other words, these molecules can surround other molecules or ions to act as host. This class of molecules are called molecular container or molecular capsules. Enzymes are naturally occurring molecular container. Synthetically, these molecules can be obtained using different strategies utilizing covalent link to non-covalent interactions such as hydrogen bonding, cation-π interaction and metal mediated coordinate bond. The usage of non-covalent interactions for creating these molecules are inspired by natural self-assembly such as DNA and proteins.

The concept of molecular capsules has been started from Cram's molecular cavitands and Lehn cryptands, which are connected via covalent bonds.[1-3] The cavitands and cryptands were used to isolate small cations and solvent molecules from bulk solvent. This area expanded and numerous molecules were reported in literature during past three decades. Few of these will be discussed in the coming sections. Researchers soon realised that poor yield, limited space and unable to release the guest are the limiting factor for these compounds to be useful. The next strategy applied to make such molecules are non-covalent interactions, which can be broken under suitable condition. Here, hydrogen bonding is used in majority because of its directionality, complementary and reversibility, more importantly predictability.

When we compare the traditional covalent and non- covalent approach for synthesizing molecular capsules, both of the methods having its own merits and demerits. For example, non-covalent approach require less number of synthetic steps in comparison

with covalent approach, self-assemble in solution without any external interference and opens up under suitable pH change are the major advantage of this method. Another advantage of non-covalent approach is the dynamic nature of non-covalent bonding, which is useful in selective uptake of molecules. However, it requires complementary functional groups to be tailored, care has to be taken for size and shape so that they assemble themselves and their instability in polar solvent, are the major constrains. The other non-covalent interaction with which capsules can be create is metalation. The major advantage of metal mediated capsules are their rigidity, water solubility, and stability of these compounds. These kind of capsules have been used as reaction vessel, isolation of molecules with unusual conformations, storage of unstable molecules. The major disadvantage of this type of capsule are their instability towards ligating molecules and solvents that breaks them apart. The other non-covalent interactions such as π–π stacking and guest induced and hydrophobic, electro static interactions can be used to synthesize the capsules.[4] Molecular capsules having its own applications starting from drug delivery, using them as reaction chambers, storing unstable molecules, sensing, separation science.

1.2 Molecular Capsules Constructed by Covalent Bond

1.2.1 Carcerands and Hemicarcirands

Cram coined the term cavitand in 1983, for molecules those contains cavity that can accommodate ions or molecules.[3] The first designed cavitand, for capturing small molecules was synthesized by Cram et al. in 1982 shown in (Figure 1.1). They use it as synthetic molecular vessels and studied its solvation properties.[3,5,6] Subsequently, they joined two cavitand to synthesize a molecule that can permanently capture guest inside and called it a carcerand.[2] In other words, carcerands may be defined as closed space

molecule, having enough void inside, to entrap the small molecules or ions permanently.[2,7] Different type of cavitands with different conformations by attaching pyrazine, quniaxoline, has been reported in literature.[8] A report from Rebek's group has described a deeper cavitand by attaching acenapthquinone, a hybrid cavitand by joining self-folding cavitand to porphyrin.[9]

Carceplexes are the *Carcerands* in which the guest molecule is imprisoned permanently and without breaking a covalent bond the guest molecule cannot escape. Hemi carceplexes are the carcerands in which the guest molecule can escape from its portals at higher temperature. Carcerands and hemi carcerands are the carceplexes and hemi carceplexes without the guest molecules inside of it.

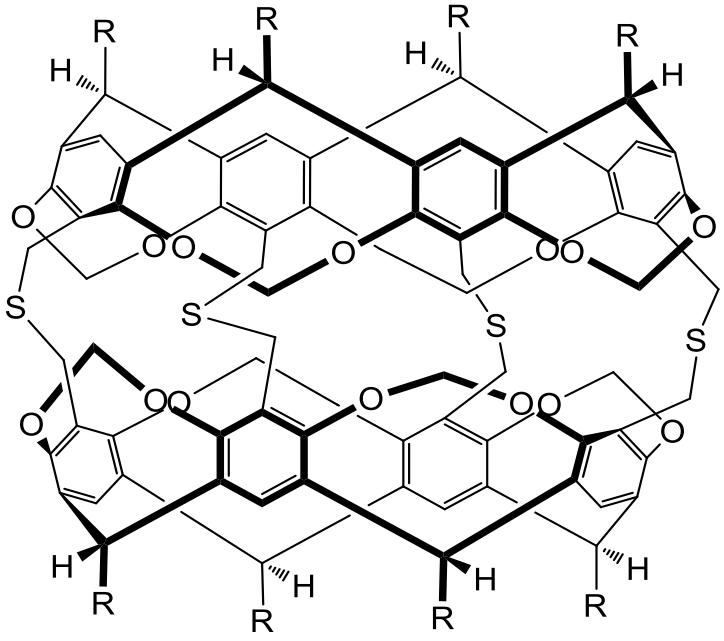


Figure 1.1. First covalently linked Carcerand

The first carceplex was synthesized by cram in 1988 that entrapped the solvent molecules used for synthesis and Cs^+ that was used as base.[10] Another hemicarceplex, with reusable cavity has been reported. Initially, it entrap the solvent molecules and on heating, they escape leaving the cavity empty. This cavity could entrap the Xe atom under suitable

condition.[11] A hemicarceplexs whose shell closure reactions depends upon the solvent used in the reaction which in turn acts as guest molecule.[12] A tetrathiol cavitand and carceplex derived it from was reported by crams group in 1995.[13] A hemi-carcerands with large internal cavity for entrapment of fullerene has been reported.[14]

A guest induced and guest resisted shell closures leads to different carceplexes, hemi-carceplexes has been reported by Cram's group.[15] Guest templated formation of a cage reported by crams group where in NMP act as poor template for cyclising using covalent approach where as pyrazine acted as best template in non-covalent approach to form a molecular capsule which is shown in (Figure 1.2.).[16] Extending the similar concept joining two of the carceplex to from a bis carceplex which has increased cavity size.[17] The bis-carceplex capped using 1, 3, 5 – (bromomethyl) mesitylene using K_2CO_3 as base lead to a giant carceplex which can entrap 3 DMF molecules.[18] The template effect in synthesizing the carcerand and carceplexs has been studied extensively.[19]

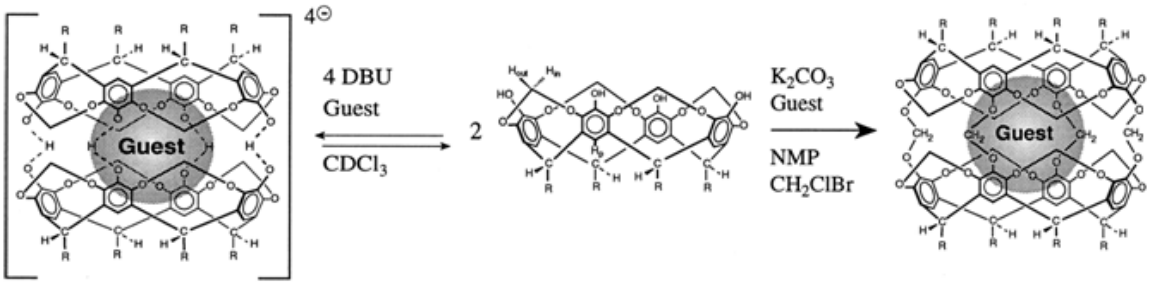


Figure 1.2. Guest induced formation of covalent molecular capsule

From a simple carcerand the covalent capsule has grown up to synthesis of super bowl container molecules in which multiple cavitand molecules were connected by covalent bond.[20,21] Recently a hemi carcerand has been converted into carcerand by photo-chemically.[22] A photo active hemi carceplexs has been synthesized in which a guest has been entrapped which is stable at room temperature and in dark upon irradiation to light

it releases the guest molecule.[23] In recent times a new cavitand system by replacing oxygen with phosphorus has been investigated and termed as Phosphocavitands.[24]

Cram's group also reported a water-soluble carcerand. This is synthesized by decorating carboxylic group on the aryl linker joining two carceplexs (Figure 1.3.a).[25,26] The evolution of water soluble cavitands and their properties such as guest binding, relation between the structures and guest binding etc are describe thoroughly in different reviews.[7,27-31]

The addition of new functional groups viz. aldehyde and boronic acid to resorcinarene cavitand leads formation of variety hemicarcerands (Figure 1.3.b). In 1991 Cram and co-workers reported condensation between a resorcinarene cavitand containing tetra-aldehyde with 1,3 diamino benzene that leads to a imine based hemicarcerand. This molecule was used to entrap variety of guest molecules ranging from ferrocene to 9,10 anthraquinone.[32] By replacing 1,4-benzenediamine with 1,3,5-tris(p-aminophenyl)benzene, various aliphatic amines resulted in rhombicuboctahedral nano capsule, octahedral nano capsules respectively.[33,34] The solvent dependence formation of octahedral nano container molecules was shown in 2006. Just by changing the solvent from chloroform to THF and DCM in presence of catalytic amount of lewis acid leads to different types of nano cages.[35] The formation of imine bond is in dynamic in nature was shown by J. Fraser Stoddart by encapsulating and releasing of the guest.[36] By replacing formyl group to boronic acid a covalent cages containing boronic acid ester linkages was formed.[37,38] A piperazine bridged resorcinarene covalent cage was reported by Kari Rissanen's group.[39] An extended cavitand based covalent chiral capsule has been synthesized which can entrap two guest molecules which form hydrogen bonding themselves has been reported by Rebek group recently.[40]

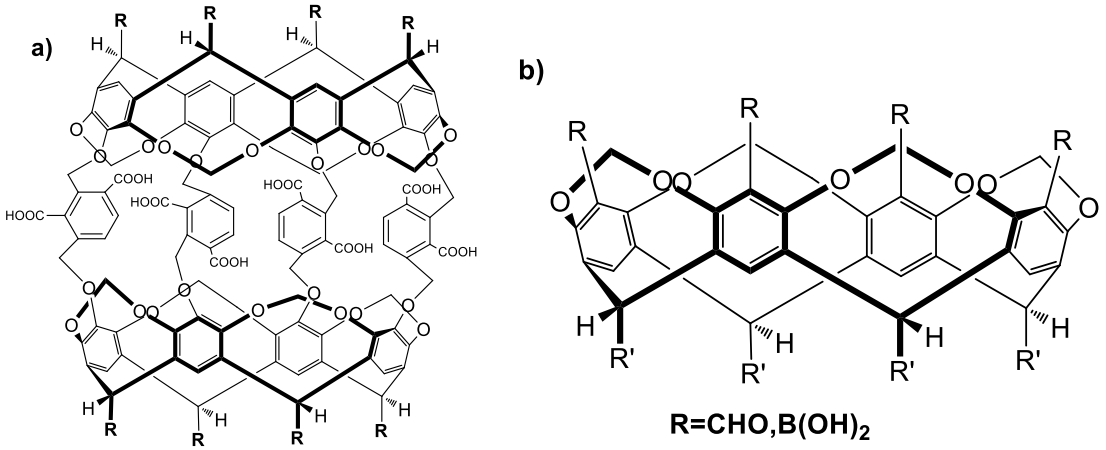


Figure 1.3. Molecular carcerands with variable functional groups

A new era of covalent capsules has been started by using calix[n]arene as a building block by Bohmer et al in 1989.[41,42] Calix[n]arene is a cone shaped molecule with rigid structure which meets the ideal criteria to be a precursor for covalent cages.[43] In 1994 Michael T. Blanda et al reported a Bis(calix[4]arene) with symmetric structure and could able to entrap *p*-xylene.[44] A prototype calix[n]arene without bridge with head to head arrangement by c-c bond formation has been reported in 1998.[45] A cocktail molecule by combining calix[4]arene and resorcinarene based cavitands has been invented and called as holand molecule (Figure 1.4.) but no guest entrapment has been found because of its rigidity.[46] A carceplex has been synthesized by joining calix[4]arene and resorcinarene, where stereoisomerism has been found with the rotation of C-N bond between amide linkages.[47] A hetrodimeric capsule by connecting calix[4]arene and resorcinarene with amide linkages in which the incarceration of the guest molecule took place in the final step of shell closure.[48] A self folding cavitand by joining two resorcinarene was synthesized and adamantyl and cyclohexyl derivatives were tested for the guest entrapment.[49]

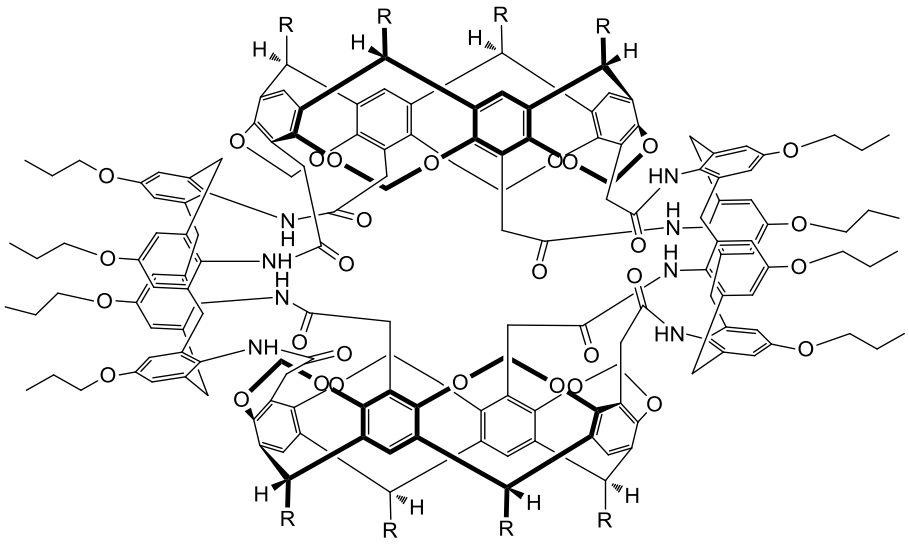


Figure 1.4. A calixrane bridged holand molecule

1.2.2 Cryptophanes

In 1915, Robinson synthesized a moleucle by reacting veratrole with formaldehyde in presence of acid and assigned the product as 2:3:6:7-Tetramethoxy-9:10-dihydroanthracene which was accepted till 1950. It has been proven wrong afterwards,[50,51] and renamed as cyclotriveratrylene with structure confirmed by x-ray strcture analysis.[52] This act as a starting material for a cryptophanes. Cryptophanes are the molecules made of two cyclotriveratrylene poining face to fact manner connecting with three bridges, releatively shorter bridges provides rigidity and spherical shape to cryptophanes **(**Figure 1.5.). Pioneering work in the cryptophanes area has been done by A. Collet and Colle`ge de France. The first cryptophanes has been synthesized by joining a cyclotriveratrylene with crown ether moleucle termed as speleands which can bind to small cations.[53]

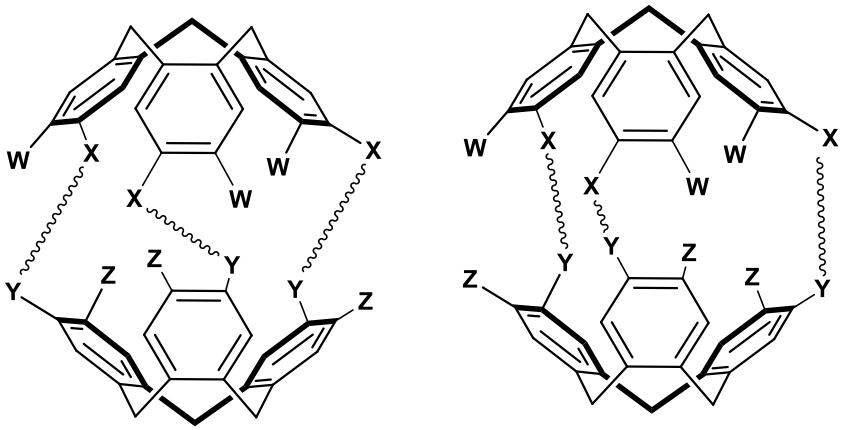


Figure 1.5. The anti and syn isomers of cryptophanes

The first cryptophanes was synthesized in 1981 by collet by joining cyclotriguaiacylene with vanillyl alochol and intermolecular cyclization lead to Bis(cyclotriveratrylenyl) Macrocage.[54] By repalcing cyclotriguaiacylene with cyclotribenzylene in 1985 collet synthesized cryptophane-C and cryptophane-D with two differnet configurations with wider windows. The cryptophane-C was used for optical resolution and to know the maximum rotation of Bromochlorofluro methane the smallest chiral molecule.[55] A water soluble cryptophane by varying the bridge lengths has been synthesized and used to entrap acetylcholine and ammoinium cations and the guest entrapment is depends upon the bridge length.[56] Cryptophane-A, Cryptophane-E was synthesized by varying the bridge length to n=2 and 3 respectively (Figure 1.6.). Methane, chloroflurocarbons were sucefully entrapped as guest in this cryptophanes.[57]

A cryptophane with aromatic bridges containing carboxylic acid groups has been syntheiszed and the cavity size is only sufficent to entrap solvent moleucles like, $CHCl_3$.[58] Following the similar strategy with exo ester m-xylyl bridged anti cryptophane has been synthsized and thermal behviour of its inclusion complex with THF has been studied. Because of short bridge units the moleucle has conformational flexibility.[59]

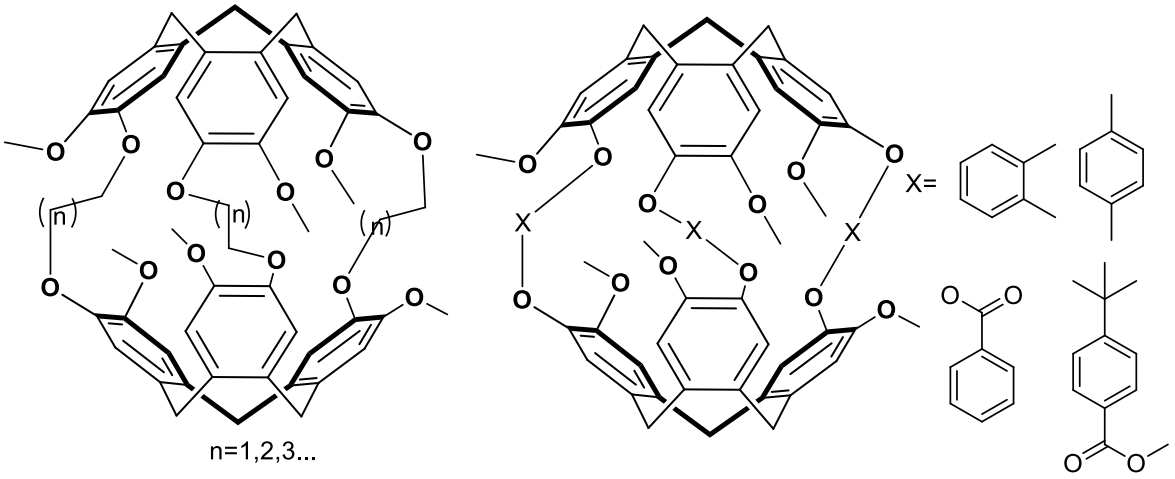


Figure 1.6. Cryptophanes of varible bridged length and functional groups

Coupling two aetylene functionalized cyclotriveratrylene moities with glasser coupling, resulted a rigid cryptophane shown in figure 1.7.,with syn and anti isomers. This cryptophane can trap the solvent organic molecules.[60] A duetrium labelled cryptophane was synthesized by Brotin and co-workers to study the environmental effects on xenon entrpment using NMR chemcial shift with ^{129}Xe.[61] By replacing the methoxy groups with thiomethoxy, a new family of cryptophanes have been syntheiszed. The bond between and C- SCH_3 can be cleaved using raney Ni which leads to formation of new functional molecules. Changing functionality varies in binding properties. These molecules are used to entrap the cations $^{+}NMe_4$, $^{+}NHMe_4$.[62] By selective demthylation of one of the methoxy group in the cryptophane leads to formation of functionalized cryptophanes cryptophanol, that can be used to join suitable functional groups for different puproses. A biotin molecule has been attached to the cryptophane (Figure 1.8.) which forms a biotin-xenon caged molecucle which binds to avidin.[63,64] A disulfide linked cryptophane cyclotrithiophenolene has been reported by joining the two cyclotrithioguaiacylene units with disulfide bond (S-Sbond) and shown to bind CH_4.[65,66]

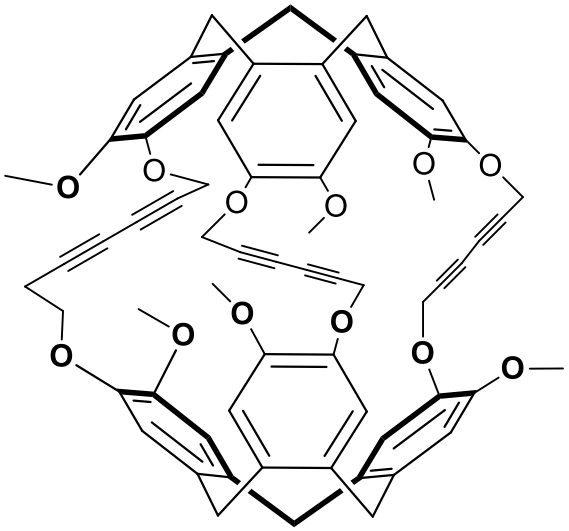


Figure 1.7. An Acetylinic bridged cryptophane

A bis cryptophane has been prepared from cryptophanol by joining them with different varieties of allkyl chains and its was tested to for ^{129}Xe binding. A notable variation has been obseverved for the encapsualtion of ^{129}Xe at two cryptophanes.[67] A functionalized cryptophane has been synthesized by attaching[Cp*Ru] to cryptophane-E (Figure 1.9.a), the cavity size has been increased because of the metallation and the π- acidic interior accepted anions as guest molecules.[68]

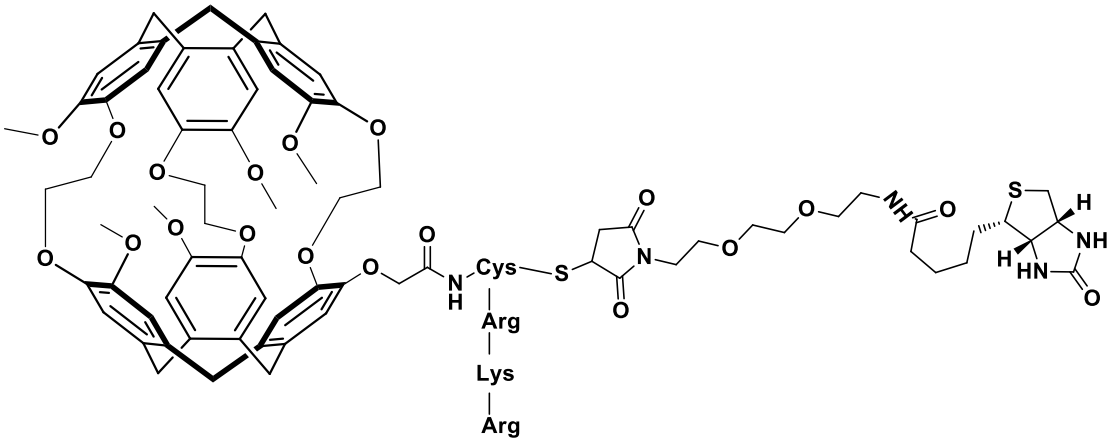


Figure 1.8. A Biotin attached cryptophane

Covalenltly linked hetro-dimeric capsule has been synthesized based on Boronate esterification. Cyclotricatchyelene is joined with boronic acid-appended hexahomo-trioxacalix[3]arene to form the covalently linked capsule. A guest molecule increase the rate of capsule formation and the capsule formation is in dynamic in nature. Also, it can be constructed and decomposed with respect to pH (Figure 1.9.b).[69] The condensation reaction is catalyzed by an acid at lower pH, that is how the capsule formation is pH dependent. A thorough discussion on cryptophanes will be covered in chapter-5. Complex formation by cryptophanes are also summarized in literature.[70,71]

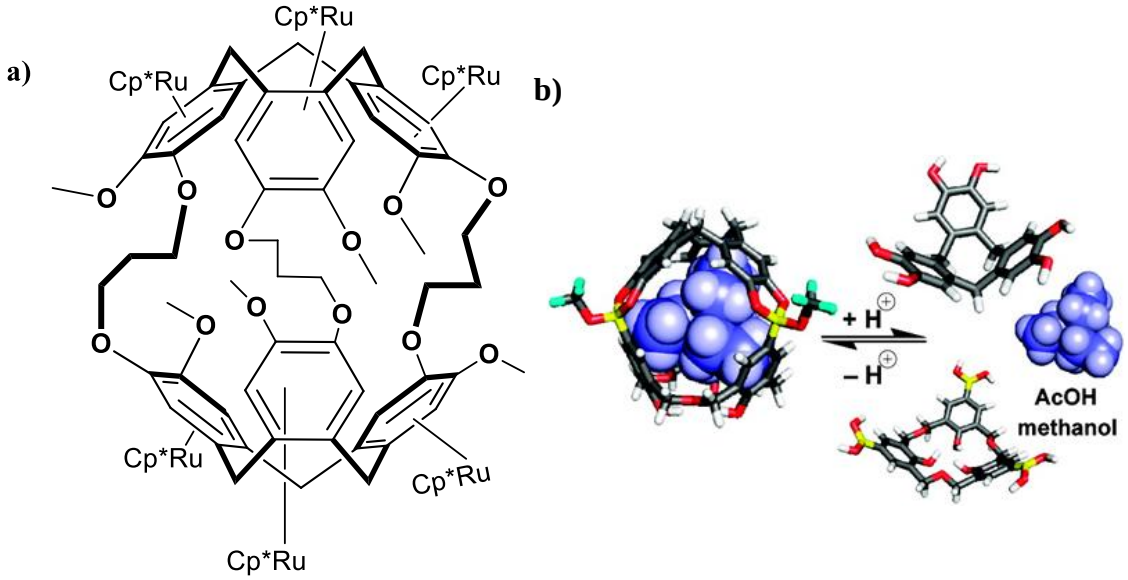


Figure 1.9. a) A Ru functionalized cryptophane b) A pH dependent cryptophane

1.3 Metalo supramolecular capsules

Molecular capsules or cages can be constructed by replacing the rigid covalent bond with flexible metal-templation. Where in the later strategy the bond formation is dynamic and in suitable solvent bonds opens up itself. A metal ion can organize a flexible ligand into different architectures raging from simple metalo-crown ethers to helciates, squares, rings, cages or capsules and recently more complicated bormean rings and solomon cube are also reported.[72-78]

1.3.1 Resorcinol[n]arenes based metalo capsules

The first metalo molecular capsule was syntheised by Enrico Dalcanale in 1997, by using tetra-cyno cavitand a half bowl shaped molecule on coordination with square planner metals Pd and Pt resulted in a rigid methylene bridged cage. The cage was confirmed by NMR and mass anyalysis. ^{19}F NMR studies revlaed the entrapement of counter anion CF_3COO^-. By extending their intial work, same group presented different varieties of cages and the anion binding effeicnecy of cages. They also prooved that the cage formation is entropy driven. In presence of a competitive ligand such as triethylamine, cage is distroyed and addition of tiflic acid that neutrlizes the base, the cage is restored.[79,80] The tetracyno cavitand and the capulse formed by using it, crystal strcture of the capsule is shown in figure 1.10.

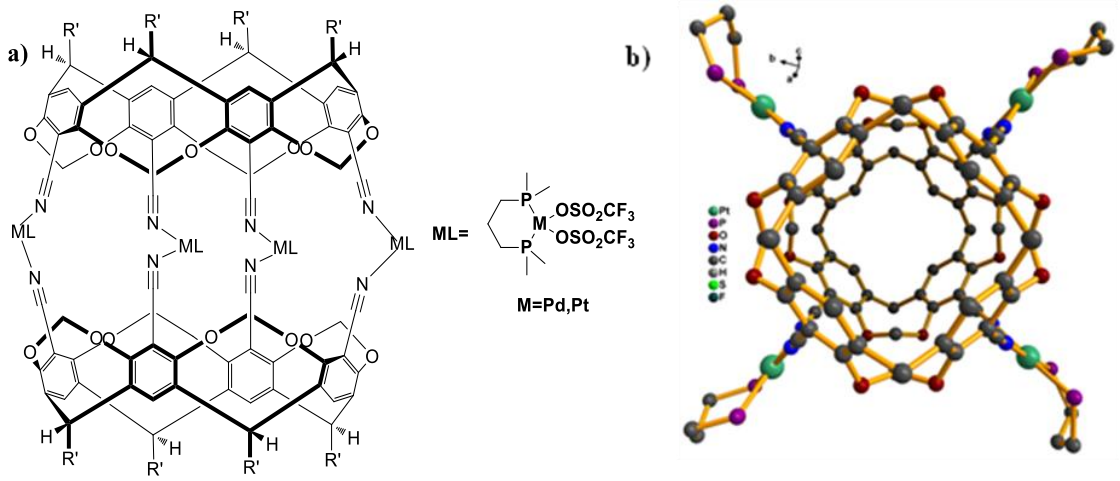


Figure 1.10. a) A tetracyano based metal capsule b) crystal strcture of the metal capsule(Hydrogen atoms are omitted for clarity)

In 1998 Roger G. Harrison reported a coordinated cage by joining imino-diacetate molecules to the upper rim of resorcin[4]arene -based cavitand (Figure 1.11.). By hydrolysing the ester groups, and addition of $CoCl_2.6H_2O$ after deprotonation of carboxylic acid functional groups with $Ba(OH)_2$, lead to coordinate cage. The same

group in 1999 reported a cage by appending $FeCl_2.H_2O$ to the resorcin[4]arene -based cavitand. This cage could entrap bromobenzene. In 2000 by extending their strategy used earlier, they could prepare coordinate cage that can entrap ethyl-benzene. The cage was tested for entrapping different organic molecules like benzene, hexane, chlorobutane, butanol, and ethyl acetate halogen-containing hydrocarbons, and polar organic molecules in water.[81-83]

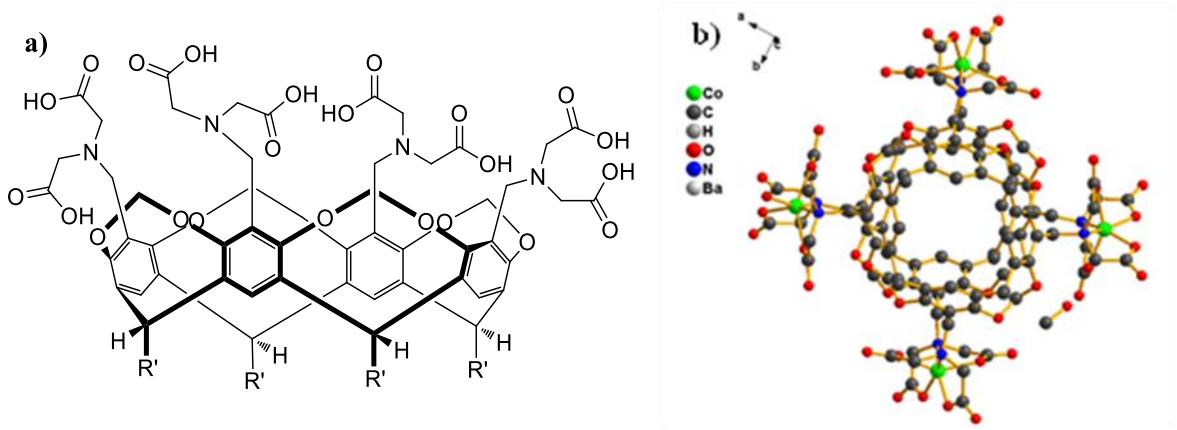


Figure 1.11. a) Schematic representation of Resorcin[4]arene cavitand appended with imino-diacid molecules b) Crystal structure of corresponding metal capsule formed with cavitand

Shinkai group utilizes the similar interactions that was used earlier by Enrico Dalcanale and demonstrated a cage by replacing the resorcin[4]arene with pyridine-containing homooxacalix[3]arene. By the complexation of Pd^{2+} with pyridine substituted homooxacalix[3]arene a cage that could entrap the fullerene molecule.[84] A porphyrin derivative containing pyridine units are shown to form a metalo cage with Pd^{2+} (Figure 1.12.a). Dipyidyl ethane formed inclusion complex with the cage with high association constant as studied by NMR.[85] A coordinated nanoscale cage has been synthesized by using tetrapyridyl-substituted resorcin[4]arene cavitand with Pd-complex (Figure 1.12.b),

N-methyl pyrdinium ion derivatives were encapsulated with the aid of cation-π interactions.[86]

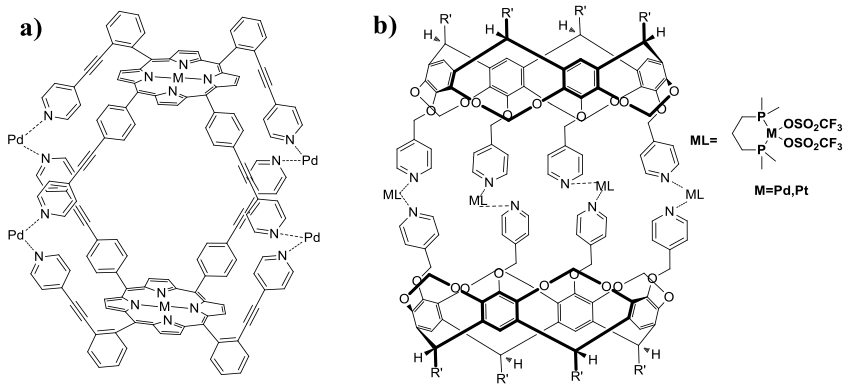


Figure 1.12. a) Molecular cage derived from porphyrin b) A metalo cage formed from pyridyl-substituted cavitand

Joining 2, 2' bipyridyl units to the resorcin[4]arene cavitand creates an extended cavity. Adding $AgBF_4$ to this molecule, a self-assembled cage molecule forms, which was confirmed by NMR, ESI-mass, the void space was proven to entrap large aromatic guest molecules (Figure 1.13.a).[87] Placing pyridine in the resorcin[4]arene cavitand as shown in figure 1.13.b, a rigid molecular structure forms. The pyridine coordinates with Pd^{2+}, lead to formation of a cage that has enugh space inside to entrap large molecule like methanol and C_{60}.[88],[89]

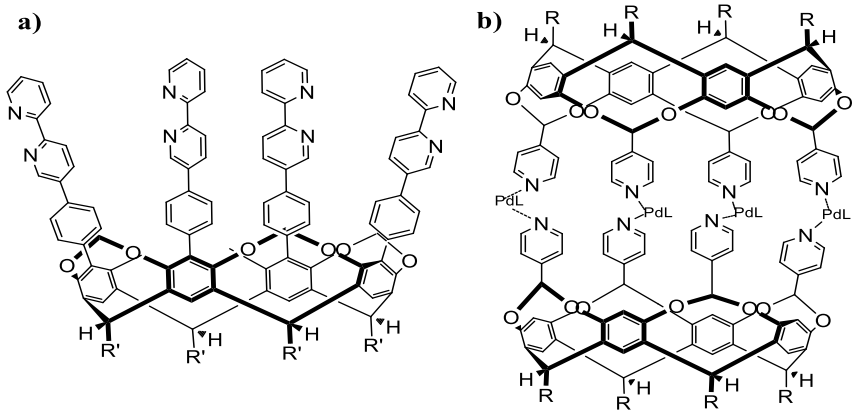


Figure 1.13. a) Schematic representation of phenyl bipyridine appended to a cavitand, which used to form deeper metal cages b) A metalo cage obtained from pyridyl resorcin[4]arene cavitand

Kobayashi group reported selective formation of homo and hetro cavitand cages via self-assembly in 2004. By mixing different functionalized cavitands in presence of metal, coordination complexes of homo or hetro cavitand were formed. Their formation was controlled by balancing kinetic and thermodynamic stabilities of cages. Addition order of cavtitand also have impact on the formation of specific cages.[90,91] In 2006, Paul D. Beer reported a polymetallic resorcinarene cage, formed by dithiocarbamate-functionalized cavitand with square planar geometry around the metals. The octa-nuclear cage (Figure 1.14.) is shown for confinement of fullerene.[92]

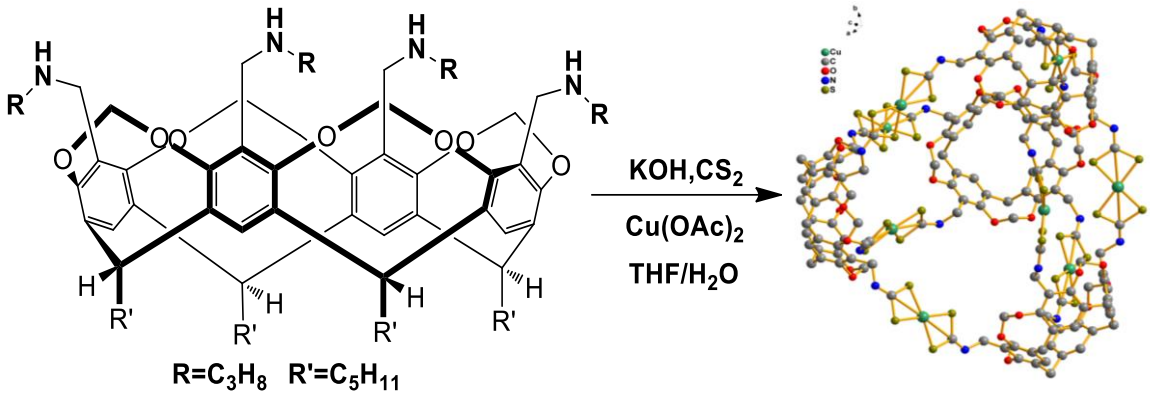


Figure1.14. Synthetic scheme of a resorcinarene cage, by dithiocarbamate-functionalized cavitand, crystal structure of the cage is shown (hydrogen atoms are omitted for clarity).

1.3.2 Pyrogallol[n]arene based metalo capsules

Pyrogallol[4]arene a polyphenolic molecule, was shown to form a giant metal cage (Figure 1.15.a), with six pyrogallol[4]arene units binding with 12 Ga(III) ions.[93] They further proved that the hydrogen bond still exits even after the metallation with gallium occurs. The capsular structures assembled due to hybrid of metal-ion coordination, and hydrogen bonds.[94] By changing the metal from Ga to Cu and attaching propyl alcohol functional groups to the lower rim of PgC_4 they got a hexameric cage which is structurally analogues to its hydrogen bonded PgC_4 capsule.[95]

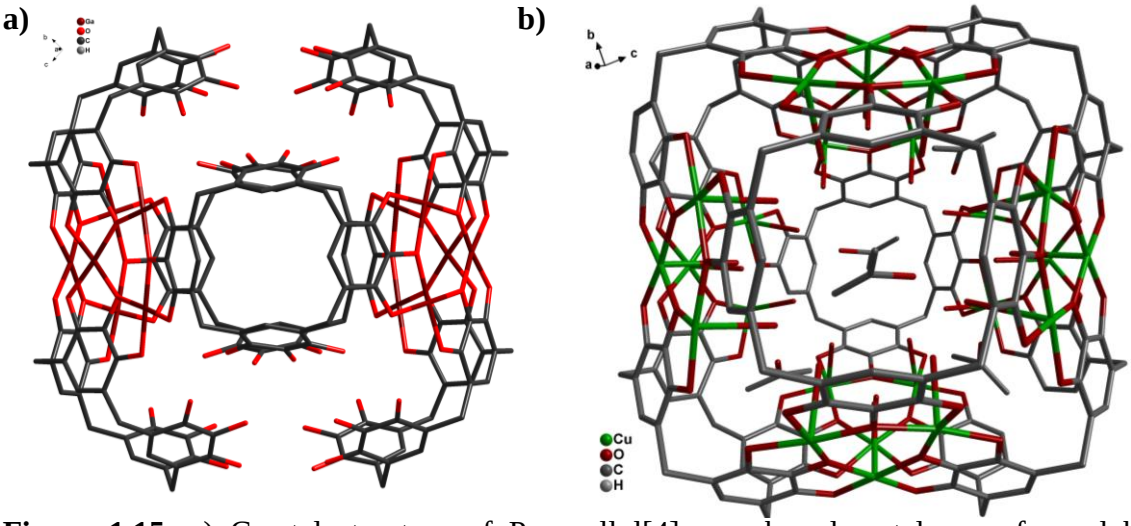


Figure 1.15. a) Crystal structure of Pyrogallol[4]arene based metal cage formed by binding with Ga(III) (hydrogen atoms are omitted for clarity) b) Crystal structure of hexameric metal cage (hydrogen atoms are omitted for clarity) formed by binding of Cu(II) with Pyrogallol[4]arene.

In 2006, the same group reported pyrogallol[n]arene based metallo-capsule with a main group metal Cs^+, two different functional groups attached to the lower rims of two different pyrogallol[4]arenes PgC_6, PgC_4Cl. Irrespective of the functional group discrimination two Pg's ended up in forming a head to head, offset molecular capsule with Cs^+ in $CH_3CN + H_2O$ mixture the CH_3CN occupies the void space.[96] Recently they further proved the sustainability of the metal cages by incorporating an external metal Cd into a preformed Ga based pyrogallol [4]arene cage. Although the Cd replaced some of the Ga in the cage and lead to an altered capsule arrangement with small portals for molecular exchange the capsular arrangement is still sustained even in the presence of a secondary incorporated metal.[97] For further details in metalo PgC cages, are available in the reviews and references cited there in.[98,99]

1.3.3 Cyclotriveratrylene based metalo-capsules

Cyclotriveratrylene a well-known molecule for its ability to form cryptophanes, can also form metalo- molecular capsules. Head to head arrangement of cyclotriveratrylene with

metal coordination have been used for this purpose. Abraham's group reported the first such cages with cyclotricatechylene. By deprotonation of cyclotricatechylene using Ca(II) as base and generating a anion that can bind to main group metal Vanadium ended up in formation of a tetrahedral type cage molecule (Figure 1.16.). [100]

In continuation of this work, they replace alkali cations to transition state metal, Cu(II) to find a highly symmetrical diamond like network of the tetrahedral cage.[101] The first report on cyclotriguaiacylene based cages was published by Yamaguchi group. They attached a pyridyl group to the upper rim of CTG and used Pd-pyridyl interactions to form a coordinated cryptophane.[102]

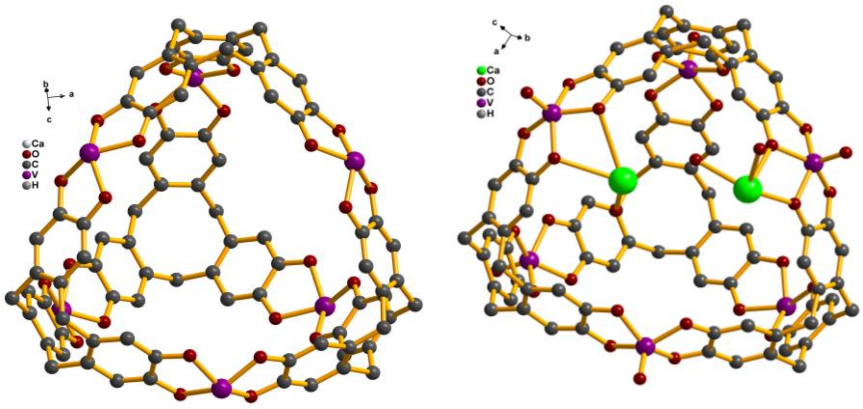


Figure 1.16. Crystal structure of tetrahedral metal cage formed by cyclotricatechylene

Michaele J. Hardie invented a new class of coordinated cages by imposing suitable metal binding site to the upper rim of cyclotriguaiacylene. A Tris-allyl-cyclotriguaiacylene molecule used to show the variable coordination modes of Ag(I) to the allyl group that resulted in discrete assemblies to more ordered cages and 3D networks, the formation of these assemblies depends on the reaction stoichiometry and reaction conditions.[103] Hardie's group introduce pyridyl derivatives to aza cyclotriguaiacylene. On binding to Ag(I) and a CH_3CN this molecule lead to formation of a dimeric capsule (Figure 1.17.a). Changing the position of hetero atom in pyridine ring resulted in different molecular architectures.[104] By incorporating isonicotinoyl groups to cyclotriguaiacylene, Hardie

group has created a tripodal ligand which on binding with Pd $(NO_3)_2$ self-assembled into an octangular cage (Figure 1.17.b).[105,106]

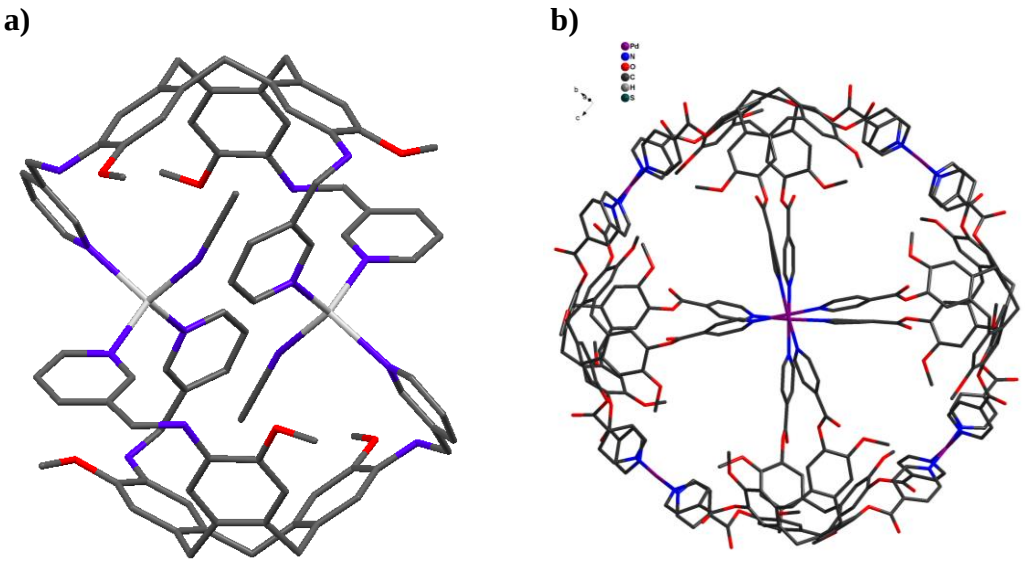


Figure 1.17. a) Crystal structure of dimeric capsule based on cyclotriguaiacylene. b) Crystal structure of octangular cage formed from cyclotriguaiacylene

Recently they reported an octangular cage with Pd(II) propyl substituted CTG. Addition of propyl group increases the solubility in a range of solvents. They have proved that the cage formation is solvent dependent and assembles in CH_3CN and CH_3NO_2 but not in the case of DMSO.[107] The same group has synthesized a metallo-cryptophane by modifying CTG with pyridine, pyrimidine (donor-N of the pyridine at 3rd position). They form either form M_3L_2 type complex or interlocked architecture on complexation with 3 equivalent of Ag(I).[108] Another metallo-cryptophane has been explored by them in 2011 by reacting CTC with methyl-3,5-bis(bromomethyl)-benzoate. On hydrolysis, it resulted a cavitand where three carboxylic acid groups are pointing outwards (Figure 1.18.a). Metallo-cryptophane with CTC are made when suitable bridge molecule viz. 1,2-bis(4-pyridyl)ethylene (BPE) are joined and metalated with $Cu(OAc)_2$, or $Co(OAc)_2$.[109] Very recently their group synthesized a metallo-cryptophane decorating with a N-hetrocyclic carbene (NHC) (Figure 1.18.b). This porous material used for single crystal to single

crystal transformation with different guest molecules such as 1,2-Dichlorobenzene and Iodine.[110,111,112]

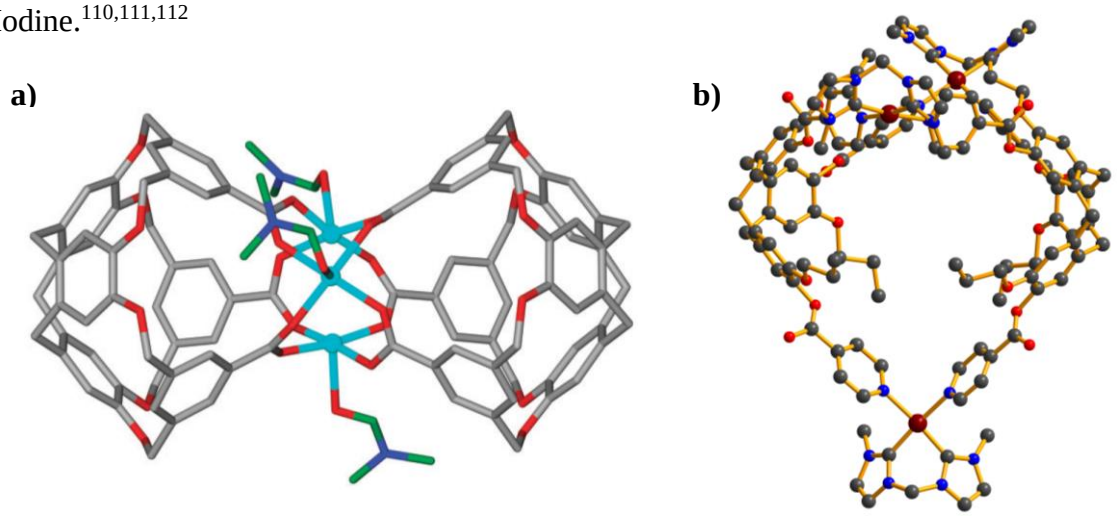


Figure 1.18. a) Crystal structure of A bow-tie metallo cryptophane(Hydrogen atoms are omitted for clarity) b) A metallo cryptophane decorated with N-hetrocyclic carbene

1.3.4 Molecular Paneling

In 1990's Makoto Fujita invented a new technique called molecular paneling, which means creating elegant 3D supramoleucalr architectures through coordination from planner molecules (Figure 1.19.). This concept showed a separate route for preparing capsular or cage like assemblies without using bowl or cone shaped molecules. In simple words in this approach, molecular tetrahedron can be created by using bringing four triangular panels together by metal coordination the same case with octahedron bringing eight triangular panels.

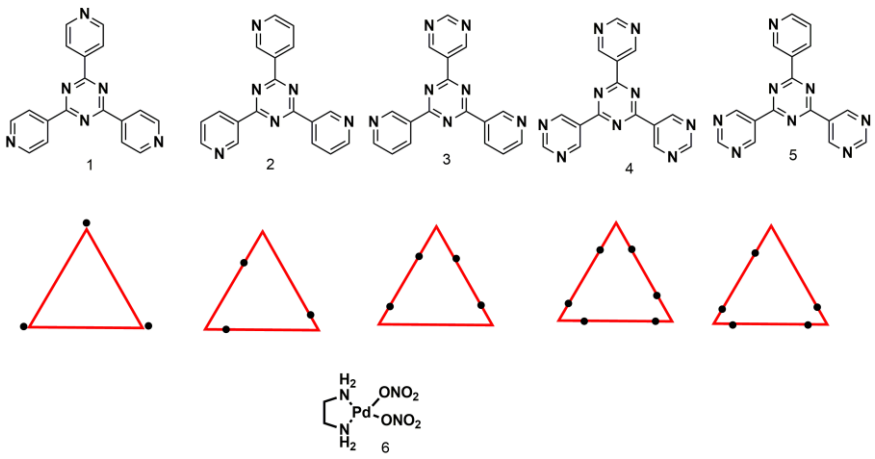


Figure 1.19. Schematic representation of Molecular panelling

The first report on molecular panelling was used to synthesize an octahedral M_6L_4 assembly where a terpyridine derivative is used. This on treatment with cis protected-Pd metal forms the cage. The octahedron cage formed by binding the metals to the corner of four terpyrdine units, the product is thermodynamically stable which conformed by excess addition of the metal did not effected the formation of the product. The cage is shown to bind large organic guest molecules such as adamantine carboxylate (Figure 1.20.).[113,114] Utilising the similar strategy, they have reported a kinetically stable cage by replacing Pd(II) with Pt(II), but the cage formation is relatively slower in this case. Increasing the temperature and presence of a guest molecule viz. adamantine carboxaldehyde increased the yield and rate of formation. The shape of the cage is preserved even after removal of the guest molecule, which is quite rare in induced formation of the cages. The cage is stable even under different harsh acidic or basic conditions.[115] Suitably designed planer molecules were used to form bowl shaped molecule with Pd(II) coordination. At the corners, these cavities are hydrophobic, because of the Pd(II) atoms but the outer surface is hydrophilic. Two of such bowl shaped molecule self-assembles in to a molecular capsule with six organic guests confined inside of it (Figure 1.21.).[116]

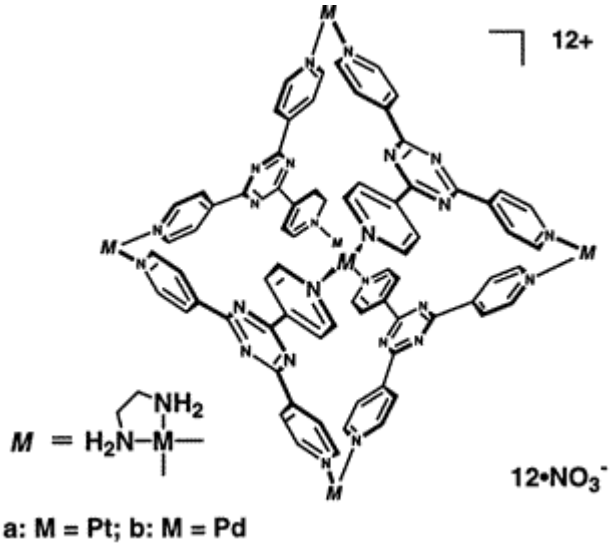


Figure 1.20. An octahedral cage formed with aid of molecular panelling concept

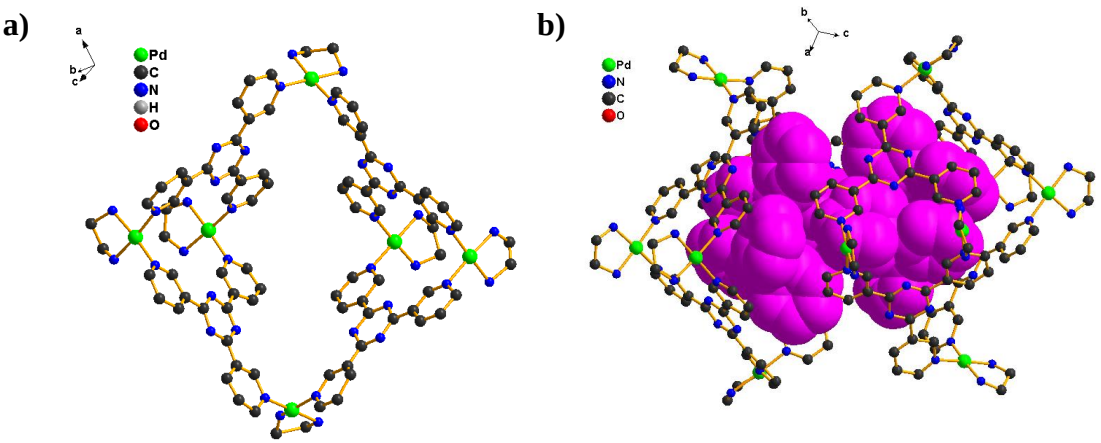


Figure 1.21. a) Crystal structure of the octahedral cage b) A dimeric capsule formed by using the cage molecule and guest molecules are shown in space-filling model (Hydrogen atoms are omitted for clarity)

A nanometer size capsule which is in hexahedral shape has been syntheiszed by Fujita group.This is generated by 24 components, out of which sixteen are metal ions. Although the cavity size is 900Å^3 because of the tightly packed arrangment neither the moleules from outside can enter into the cage nor the molecules trapped inside of the cage can leave.[117] By modifying the the earlier strategy and leaving one binding site free in the panel molceule as shown in figure 1.22., the same group synthesized a coordinated cage with clefts.Through this clefts the guest molecule can go and leave the host molecule.[118] Similar concept has been applied for preparing different molecular cages.[119-123]

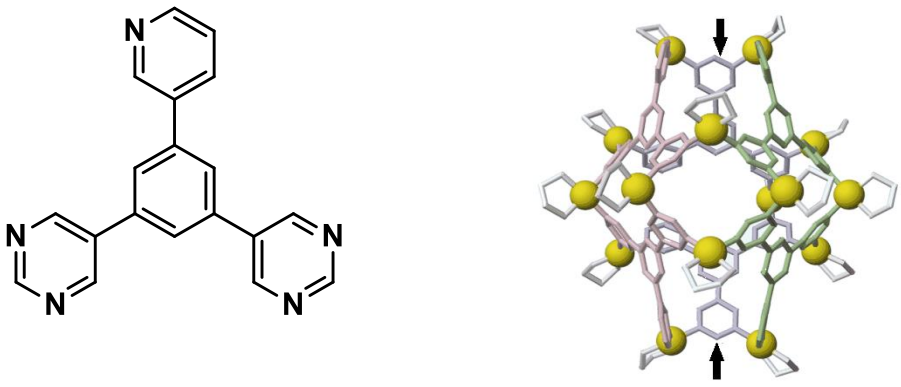


Figure 1.22. Chemical strcture of the ligand used to synthesize a moleuclar cage with clefts, crystal structure of the cage molecule.

1.4. Self Assembled Moleuclar capsules

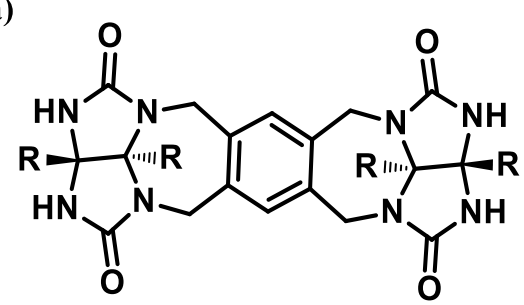
1.4.1. Glycouril capsules

Although molecular capsules can create via self assembly of metal ligand interactions it has its own pros and cons. On positive side, it can be water soluble, stable in polar solvents and reversible. But its rigidity and instability in ligating solvents are the nagetive side. There are different forces which can lead to self assembly viz. Hydrogen bonding, π–π interactions, hydrophoblic effect, guest induced, vanderwalls forces etc. Self assembly through hydrogen bonding occupies the majority of all, because of its directionality, complementry nature, reversiblity and plastity of this bonding which can open in change in environments. In this section we will dicuss the role of self assembly in molecular capsules leaving the metal ligand which already has been discueesd earlier.

We can define self-assembling capsules as assembly with enclosed cavities that are formed by the reversible non-covalent interaction of two or more, not necessarily identical, subunits. Because of large number of reports and to simplify this topic, we will divide this section two parts. 1) we will discuss about the non bowl shaped molecules converted in to bowl shaped capsules with aid of complementary nature of the functional groups and 2) capsules formed by cyclic shaped molecules, which are in bowl shaped.

The first hydrogen bonded molecular capsule based on non-cyclic molecules came into picture after the discovery of Rebeck's glycouril based spherical assembly. They named it as tennis ball, which is a result of glycouril unit with two complimentary functional groups joined by a durene unit.[124] The halve moiety of the tennis ball (seven member ring between the glycouril unit and phenyl group gave the curvature shape to the half unit) dimeriszed and form the capsule (Figure 1.23.). This capsule is characterised in solution phase by NMR and Mass spectroscopy.

a)



b)

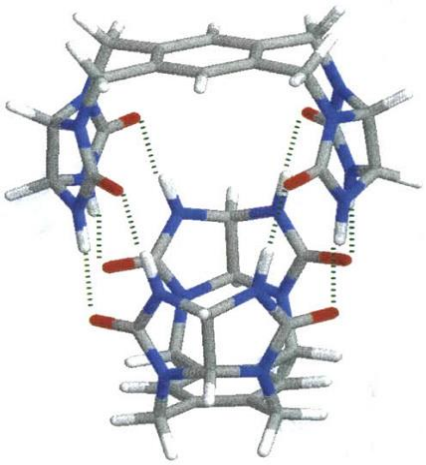


Figure 1.23. Two glycouril molecules joined by a durene molecule b) Cartoon representation of the glycouril units self-assemble to form a capsular structure.

Continuing their work, they further proved that the cavity space was sufficient to entrap small molecules viz. CH_4 confirmed by the up field shift of NMR peak.[125] Different verities of glycouril monomer molecules with various functional groups, varying the bridging and spacer group have been synthesized. The monomers shown to form dimeric capsule with the aid of hydrogen bonding, different hetro dimeric capsules were also formed by mixing two different monomers. The formation of the specific capsules can be controlled by guest molecule addition. Selective absorption of methane over ethane has also been reported.[126] Increasing the solubility of the capsule by imposing suitable functional groups to the glycouril units, reversible encapsulation of Xe controlled under acidic- basic conditions has been reported by the same group.[127]

To increase the void space of the capsule to encapsulate larger molecules, Rebek and his co-workers have created a new type of assemblies and named it as soft balls. By increasing, the size of the spacer between the glycouril units retaining the curvature shape for dimerisation to occur, they synthesized soft ball with 13 fused and 1 bridged rings. The soft ball dimerized in benzene-d6 which itself acted as a guest molecule. However, in toluene-d_8 case the capsule was not formed. They studied different guest

molecule as guest. Out of which they found adamantine carboxylic acid, ferrocene carboxylic acid are the best for dimerizing the capsule.[128] They further improved their strategy by introducing hydroxyl functional group to the soft ball (Figure 1.24), to increase the number of hydrogen bonding sites. Due to more hydrogen bonding, the capsular arrangement is preferred over aggregates. The soft ball was shown to exchange of the guest molecule under NMR scale, binding of guests by this capsule is also entropically driven.[129]

a) **b)**

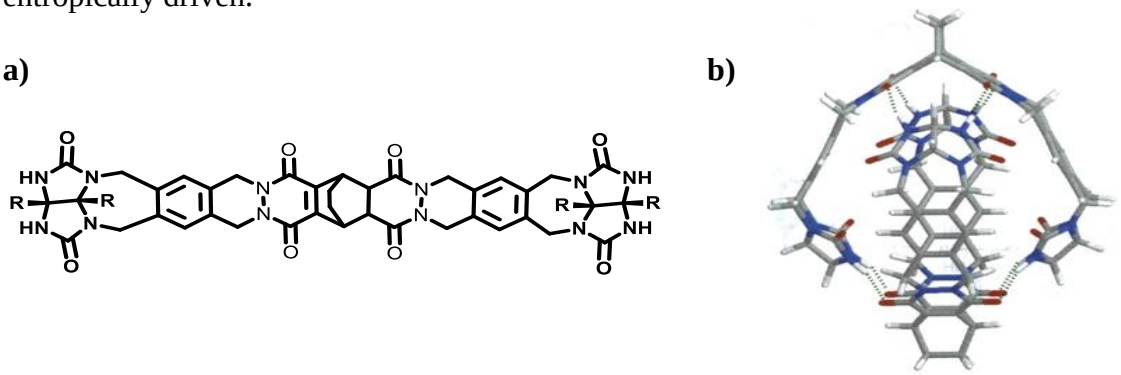


Figure 1.24. a) Chemical structure of the precursor used for synthesizing softball b) Schematic representation of softball

A chiral capsule has been synthesized by the same group by incorporating different R groups to the two ends of glycouril tape monomers, on association they formed a chiral capsule which can clatharate naturally occurring chiral molecule camphor and its derivatives.[130] The capsule size was controlled by changing the bridging group from phenyl group to ethylene. They used two bridging groups in the same monomer; even though symmetry has been reduced, but the monomers self-assemble themselves resulting in chiral capsules. By varying the guest size, the specific diastereomeric complexes formed preferentially over the other. Guest with functional groups which can form hydrogen bonding with them were the ideal guests to entrap in.[131] A structural modification to the tennis ball by joining them via triphenylene units lead to a new class of monomer, which on dimerisation leads to a new assembly called Jelly Doughnut.

Cylcohexane was chosen as suitable guest to bind reversibly and they have studied the ring inversion dynamics of cyclohexane in the capsule.[132,133]

A non-chiral capsule has been synthesized by adding sulfamide and hydroxyl group to the bridge phenyl ring, which on self assembly, leads to a capsule shown in Figure 1.25b. Inside environment is chiral which can distinguish two entatiomers, having special affinity for ketones.[134] The readers can find more details about glycouril based capsules in the reviews and reference cited there in.[135-137]

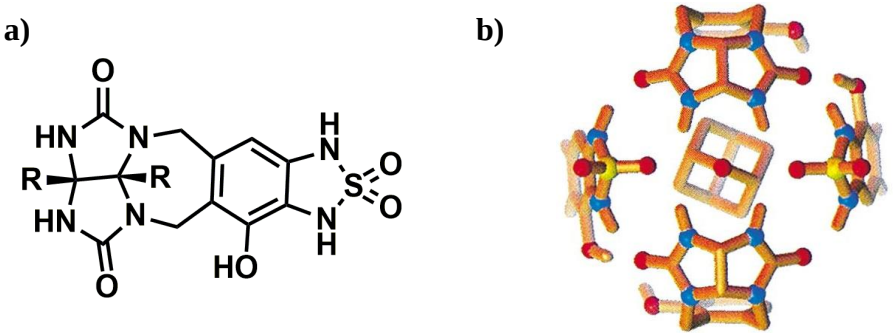


Figure 1.25. a) The chemical structure of glycoluril with cyclic sulfamide functionalities b) Energy-minimized structure of a tetrameric assembly of **1.25a** and entrapment of 2-adamantone

1.4.2. Cyclophane based self assembled moleuclar capsules

In cyclophane based molecular capsules, we will focus on moleucles which are bowl shaped, half spherical, cone or cylindrical shaped which on assembly leads to a closed capsule like structure. Calix[n]arene, Resorcin[n]arene, Pyrogallol [n]arenes, cavitands and cyclotriveratrylene derivatives based capsules will be explored in this section. Calix[n]arenes possess a bowl shaped conformation, which is similar to half-closed capsular topology. When two of such molecules are brought together in rim-to-rim arrangement with complementary functional groups, it ends up forming capsule with aid of hydrogen bonding.

Julius Rebek reported a calix[4]arene based capsule, where in they functionalized the upper rim with 4 urea groups, which offers 8 hydrogen bonding sites. (Figure 1.26.) The half molecule on dimerization leads to formation of capsule with 16 hydrogen bonds, the cavity was sufficient to entrap ethyl benzene or *p*-xylene.[138,139]

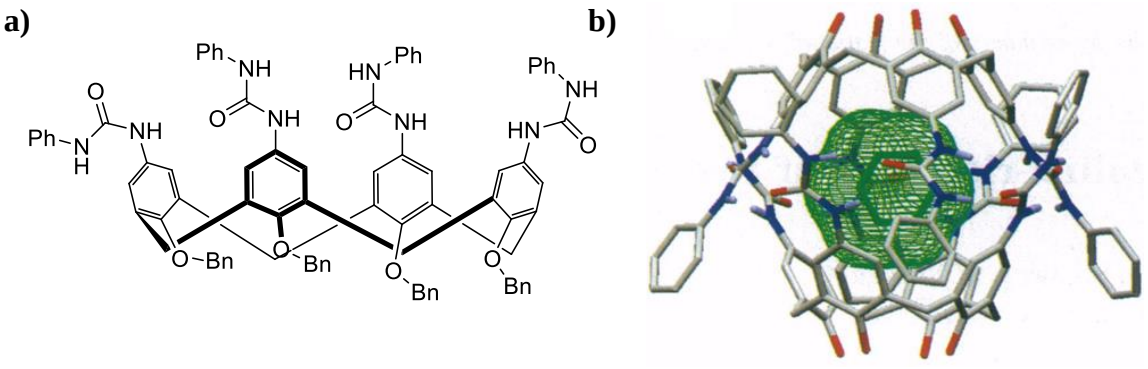


Figure 1.26. a) Chemical structure of calixarene used for formation of dimeric capsule b) Energy minimized structure of the capsule and entrapped benzene molecule is shown in van der Walls' surface

Crystal structure of different lower rim substituted calix[4]arene has proved beyond doubt that the capsule structure exists in solid state. The solution phase capsular structure was proven by Volker Bohmer. A calix[4]arene based dimeric capsule which can bind the guest molecule in reversible way was shown by Rebek and his co-workers in continuation to their work.[140,141] A hydrogen bonded molecular capsule that is stable, even in DMSO has been reported by Bohmer. By stitching tri- and tetra-phenyl groups to the upper rim urea moiety which entraps the $^{+}NMe_4$ cation, offering stability to the capsule by cation-π interactions; so much so that this capsule is stable up to 4 days.[142] By changing urea functional groups to sulfonyl functional groups, Rebek and his co-workers synthesized a new class of calix[4]arene. This can form dimeric capsules and joining the lower rim covalently, formed a polycap structure. The same group reported a

heterodimeric capsule; by mixing two different functional calix[4]arenes, naturally occurring chiral molecules were entrapped inside.[143,144]

Functionalizing calix[4]arenes with carboxylic acid groups which can dimerise, formed a capsular assembly confirmed by crystal structure. Replacing the methylene bridged with SH group and introducing carbamoylmethylphosphineoxide functional group at the wider rim (Figure 1.27.a) resulted in capsular structure.[145,146] Extending the size of calix[4]arenes to calix[6]arenes, with three carboxylic acid at the upper rim, created a new cage compounds with extended interior volume. By incorporating suitable amino acid groups via peptide bond to the upper rim of the calix[4]arenes, which self-assembled as capsules assisted by hydrogen bonding.[147,148] Hong and co-workers have reported a heterodimeric molecular capsule based on the charged hydrogen bonding interaction between two different CTV monomers. TMS served as guest molecule which was shown to release by increasing the temperature or change in pH.[149] Recently, Ananchenko reported a amphiphilic para-hexanoylcalix[4]arene based molecular capsule, in which they observed, guest exchange at the solid-liquid interface without degrading the original structure.[150] Calix[4]arenes with two oppositely charged molecules i.e amidinium functionalised on one side and the complementarily negatively charged sufonyl groups place on the other side of the capsule resulted in formation of capsular assembly with ionic interactions in polar solvents.

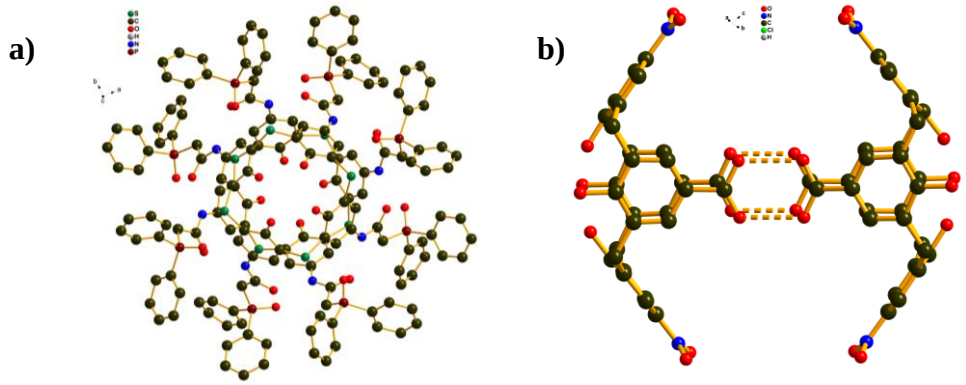


Figure 1.27. a) Functionalised calixarene dimeric capsule b) Carboxylic acid functional groups at the upper rim of calixarene forming a capsule by hydrogen bonding.

These capsules showed binding affinity for charged species like acetylcholine, tetramethyl ammonium (TMA), N-methylquinuclidinium as reported by Reinhoudt in 2002.[151] The same group reported a similar capsule, which is soluble in water, (Figure 1.28.a) by replacing anion counterpart. They functionalized the upper rim with L-alanine moieties, the carboxylate group of (alanine) on one side and retaining the amidinium functionalised calix[4]arenes on the other side, N-methylquinuclidinium cation entrapped inside the cavity.[152] Using similar strategy, adding anilium cation on one side of the calix[4]arene and tetraphosphonate on the other side of the calix[4]arene also leads to formation of a capsule (Figure 1.28.b) in polar solvents.[153] The readers can find more details about the calix[4]arenes based molecular capsules from the reviews and references cited there in.[154-156]

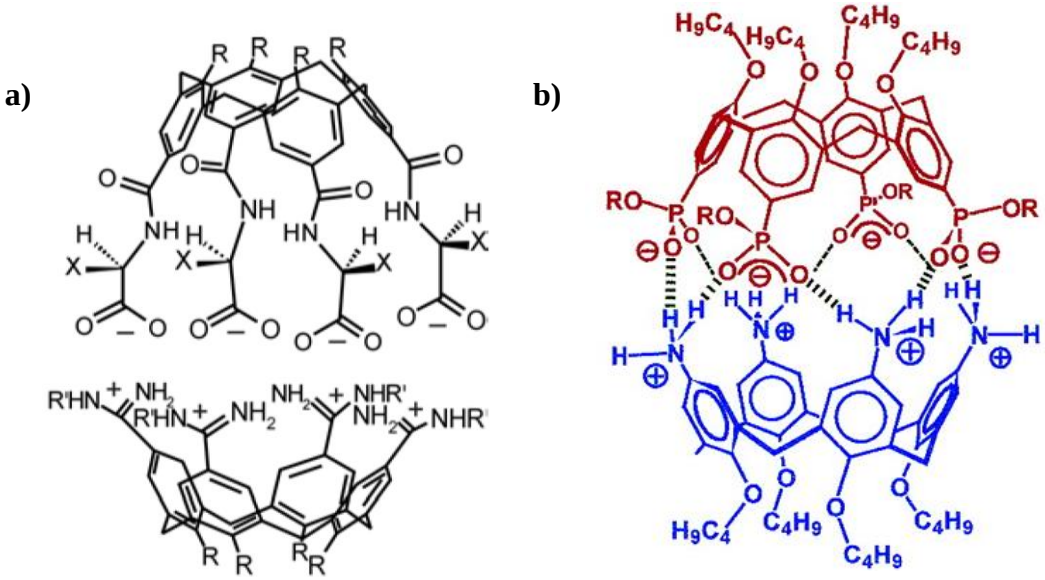


Figure 1.28. Calixarene based water soluble molecular capsules formed by ionic interactions a) with caroxylic acid and amine functional groups b) with phosphoric acid and anilium functional groups

Rebek and co-workers synthesized a vase shaped cavitand with four imide functions to the upper rim by implementing Cram's Dalcanale strategy of cavitands, which dimerizes

rim-to-rim fashion through hydrogen bonding to a molecular capsule. Because of the cylindrical shape of the capsule, elongated guest were suitable to be enclosed inside the cavity, in presence of benzene, toluene, and p-xylene. Binding in benzene - *p* xylene was preferred over the other combinations.[157] Resorcinarene based cavitand, decorated with four carboxylic acids, was shown to form capsule. Amino pyrimidne served as hydrogen bonding bridges, two nitrobenzene molecules were encapsulated in side capsule.[158] Resorcinarene molecule, which contains both hydroxyl and ester groups, that serve as hydrogen bonding donors and acceptors is self-assembled as capsule (Figure 1.29.**)** in presence of a guest molecule.[159] Rebek and his co-workers has reported simultaneous encapsulation of two guests termed as co-encapsulation, where in the two individual guest molecules alone could not entrap inside on the other hand simultaneously they were shown to be entrapped.[160-162]

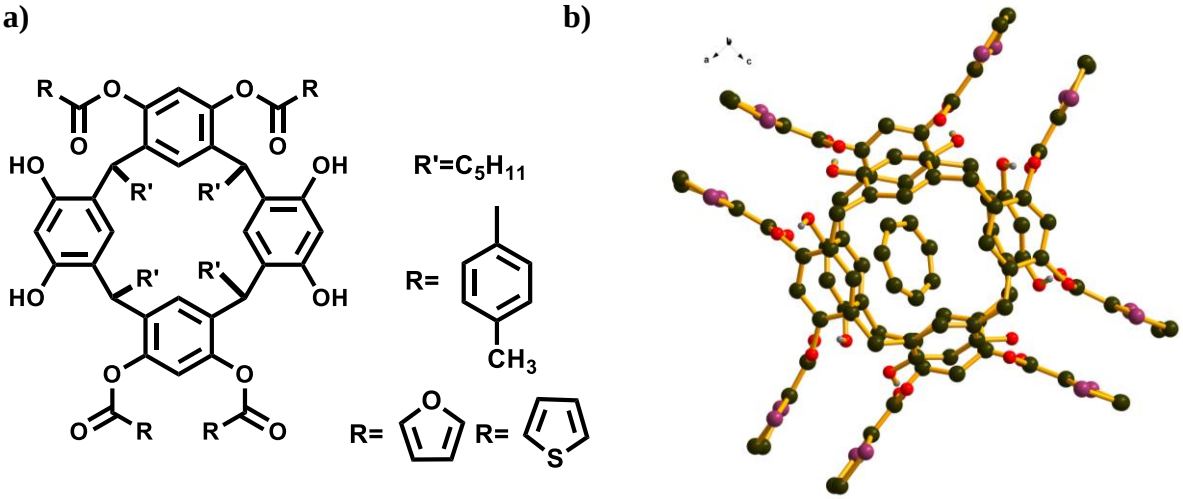


Figure 1.29. a) Chemical strcture of resorcinarene molecule, which contains both hydroxyl and ester functional groups b) self assembly of the moleucle to form a capsule and entrapment of tropylium cation.

A hybrid supramolecular capsule has been synthesized by coupling a glycouril unit to a resorcinarene cavitand, which self assembled through hydrogen bonding. The large interior volume is sufficient to entrap ionic cryptets inside.[163] They have reported a

reversibly expanded capsule, by incorporating four glycouril units in between the cylindrical cavitands (Figure 1.30.) which forms hydrogen bonding between two tetraimide cavitands and gave ample space for long chain alkanes of chain length $C_{21}H_{44}$.[164] Continuing their work, they further proved that the extension of the capsule is reversible by keeping suitably functionalised glycoluril units with dibutyl aniline groups, the extension can be controlled on acid- base chemistry.[165] Using these capsules Rebek and his co-workers showed different conformations of normal alkanes, ranging from bent to coiled and compressed which were not found in the bulk solvent environment.[166,167] Rebek and his co-workers synthesized a wider capsule by appending thiourea functional to the resorcinarene cavitands. This on dimerization leads to a wider capsule than corresponding imide cavitands (Figure 1.31.) and longer chains can be accommodated.[168]

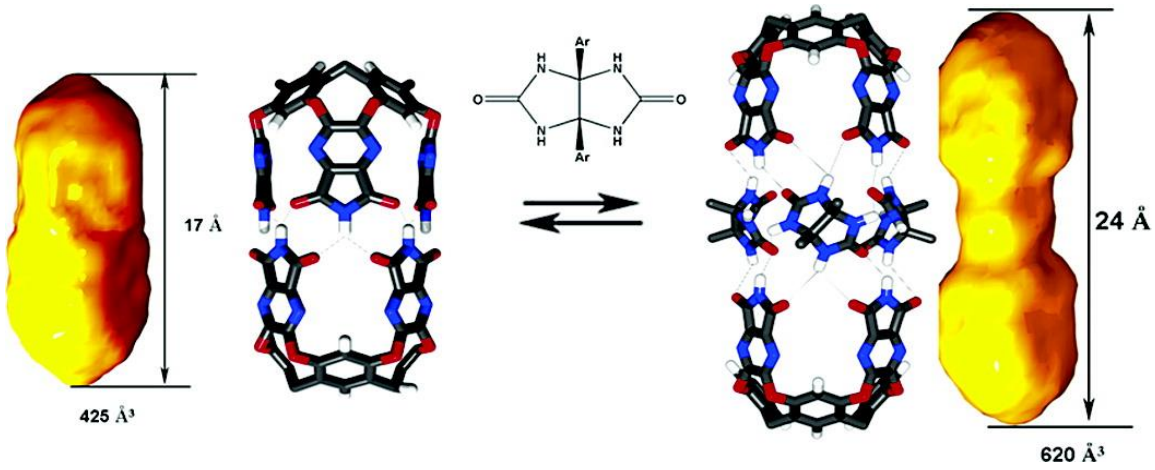


Figure 1.30. Proposed scheme for the expanding the length of the capsule.

In 2013, Rebek and his co-workers invented a new type of water-soluble version of hydrogen-bonded capsule, by attaching a pyridinium salt to the bridged methylene group. The capsule entraps hydrophobic guest molecules in water viz. dimethylstilbene. Quenching of fluorescence inside the cavity and down field shift of NMR peaks in D_2O further confirmed the entrapment of the guest.[169] For more details in cavitand based

hydrogen bonded molecular capsules, the readers can follow the reviews and references cited there in.[30,135,170-172]

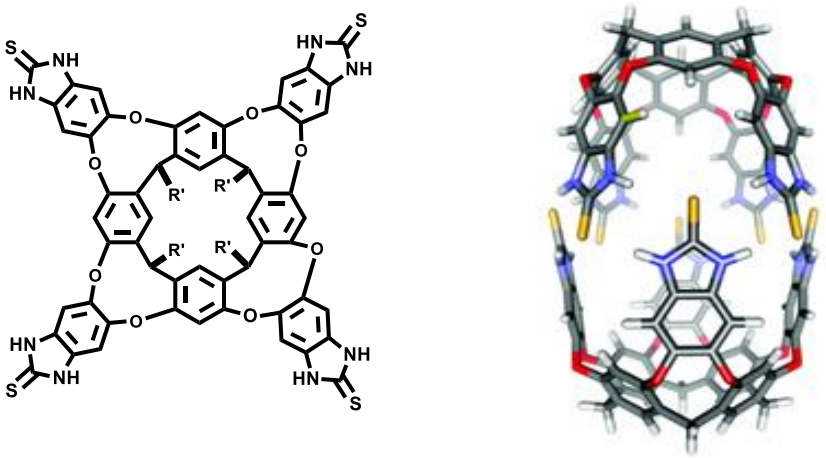


Figure 1.31. Thiourea-containing cavitand, it's self-sssembly via H-bonding into a cylindrical capsule

1.4.3. Resorcin[n]arenes and Pyrogallo[n]arenes

Resorcinarenes have been used as a vital molecule for construction of molecular capsules because of its rigid bowl shape, suitably placed hydroxyl groups that can form hydrogen bond with suitable acceptors. Atwood and co-workers have reported first resorcinarene molecular capsule based on hydrogen bonding, where in they reported capsule formation via hexameric assembly of resorcarene units with 60 hydrogen bonds between them and with 8 water molecules (Figure 1.32.a).

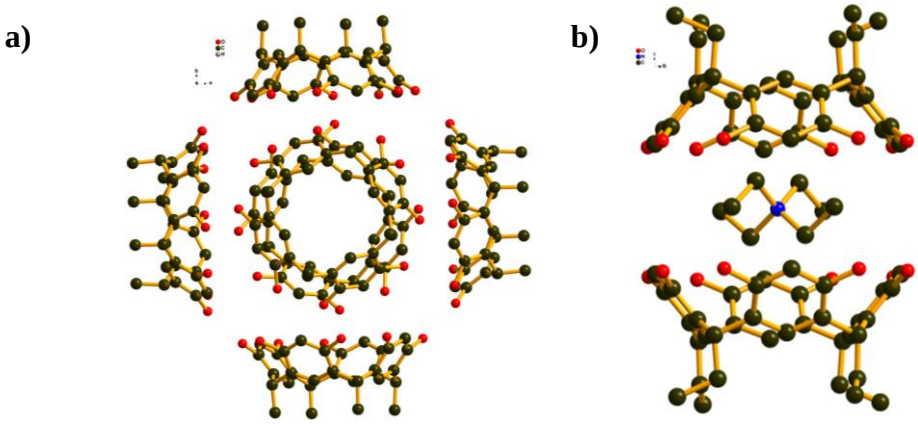


Figure 1.32. a) Crystal structure of the Resorcinarene based hexameric cage with hydrogen bonding b) a dimeric capsule formation with aid of hydrogen bonding and entrapping a guest molecule (Hydrogen atoms are omitted for clarity)

The crystal topology resembles that of a spherical virus, the central cavity volume is 1375Å^3 that is sufficient to enclathrate large organic molecules viz. fullerene, porphyrins.[173] Rebek and his co-workers further investigated the guest molecule studies of hexameric capsule in solution phase and proved variety of aromatic molecules are co-encapsulated with Bu_4SbBr in the capsule.[174] Kari Rissanen and co-workers have reported a resorcarene capsule formed by hydrogen bonding with ten water molecules which entraps Et_3NH^+ inside the cavity, tetraethylresorcin[4]arene units formed capsule by hydrogen bonding with water molecules. The capsule is guest driven through cation-π interactions between resorcarene and tetra ethyl ammonium.[175,176]

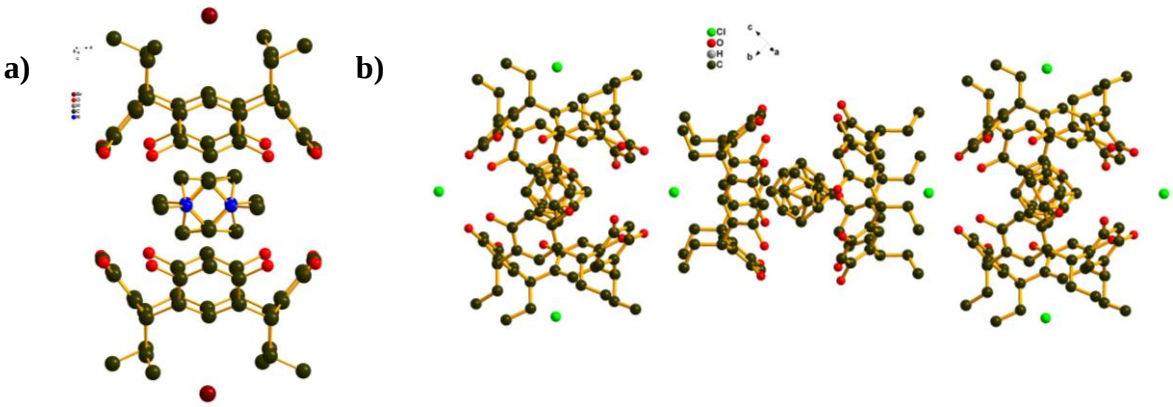


Figure 1.33. Crystal structure of Ethyl resorcinarene molecule forming hydrogen bonds with anions and entrapping guest (DABCO) a) Bromide b) Chloride (hydrogen atoms are omitted for clarity)

Two ethyl resorcinarene molecules formed a dimeric capsule aid of hydrogen bonding with MeOH, H_2O molecules; $DABCO^+$ cations was found inside the capsule shown in figure 1.33. The counter anions are forming hydrogen bonding with the resorcarene units besides solvent molecules.[177] The reversible encapsulation of different guest molecules in hydrogen bonded resorcarene capsule has been shown.[178,179]

Appending suitably bridged acceptors can increase cavity size of the capsule. L. R. Macgillvray and co-workers use 4,4'-bipyridne molecule as bridge between two C-methylcalix[4]resorcinarene (Figure 1.34.a) through hydrogen bond, increasing the size of the cavity. The interior of the capsule is large enough to be occupied by nitrobenzene with π–π stack.[180] Replacing pyridine group in the calix[4]resorcinarene resulted in octahydroxypyridine[4]arenes which dimerize through hydrogen bonding (Figure 1.34.b). Different guest were shown to entrap inside as studied by mass spectroscopy.[181,182] Various capsule with hydrogen bond, extended chain capsule is reviewed recently.[183]

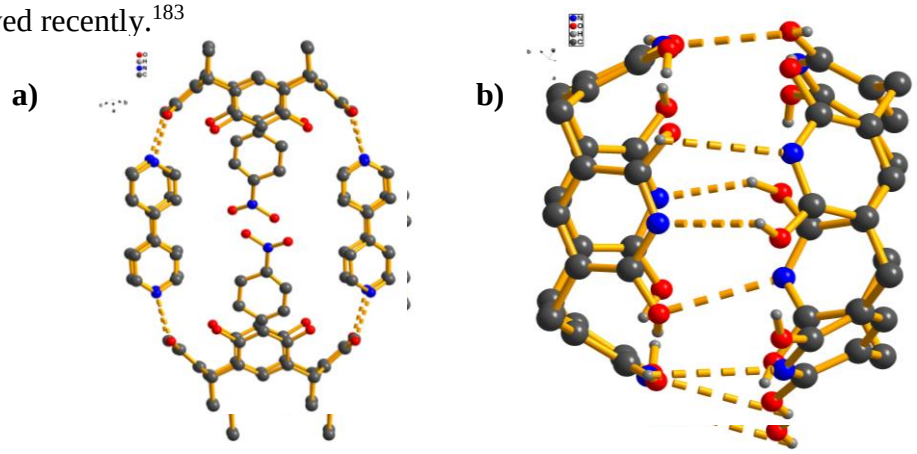


Figure 1.34. a) Crystal structure of the resorcinarene based capsule with aid of hydrogen bonding between 4,4'-bipyridine, 2 nitrobenzene molecules are entrapped inside the cavity (hydrogen atoms are omitted for clarity) b) Self assembled capsule of Octahydroxypyridine[4]arenes

Adding additional hydroxyl groups to resorcinarene resulted in pyrogallo[4]arenes, which is having more number of hydrogen bonding sites. In 2001, Jerry L. Atwood and co-workers have reported a hexameric robust capsule (Figure 1.35.a), formed by pyrogallo[4]arenes with hydrogen bonding that is stable even in polar solvents. [184] Rebek and co-workers proved that pyrogallo[4]arenes molecules form dimeric capsules (Figure 1.35.b), and encapsulate tropylium and tetramethylammonium cations in both solution

and solid phases.[185] By continuing their early work, Jerry L. Atwood and co-workers have shown two fluorescent guest molecules pyrene and butyric acid entrapment into a hexameric capsule (Figure 1.36.a) both in solid and solution state.[186] Replacing the guest fluorophore to substituted anthracene moiety, they further proved that the guest molecule could be inside or outside the cavity; they studied the arrangement of the capsule in solution phase through fluorescence spectroscopy.[187] Different supramoleuclar architectures were shown with pyrogallo[4]arenes in presence of guest molecule and in absence of guest molecules. In presence of guest molecule, tubular structure form but in absence of guest molecule spheroid assembly forms (Figure 1.36.b). Further details on pyrogallo[4]arenes based capsules, can be found in the review, references cited there in.[97]

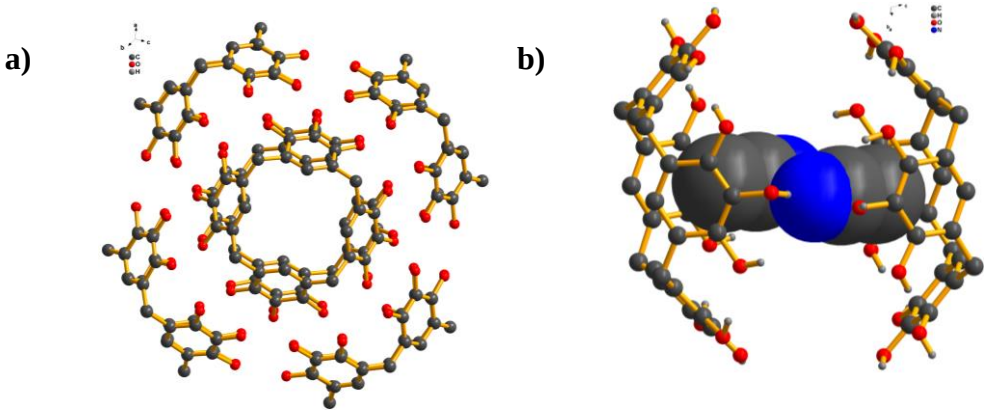


Figure 1.35. a) Crystal Structure of self assembled pyrogallo[4]arenes forming a hexameric capsule b) Crystal Structure of Dimeric capsule of pyrogallo[4]arenes encapsulated acetonitrile molecules shown in space filling model (hydrogen atoms are omitted for clarity)

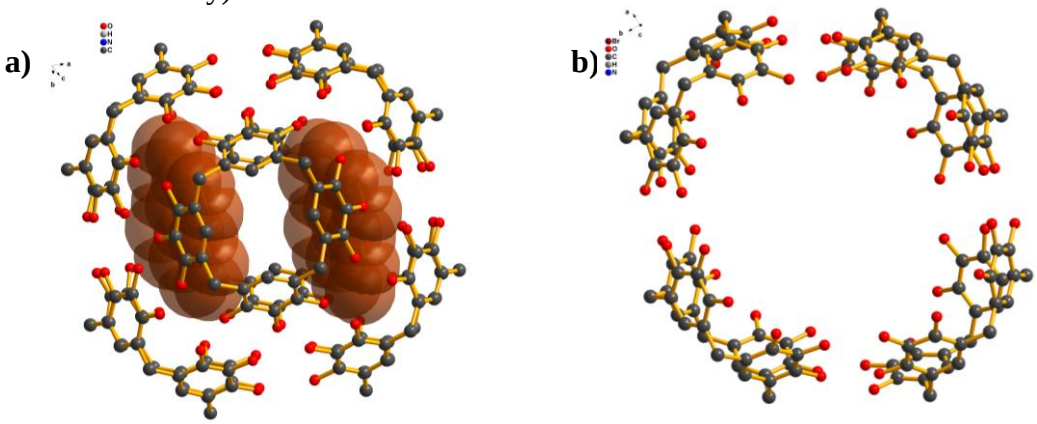


Figure 1.36. a) Crystal Structure of hexameric capsule by entrapping pyrene butyric acid as guest (shown in space filling model) b) Crystal Structure of spheroid formed in the absence of guest molecule (hydrogen atoms are omitted for clarity)

The structurally similar and conformationally different molecule, cyclotriveratrylene and its derivatives are also used for formation of hydrogen bonded capsules. B. F. Abrhams and co-workers reported the first such capsule. They used the demethylated version of CTV, namely CTC, to self-assemble a capsular structure by hydrogen bonding, the cavity is occupied by Rb^+ (Figure 1.37.a).[188] By joining ureido-pyrimidinone scaffold, one of the best hydrogen-bonded self-complementary units to substituted cyclotriveratrylene, resulted in half bowl shaped molecule. On dimerization, it leads to formation a self-assembled capsule (Figure 1.37. b and c) which shows a potential application to bind, separate selectively C_{70} from mixture of C_{70} and C_{60}.[189] A more elaborate discussion on hydrogen bonded molecular capsules is given in chapter **1** and **2.**

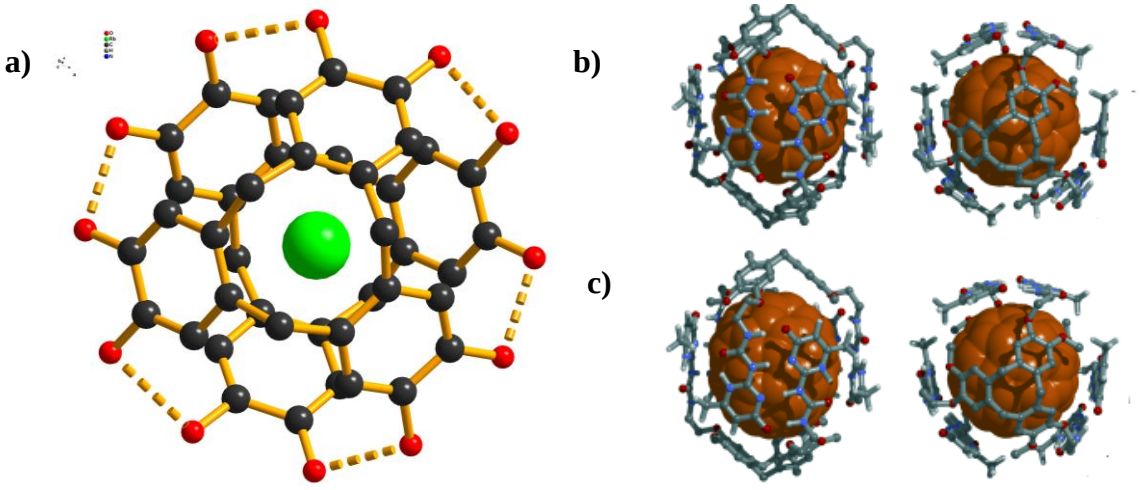


Figure 1.37. a) Crystal structure of the molecular capsule formed by cyclotricatechylene with hydrogen bonding and entrapping Rb^+ cation which is shown in green colour (hydrogen atoms are omitted for clarity) b) DFT-calculated molecular structures of the hydrogen-bonded capsules capsule entrapping C_{60}, c) entrapping C_{70}

1.5. Hydrophobic effect

Bruce C. Gibb and co-workers studied the cage formation by hydrophobic effect. They synthesized a deeper cavitand, that possesses an external carboxylic acid groups, and having hydrophobic cavity internally. By adding a steroid molecule in water to the cavitand (Figure 1.38.), it dimerised to entrap the steroid confirmed by NMR studies. The size and shape of the capsule has been probed by varying guest molecules.[190] By changing template from steroid to a gas molecule also resulted in formation of capsule by trapping the gas molecule inside and its discrimination of the different gas molecules showed that these capsule can be used for gas separation.[191] They further extended strategy by adding dendrimers to the side chains of cavitands, which is having hydroxyl groups at the end of the chain. In presence of different guest molecules, the dendrimeric cavitand self-assembled to form a capsule, encapsulating the guest molecule. They proved that the guest molecule size is having impact on capsule formation. In case of comparatively small molecule such as cyclohexane, they observed opening up of the capsule.[192] In recent reviews, hydrophobic driven molecular capsules discussed extensively.[4,193,194]

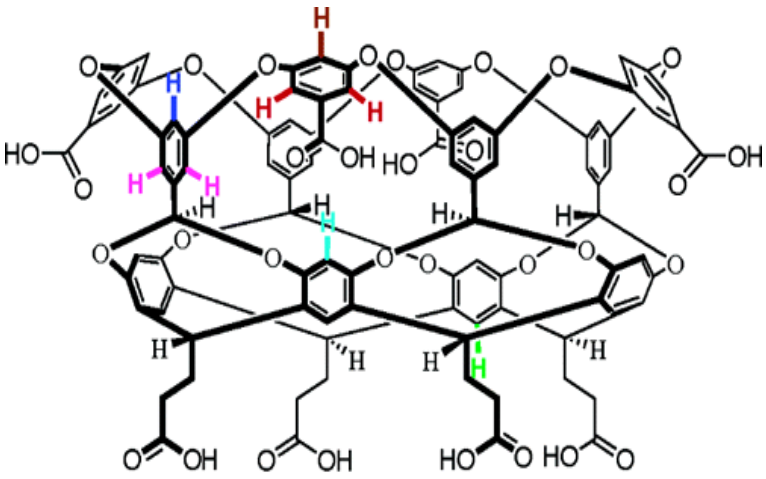


Figure 1.38. Deep-cavity cavitand dimerizes on addition of hydrophobic guest moleucles

1.6 Functional Properties

As we discussed in the introduction of this chapter, these cage molecules can be used in drug delivery, reaction chambers, storing unstable molecules, sensing, separation science, to name a few. In this section, we will discuss these applications of the capsules and cages.

1.6.1 Molecular containers as reaction vessels

Molecular cages with well-defined cavities can be used as reaction chambers. In 1998, Warmuth reported a Diels-Alder reaction of benzyne with walls of hemicarcerand molecule in which it is incarcerated.[195] They further used the hemicarcerand for reduction of borane, addition of methyl lithium to benzaldehyde, benzocyclobutenone, benzocyclobutenedione, by entrapping the individual moieties. In case of benzocyclobutenedione they observed reduction of one keto group and monomethylation.[196] Rebek and co-workers showed a self-assembled soft ball that accelerated Diels–Alder reaction by two orders of magnitude at room temperature. Because of the strong binding affinity of the product in the capsule the true catalytic behaviour of the capsule could not be studied.[197] They further showed the hydroxyl functionalised soft ball catalyzed the Diels–Alder reaction, which shows real catalytic behaviour (Figure 1.39.). In this case, product was not strongly bonded compared to reactants inside the capsule.[198] They showed the ability of capsule to catalyze 1,3 dipolar cycloadditions by entrapping phenylazide and phenylacetylene that leads exclusively to 1,4-triazole at room temperature in three days; in the absence of the capsule the reaction takes years at room temperature.[199] Recently they showed a cavitand molecule templating the cyclization of ω-amino acids into lactams in water irrespective of the high dilution condition which is generally used for cyclization process over polymers.[200]

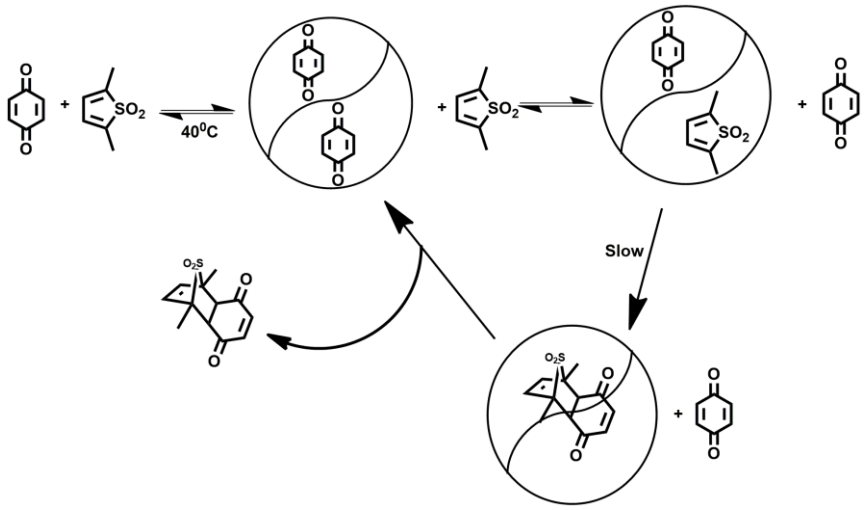


Figure 1.39. The Rebek's cage catalysing Diels-Alder reaction.

Fujita and co-workers have used metal cages as nanoreactors, where in they performed highly stereoregulated [2+2] photo-dimerization reaction of acenaphthylenes, naphthoquinones in aqueous medium that give rise to only syn and head-to-tail isomers.[201] Continuing their work, they further showed highly selective [2+2] cross-photodimerization of olefins within a self-assembled coordination cage that acts as a molecular flask in an aqueous medium.[202] They further observed the photo-dimerization of acenaphthylenes via in situ crystallography, where in two acenaphthylenes molecules were encapsulated in a pre-organised metal cage on irradiation to light (at 300–365 nm). They found that guest molecule was dimerized, confirmed by crystal diffraction.[203]

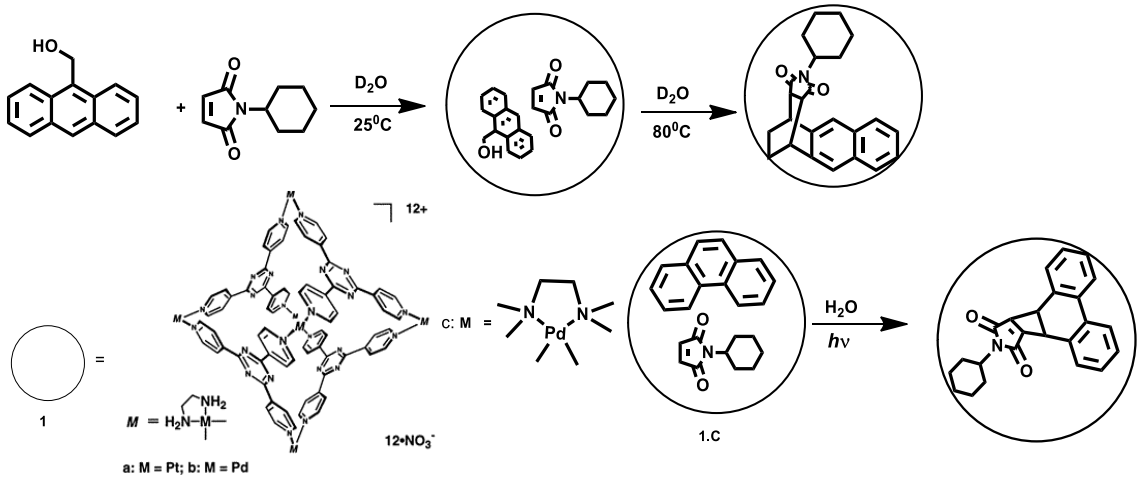


Figure 1.40. Fujitha's cage catalysing diels alder reaction,

Besides photo chemical reactions, Fujita and co-workers have reported a water soluble host-mediated Diels-Alder coupling of anthracenes and phthalimides. It yields an unusual regioselective adduct, bridging at 1,4 position, where as in bulk solvent environment it has shown to form an adduct bridging at the centring 9,10-position (Figure 1.41.) of the anthracene.[204] Extending the strategy in 2007, they showed the Diels-Alder reaction between arenes viz triphenylene, perylene etc and N –cyclohexylmaleimide, and by tuning the metal complex by imposing methyl groups they synthesized a cage which was used as container molecule for [2+2] photo-dimerization shown in Figure 1.40.[205] Recently, it has been shown that resorcinarene capsule by mimicking the cyclase enzyme can catalayze tail-to-head terpene (THT) cyclization, isomerization of a geranyl cation to the cisoid isomer was also been found where in the bulk solvent environment. The isomer is unlikely to be feasible.[206] More details about reactivity in a confined space, supramolecular catalysis can be found in reviews and reference cited there in.[120,207-209]

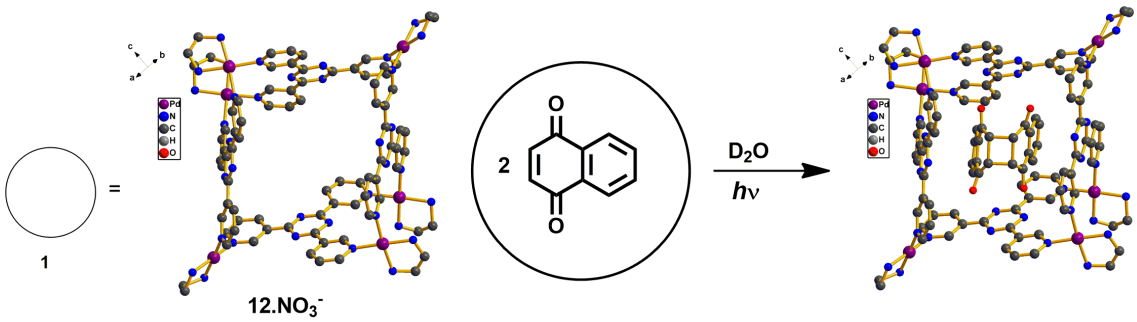


Figure 1.41. A metallo cage synthesized by fujitha catalysing [2+2] cyclo addition reaction, Crystal structure of the entrapped adduct is shown (hydrogen atoms are omitted for clarity)

1.6.2 Molecular containers for prevention of reactive species

Molecular cages can be used to store unstable or reactive species in bulk solvent environment. Cram's group has generated cyclobutadiene as *in situ* inside of a hemicarceplex and performed reactions with cyclobutadiene inside the cage.[210]

Following the similar strategy in 1997, R. Warmuth has isolated one more reactive intermediate benzyne by the photolysis of benzocyclobutenedione, through incarceration inside a molecular container and studied the structural and electronical properties.[211] They further isolated 1,2,4,6-cycloheptatetraene, generated from photochemical reaction of phenyldiazirine inside hemicarcerand and proven to be stable at room temperature.[212] Rebek and co-workers have isolated tetrahedral intermediate hemiaminal formed in a cavitand by encapsulating alkyl-substituted primary amines, that orient themselves towards a covalently tethered aldehyde, resulting in hemiaminal confined from the bulk solution and characterized at ambient temperature.[213]

In 1998, Fujita and co-workers showed neutral organic molecules viz. azobenzene, stillbene are incarcerated in a metal cage and exits in a unusual cis dimer inside of it.[214] They further showed the cyclic trimer of trialkoxysilanes can be prepared and stored inside the cage. The cyclic trimer inside the cage is stable at neutral and even acidic conditions.[215] In 2009, Jonathan R. Nitschke and co-workers have isolated highly reactive white phosphorus inside a tetrahedral capsule (Figure 1.42.) and showed that it is stable at room temperature even after expositing to air.[216]

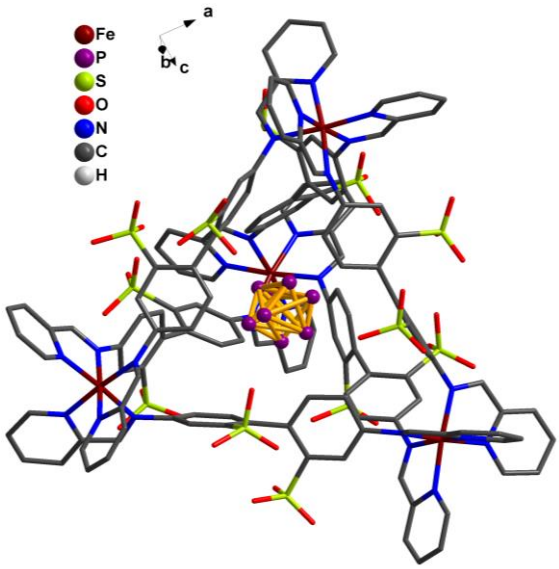


Figure 1.42. Crystal structure of the molecular cage used for entrapment of reactive white phosphorous

1.6.3. Other applications

Julius Rebek and co-workers have reported a calix[4]arenes based FRET sensor for small molecules at nano molar concentration. They functionalized calix[4]arenes with ureas on their wider rims which dimerize in organic solution, via intermolecular hydrogen bonding. They imposed calixarene molecule with a donor fluorophore on one side and the other with an acceptor. When a suitable guest molecule was added, two calixarene molecules comes close enough for energy transfer to take place (FRET), (Figure 1.43.) which was monitored by wavelengths of the acceptor, donor and the complex.[217] Continuing their work, they used FRET as the tool for studying dynamics of heteromeric capsule formed by self-assembly of cavitands labelled with pyrene as donor and perlyene as acceptor fluorophore. [218]

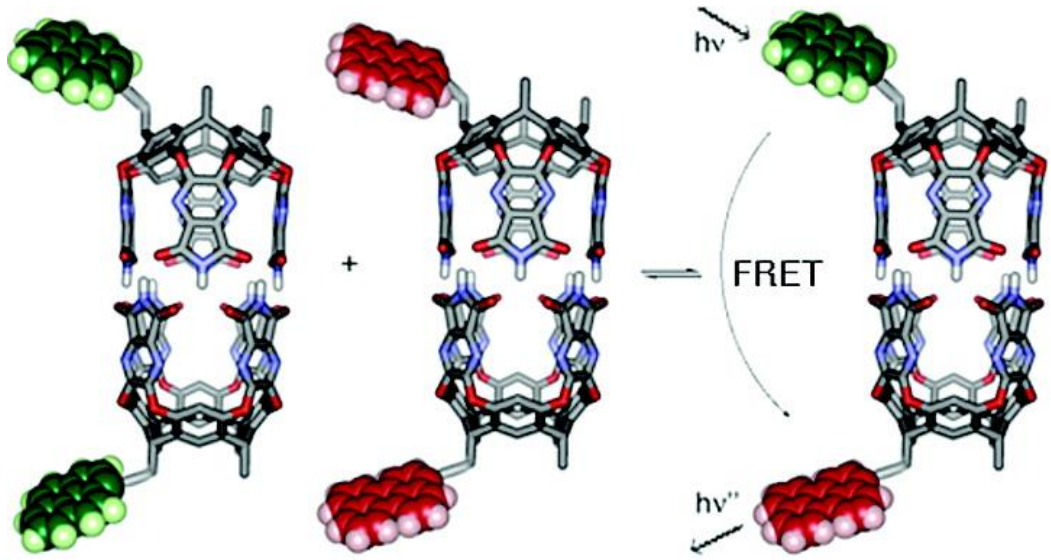


Figure 1.43. FRET occurring through hydrogen bonded molecular capsules

They used the similar technique and studied the dynamics of Mac Gillivray and Atwood's hexameric capsule formed by self-assembly of resorcinarene. They labelled two resorcinarene units with Pyrene and perylene as the donor and acceptor fluorophores and employed FRET to study the dynamics and entrapment of a fluorophore guest

molecule inside the cavity.[219] Supramolecular capsules are also used as drug delivery vehicles and nano carriers and hydrogel materials.[220]

1.7.Objective of the present thesis

As discussed, molecular capsules are a matter of intense study because of its possible interdisciplinary applications during the last few decades. Different molecular capsules have been reported from covalently linked Cram's molecular cavitands and Lehn's Cryptands to capsules based on non-covalent forces. Cyclotriveratrylene(CTV) and its derivatives which are stable in the bowl shape were shown to form cryptophanes, connected by covalent bond and metal mediated cages. The main objective of the thesis is to explore about cyclotriveratrylene (CTV) derivative molecular capsules with covalent or non-covalent interactions. Cyclotricatechylene (CTC), the demethylated version of CTV, based capsules and guest entrapment with aid of non-covalent interactions viz. hydrogen bonding, π–π interactions has been discussed in Chapter-2. Partial demethylated derivative of CTV i.e. Cyclotriguaiacylene (CTG) based capsules by mimicking A-T base pairing found in DNA, is extensively discussed in Chapter-3. Chapter-4 deals with guest induced capsular formation of CTC, while Chapter-5 deals with the synthesis of CTG based triazole bridged cryptophanes.

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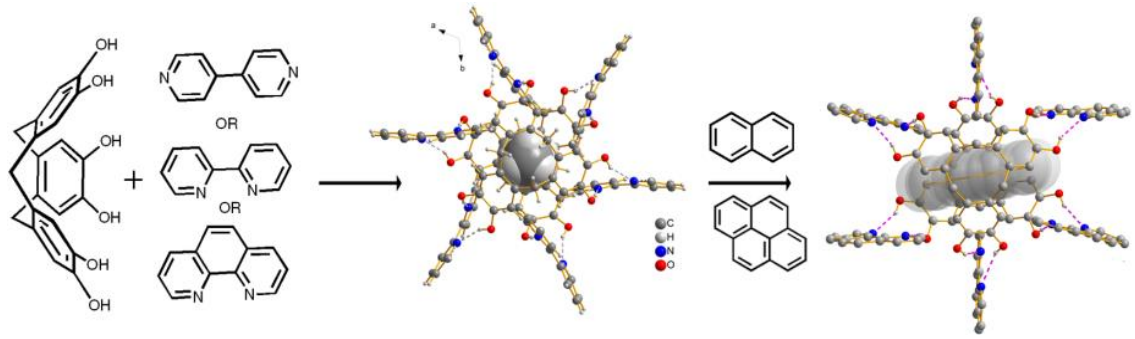
CHAPTER 2

Propeller Shaped Self-Assembled Molecular Capsules: Synthesis and Guest Entrapment; Cyclotricatechylene based supramolecular assembly

2.1 ABSTR ACT:



Molecular containers or supramolecular capsules are a subject of great interest because of their potential utilizations in various fields of chemistry, medicine and nano science. They have been utilized as nano vessel for reactions and targeted drug delivery in recent years. Cyclotricatechylene (CTC), is a bowl shaped molecule in its crown structure. It has six phenolic groups as potential hydrogen bond donors. In this work, we utilize this hydrogen bonding capability of CTC to generate the supramolecular complexes with hydrogen bond acceptors such as 4,4'-bipyridine, pyrazine, 2,2'-bipyridine and phenanthroline. These supramolecular entities are studied in solid state by X-ray crystallography and scanning electron microscopy. They are not soluble in low polar solvents. Therefore, hydrogen bonding behavior in solution could not be studied by NMR. Except in case of pyrazine, capsular supramolecular assemblies were formed in all the cases. One of these capsules was studied for guest entrapment. Planar molecules like naphthalene and pyrene, phenantrene were trapped inside its cavity with a little reorganization of the capsular assembly. We further studied the effect of changing phenanthroline to 9,10-phenanthraquinone where the two more oxygen atoms have been imported capable of forming hydrogen bonds to phenolic hydrogen atoms besides nitrogen atoms of phenanthroline.

2.2 Introduction:

Molecular capsules are macro-molecules or supra-molecules, which have space inside to encapsulate other molecules as guests and they generally do not expose them to outside environment. The interaction between them is of covalent bond (i.e. cryptands),[1] ionic interactions,[2] metal ligand coordination,[3-5] hydrogen bonding,[6-10] hydrophobic effects,[11] or combination of them.[12] Also, in some cases the guest entrapment causes the capsule fomation.[13,14] Studies of capsules are of great interest because of their potential application in many fields such as using as nano reaction vessel,[7,8,15-17] stabilizing unstable molecules inside the cavity,[18,19] sensing of molecules and ions.[20] However, design of capsule with predefined shape and size is difficult and still remains a challenge for chemists.[21]

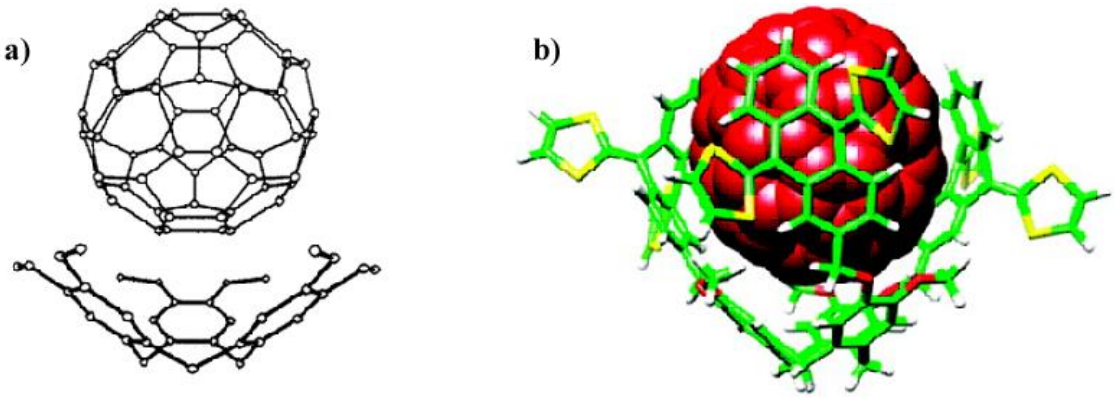


Figure 2.1. a) Crystal structure of CTV inclusion complex with C_{60} (hydrogen atoms are omitted for clarity) b) Energy-minimized structures (DFT) of C_{70}@exTTF-CTV side view.

Macrocyclic based systems such as cyclodextrins, carcerands, calix[4]arenes, resorcinol based systems are extensively used for making capsules.[12] Cyclotriveratrylene (CTV) (Scheme 1a), a cyclic trimer of veratrylene is conformationally similar to Calix[4]arenes molecules. CTV in its crown conformation adopts a bowl shape. Due to its cavity, CTV

and its cryptand like derivatives have been reported to form self clatharates (Figure.2.4.) and clathrates with many solvent molecules.[22,23] Jerry.L.Atwood and co-workers have shown CTV forms 1:1 inclusion complexes with C_{60} because of its affinity to form π–π stack, which was confirmed by crystal structure, the bond distance between CTV and fullerene being 3.51Å supportins the π–π stack shown in (Figure 2.1.a.)[24] Javier de Mendoza and co-workers recently attached a concave aromatic surface 2-[9-(1,3-dithiol-2-ylidene)anthracen-10(9H)-ylidene]-1,3-dithiole which resulted in a tweezer-like design that can bind C_{70} more efficiently over C_{60},. Because of the concave surfaces of both the CTV and the ex TTF subunits, they nicely wrap around the entrapped fullerene guests shown in (Figure 2.1.b.)[25]

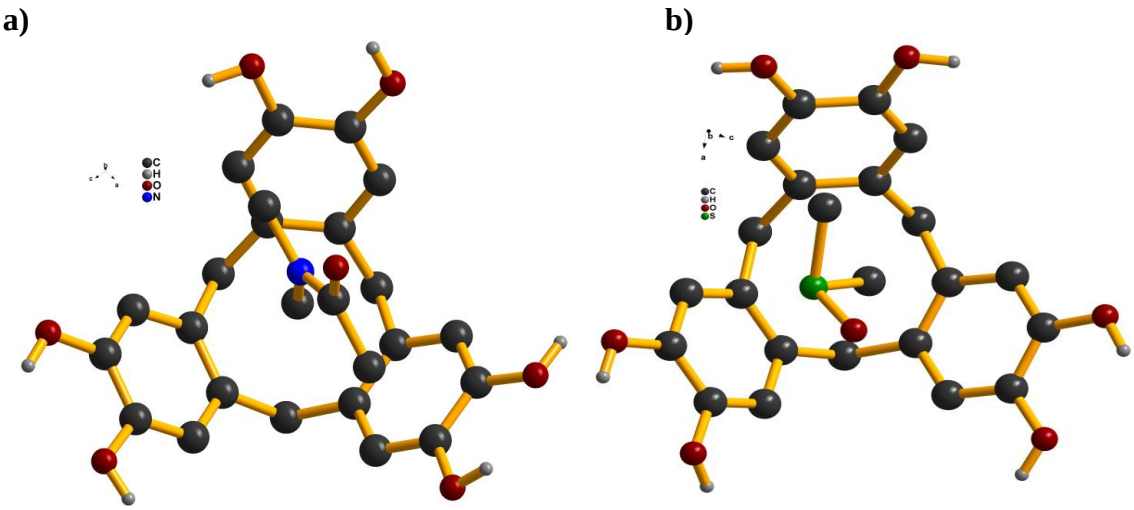


Figure 2.2. a) Crystal Structure of cyclotricatechylene (CTC) forming clathrates with solvent molecules a) DMA(Dimethyl acetamide) b) DMSO (Dimethyl Sulfoxide)

Demethylation of CTV gives cyclotricatechylene (CTC), which has six phenolic hydrogen atoms (Scheme 1b).[26,27] Michaele J. Hardie and co-workers have shown that CTC can also form clathrates with different solvent molecules (Figure 2.2.) like its parent molecule; the hydroxyl groups of it can form donor-acceptor complexes with suitable

acceptors viz. tetracyanoethene, (Figure 2.3.a) tetracyanoquinodimethane (Figure 2.3.b).[28] Although, bowl shape of CTC is advantageous for capsule formation, such efforts have been reported recently and only few examples exist. They are; a heterodimeric capsule with boronic acid-appended hexahomo-trioxacalix-[3]arene;[29] molecular capsule due to dimerization by hydrogen bonding which holds an Rb^+ cation in the cavity;[30] deprotonation of phenolic hydrogen atoms and subsequent metalation with Cu^{2+} and Mn^{2+} ions in presence of Ca^{2+} and Cs^+ ions.[31,32]

We envisaged that generating different capsules from CTC would be possible, if suitable spacers can be put between them, which would connect two CTC molecules. Such strategy should give capsules with different size depending on the spacers used. On the other hand molecules with suitable hydrogen bond acceptor from phenolic hydrogen atoms of CTC may act as ideal spacers under suitable proportion and condition. We thought of simple linear systems such as pyrazine and 4-bpy. Both of these molecules have two nitrogen atoms as hydrogen bond acceptors, may be suitable for this purpose, where π–π stacking is likely to further stabilize the supra structure. Recently, capsules were made using similar hydrogen bonding strategy where hydrogen bonding among the spacers leads to hyper-extended capsule from calixarene derivative.[6,33] In this chapter, we describe the synthesis and characterization of four novel supramolecular complexes of CTC with pyrazine, 4,4'-bipyridine (4-bpy), 2,2'-bipyridine (2-bpy) and phenanthroline (phen) formed due to hydrogen bonding and π–π stacking interactions. Except pyrazine, all of them forms capsular assemblies in solid state. The inability of pyrazine in formation of capsule could be attributed to its shorter length may not be sufficient to hold two CTC molecules together. The capsule of CTC with phen is capable of encapsulating naphthalene and pyrene.

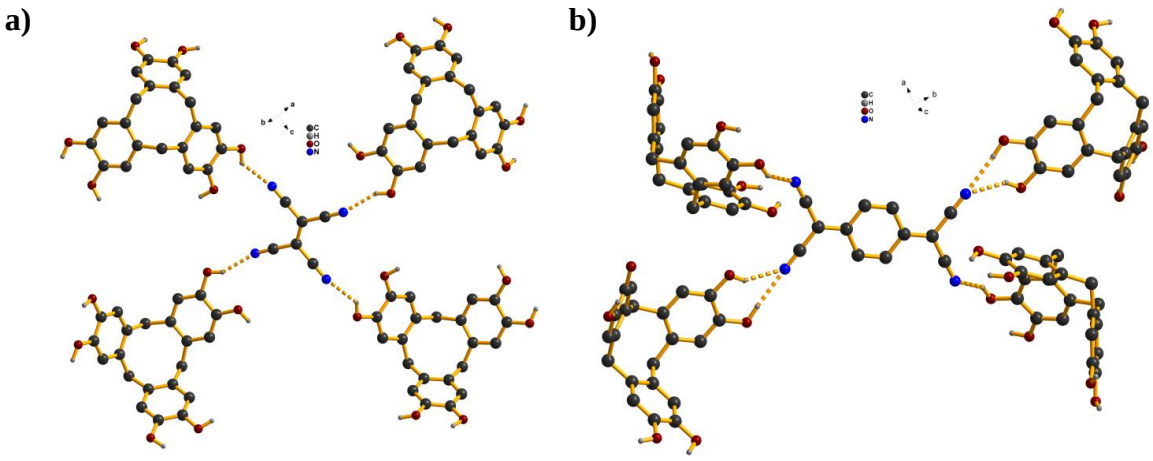


Figure 2.3. Cyclotricatechylene (CTC) forming donor acceptor complexs with a) tetracyanoethene b) tetracyanoquinodimethane.

2.3 Experimental Section

Materials: Reagent grade and metal salts were acquired from Aldrich and used as received. All solvents were procured from S. D. Fine Chemicals, India. Solvents were purified prior to use following standard procedures.

Physical Measurements: NMR was recorded at Bruker 400MHz instrument. Single crystals X-ray diffraction studies were done on a Bruker APEX-II diffractometer equipped with a CCD detector, the X-ray source being Mo K_α (wave length 0.71073 Å) at room temperature. Data collection was monitor with Apex II software and preprocessing was done with SADBS integrated with Bruker-Apex II.[34]

2.3.1. Synthesis of Cyclotriveratrylene: CTV was synthesized by following literature procedure from veratrole (Scheme 1).[35] Veratrole in acidic medium trimerizes with formaldehyde to form CTV. In a typical procedure veratrole (10 g, 72.37 m.mol), formaldehyde (14 g, 0.466mol) (30% aq.solution) was taken in a 250 mL round bottom flask, at 0^{O}C. To this H_2SO_4 (70%) was added drop by drop with vigorous stirring, after

the finishing of addition the reaction was kept at room temperature for 2 hours. During which the reaction colour changed from rose to purple, reaction mixture solidifies, and the product can be isolated by adding ethanol to this solid and refluxing. After cooling to room temperature the white solid was filtered, washed with ethanol and dried under vacuum. Yield of the compound: 10 g (36.7%).

^{1}H NMR (400 MHz, CDCl3, 27°C): δ = 3.57 (Heq) and 4.78 (Hax) (d, 6H, Ar*CH2*Ar), 3.84 (S, 18H, *OCH3*), 6.83 (s, 6H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 36.6, 56.1, 113.1, 131.8, 147.8

a) **b)**

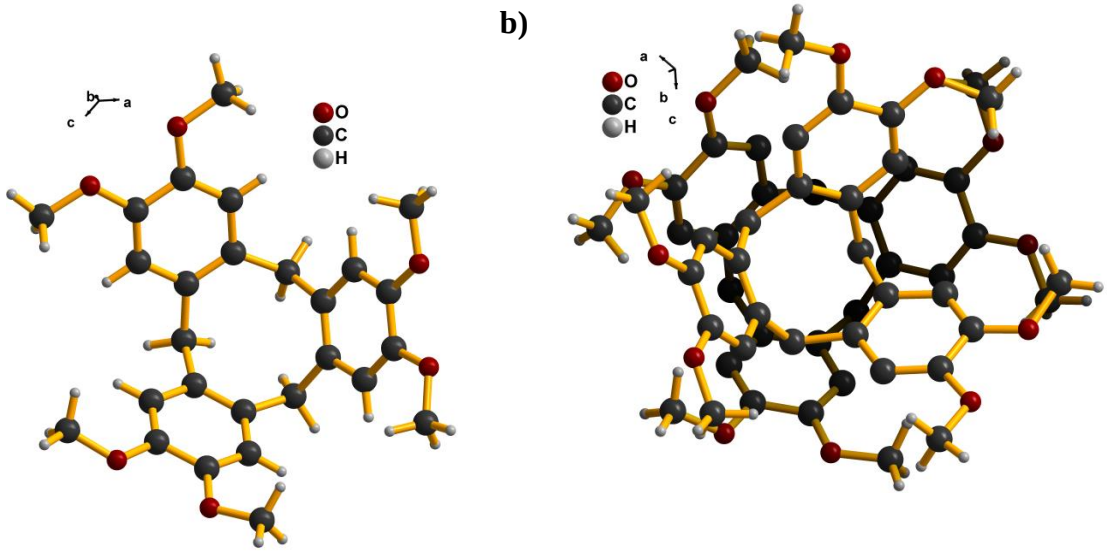


Figure 2.4. a) Crystal strcture of CTV b) CTV forming self clatharate strctures.

2.3.2.Synthesis of Cyclotricatechylene: Into a stirred solution of 40 mL dry CH_2Cl_2 in a 250 mL r.b, BBr_3 (3.8 mL, 39.96 mmol) was added, to this (2 g, 4.44 mmol) of CTV dissolved in 40 mL of dry CH_2Cl_2 was added dropwise under nitrogen at -40°C, The slightly purple reaction mixture was brought to RT after finishing the addition, and then refluxed for 10 h. The reaction mixture was quenched by slow addition 20-25 mL H_2O at 0 °C. The resulting slurry was filtered and washed with H_2O. The crude wet solid was recrystallized from aqueous EtOH to yield 1.2 g (73.8%) of slightly brownish colored solid.

^{1}H NMR (400 MHz, DMSO-d_6, 27°C): δ = 3.22 (Heq) and 4.49 (Hax) (d, 6H, ArCH2Ar), 6.65 (s, 6H, Ar-H) , 8.60 (s, 6H, OH) ;

^{13}C NMR (100 MHz,DMSO-d_6, 27 °C): δ = 35.0,116.7, 130.8, 143.5

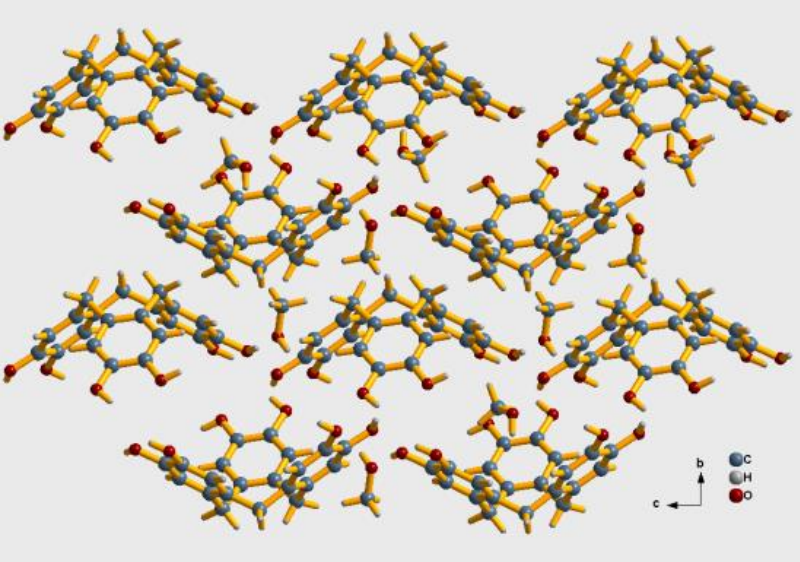


Figure.2.5. Crystal structure of CTC, showing molecular arrangement along crystallographic a-axis

2.3.3. 1,10-Phenanthroline-5,6-dione: The compound was prepared according to a literature method.[36] In a 250 mL r.b 1,10-phenanthroline (4 g, 22.2 mmol) was taken to this, an ice-cold mixture of concentrated H_2SO_4 (40 mL) and HNO_3 (20 mL) was added slowly, to this mixture KBr (4.03 g , 33.9 mmol) was added. The mixture was heated at reflux for 3 hours. The yellow solution was poured over ice and neutralized carefully with NaOH until pH is neutral to slightly acidic. The water layer was extracted with $CHCl_3$ followed by drying with Na_2SO_4, evaporated the solvent under reduced pressure gave 4.3 g (92.1%) of the title compound.

^{1}H NMR 400 MHz ($CDCl_3$): δ 9.13 (dd, 2H), δ8.52 (dd, 2H), δ 7.60 (q, 2H). ^{13}C NMR 400 MHz ($CDCl_3$): δ = 125.61, 128.07, 137.30, 152.90, 156.41, 178.66

2.3.4. Synthesis of complexes: For all the compounds similar procedure was adopted. In a typical procedure, CTC (10 mg, 0.027mmol, 1 equiv.) was dissolved in 3 mL acetonitrile, respective spacer (3.3 equiv.) was also dissolved in 3 mL acetonitrile. Both the solutions were mixed and stirred at room temperature. In half an hour precipitate started coming out. It was further stirred till TLC shows no CTC in the solution, which takes about 4-12h depending on the spacer. Then the precipitate was filtered and washed with acetonitrile. The crystals were grown by re-dissolving the solid in 1:1 mixture acetonitrile and methanol and kept undisturbed. Crystals were formed in a week. For encapsulation studies, preformed capsule and 2 equivalent (with respect to capsule) of guest are dissolved in methanol, sonicated till everything dissolves and kept undisturbed. Crystals of host-guest complex along with the excess guest comes out in about a week. The data was solved by SIR2002,[37] and expanded using Fourier technique. In case of **1** and **4**, disordered solvent molecules were present which were taken out using SQUEEZE command in PLATON.[38] All these software were integrated in wingx package.[39]

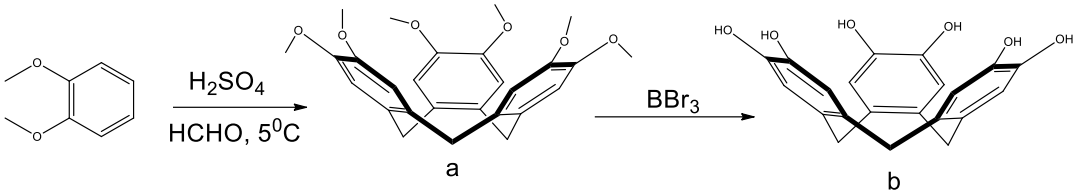
2.3.5. Crystal data of complexes; **Table 2.1.** Crystal data of complexes 1-5

compound	**1**$(ctc)_2(4\text{-}bpy)_3$	**2**(ctc) $(pyrazine)_2$	**3**$(ctc)_2(2\text{-}bpy)_6$	**4**$(ctc)_2$ $(phe)_6$	**5** CTC_PAQ)
Empirical formula	C_{36} H_{30} N_3 O_6	C_{27} H_{24} N_3 O_6	C_{106} H_{90} N_{13} O_{12}	C_{57} H_{42} N_6 O_6	$C_{78}H_{54}$ N_6 O_{18}
Formula weight	600.63	486.49	1737.93	906.32	1363.27
Crystal system	Triclinic	Triclinic	Trigonal	Trigonal	Triclinic
Space group	P-1	P-1	R-3	R-3	P1
a (Å)	9.618(5)	7.893(5)	16.530(5)	16.501(5)	8.90(7)
b (Å)	11.523(5)	9.402(5)	16.530(5)	16.501(5)	12.379(10)
c (Å)	14.750(5)	16.192(5)	27.774(5)	63.704(5)	17.042(13)
α (deg)	78.948(5)	95.101(5)	90.000(5)	90.000(5)	109.23(4)
β (deg)	76.273(5)	97.947(5)	90.000(5)	90.000(5)	97.04(5)
γ (deg)	79.236(5)	104.476(5)	120.000(5)	120.000(5)	93.94(5)
V ($Å^3$)	1541.4(12)	1142.7(10)	6572(3)	15022(7)	1747.5(15)
Z	2	2	18	18	1
D(g. cm-3)	1.294	1.414	1.317	1.203	1.295
m mm^{-1}	0.089	0.101	0.088	0.079	0.093mm^{-1}
F(000)	630	510	2739	5688	708
θ max	28.35°	30.51°	30.55°	27.21°	26.36°
Reflections collected	22832	17394	38321	79906	22809
Independent reflections	7659	6838	4458	7444	12028
GOOF	1.040	1.033	1.032	1.071	0.982
R1 and wR2 [I>2σ(I)]	R1=0.0509, wR2=0.1245	R1 = 0.0483, wR2= 0.1089	R1=0.0506, wR2 = 0.1383	R1 = 0.0666, wR2= 0.1920	R1 = 0.0648, wR2 = 0.1719
R1 and wR2 (all data)	R1=0.0972, wR2=0.1398	R1 = 0.0846, wR2= 0.1246	R1=0.0674, wR2=0.1544	R1 = 0.0971, wR2= 0.2124	R1 = 0.1041, wR2 = 0.1947

Compound	**6** $(ctc)_2(phe)_6$ (Nap)	**7** $(ctc)_2(phe)_6$ (Pyrene)	**8**$(CTC)_2(phe)_6$ PHE)
Empirical formula	C_{62} H_{46} N_6 O_6	C_{65} H_{47} N_6 O_6	C_{64} H_{46} N_6 O_6
Formula weight	971.05	1008.09	995.07
Temperature	296(2) K	296(2) K	296(2) K
Wavelength	0.71073 A°	0.71073 A°	0.71073 A°
Crystal system	Triclinic	Triclinic	Triclinic A°
Space group	P-1	P-1	P-1
a (Å)	14.128 (5)	14.085(5)	13.953(4)
b (Å)	14.272 (5)	14.344(5)	14.339(4)
c (Å)	14.349 (5)	14.389(5)	14.342(4)
α (deg)	71.371 (5)	73.233(5)	73.574(10)
β (deg)	72.949(5)	72.028(5)	72.863(10)
γ (deg)	69.739 (5)	69.400	70.128(10)
Volume ($Å^3$)	2517.19(15)	2535.0(15)	2525.0(15)
Z	2	2	2
Density (calculated)	1.28109	1.321	1.309
Absorption coefficient	0.084	0.086	0.085 mm^{-1}
F(000)	1016	1054	1040
θ max	20.27	27.74°	27.16°
Reflections collected	29292	39161	33666
Independent reflections	9204	14827	11143
GOOF	1.009	1.039	1.034
Final R indices [I>2σ(I)]	R1 = 0.0770, wR2 = 0.2312	R1 = 0.0581, wR2 = 0.1467	R1 = 0.0573, wR2 = 0.1564
R indices (all data)	R1 = 0.1263,wR2 = 0.2610	R1= .1131,wR2 =0.1729	R1 = 0.1028, wR2 = 0.1885

Table 2.1. Crystal data of complexes 6-8

2.4. Result and Discussions:



Scheme 2.1. Synthesis of CTC

CTC was synthesized in two steps by following literature procedure from veratrole (Scheme 1).[26,35,40] Veratrole in acidic medium trimerizes with formaldehyde to form CTV. CTV was then demethylated using BBr_3 to give CTC. Mixing of CTC with 4-bpy (1:3) in acetonitrile, affords complex **1** as a precipitate. It started forming in half an hour and takes about 12 h to consume all CTC as monitored by thin layer chromatography. This precipitate is only soluble in high polar solvents like methanol and DMSO. The ^1H NMR in DMSO-d_6 shows 2:3 ratio of CTC and 4-bpy (Figure.2.6.), suggests three molecules of 4-bpy and two units of CTC are making complex **1**. However, no hydrogen bond information could be ascertained due to high polarity of DMSO. Also, the ESI mass spectroscopic investigation did not provide any information about the capsular assembly. This is true for all supramolecular structure reported here and therefore, it was not possible to investigate their structure and behaviour in solution. Thus, we have studied them with X-ray crystallography and Scanning electron microscopy (SEM) in solid state.

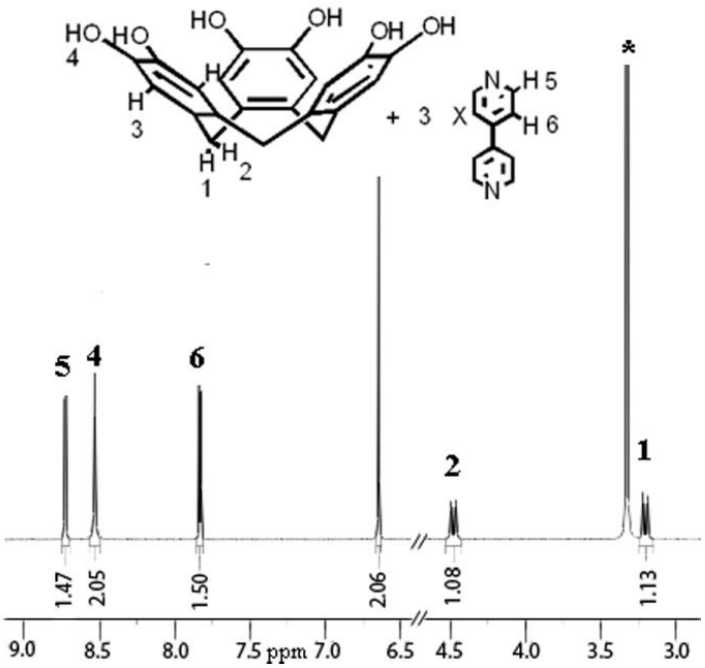


Figure.2.6. NMR spectra of complex 1 in DMSO-d_6. The starred peak is water peak. Numbers in the structure correspond to the number in the spectra.

We have grown the crystal of **1** by slow evaporation method after preparing a dilute solution in methanol and acetonitrile (1:1). This assembly is crystallized in Triclinic, *P*-1 space group (No. 2). As observed form ^{1}H NMR spectral analyses, each capsular unit consists of two CTC and three 4-bpy molecules. To our surprise, the arrangement is completely different from our expectation. When viewed along crystallographic *a*-axis, the following observation can be made. Three 4-bpy and two CTC units are forming a capsule due to combination of π–π stacking and hydrogen bonding. None of the 4-bpy units are connecting both the CTC units. Out of three, the middle 4-bpy do not form hydrogen bonds to any of the CTC units within the capsule but have a π-stacking interaction with other two molecules of 4-bpy, distance being 4.5Å. Each of the other two 4-bpy, is forming one N...H-O hydrogen bonding (1.86Å) with opposite CTC units (Figure.2.7.a). All the three 4-bpy molecules form hydrogen bonding with different capsular units (Figure.2.7.c). The hydrogen bonding with similar distances are considered to be strong.[41] Each CTC molecules are having eight hydrogen bonds, one

with inside 4-bpy and other with the neighbouring CTC and 4-bpy molecules (Figure.2.7.b). Although CTC and 4-bpy gives a capsular assembly, the cavity is filled by 4-bpy itself and solvent accessible void is ~136 $Å^3$ for **1** which is 9% of the unit cell volume**.**

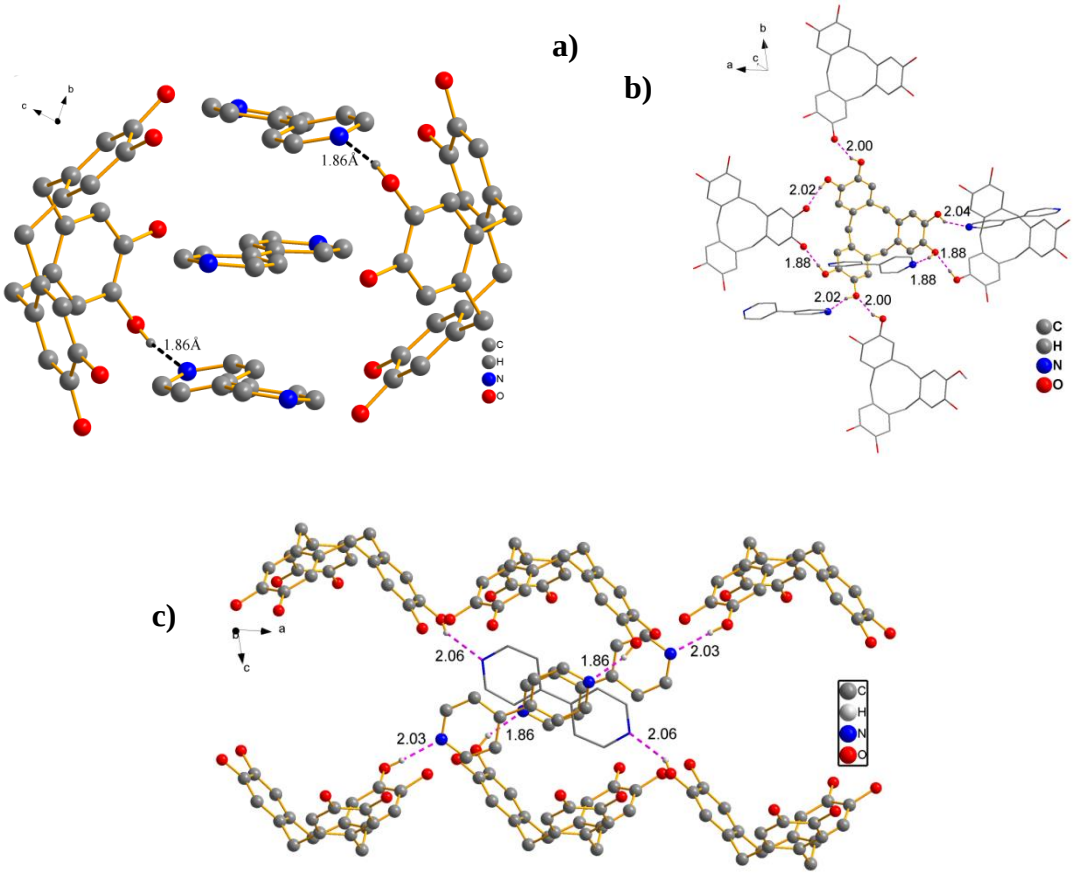


Figure.2.7. X-ray structure of complex **1**. Hydrogen atoms except those forming hydrogen bonds are omitted for clarity. Hydrogen bonding is shown as dotted lines. The text shows the N...H-O distance. Viewed along *a*-axis.

Crystals of complex (**2)** between CTC and pyrazine suitable for X-ray studies, were grown similar to complex **1**.The asymmetric unit contains one molecule of CTC and two molecules of pyrazine. One of the pyrazine molecules is sitting in the cavity and the other one is positioned adjacent to a catechol unit. Each pyrazine molecule is making two hydrogen bonds via their nitrogen atoms. The O-H...N distances of 1.97Å and 2.01Å for one, while other forms two equal hydrogen bond distance being 2.05Å. The hydrogen

bonding between CTC molecules can be clearly seen when viewed along crystallographic *b*-axis. However, no capsule structure could be established may be because of shorter length of pyrzine, less number of π–π electrons to form π–π stack (Figure.2.8.).

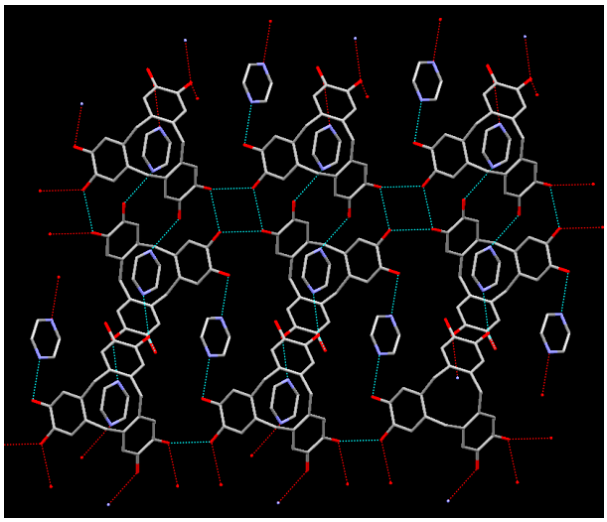


Figure.2.8. Crystal Structure and hydrogen bonding in **2**. Broken bond shows hydrogen bonding.

Capsule (**1**) forms in spite of 4-bpy did not unite two CTC molecules and hydrogen bonding along with π–π stacking played an important for its formation. This result encouraged us to investigate supramolecular structure of CTC with 2-bpy and phen. In these cases, the nitrogen atoms are placed closely; as a consequence both of them are capable of forming hydrogen bonds with the closely placed phenolic hydrogen atoms in CTC but will not be able to unite two CTC molecules. The only difference between 2-bpy and phen is C-C bond rotation in 2-bpy which is restricted in phen. Complex **3** was synthesized by mixing 1:3 equivalents of CTC and 2-bpy respectively in acetonitrile this also comes as a precipitate. The crystals of CTC with 2-bpy was grown in methanol and acetonitrile (1:1) by similar method as for **1**. This assembly is crystallized in trigonal, *R-3* space group (No. 148). As perceived, nearby phenolic hydrogen atoms are bonded to one 2-bpy by hydrogen bonds, thus, each CTC is bonded to three 2-bpy (Figure.2.9.).

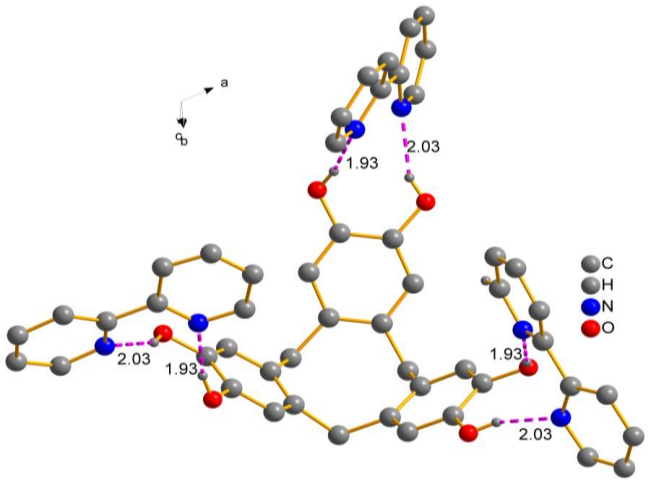


Figure.2.9. Hydrogen bonding and distances in **3**

The O-H...N distances are 1.93Å and 2.03Å. Altogether, the capsule has a propeller like structure with six pyridyl units coming out and inside the cavity is occupied by a positional disordered acetonitrile molecule (Figure.2.10.a). The acetonitrile molecule is placed with its methyl group heading towards the cavity of CTC. This is probably the stability gained due to hydrophobic effects. The 2-bpy molecules are not planar as the rings are tilted at an angle of 20° with respect to each other. This may be happening to have best possible hydrogen bonding. In the absence of acetonitrile solvent molecule, the void size is 471Å^3, 7% of the unit cell volume.

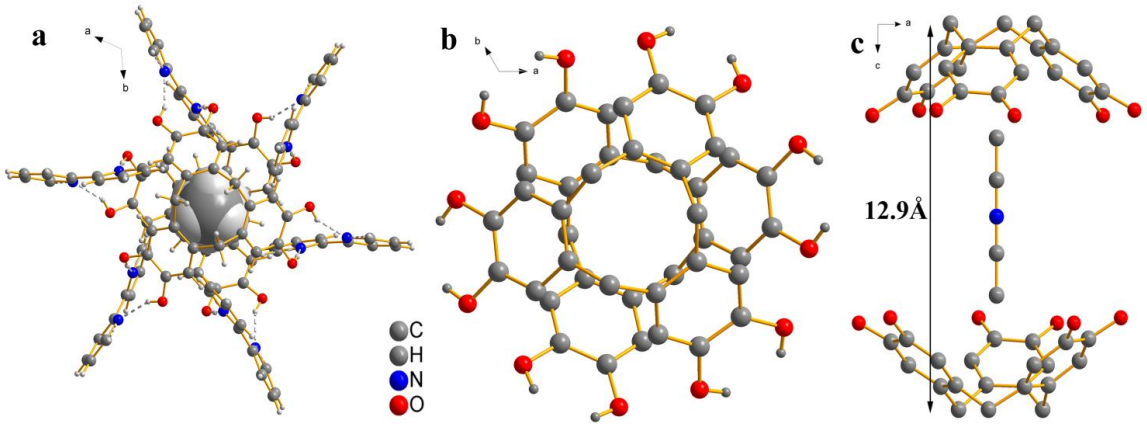


Figure.2.10. a) View of Capsule formed in 3 along *c*-axis. The cavity holds an acetonitrile molecule (space filling model). Hydrogen bonds are shown in dotted lines. b) 3 without solvent and spacer (2-bpy) are viewed along *c*-axis. Hydrogen atoms attached

to carbon are omitted for clarity. c) 3 without 2-bpy are viewed along *b*-axis. Hydrogen atoms are omitted for clarity. Arrow shows the length of the capsule.

The catechol units in CTC molecules, in the capsule are arranged in a staggered like conformation as shown in (Figure.2.10.b.) The distance between the CTC molecules is 12.9Å. A side view of the crystal without 2-bpy shows inclusion of solvent molecule inside the cavity (Figure.2.10.c.). The stability of the capsule is mostly by π–π stacking between 2-bpy rings of adjacent capsules (Figure.2.11.a).

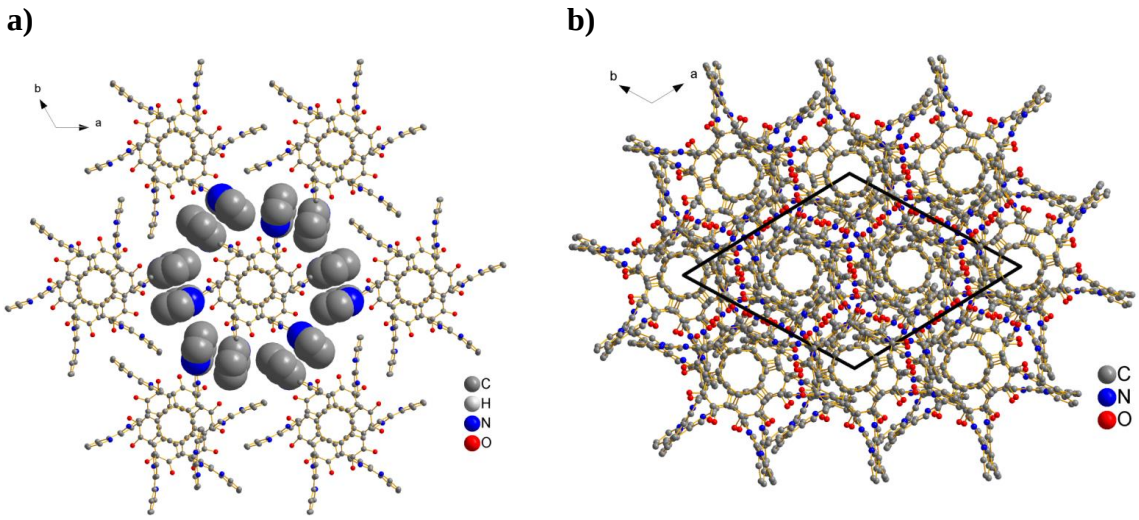


Figure.2.11. Packing in **3**, showing the π–π stacking interactions. Rings having π–stacking interaction to the central capsule are shown in spacing filling model(b) **:** Unit cell packing of **3**. Hydrogen atoms are omitted for clarity.

The formation of the complex 4, between CTC and phen was realized by the precipitation when CTC is added to phen in acetonitrile. The precipitation is faster than the previous complexes and completes in about 4h. Crystals suitable for X-ray diffraction were grown similarly to 1. The overall arrangement is similar to 3. As a result of restricted bond rotation, the N...H-O hydrogen bonding is weaker than 3, distances are 2.0Å and 2.1Å. The phen molecules are inclined to each other by 60 degrees; as a result 1st and 4th rings which are bonded to opposite CTC molecules are parallel to each other

(Figure.2.12.a,b). This arrangement of phen molecules making the capsule look like a propeller. The capsules are arranged in such a way that the phen in one capsule interacts with adjacent capsules by π–π stacking with distance 3.5Å, which stabilizes them (Figure.2.12.c). The distance between the CTC units in 4 is 13.1Å, little larger than in 3. The void size is 1705Å^3 which is 11% of the unit cell volume. This is the highest among all three capsules reported here.

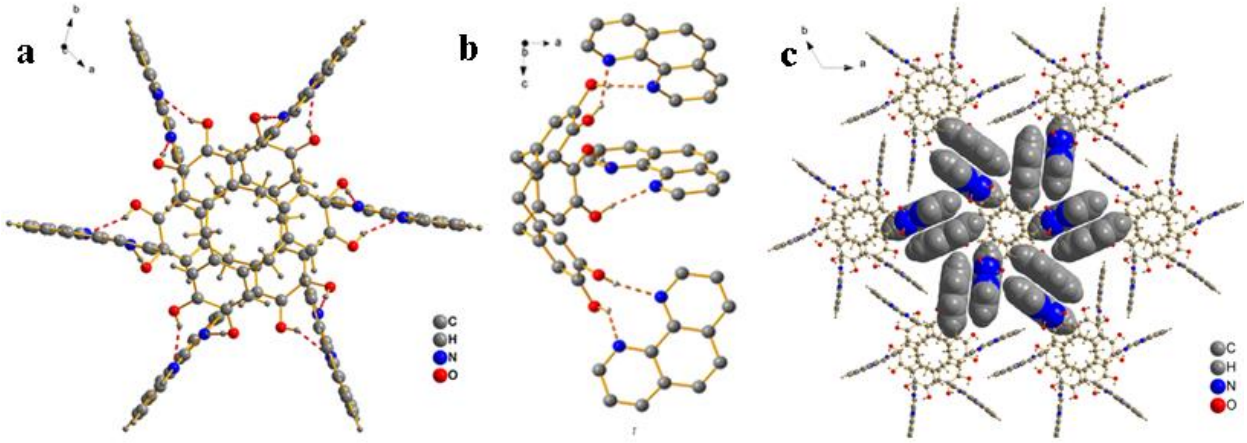
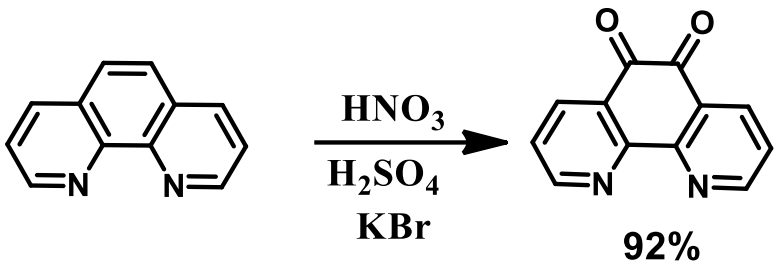


Figure.2.12. Solid sate structure of **4.** a) Capsule as viewed from *c* –axis. b) Hydrogen bonding of CTC and phen in half of the capsule. c) Relative arrangement of capsules and π–π stacking among them. Groups having π–π stacking with the central capsule is shown in space filling model. Hydrogen atoms in b except those forming hydrogen bond are omitted for clarity.

We were interested in studying the effect of changes in the capsule formation with a little change in phen. We choose 9,10-phenanthraquinone to replace phen, where the two oxygen capable of forming hydrogen bonds to phenolic hydrogen atoms are also present along with nitrogen atoms.



Scheme2.2. Synthesis of 9,10-phenanthraquinone

Complex 5 was synthesized by similar manner to complex **1** but replacing phen with 9,10-phenanthraquinone which was synthesized as shown in Scheme2.2. It was obtained as reddish brown crystals in about 2 weeks time and found to crystallize in triclinic crystal setting. Although the highest symmetry space group found was P-1(No. 2), the crystal could not be properly solved in this space group as one of the 9,10-phenanthraquinone was highly disordered. Changing the space group to P1 (No. 1), helped in solving the structure without any disorder. Also, squeeze command was used to take out the electron density of disordered solvent molecules. The capsular structure does not form as seen in the packing of this complex. From the crystal structures, the distance between the nitrogen atoms in phenanthroline and oxygen atoms in 9,10-phenanthraquinone are very similar (2.67Å and 2.68 Å respectively).

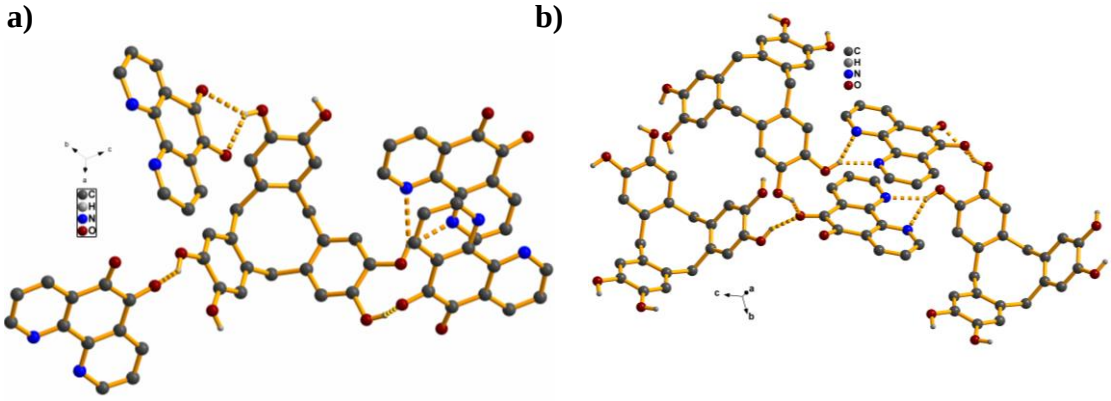


Figure.2.13. a) Hydrogen bonding between CTC and 9,10-phenanthraquinone, Dotted lines shows the hydrogen bonding b) π–π stack between the 9,10-phenanthraquinone units

Therefore, if both the oxygen atoms form hydrogen bonds with phenolic hydrogen atoms of CTC, a capsular structure might be expected. However, this is not happening, may be due to the drastic change in molecular properties of 9,10-phenanthraquinone form phen due to the carbonyl groups. Figure.2.13.a. shows the structure for complex 2. The phenolic hydrogen atoms of CTC are now have hydrogen bond with nitrogen and oxygen atoms of 9,10-phenanthraquinone. This forms a 2D network of hydrogen bonded molecules as shown in Figure.2.13.b. Another feature of this unit cell is π–π stacking. interactions between CTC and 9,10-phenanthraquinone with a centroid to centroid distance of ~3.5Å.

Considering the hydrophobic nature of the CTC cavity, strong π–π intearctions between the phen moleucles, we thought of encapsulating small aromatic molecules in side its cavity. We could successfully encapsulate naphthalene in the cavity. When 1:2 molar ratios of preformed capsule and naphthalene respectively, was dissolved in methanol and kept for slow evaporation, in about two

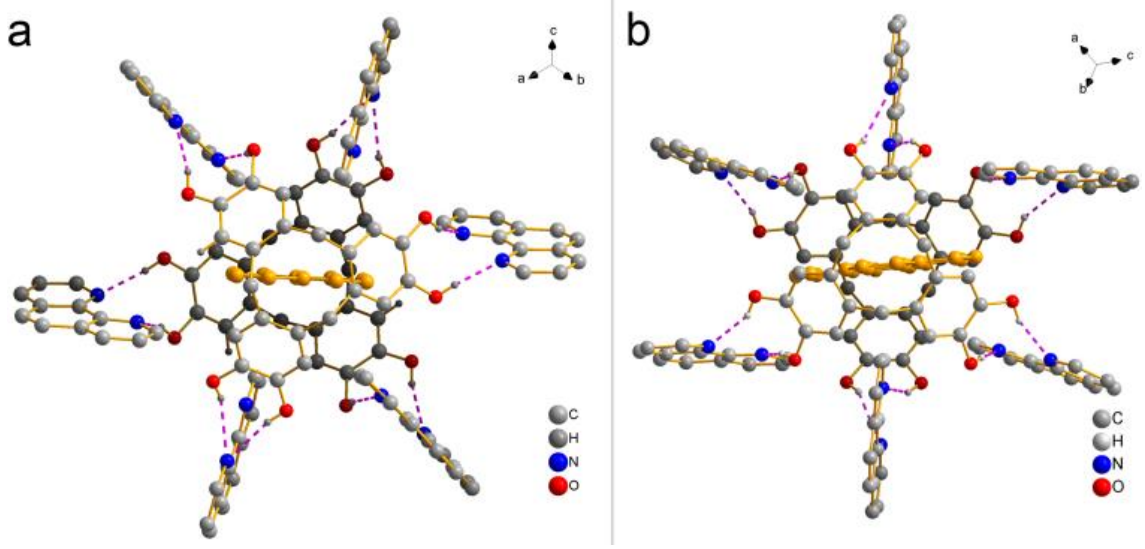


Figure.2.14. X-ray crystal structure of a) **6** and b) **7** with depth cueing**.** Dotted bond shows the hydrogen bonding. The guest molecules are shown orange color. Hydrogen atoms not forming hydrogen bonds are omitted for clarity.

weeks crystals of complex **6** was formed. We chose to put preformed capsule to avoid excess of phenanthroline in the solution. Morphologically, it seems to have two kinds of crystals. One was similar and another different from **4**. During initial investigation with X-ray, it was found that crystals those have different morphology have different cell dimensions as compared to **4**. Complex **6** also belonged to triclinic P-1 space group (Figure.2.14.a) Naphthalene molecule is occupying the cavity with the hydrogen atoms pointing towards the CTC molecules.

Two opposite phen rings are displaced when compared with **4**. The distances between the displaced phen rings with nearby CTC unit is 3.63Å, while other rings are stacked at 3.92Å. The hydrogen bonding distances and angles are given in table 2.2. Most possibly hydrophobic forces are holding the guest in the cavity. We also found that pyrene can be put inside the cavity to form complex **7**. We crystallized pyrene encapsulated capsule **7** in a similar manner to **6** (Figure.2.14.b). For **7**, four rings are displaced as compared to parent capsule **4,** which makes a cavity for pyrene to stay. Due to this arrangement the capsule with guest are no more propellers shaped. The $\pi-\pi$ stacking distance between phen moieties in nearby capsule is 3.78Å. Figure 2.14 presents capsule **6** and **7** with guest inside.

The encapsulation of naphthalene and pyrene in the capsule formed with CTC and phen encouraged us to investigate the encapsulation of phenanthrene. Phenanthrene was dissolved in methanol and mixed with re-dissolved capsule solution. Brown colored crystals of complex 8 were formed in about 2 weeks time. They belonged to P-1 (No. 2) space group in triclinic crystal system. Table 2.1 contains the crystal data for the complex. As expected, the assembly is found to form a capsule, inside which phenanthrene is encapsulated (Figure.2.15.). Two carbon atoms on phenanthrene were found to have positional disorder.

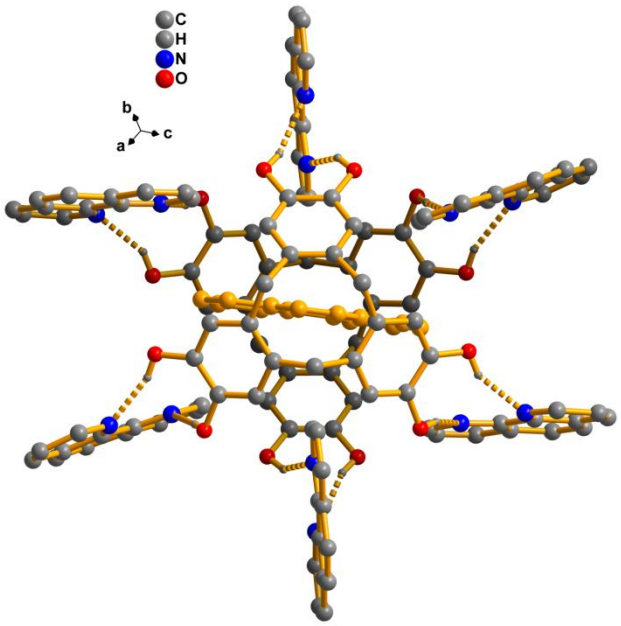


Figure.2.15. X-ray crystal structure of **8** with depth cueing**.** Dotted bond shows the hydrogen bonding. The guest molecules are shown orange color. Hydrogen atoms not forming hydrogen bonds are omitted for clarity

This is due to the energetically two similar position of phenanthrene inside the capsule. The disordered was resolved by giving half occupancy to each of the carbon and refining them. The occupancies were converged at 0.509 and 0.491 for these carbons.

The CTC unit forms six hydrogen bonds with three phen moieties, thereby forming half of the capsular structure (Figure.2.16.a). The hydrogen bonding distances are given in Table 2.2 Two half of these capsular units are joined together by π–π stacking interactions with phen to form other capsules (Figure.2.16.b). The distance between the planes passing through the methylene groups of CTC in participating capsules are 12.9 A°. This distance may be regarded as the length of the capsule. The phenanthrene captured inside in a manner that the hydrogen atoms of the middle ring are pointing towards CTC molecules, thereby almost parallel to the four phen moieties and perpendicular to two of them. Four phen which are parallel to phenanthrene are having a

week π–π stacking interactions (Figure.2.16.b). These phen molecules are holding the guest from slipping away. As a whole the phenanthrene is captured inside the molecules due to hydrophobic forces of CTC and π–π stacking of phen molecules.

a) **b)**

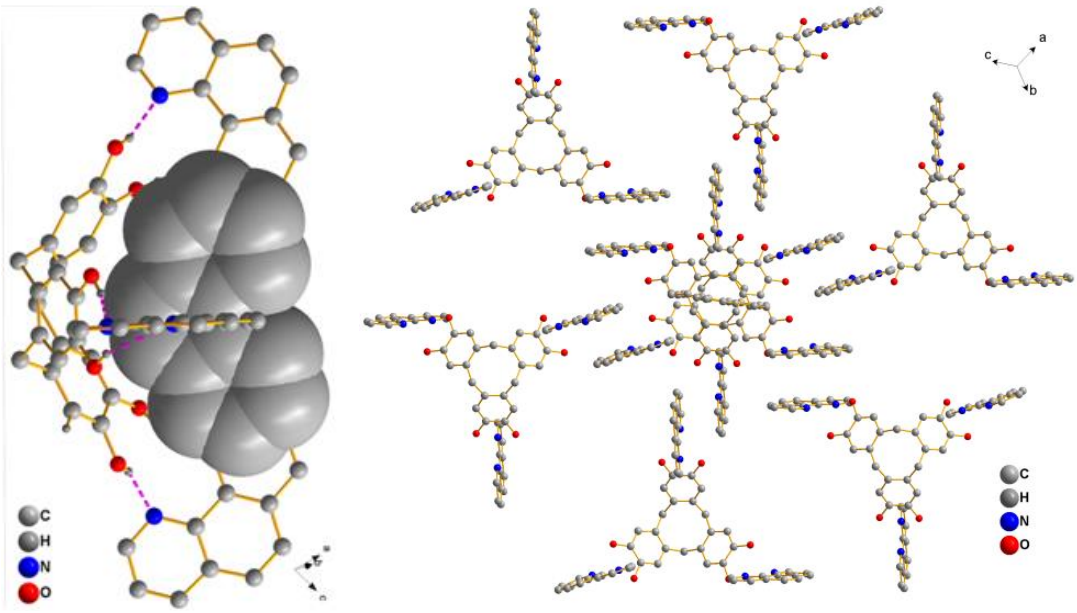


Figure.2.16. a) Half of the capsule showing phenanthrene encapsulation. Dotted line indicates hydrogen bonding. Hydrogen atoms except those forming hydrogen bonding are omitted for clarity b) Crystal lattice of complex **8**, showing the π–π stacking which holds the capsular structure. Hydrogen atoms are omitted for clarity.

2.5. SEM studies: To know the morphology of the selected complexes in powder, particularly for CTC, capsular complex **4** and pyrene entrapped complex **7**, we examine their bulk product through scanning electron microscope. The sample was prepared by dissolving 1mg of the precipitate in 1ml of methanol and filtered through a micro filter. 20μl of the solution was placed on to a 100 silicon wafer surface. The solution was evaporated by air and the sample was kept in vacuum for 8h. It was then imaged. Only CTC shows crystalline morphology (Figure.2.17.) and micro crystals were deposited all over the surface.

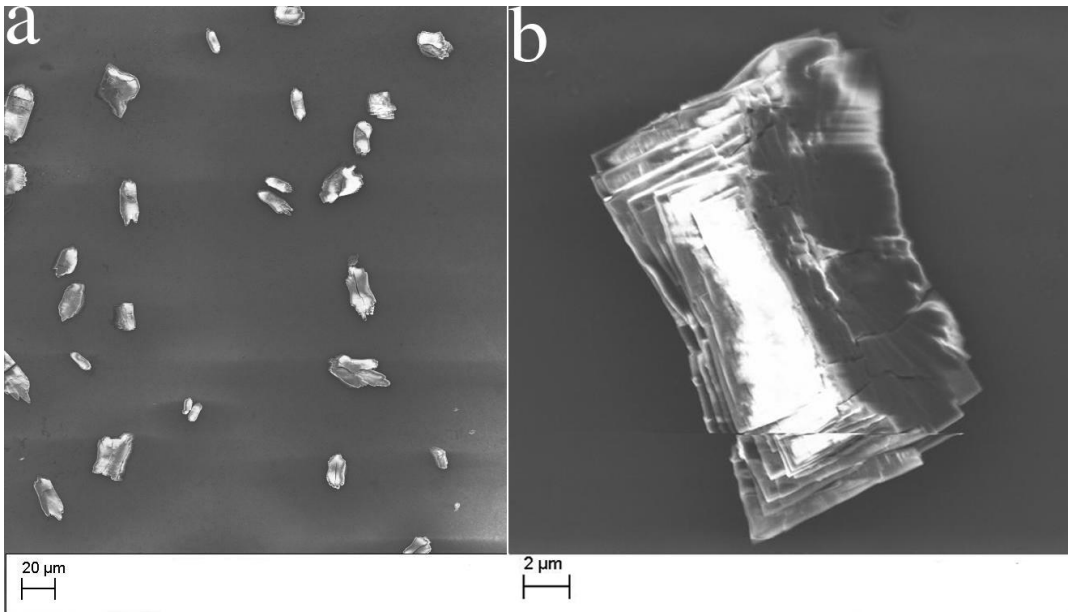


Figure.2.17. SEM pictures of only CTC. a) At Low magnification; b) at higher magnification.

Capsule **4**, shows spherical structure of different size ranging from 0.5-1.5 micron in size deposited all over the surface (Figure.2.18). This indicates that the self assembled structures are growing in three dimensions to retain the structure at atomic level. Stabilization of the spherical structure at bulk may be attributed to the large number of strong π–π stacking in case of **4**. In case of **7**, the SEM image shows linear crystalline structure which are composed of small crystalline structure. The distortion in the structure due to the entrapment of a larger molecule like pyrene, which resulted in relatively weaker π–π stacking, may be responsible for destruction of spherical structure in bulk(Figure.2.18).

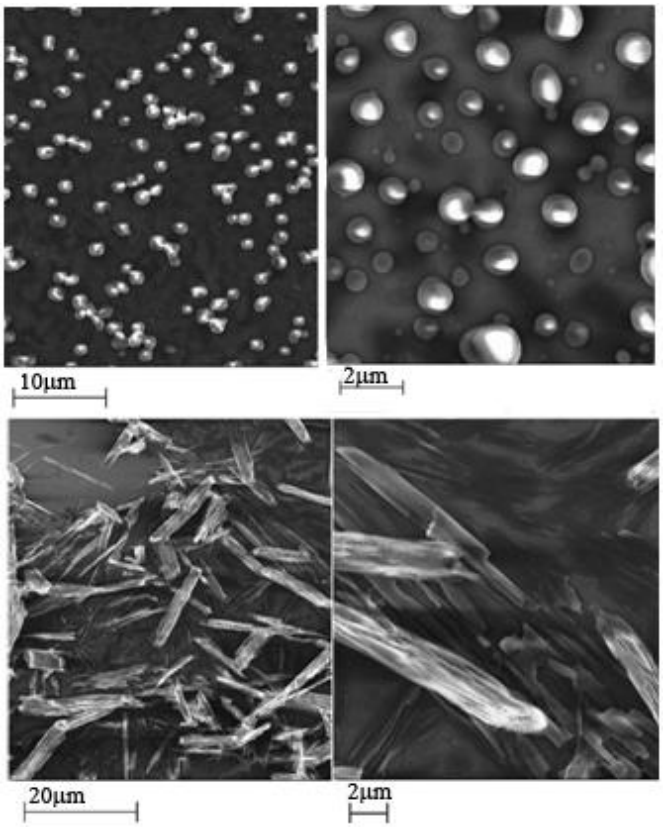


Figure.2.18. SEM images a) **4** at low magnification, b) **4** at higher magnification c) **7** at low magnification and d) **7** at higher magnification.

2.6. Conclusions: In conclusion, we have reported here through single crystals studies, supramolecular assemblies of CTC with suitable hydrogen bonding heterocyclic compounds forming capsular structures. We also noticed that modifying 1, 10-Phenanthroline and synthesizing 9, 10- phenanthraquinone which is having more number of hydrogen bonding acceptors has destroyed the capsular structure ended up in forming supramolecular assembly. Capsule formed by CTC, 1, 10-Phenanthroline is capable of encapsulating planar molecules naphthalene, pyrene, phenanthrene.

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2.7. Spectral Data

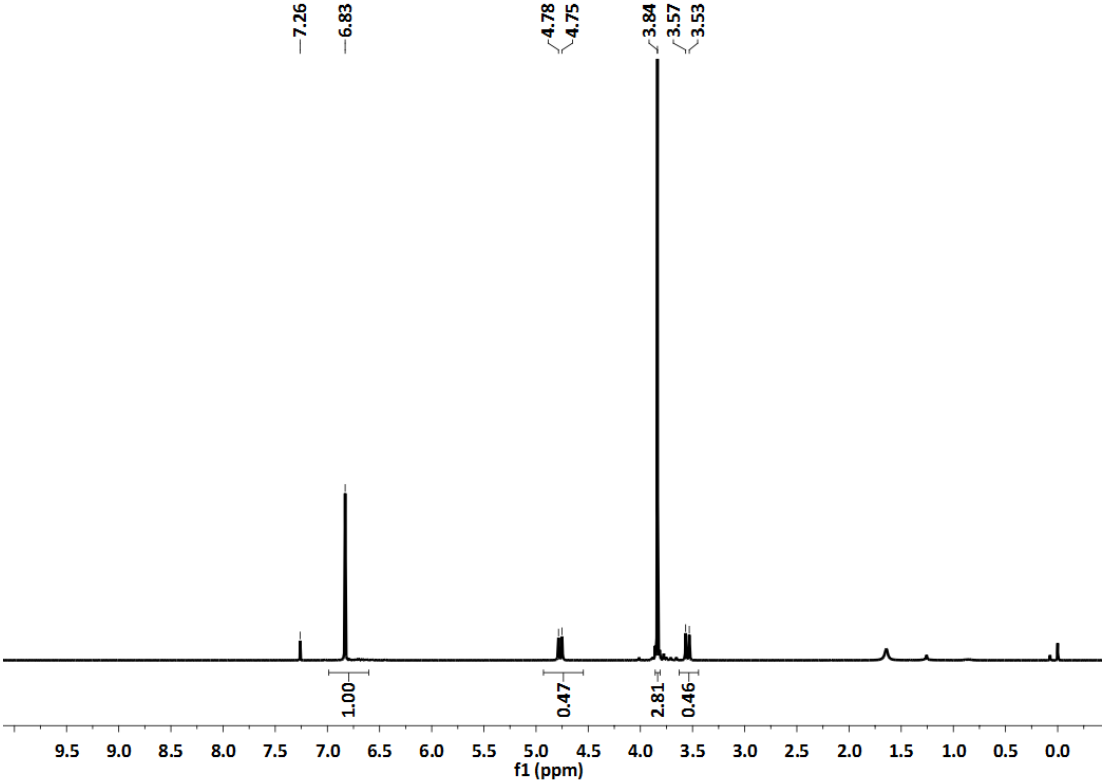


Figure.2.19. ^{1}H NMR spectra of CTV in $CDCl_3$

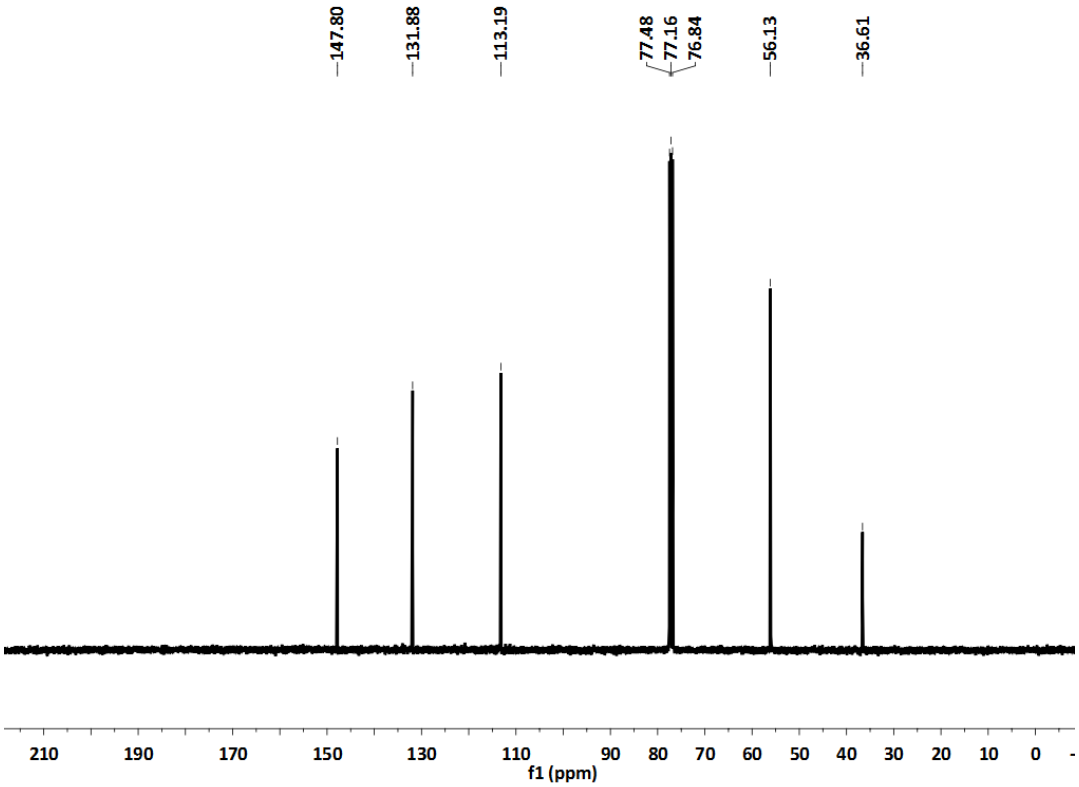


Figure.2.20. ^{13}C NMR spectra of CTV in $CDCl_3$

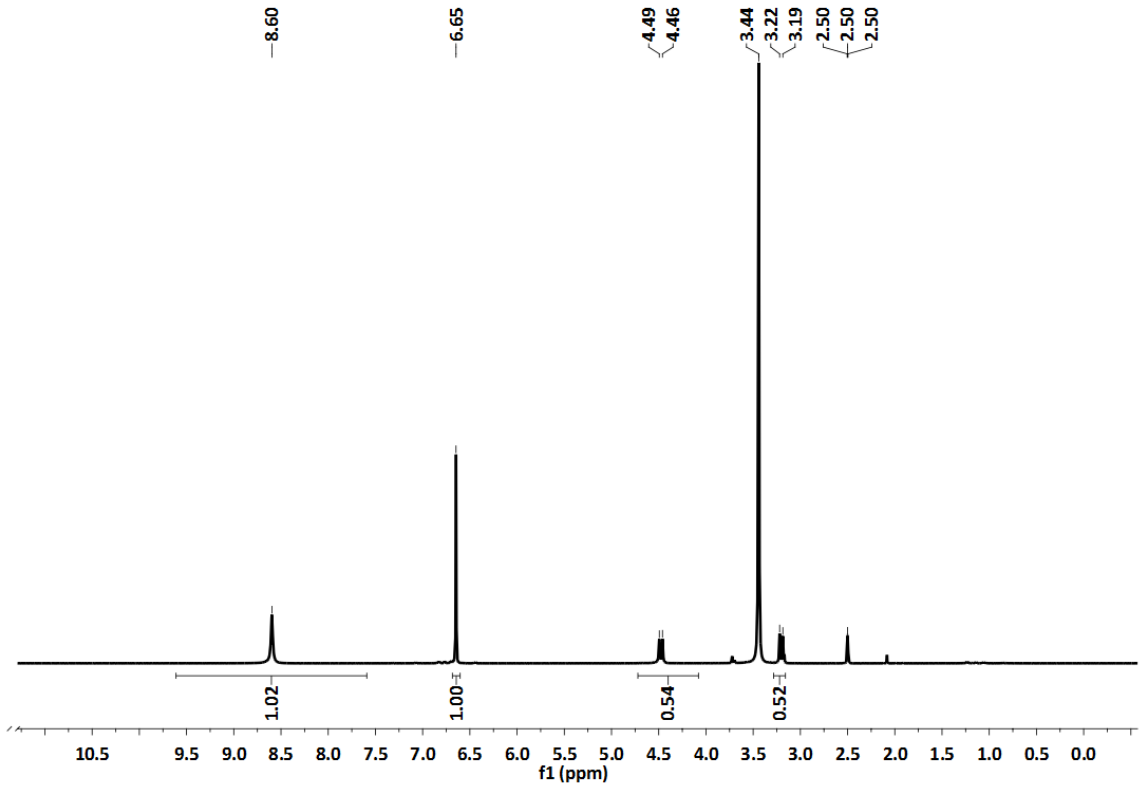


Figure.2.21. ^{1}H NMR spectra of CTC in DMSO-d_6

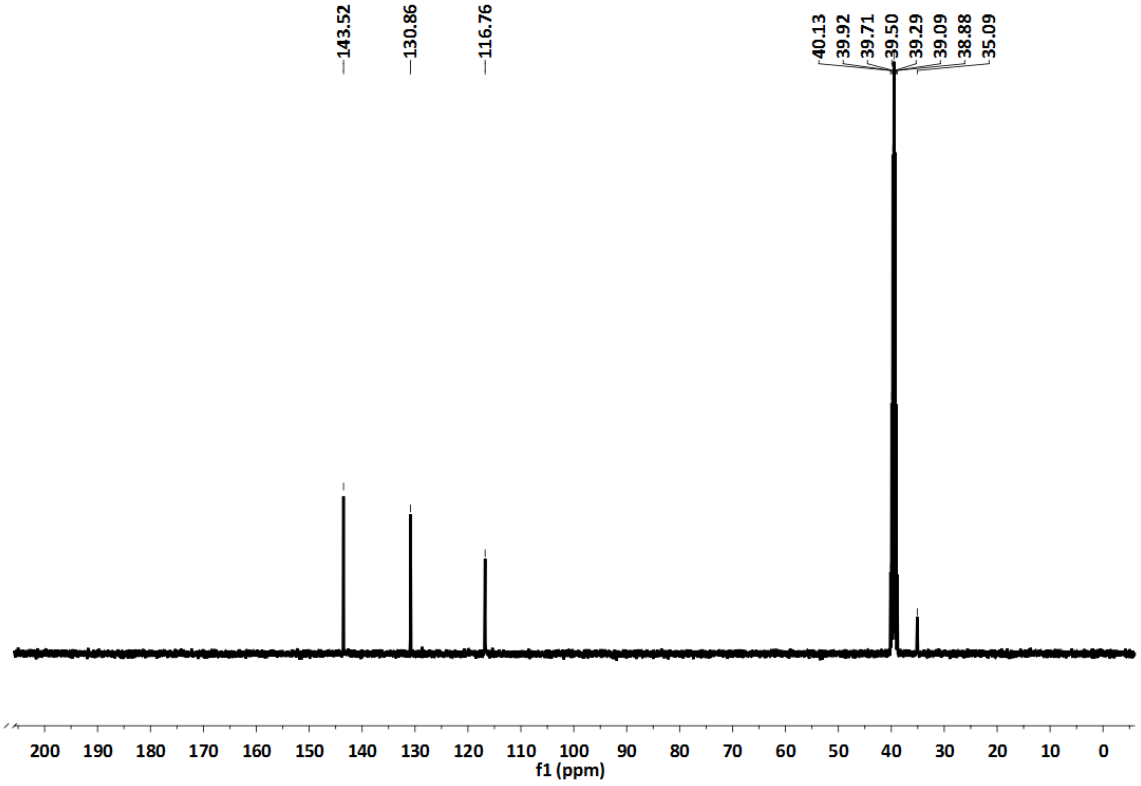


Figure.2.22. ^{13}C NMR spectra of CTC in DMSO-d_6

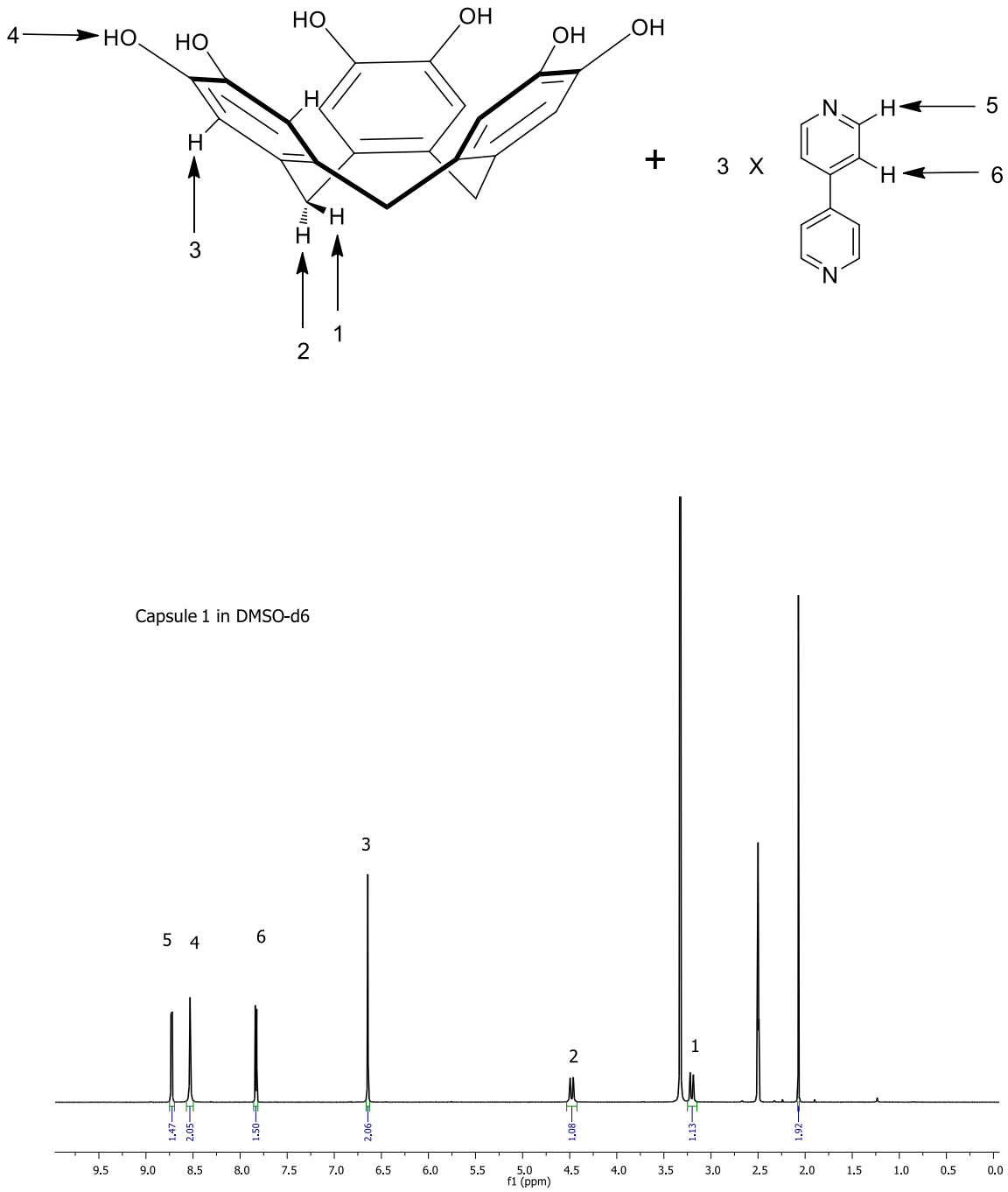


Figure.2.23. [1]HNMR of **1.** Starred peak is solvent residual peak.

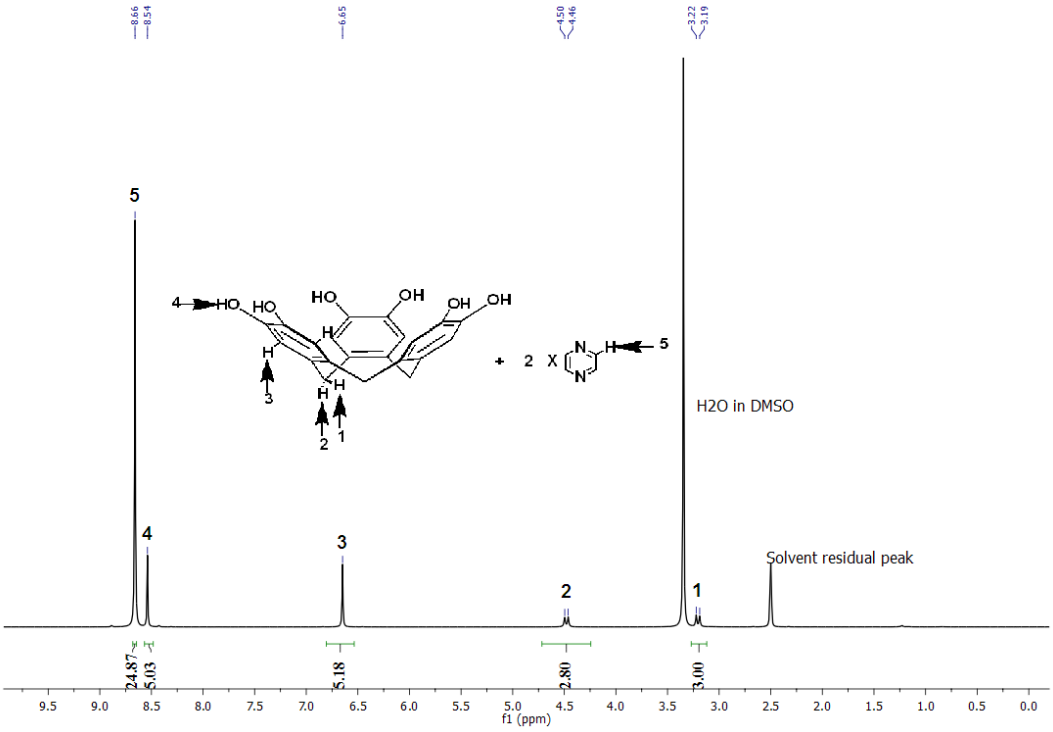


Figure.2.24. ^{1}H NMR of complex **2**

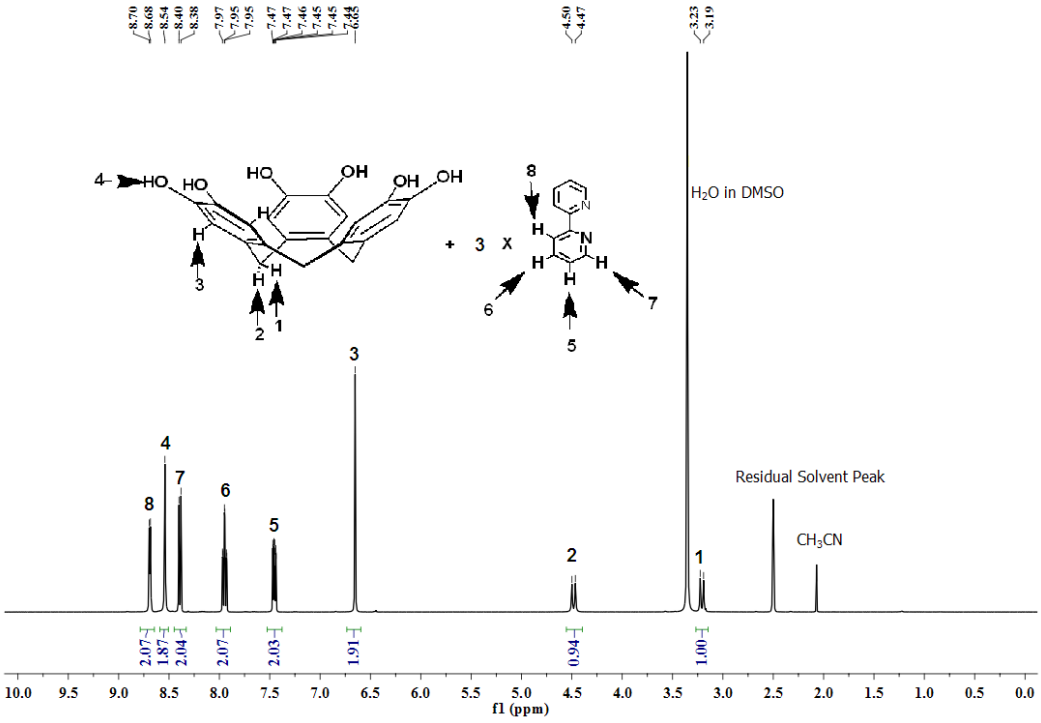


Figure.2.25. ^{1}H NMR of complex **3**

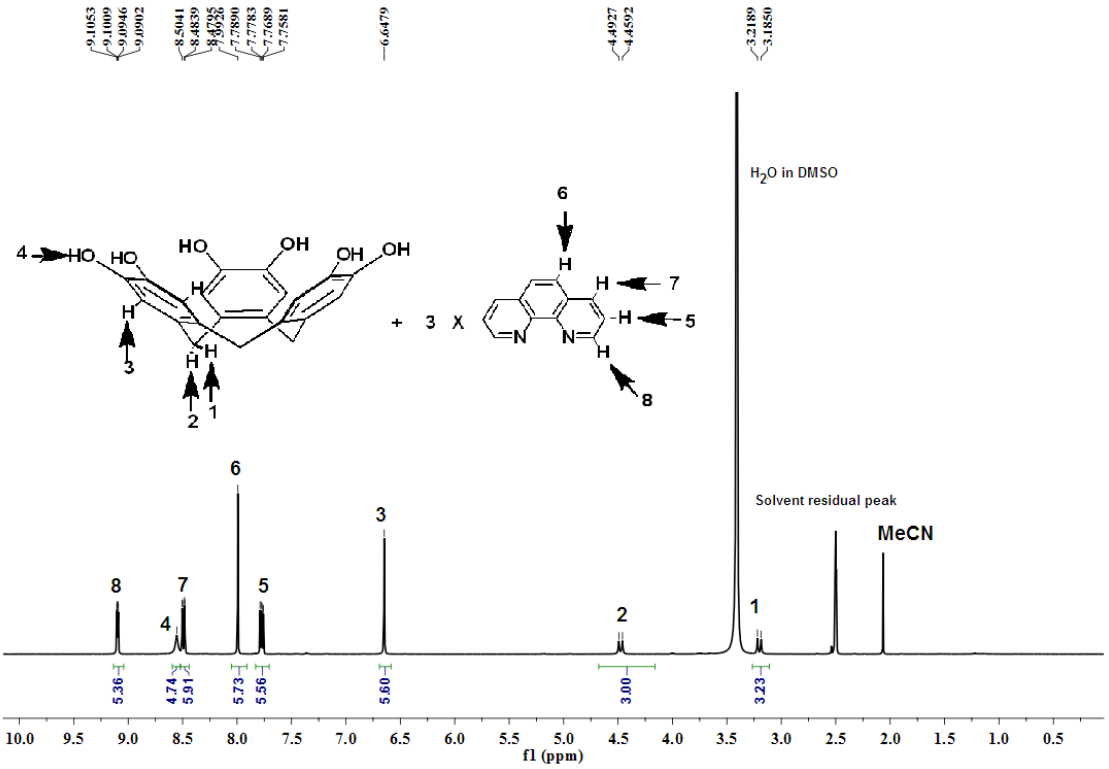


Figure.2.26. [1]HNMR of complex **4**

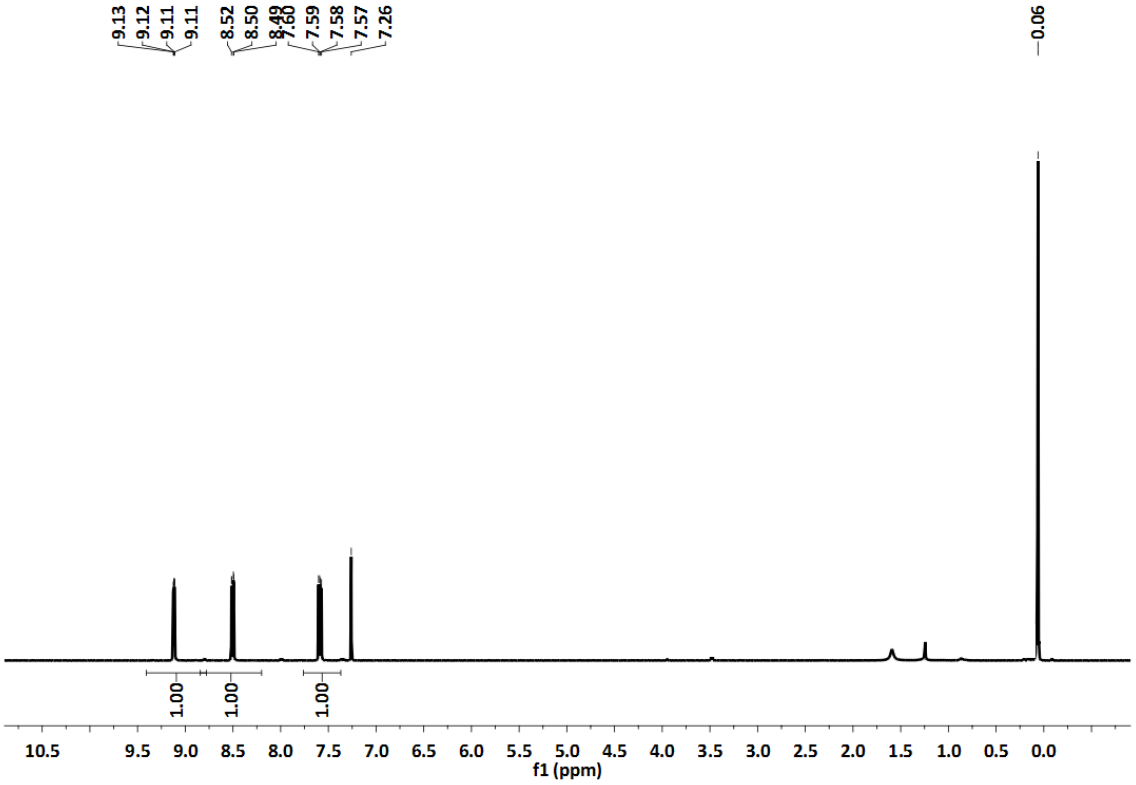


Figure.2.27. [1]H NMR of PAQ $CDCl_3$

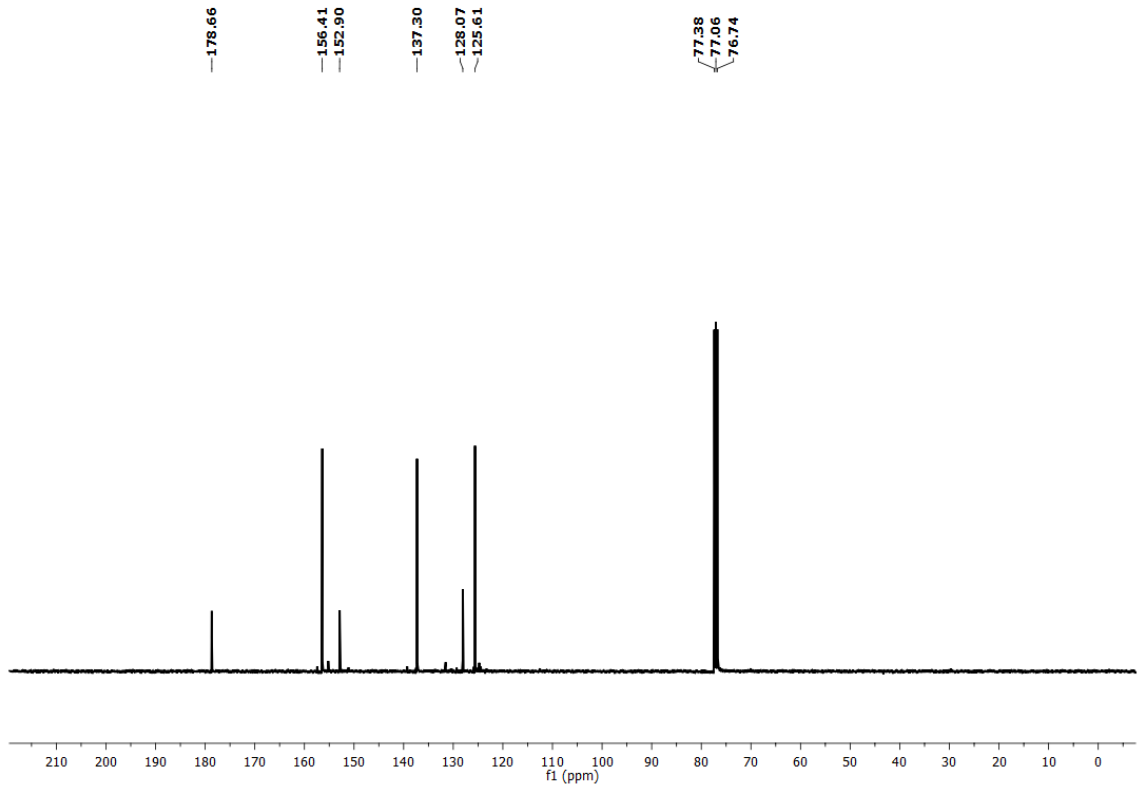


Figure.2.27. ^{13}CNMR of PAQ in $CDCl_3$

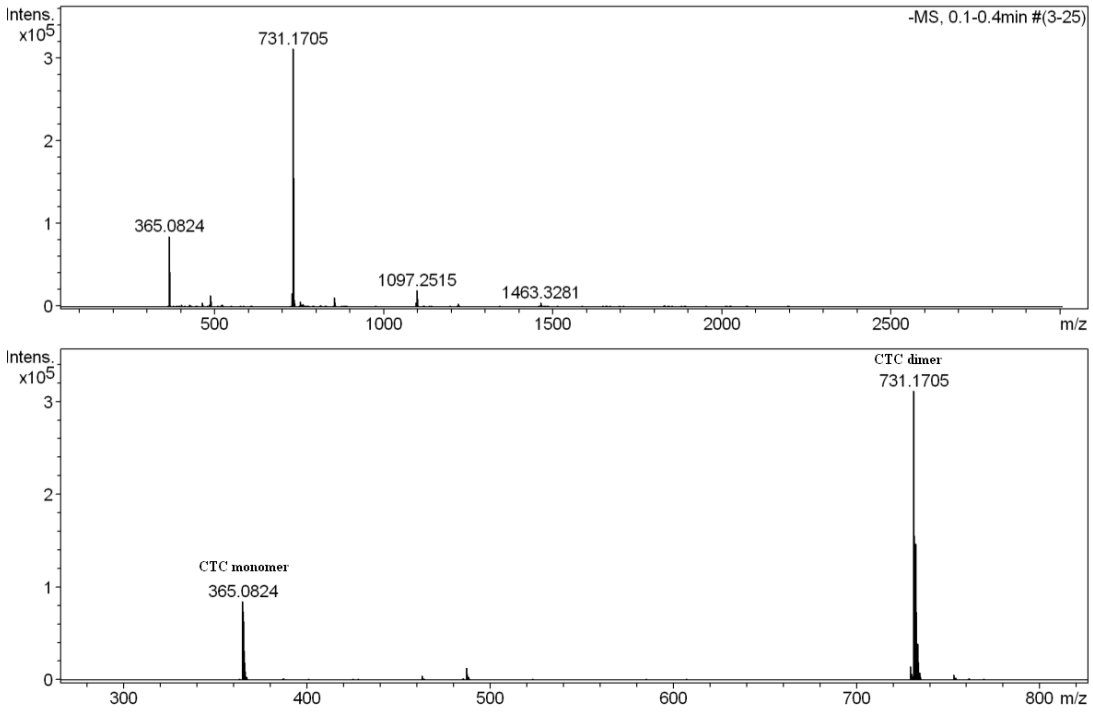


Figure.2.28. ESI-Mass Spectra of (-ve Mode) **CTC** in Methanol

Complex 1				
D-H…A	**D-H**	**H…A**	**D…A**	**D-H…A**
O(1)...H(1)…N(3)	0.82	2.04	2.772(3)	148
O(2)...H(2)…N(2)	0.82	1.87	2.670(3)	166
O(3)...H(3`)…N(1)	0.82	2.02	2.808(3)	161
O(4)...H(4)…O(2)	0.82	1.88	2.696(2)	170
O(5)...H(5)…O(1)	0.82	2.02	2.832(2)	168
O(6)...H(6`)…O(3)	0.82	2.01	2.770(2)	155
C(28)...H(28)…O(3)	0.93	2.51	3.348(3)	151
Complex 2				
O(1)...H(1)…N(3)	0.82	2.06	2.866(3)	167
O(2)...H(2A)...O(4)	0.82	2.09	2.794(2)	143
O(3)...H(3)...N(1)	0.82	1.99	2.791(2)	164
O(4)...H(4)…O(2)	0.82	2.25	3.015(2)	156
O(5)...H(5A)…N(2)	0.82	1.97	2.760(2)	162
O(6)...H(6)…O(5)	0.82	2.09	2.861(3)	157
Complex 3				
O(1)...H(1)…(1)	0.82	1.93	2.723(18)	162
O(2)...H(2)…N(2)	0.82	2.03	2.794(2)	154
C(3)...H(3)…O(1)	0.93	2.56	3.401(2)	151
C(6)...H(6)…O(1)	0.93	2.54	3.435(2)	160
Complex 4				
O(1)...H(1)..N(4)	0.82	2.02	2.763(4)	151
O(2)...H(2)..N(3)	0.82	2.00	2.814(4)	169
O(3)...H(3A)..N(2)	0.82	2.07	2.846(3)	158
O(4)...H(4)..N(1)	0.82	2.05	2.817(3)	156
Complex 5				
O(2)—H(2)..O(17)	0.82	2.14	2.854(7)	146
O(2)—H(2) ..O(18)	0.82	2.39	2.884(6)	120
O(3)—-H(3A) ..O(16)	0.82	2.37	3.024(5)	137
O(5) —H(5) ..O(13)	0.82	2.41	3.136(6)	149
O(5)—H(5) ..O(14)	0.82	2.35	2.947(6)	131
O(6)—H(6A) ..N(3)	0.82	2.60	3.274(7)	141
O(6) --H(6A) ..N(4)	0.82	2.07	2.768(6)	143
O(7)—H(7) ..N(5)	0.82	2.08	2.845(7)	155
O(9)— H(9) ..O(14)	0.82	2.28	2.931(5)	137
O(11)—H(11) ..O(15)	0.82	2.43	3.185(7)	155
O(11)—H(11) ..O(16)	0.82	2.49	3.013(7)	123
O(12)—H(12) ..N(1)	0.82	2.58	3.198(6)	134
O(12)—H(12) ..N(2)	0.82	2.00	2.722(6)	147

Complex 6				
O(1)...H(1)...N(5)	0.82	2.08	2.874(5)	164
O(2)...H(2)...N(6)	0.82	2.06	2.839(6)	159
O(3)...H(3)…N(1)	0.82	2.33	3.078(4)	151
O(3)...H(3)…N(2)	0.82	2.33	2.989(5)	137
O(4)...H(4)...N(1)	0.82	2.16	2.958(4)	166
O(5)...H(5)...N(3)	0.82	1.96	2.767(5)	166
O(6)...H(6)...N(3)	0.82	2.59	3.219(6)	135
O(6)...H(6)...N(4)	0.82	2.09	2.831(5)	151
C(1)...H(1B)...O(1)	0.97	2.52	3.485(4)	176
Complex 7				
O(1)...H(1)…N(5)	0.82	2.01	2.813(3)	166
O(2)...H(2)…N(6)	0.82	2.04	2.825(3)	162
O(3)...H(3A)…N(1)	0.82	2.27	2.950(2)	140
O(3)...H(3A)…N(2)	0.82	2.34	3.055(2)	147
O(4)...H(4)…N(1)	0.82	2.32	3.013(2)	143
O(4)...H(4)…N(2)	0.82	2.31	3.012(3)	145
O(5)...H(5)...N(3)	0.82	2.01	2.759(2)	151
O(6)...H(6A)…N(4)	0.82	1.99	2.762(2)	156
C(15)...H(15B)…O(6)	0.97	2.55	3.469(3)	159
C(28)...H(28)…O(1)	0.93	2.42	3.227(4)	145
Complex 8				
O(1) — H(1) ..N(3)	0.82	2.04	2.823(9)	161
O(2)— H(2) ..N(4)	0.82	1.99	2.810(1)	176
O(3)—H(3A) ..N(5)	0.82	2.49	3.067(5)	128
O(3)—H(3A) ..N(6)	0.82	2.16	2.930(8)	158
O(4)— H(4) ..N(5)	0.82	2.32	2.999(1)	140
O(4)— H(4) ..N(6)	0.82	2.29	3.005(3)	147
O(5)—H(5) ..N(1)	0.82	2.00	2.749(4)	152
O(6)—H(6A) ..N(2)	0.82	1.98	2.758(2)	159

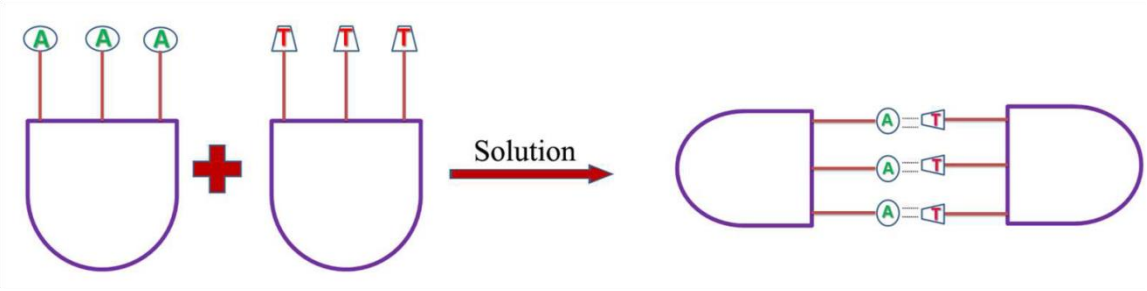
Table 2.2. Hydrogen bonding distances and angles of the complexes **1**-**8**.

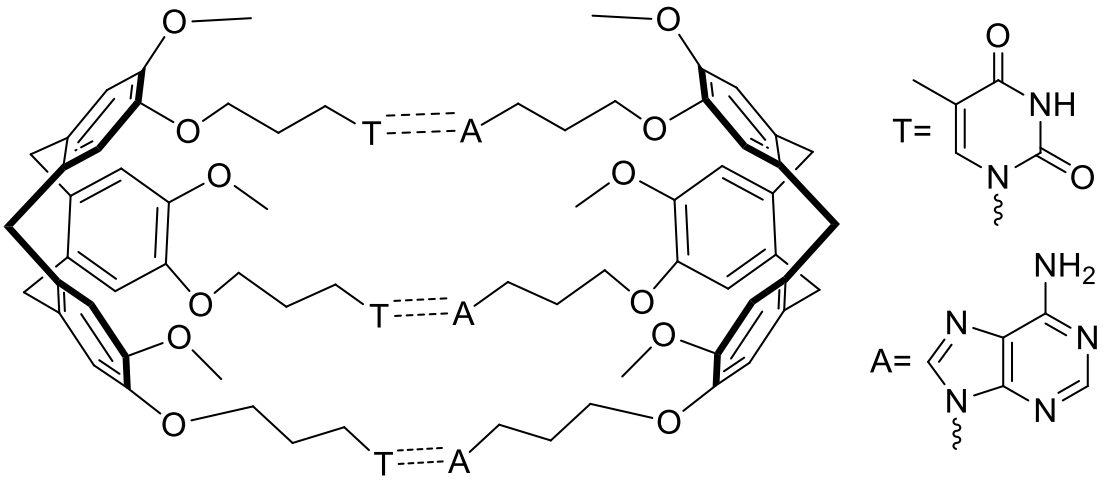
CHAPTER 3

Bio-inspired self-assembled molecular capsule

3.1 Abstract

In this chapter we will discuss the molecular capsules synthesized, by inspiring from biologically relevant molecules. We synthesized hydrogen bonding based capsule which is a mimic of A-T base pairing of DNA. Bowl shaped molecules are useful for making molecular capsules with suitable non-covalent bond. Bowl shaped Cyclotriguaiacylene can be suitably modified at its phenolic groups for attaching differentfunctionality to construct molecular capsule. In this work, a molecular capsule has been prepared by appending adenine and thymine in cyclotriguaiacylene. These blocks when mixed in mixture of solvents give a molecular capsule, as ascertained by mass and NMR spectroscopy.





3.2Introduction

3.2.1 Supramolecular assemblies with A-T base pairing

Molecular capsules have recently emerged as a subject of great interest due to their possible applications in various fields. For example, their ability to carry guest molecules, and release them under mild change in condition, is an important feature in drug delivery.[1-4] Molecular capsules when used as reaction vessels, can accelerate the reaction speed as compared to the bulk solvent environment,[5-7] and can trap the unstable molecules or reactive intermediates at room temperature.[8-10] Self-assembled molecular capsules can also be used for molecular recognition and as sensing materials.[11-13] Molecular capsule formed by non-covalent interaction(s) such as hydrogen bonding, is highly desirable as these bonds can easily be broken by subtle change in environment.

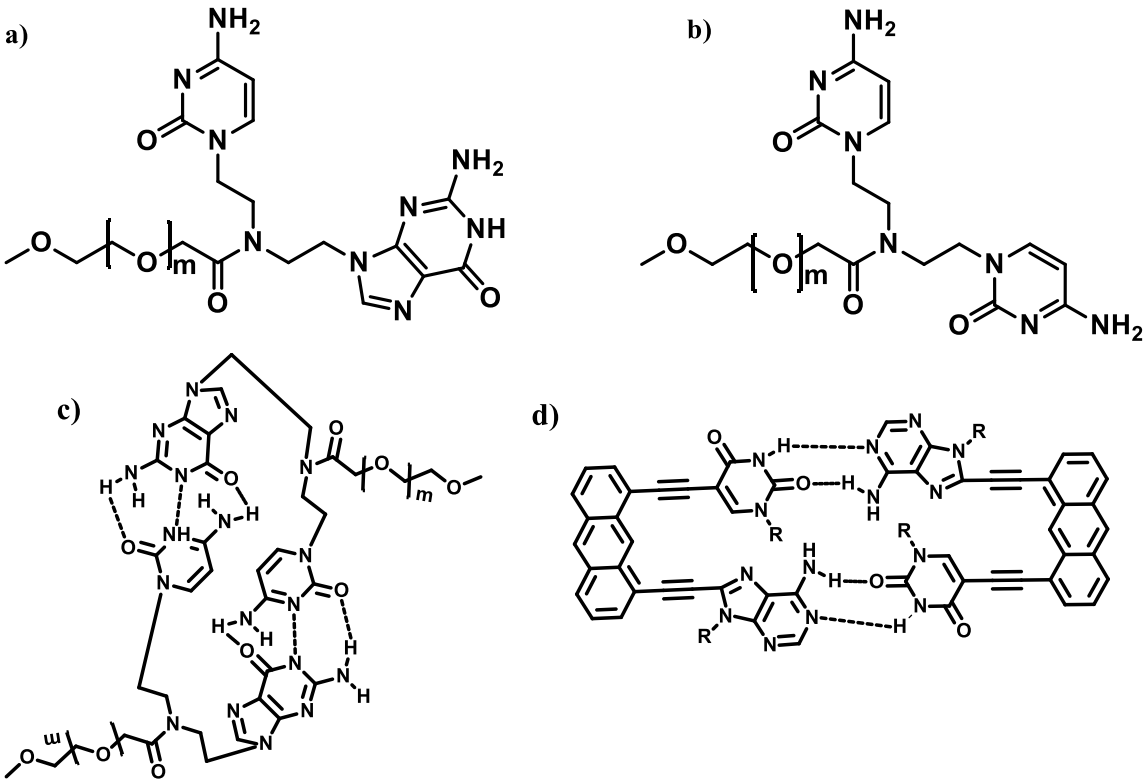
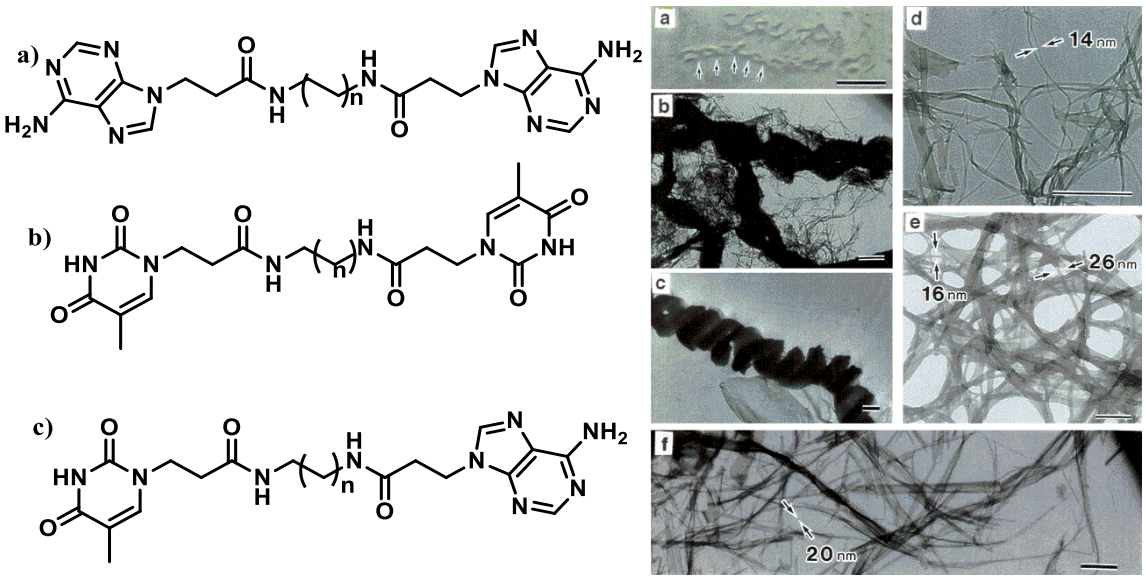


Figure 3.1.a) Nucleobase hetero monomers attached to PEG **b)** Nucleobase homo monomers attached to PEG **c)** self-association of heterodimer **d)** Anartificial dinucleotide duplex formed by complimentary base pairing

3.2.2 Molecular recognition with A-T base pairing

Molecular recognition and self-assembly is strongly governed by the molecular components they contain and the type of interaction(s) that hold them together. Among naturally occurring molecules, nucleobases are well known for their specific Watson-Crick hydrogen bonding. Due to directionality and specificity in Watson-Crick base pairing and π–π stacking capability of nucleobases, they hold DNA single strands to form a double helical structure in cellular milieu that helps DNA to replicate and preserve genetic code. The self-complementary nature of nucleobases can be used for molecular recognition and nanotechnology. Chemists used this interaction beyond natural realm to assemble molecular building blocks.[14,15]By attaching two complementary bases cytosine and guanine on two sides of short aliphatic chainshomodimers,guanine cytosine hetrodimers,(Figure 3.1.a-c)have been synthesized,which dimerizesanalogues todinucleotides based on molecular recognition.[16]



d)

Figure3.2.a-c) Bolaamphiphile molecules with different nucleobase composition **d)** TEM images of the different supra molecular architectures ranging from a helix to nanofibers

By changing the aliphatic side chains to 1, 8 diethynylanthracene and keeping two complementary bases(Figure 3.1.d)on both sides of rigid acetylinic spacer results in duplex-likeensemble, which forms artificial dinucleotide duplex.[17]Nanofibers can be formed by attaching the complementary adenine, thymine on both sides of 1,n-diaimino alkanes(n=10-12) shown in(Figure 3.2.).[18]An artificial receptor for nucleic acids was synthesized by attaching the nucleobases to 1,3,5 –cyclohexane tri carboxylic acid.[19]Suitably stitched aromatic surface that allows simultaneous base-pairing and aryl stacking interactions which make the molecule recognize 9-ethyl adenine.

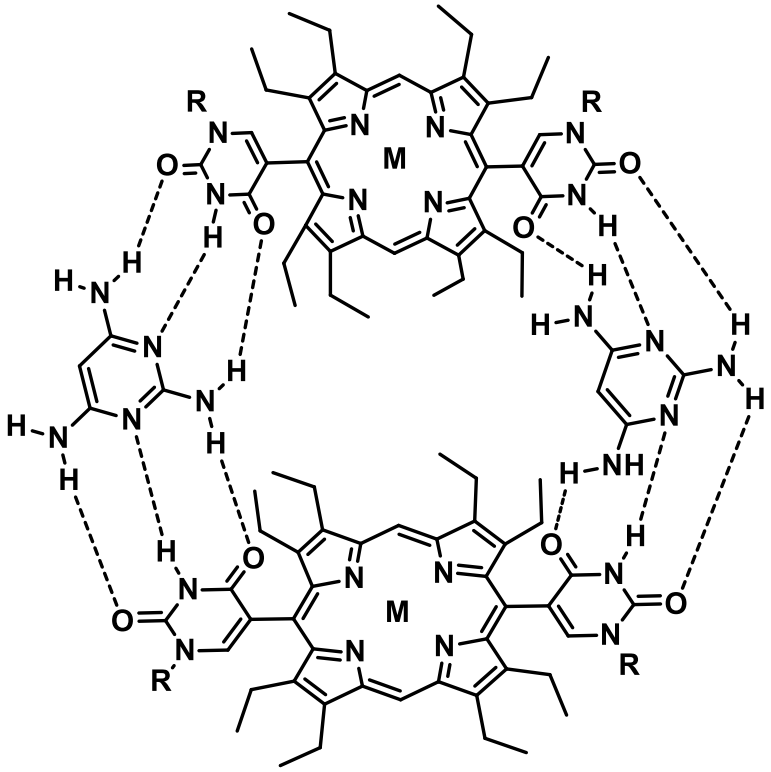


Figure3.3. Supramolecular cage-like structure, formed by the self-assembly of two porphyrins containing 5-alkyluracil

A molecular cage(Figure 3.3.)has been synthesized by attaching hydrogen bonding uracil moieties to the porphyrin ring.The hydrogen bonding interactions with complementary molecule 2,4,6 triamino pyrimidine was used as glue to join the two half in this case.[20]By appending the complementary adenine, thymine units to the end arms of the crown ethers different structures, A-**O**-A, T-**O**-T, A-**O**-Twhere '**O'** represents crown ether, have been synthesized.[21]Association of the nucleotide bases afford molecular boxes, by inter and intra molecular interactions, diammonium salt was shown an induced-fitbetween A-**O**-A and T-**O**-T.Many examples such as triblock copolymer,[22] biocompatible materials with embedding nucleobase to poly(e-caprolactone),[23]molecular recognition motif,[16,19-21] energy- and electron-transfer systems have been reported in literature.[24] Chemists also use them as metal coordinating ligand for formation of different super structures;[25-29] constructs MOF and use their coordination polymer as catalyst, absorption materials, and drug delivery vehicles.[30-33] The major challenge, however, remains with preparation of predefined super-structures that are soluble in suitable solvent.[34]

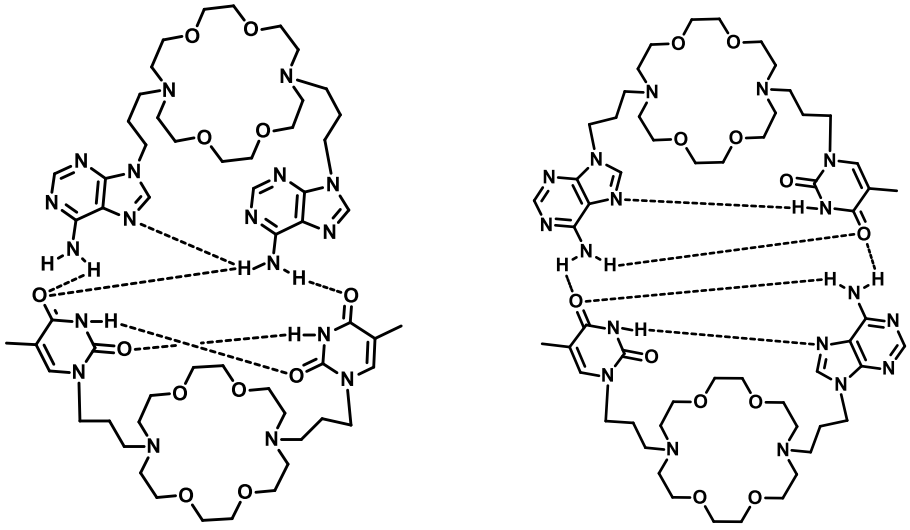


Figure 3.4. Molecular boxes formed by hydrogen bonding between the complementary nucleobases

Macrocyclic-based systems such as cyclodextrins, carcerands, calix[4]arenes, and resorcinol-based systems are extensively used for making capsules.[35-38]Bowl shape of cyclotriguaiacylene (CTG) (Scheme1.), a calixarene analogue, is considered appropriate for making such molecular capsules due to its bowl shape. Recently,two adenine moieties attached to calixarene shown in figure 3.5,was used as receptor for cations viz. Zn^{2+} and Mn^{2+} ions through 1:1 binding stoichiometry.[39]Few examples are known to form complex by means of covalent bond, hydrogen bond, and due to coordination with metal ions.[40-45]Some of them are also known to capture metal ion, organic molecules in their cavity.[46] In continuation of our work,[47,48]we modified the CTG, to append nucleobase adenine and thymine, so they can form molecular capsule upon combination in a solution. Very few studies with calixarinenucleobase conjugates are reported in literature. The conjugates are evaluated for various functions.[49-53] No attempt has been made so far to make nucleobase CTG or related molecules to the best of our knowledge

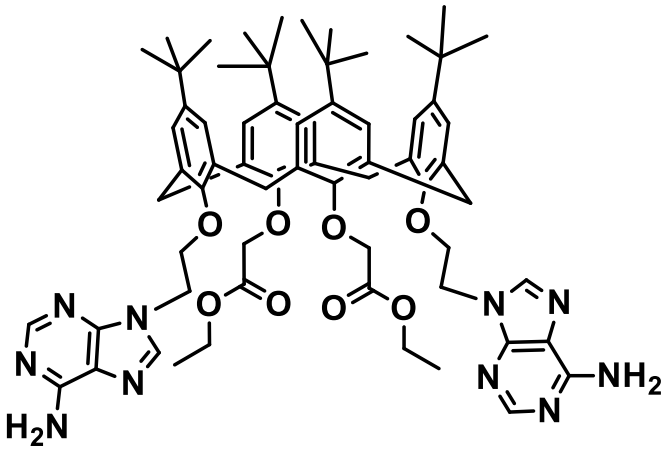
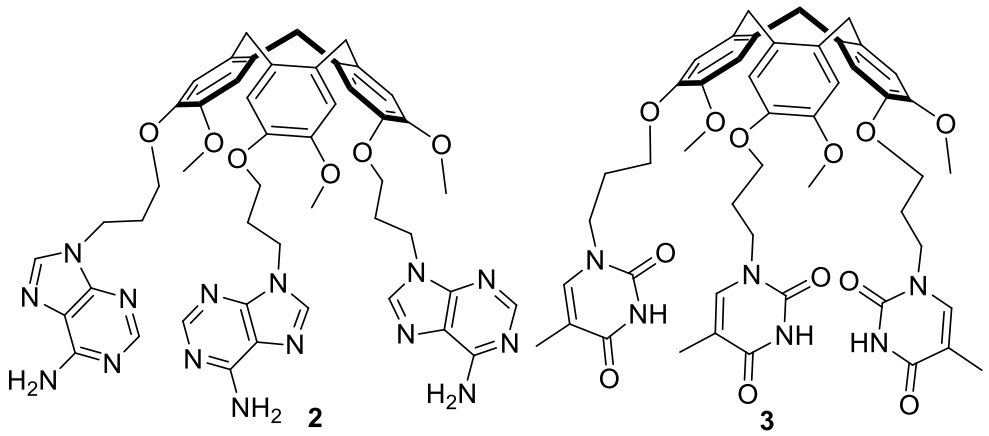
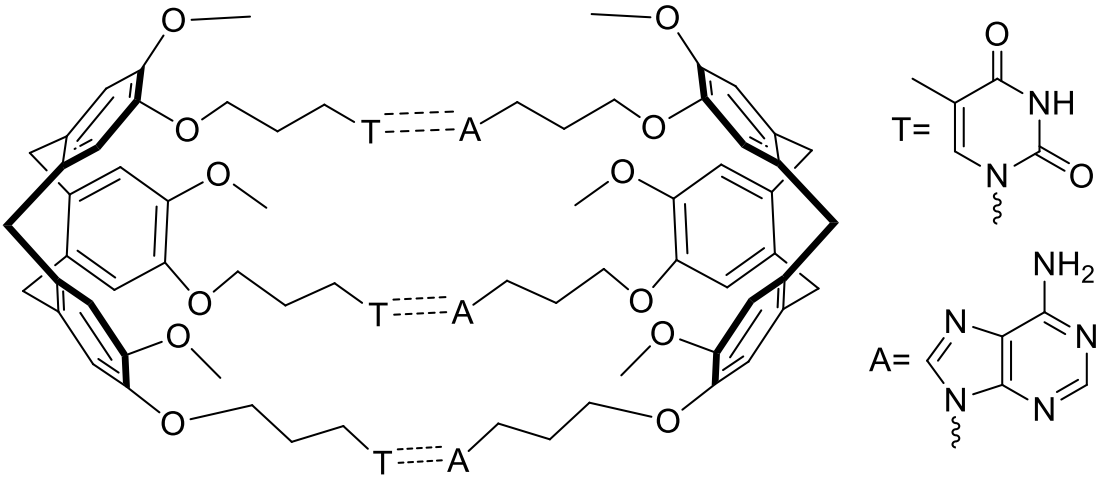


Figure 3.5. Chemical structure of calixarene molecule appended with Adenine



2 **3**



1

Scheme3.1. Schematic representation of the capsule **(1)** and the precursors**(2&3)** used to synthesize the capsule

3.3 Experimental Section

3.3.1 NMR experiments: All NMR experiments were carried out on a 9.39Tesla 400MHz AVANCE-III Bruker liquid state spectrometer equipped with BBFO-Plus broadband probe. The maximum gradient strength allowed by the probe is 50 G/cm. Experiments were performed at ambient temperature (27^{o}C). During experiments it was found that the machine could not automatically lock the sample as the sample was prepared in a mixture of two differentdeuterated

solvents (CD_3CN andCD_3OD). A manual lock was therefore performed by suitably adjusting the Z_0 field value. The diffusion experiments were performed with 8 scans for each gradient strength and with 16 different gradient strengths varied linearly from 2% to 95% of the maximum gradient strength. Duration of gradient pulses was 1500 μs and diffusion delay of 70 ms was used for all experiments. As identical diffusion delay was used for all experiments, relaxation effect did not interfere with the calculation of D.

3.3.2 SEM experimental details: The sample was prepared by dissolving 1mg of the corresponding compound in 1ml of methanol and chloroform (1:1, v/v) filtered through a 0.22micron syringe driven filter.20μL of this solution was deposited on a clean 100 silicon wafer, dried by air and kept in vacuum desiccators for 8h. This was then imaged through a FESEM (Carl Zeiss, Germany).

3.3.3 Synthesis of the compounds:

(3-(3-bromopropoxy)-4-methoxyphenyl)methanol(5):[54]

Vanillylalcohol (5 g, 32.45 mmol) was dissolved in 30 mL of dry acetone and anhydrous K_2CO_3 (5.4 g, 38.94 mmol) was added under N_2 atmosphere, to this solution 1, 3 dibromo propane (30.485 g, 162.25 mmol) was added and refluxed overnight. The reaction mixture was filtered and solvent was evaporated under reduced pressure, to this diethyl ether was added most of the di-alkylated product was precipitated and filtered .The diethyl ether layer was washed with water and ether layer was passed through a short alumina column and evaporated resulting in a white coloured solid (6.7 g, 74%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.27-2.38, m, 2H), (3.61, t, 2H), (3.86, s, 3H), (4.13, m, 2H), (4.61, s, 1H), (6.85-6.94, m, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.27, 32.49, 56.05, 65.35, 67.00, 111.16, 113.80, 119.56, 134.33, 147.84, 149.87).

2,7,12-tris(3-bromopropoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene(CTG-Br(4)):

CTG-Br was prepared according to a reported procedure.[55] The alkylated vanilly alcohol (5) (6.6 g, 23.98 m.mol) was dissolved in dry acetonitrile (15 mL) under N_2 atmosphere, to this solution $Sc(OTf)_3$(118 mg, 0.239 m.mol) was added and kept at 70^{O}C for overnight. The solution was evaporated under reduced pressure to this DCM was added and washed with water.The DCM layer was dried under anhydrous Na_2SO_4 and the DCM was evaporated under reduced pressure. The crude product purified by column chromatography (silica 100-200) DCM as eluant yielded a white coloured solid (3.5g, 19%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.29-2.37, m, 2H), (3.54, d, J=16Hz, 1H), (3.59-3.64, m, 2H), (3.83, s, 3H), (4.09-4.17, m, 2H), (4.74-4.78, m, 2H), (6.85, s, 1H), (6.91, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.45, 32.28, 36.46, 56.24, 67.08, 113.70, 115.88, 131.84, 132.66, 146.85, 148.47).

9,9',9''-(((3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triyl)tris(oxy))tris(propane-3,1-diyl))tris(9H-purin-6-amine) (2)):

Adenine (522 mg, 3.862 mmol) was suspended in 10 mL dryDMF, to this suspension anhydrous K_2CO_3 (533 mg, 3.862m.mol) was added and kept under N_2 for 30 min. To this suspension CTG-Br (0.9g, 1.17 mmol) dissolved in 15ml dry-DMF was added and kept at 80^{O}C for 48 hours and filtered, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica 100-200) DCM:MeOH (92:8) the product obtained as a white coloured solid(300mg, 27.5%).^{1}HNMR (400MHz, DMSO-d_6) δ: (2.21-2.28, m, 2H), (3.43, d, J=12Hz, 1H), (3.62, s, 3H), (3.83-3.96, m, 2H), (4.27-4.30, t,

2H), (4.64, d=12Hz, 1H), (7.00, s, 1H), (7.03, s, 1H), (7.21, s, 2H), (8.10, s, 1H) (8.15, s, 1H).

^{13}CNMR (100MHz, DMSO-d_6) δ: (28.88, 34.98, 48.57, 55.82, 65.89, 113.83, 115.60, 118.82, 131.92, 132.62, 140.91, 146.13, 147.73, 149.51, 152.32, 155.92); ESI-HRMS: m/z calculated for $C_{48}H_{51}N_{15}O_6$ ($M+H^+$) is 934.4220, found 934.4244.

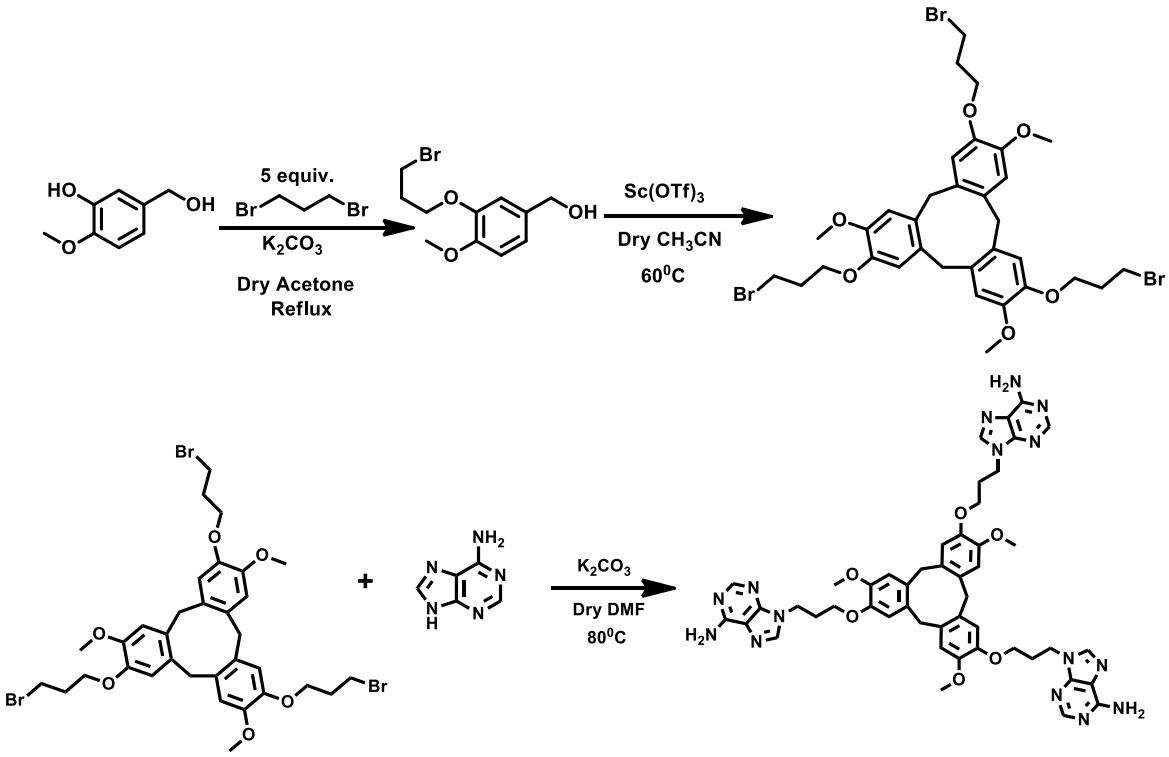
1,1',1''-(((3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triyl)tris(oxy))tris(propane-3,1-diyl))tris(5-methylpyrimidine-2,4(1H,3H)-dione)(3)):

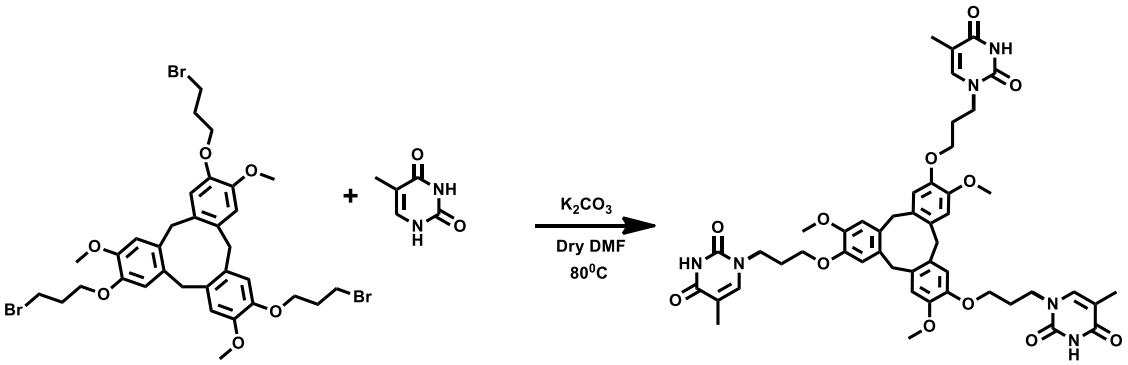
Thymine (541mg, 4.29m.mol) was suspended in 10ml dry-DMF, to this suspension anhydrous K_2CO_3 (593.8 mg, 4.29m.mol) was added and kept under N_2 for 30 min. To this, suspension CTG-Br (1g, 1.30m.mol) dissolved in 15ml dry-DMF, was added and kept at 80^{O}c for 48 hours and filtered, the solvent was evaporated under reduced pressure. The product was partitioned between DCM and water, DCM layer was washed with conc.HCl and organic layer was dried under anhydrous Na_2SO_4 the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica 100-200)DCM:MeOH(94:6) the product obtained as a white coloured solid(250mg, 21.2%).^{1}HNMR (400 MHz, DMSO-d_6) δ: (1.68, s, 3H), (1.97, m, 2H), (3.46, d, J=16Hz, 1H), (3.67, s, 3H), (3.74, t, 2H), (3.91-3.95, m, 2H), (4.66, d, J=12Hz, 1H), (7.04, s, 1H), (7.07, s, 1H), (7.45, s, 1H), (11.18, s, 1H). ^{13}CNMR (100MHz, DMSO-d_6) δ: (11.83, 28.10, 35.01, 44.97, 55.86, 66.14, 108.36, 113.83, 131.92, 132.57, 141.44, 146.15, 146.41, 147.71, 150.90, 164.27)

ESI-HRMS: m/z calculated for $C_{48}H_{54}N_6O_{12}$ ($M+H^+$) is 907.3872, found 907.3846.

3.4 Results and discussions:

Being bowl shaped, CTG is a good candidate for preparation of molecular capsule. Also, it has phenolic functional groups that caneasily be modified to desired functional group. We planned to prepare two molecules by introducing two complimentary nucleobase on CTG by modifying the phenolic group. The central idea behind introducing two complimentary nucleobases is that, these modified CTG would then dimerize by well-known Watson-Crick hydrogen bonding to give a supramolecular capsule when brought together in a solution.(Scheme 1). We chosen adenine and thymine for incorporation. This was done by reacting dibromopropane with vanillyl alcohol to produce alkyl halide suitable for trimerisation using literature procedure. Briefly, trimerisation was carried out using $Sc(OTf)_3$ as a lewis acid in acetonitrile to get the trialkylhalide derivative of CTG with 19% yield. It was then reacted with adenine or thymine under basic condition to get the desired molecules (Scheme 2).





Scheme 3.2: Synthetic scheme appended to prepare the precursors **(2&3)**

To verify our assumption that these monomers will indeed give molecular capsule through formation of AT dimer, we recorded HRMS spectra. Well characterized monomer solutions were prepared in CH_3CN:CH_3OH (1:1, v/v) and mixed in 1:1 ratio. The solvent mixture was necessary to solubilise the molecules.

They were sonicated for one hour at 50°C, cooled to room temperature, filteredand then injected for recording mass spectra(Figure 3.6.). The spectrumcontains a peak at 1841.8 which corresponds to the desired capsule mass, along with another peak at 1868.83that matches well with AA dimer. No peak corresponding to TT dimer was observed.

To prove further, that the self assembly exists in solution, we carried out a NMR experiment, namely, Diffusion-Ordered SpectroscopY (DOSY). This method is being used as a powerful non-invasive technique to estimate the effective size and molecular weight of a molecular species in a given set of conditions and with the assumption that the molecule is spherical.[56,57]The poor solubility of the compounds in both low polar and high polar solvents imposed a constraint for NMR studies in any single NMR solvent. To overcome this, we have chosen a mixture of polar and non-polar solvents(CD_3OD and CCl_4) in 1:1 (v/v) ratio, to perform the NMR experiment.

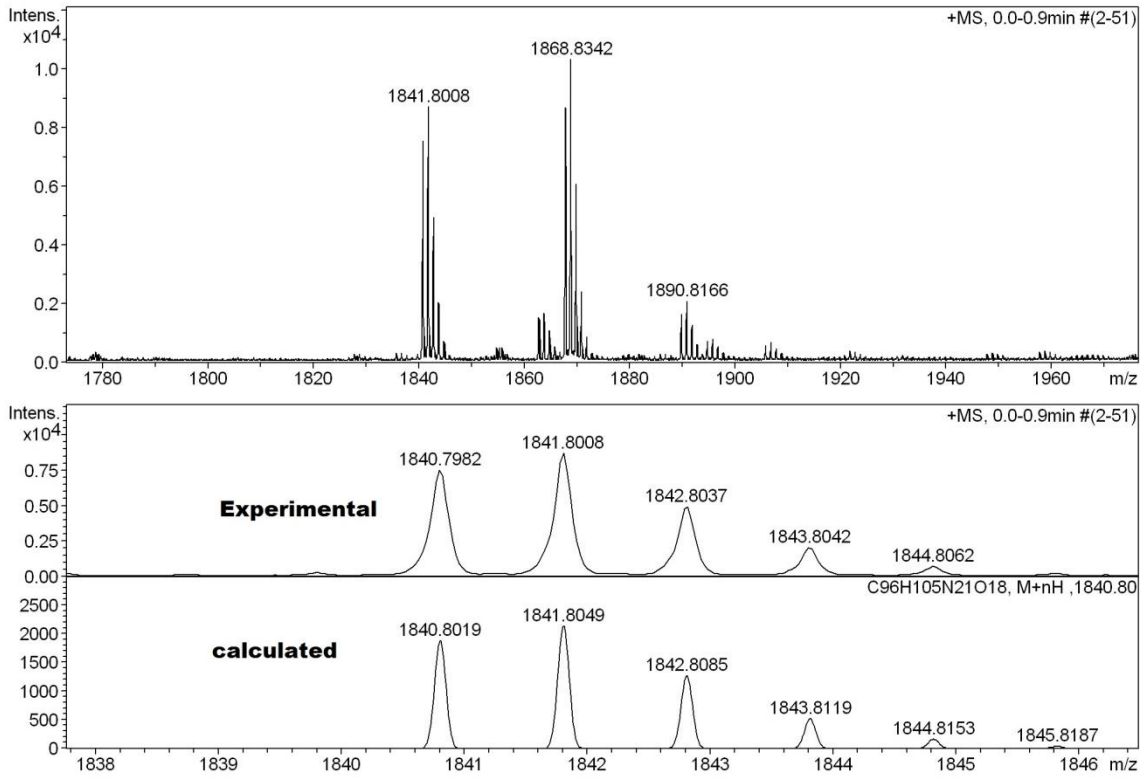


Figure 3.6. ESI-mass spectra of capsule**1**

The famous Stokes-Einstein formula for translational diffusion coefficient (D) of spherical solute molecules that are large compared to the solvent molecules relates D with radius of solute molecule (a) as, $D=(kT)/(6\pi\mu a)$, where, k is the Boltzmann constant, T is absolute solvent temperature, μ is the coefficient of viscosity of the diffusion medium.[58] The radius a, in turn relates to the mass, M, of the solute molecule as $M=4\pi a^3\rho/3$, ρ being the density. Two molecules with different masses, M_1 and M_2, would then give two translational diffusion coefficients, D_1 and D_2, related as $D_1/D_2=(M_2/M_1)^{1/3}$, provided all other experimental conditions remain unaltered. In the present system, the monomers are having nearly identical molecular weight. Therefore, if the dimer which would be a self-assembled molecular capsule, exists in solution, can be easily known by this technique, comparing the ratio of diffusion coefficients.

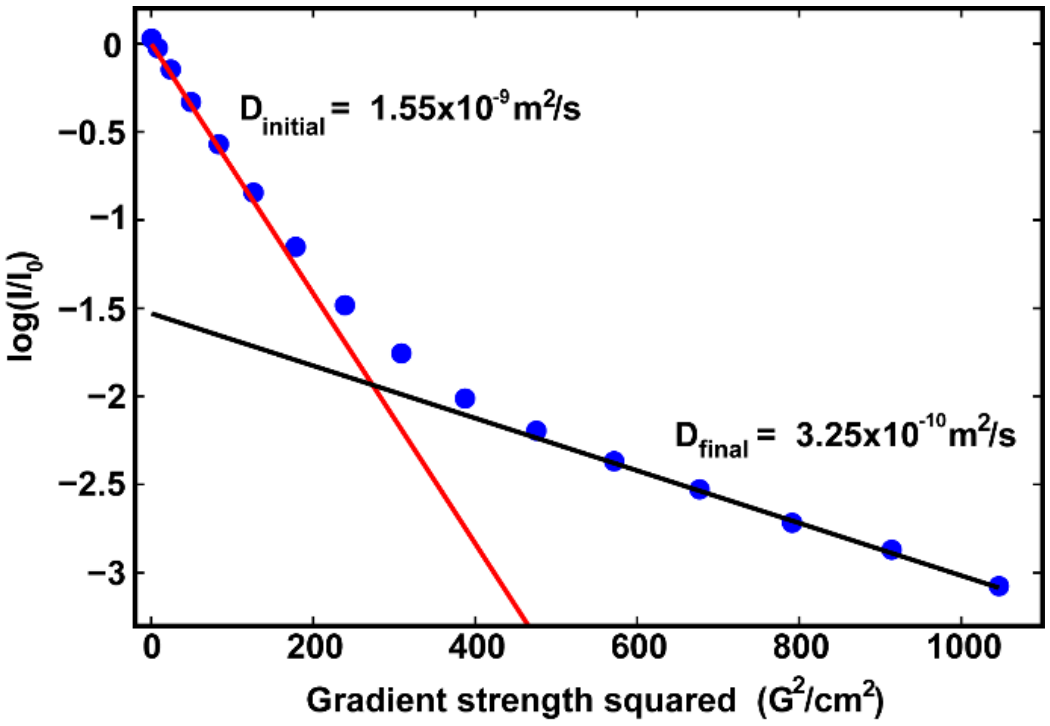


Figure 3.7. Diffusion coefficient measured for a fresh mixture of **2** and **3**. The existence of two slopes indicates formation of the capsule.

The translational diffusion coefficients were measured using the Pulsed field Gradient Stimulated Echo (PGSE) experiment with bipolar gradients to minimize eddy current caused by the gradients. In this experiment attenuation of a NMR resonance signal is measured as a function of gradient strength. The peak intensity (I) for any particular gradient strength (g), normalized with respect to the non-attenuated intensity (I_0) follows a relationship $I/I_0=\exp(-D\zeta g^2)$. ζ is a constant that depends on the gyromagnetic ratio of the spins under investigation and few experimental parameters and can easily be calculated.

Log of (I/I_0) plotted against squared gradient strength (g^2) gives a straight line with a negative slope of $D\zeta$ from where D is calculated. During the experiments, we have recorded diffusion coefficients of **2** to be $3.9\times10^{-10}m^2/s$.

The corresponding value for a mixture of **2** and **3**, prepared the previous night, was found to be 3.25×10^{-10} m^2/s (Figure 3.7.)The ratio of these values is 1.2 which agrees reasonably well with the theoretical value of $2^{1/3}$=1.25, expected for a capsule of double molecular weight of that of the corresponding monomers.

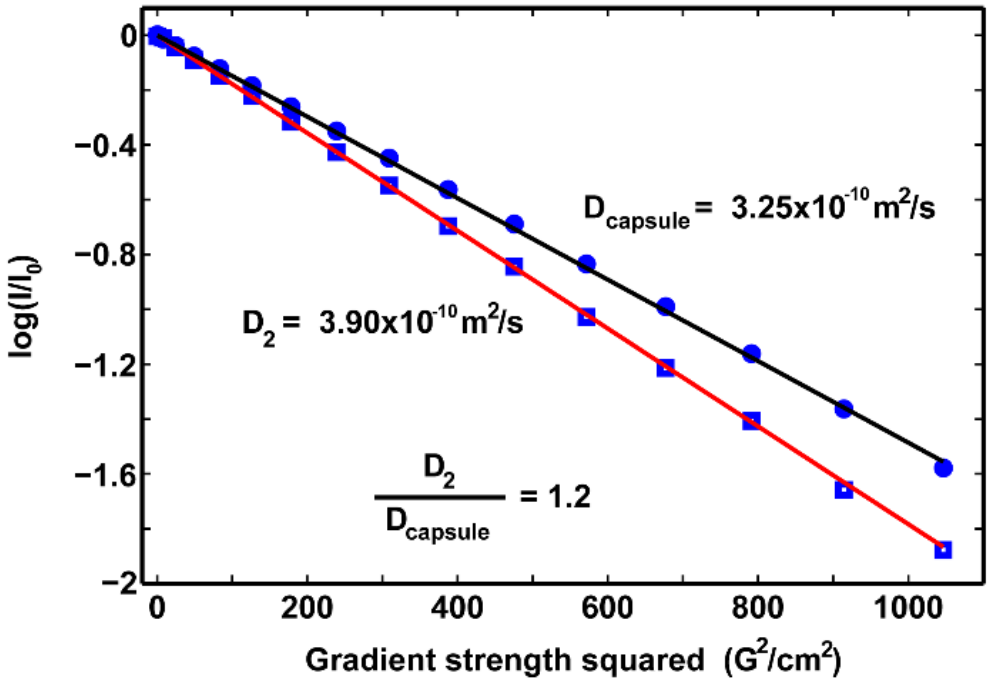


Figure 3.8. Logarithm of normalized peak (at 8 ppm) intensity as a function of squared gradient strength. The slopes determine diffusion coefficients for the capsule of **2**. The ratio of coefficients is 1.2 against theoretically expected value of 1.25

We also measured the diffusion coefficient of a freshly mixed monomer solutions to capture the formation of the capsule through gradual change of diffusion coefficient from the monomeric value to the value of the capsule. The experiment gave an interesting result(Figure 3.8.)While the final data points fit to a slope matching with the D for a fully formed capsule, the initial data points give a D that is one order of magnitude larger than that of the monomers. A possible explanation could be the pockets of high temperature generated within the solvent due to the formation of hydrogen bonds (exothermic

reaction) in the process of the capsule formation.It is rather expected that the Stokes-Einstein formula would be violated if solvent temperature does not remain constant during the entire experiment.

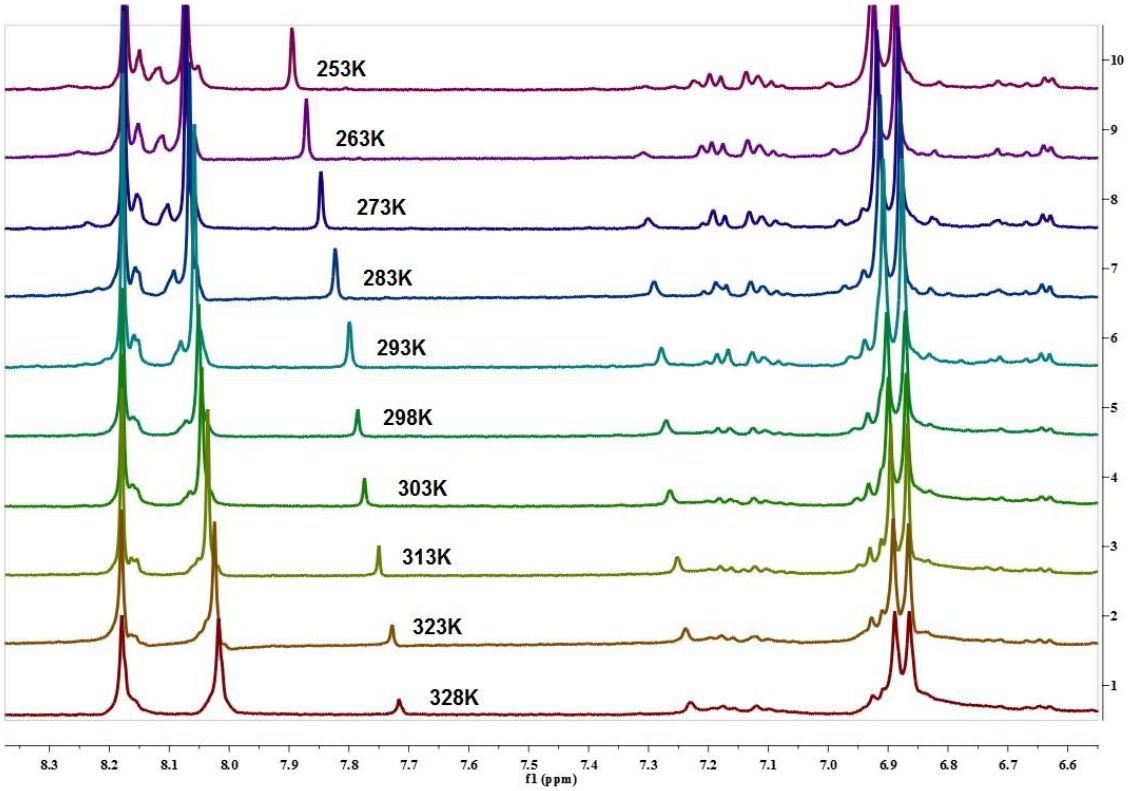


Figure 3.9. The temperature dependent NMR of the (1:1 of 1:2) complex from 328 k to 253K from bottom to top.

It is well known that AT dimer is more stronger than AA or TT dimer and easily emerge under suitable condition.[59] From the DOSY data, it is quite evident that the dimer exists in solution. Most possibly, a capsule is forming due to hydrogen bonding between adenine and thymine residue in the molecules. To confirm this, we carried out a variable temperature NMR experiment. In Watson-Crick hydrogen bonding, the exocyclic N^6 hydrogen atoms of adenine get involved. As the strength of hydrogen bonding depends on temperature, a temperature dependent NMR would reveal the participation of adenine-

N^6 in dimer formation, which in turn will prove the formation of Watson-Crick type of bonding between the monomers.

We deliberatelydid not change the solvent system from that used in DOSY experiment, in spite of the possibility of deuterium exchange, causing reductionin the signal intensity. For this experiment, initially, ^{1}H NMR was recorded for compound **2**. A broad singlet peak at 7.7ppm can be attributedto the NH_2 of adenine. A mixture of 1:1 molar ratio of **2** and **3**is used to record a 1H NMR at 298K and the peak at 7.7ppm was shifted to 0.1ppmdownfield to 7.8ppm. With varying temperature from 253K to 328K the amine peak was shifted from 7.9ppm to 7.72ppm whereas the other peak positions remained unchanged(Figure 3.9.)This indicates the involvement of adenine exocyclic amine group in hydrogen bonding. As expected, the signal intensity decrease with increase in temperature but the shift could be well established

Several attempts to grow suitable single crystals of the compounds for X-rayanalysis were not successful. Therefore, weexamine the morphology in solid stateof the compounds,byusing Scanning Electron Microscopy(SEM). Images of theindividual half moieties and the capsule **1**were recorded (Figure 4.0.)**.** Same concentrations of samples were prepared inCCl_4:CH_3OH (1:1, v/v) and capsule was prepared by mixing 1ml of **2**with 1ml of **3** and kept for overnight. From these solutions, 30μL was taken and deposited on a 100 silicon wafer, dried for 12 hours in a vacuum desiccator, then imaged. **2**showsextensive microfibers all over the surface (Figure 3.10.a and b), while**3** shows aggregated spherical structures.The combined solution supposedly, capsule or spheres were not found but rather look like a combination of **2** and **3,** with spheres are linked with fibre.This might be due to the evaporation of solvent molecules causing the spheres tocollapse. However, in absence of single crystal X-ray analysis, it is difficult to find the possible cause.

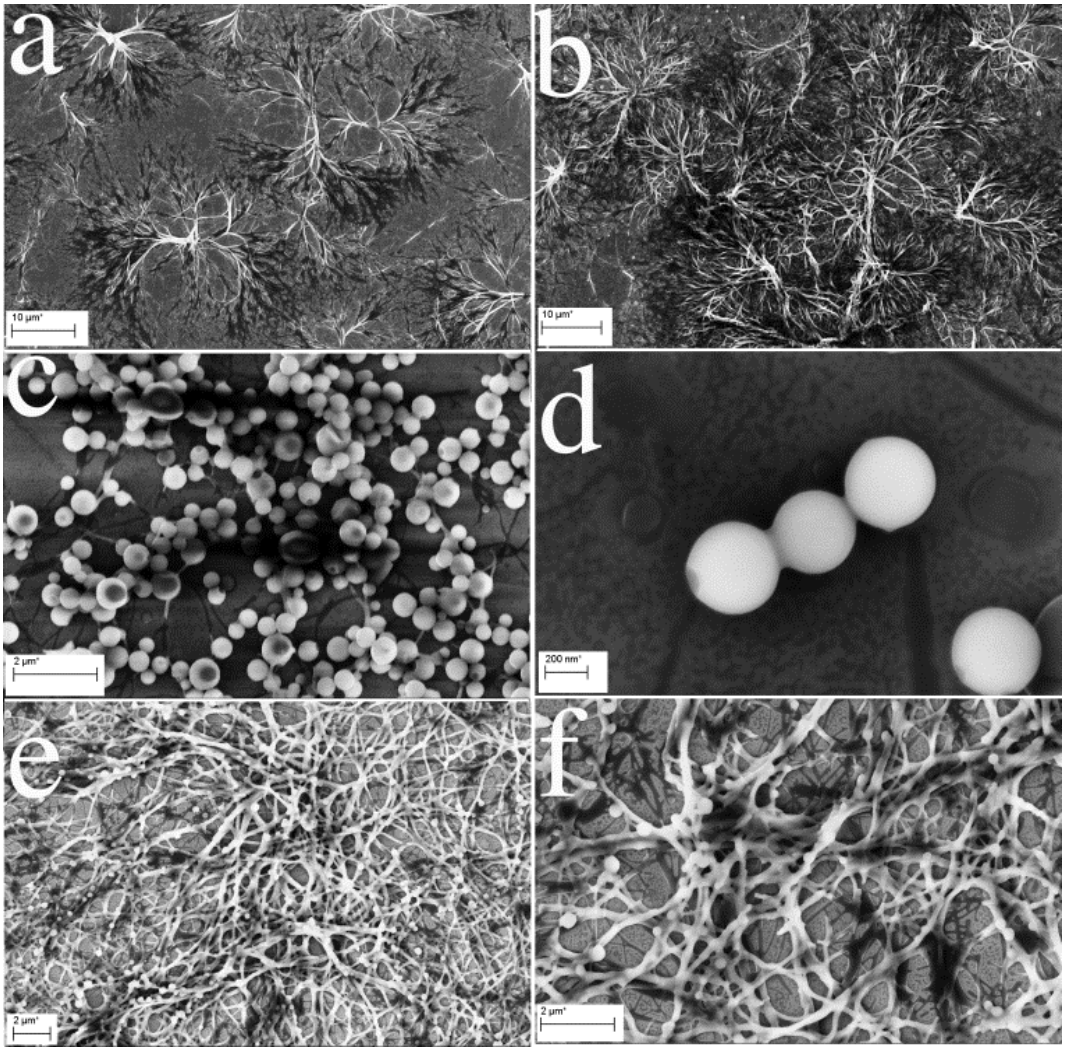


Figure 3.10. SEM images of 2, (a and b):3, (c and d):1,(e and f)

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3.6 Spectral data

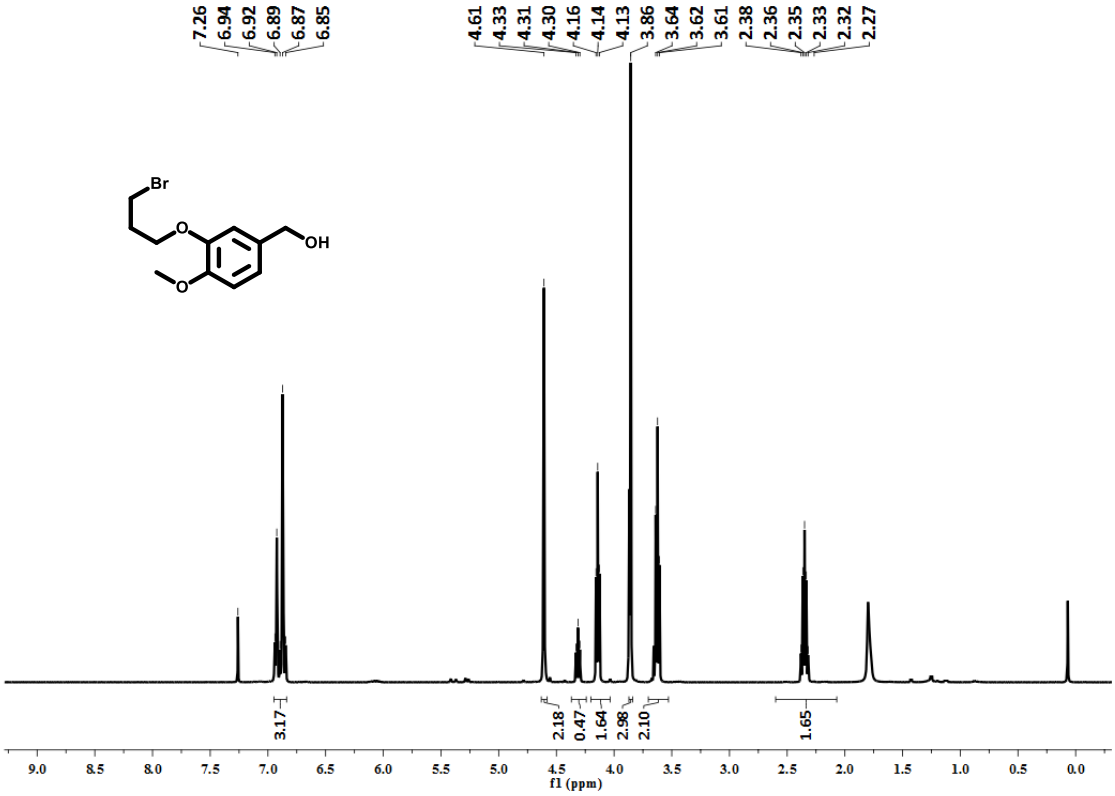


Figure 3.11. ^{1}H NMR spectrum of 5 in $CDCl_3$

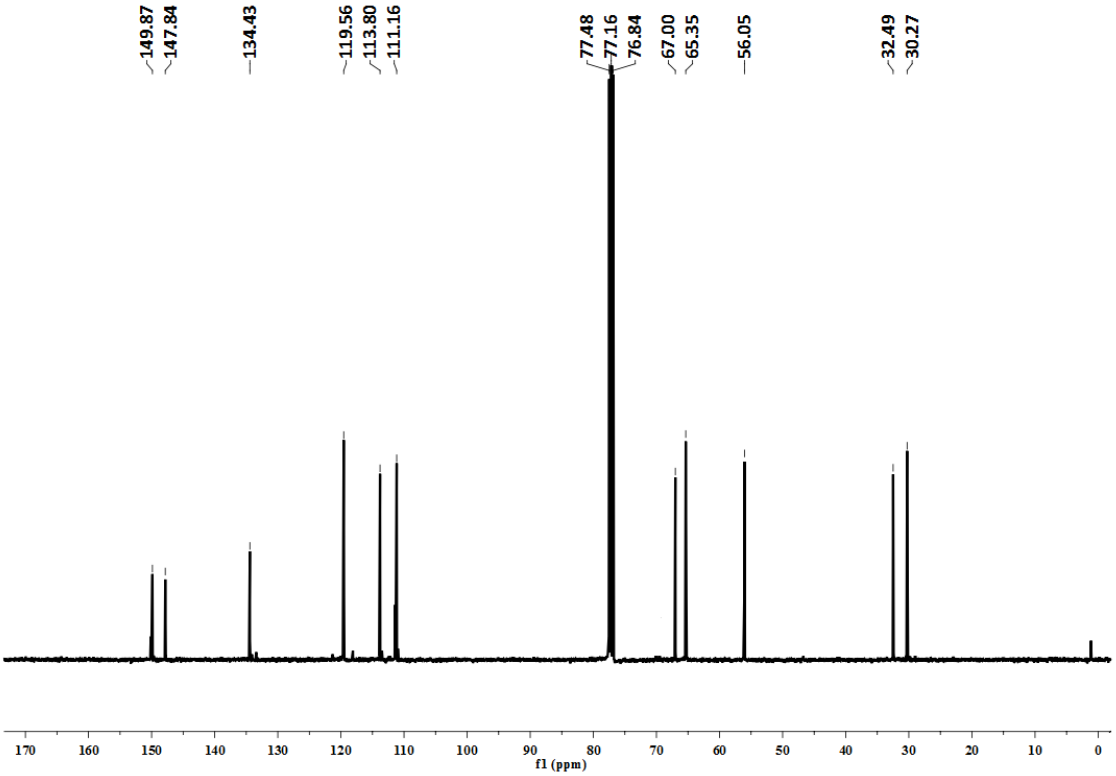


Figure 3.12. ^{13}C NMR spectrum of **5** in $CDCl_3$

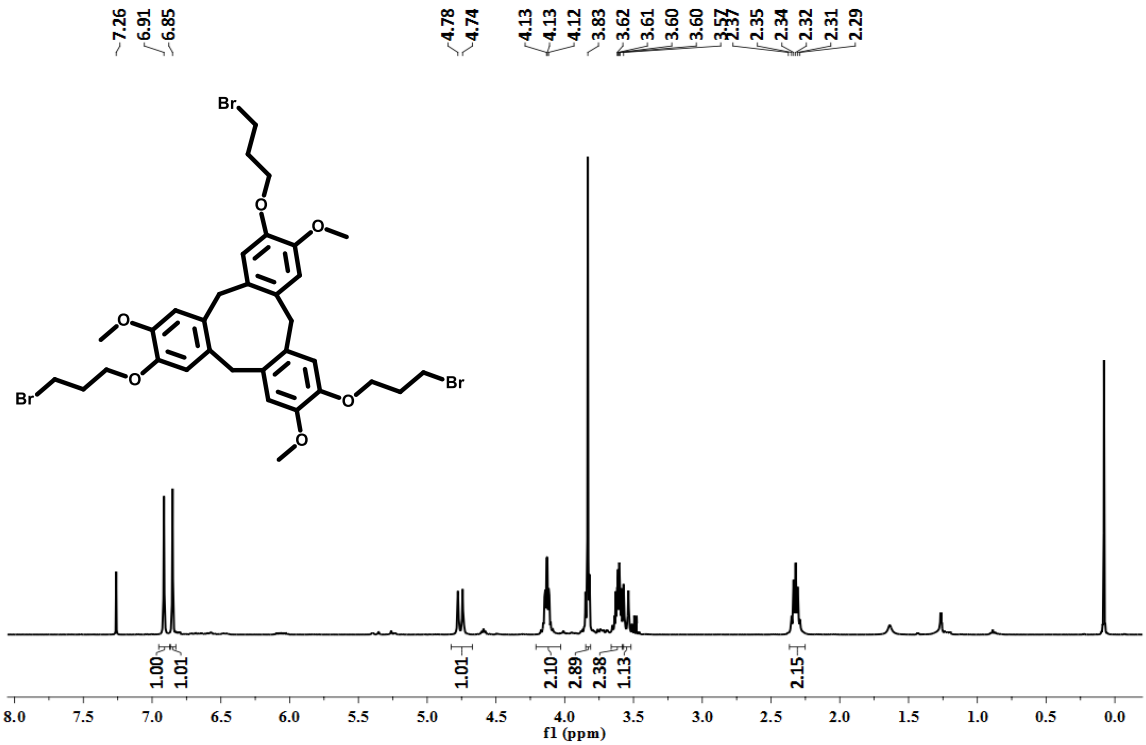


Figure 3.13. ^{1}H NMR spectrum of **4** in $CDCl_3$

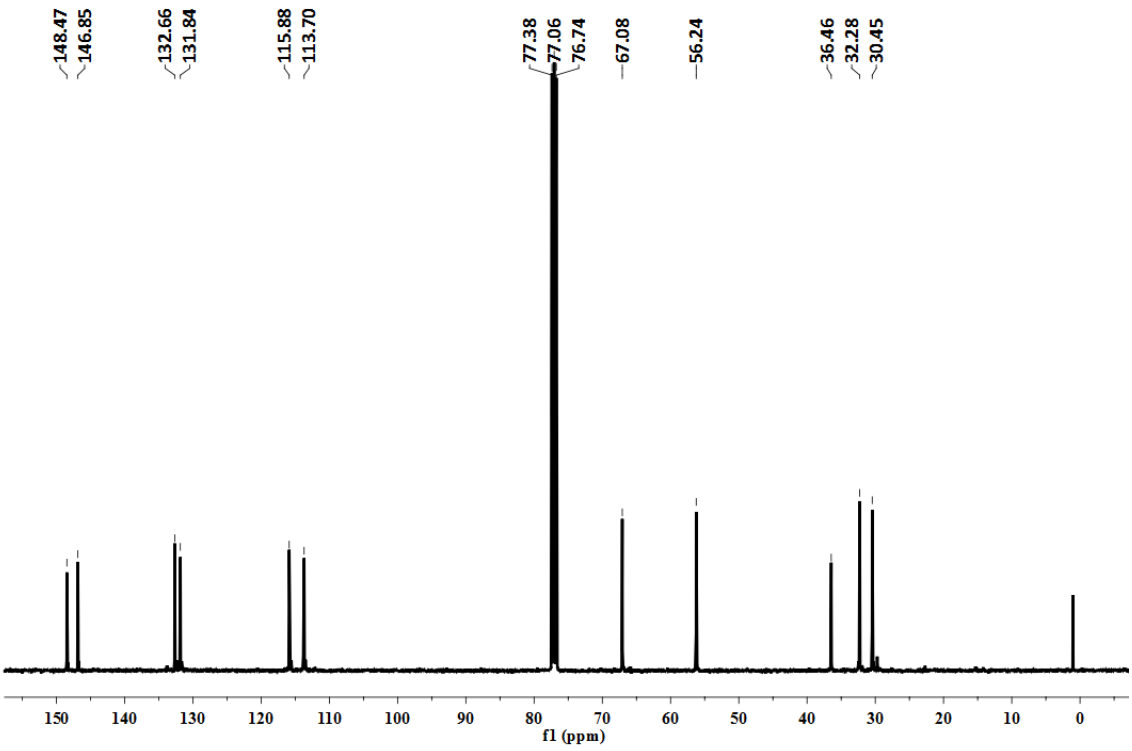


Figure 3.14. ^{13}C NMR spectrum of **4** in $CDCl_3$

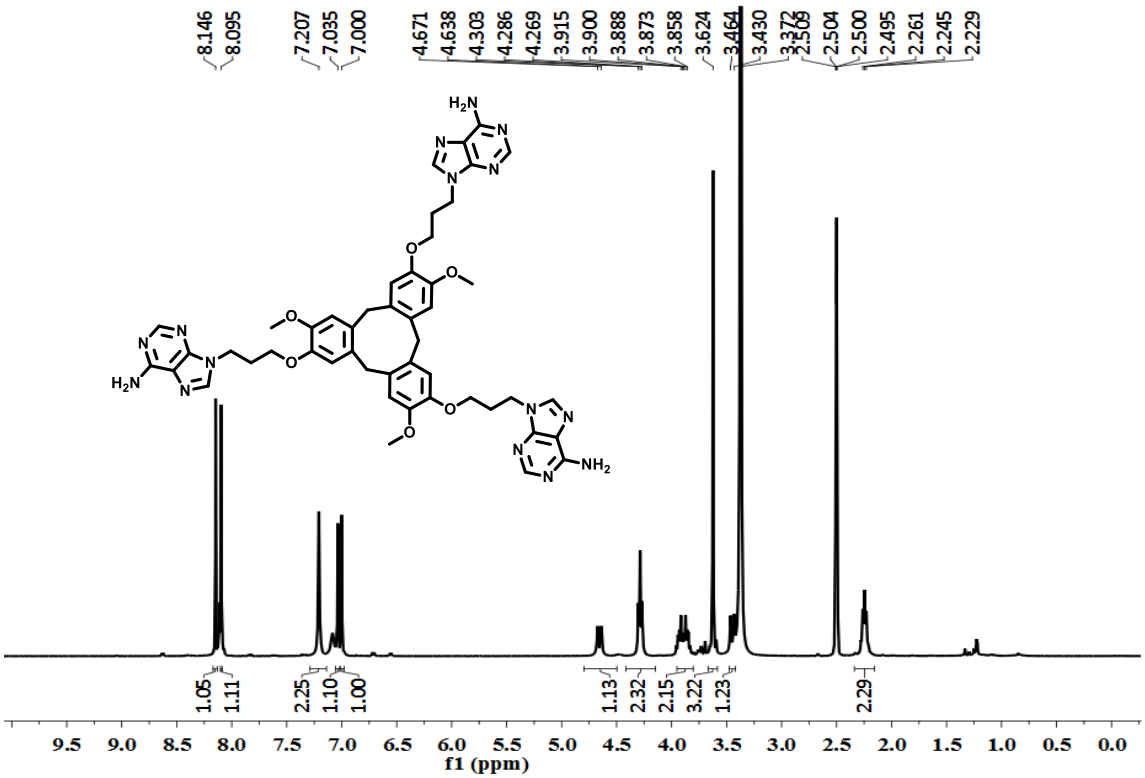


Figure 3.15. ^{1}H NMR spectrum of **2** in DMSO-d_6

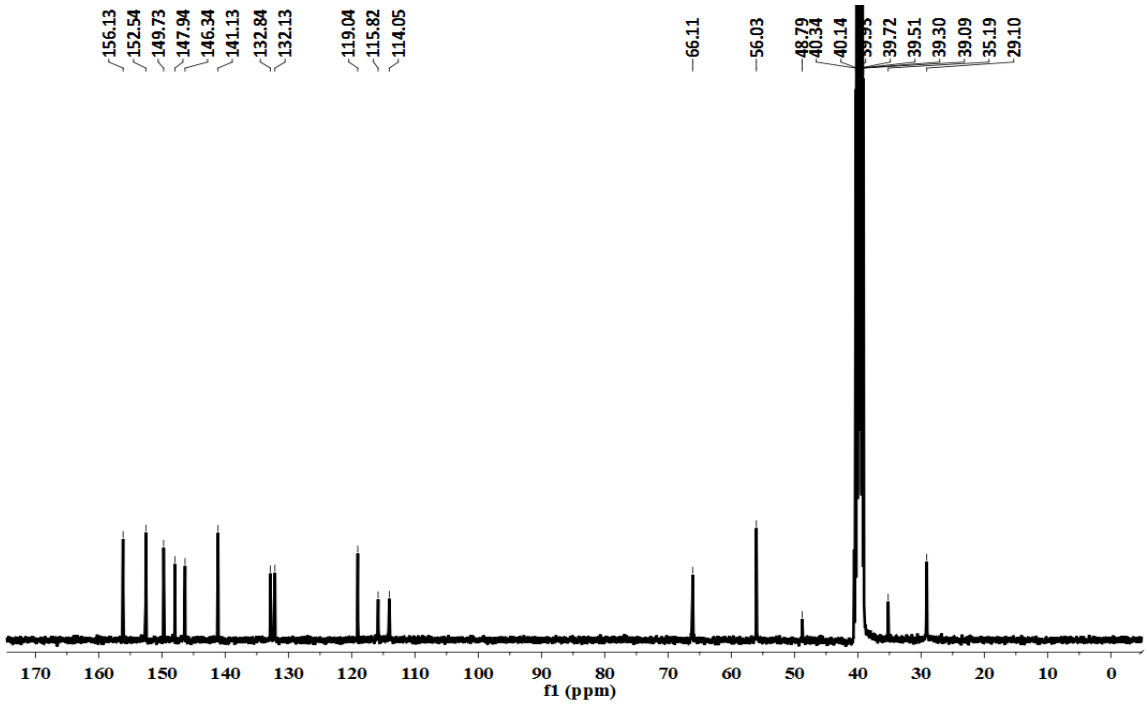


Figure 3.16. ^{13}C NMR spectrum of **2** in DMSO-d_6

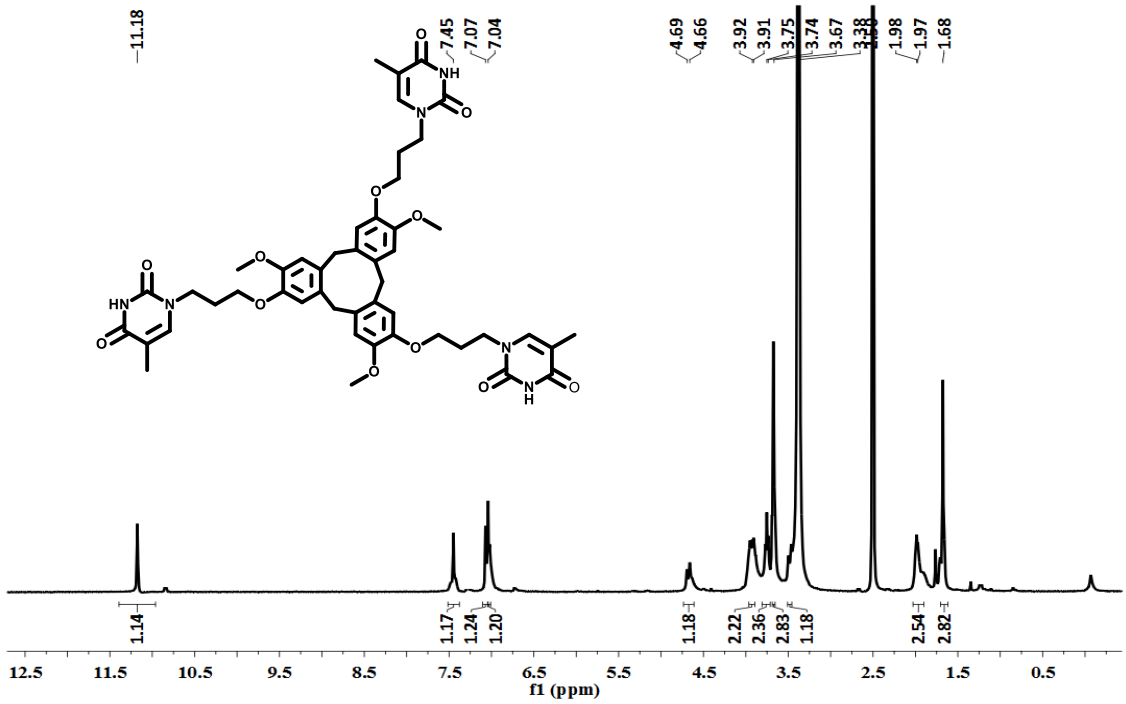


Figure 3.17. ^{1}H NMR spectrum of **3** in DMSO-d_6

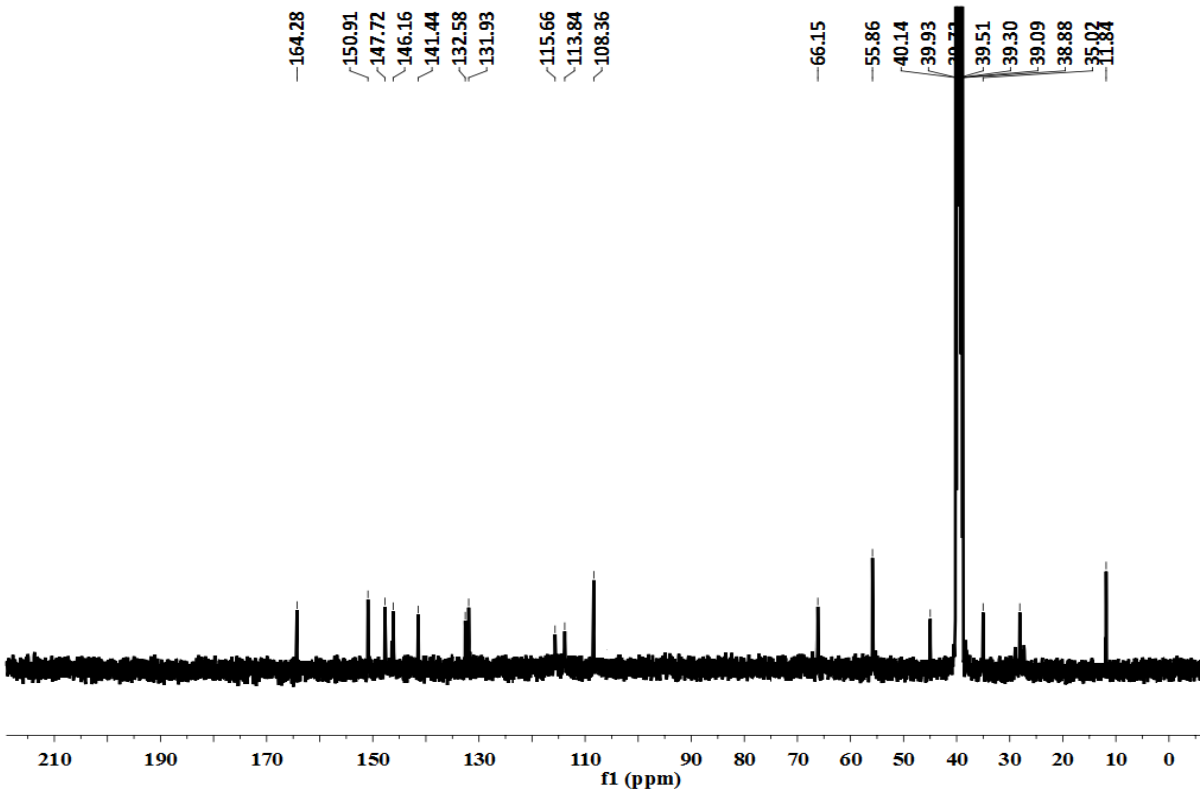


Figure 3.18. ^{13}C NMR spectrum of **3** in DMSO-d_6

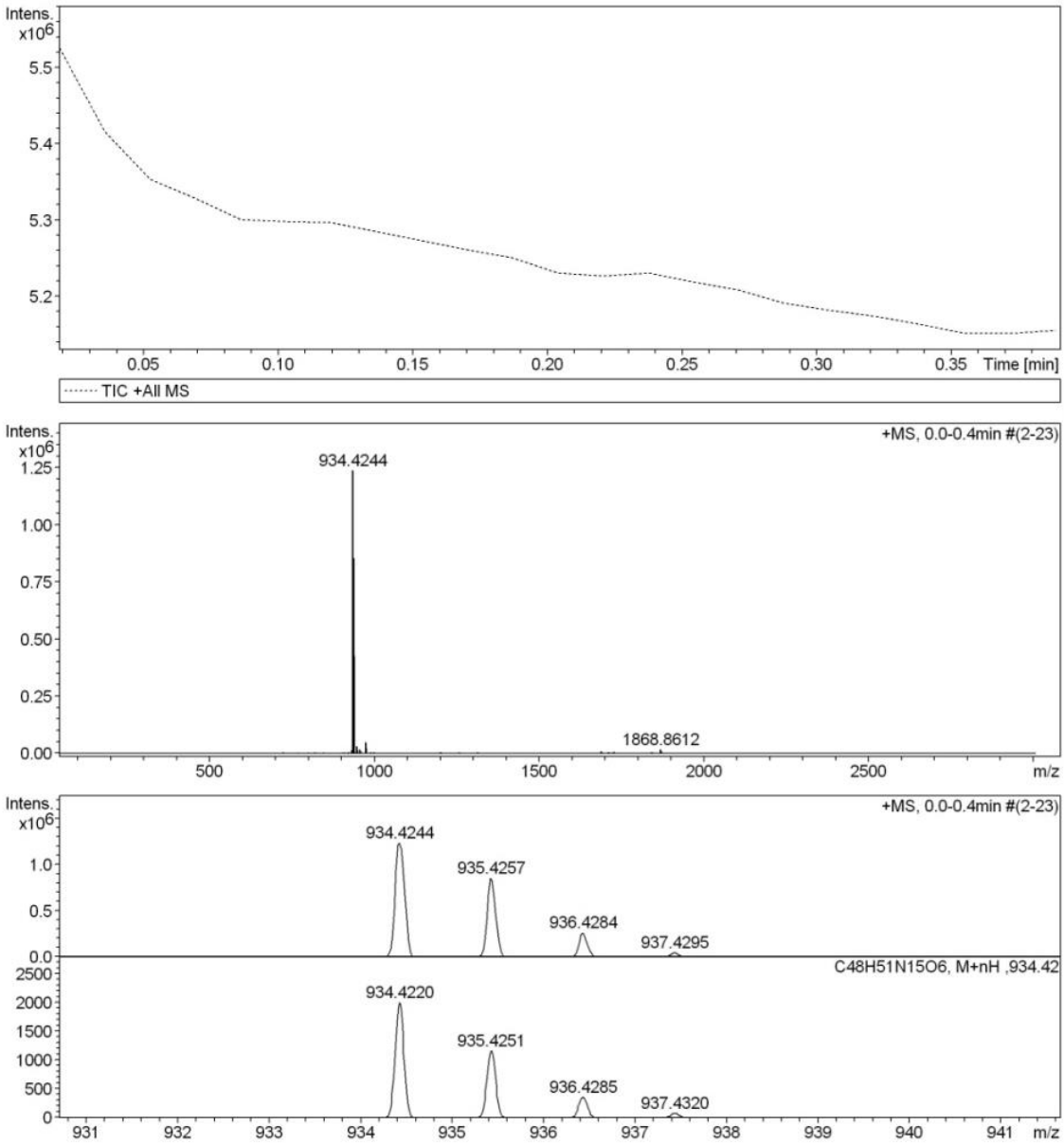


Figure 3.19.HRMS (ESI) Spectrum of **2**

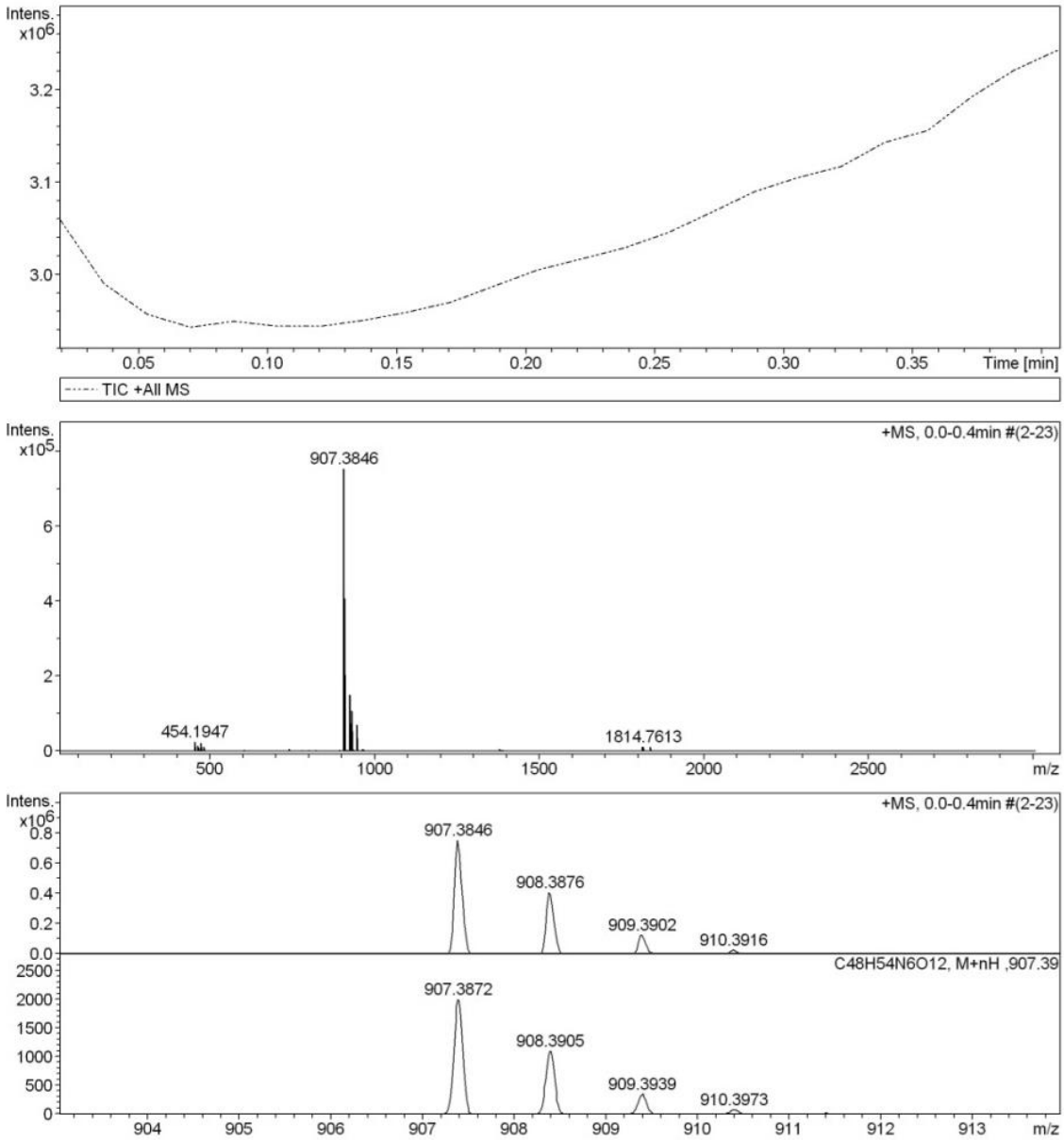


Figure 3.20.HRMS (ESI) spectrum of **3**

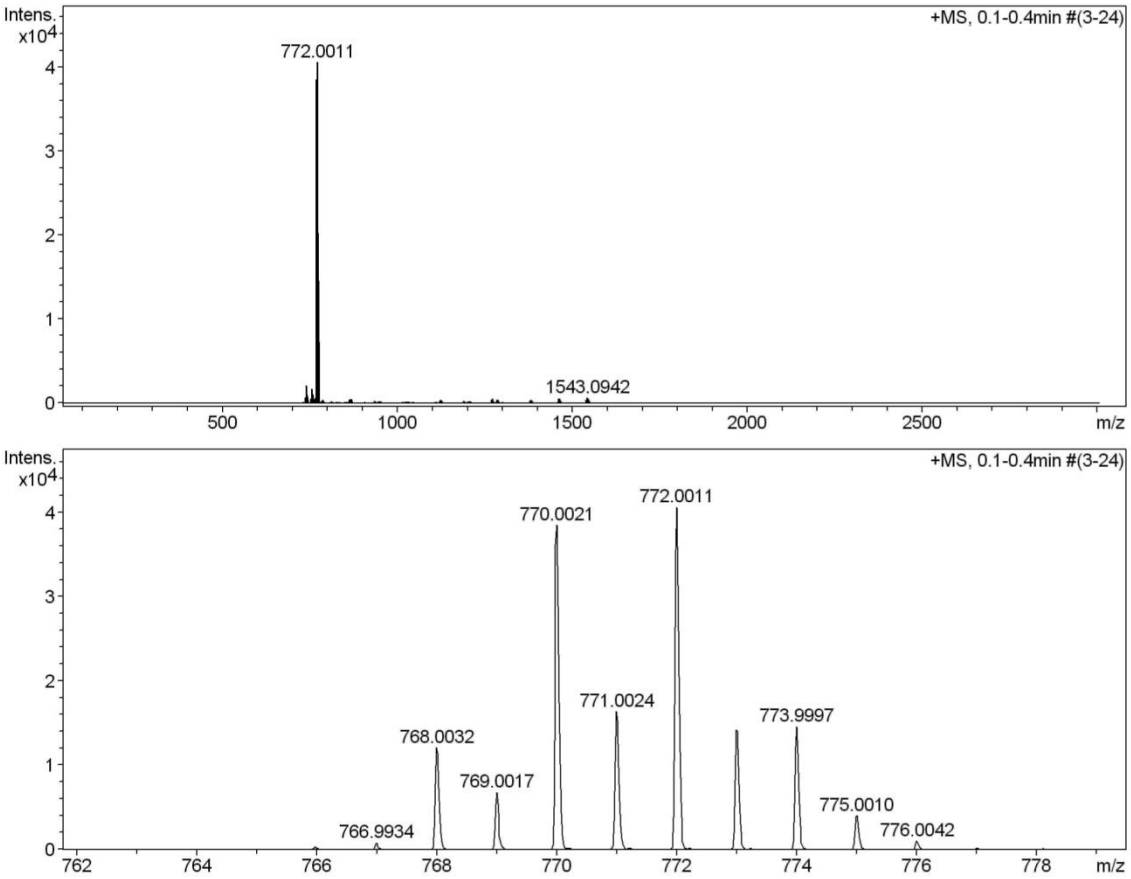


Figure 3.21.ESI – (SOLID STATE) mass spectrum of **4**

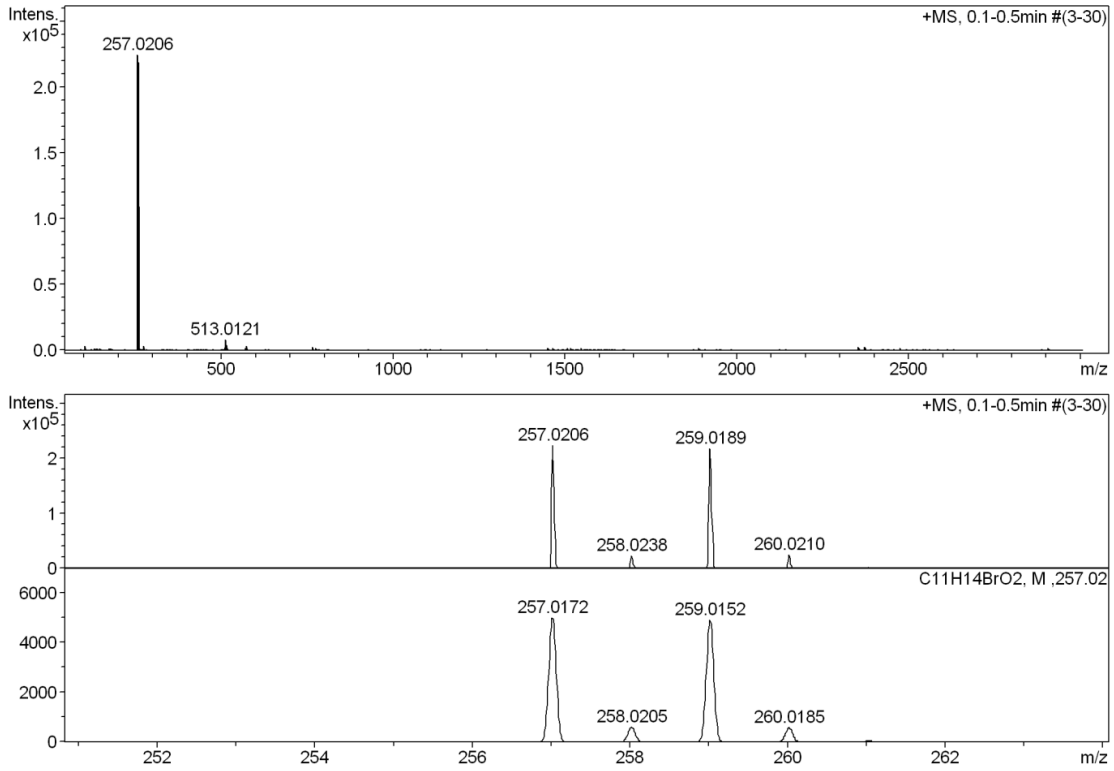


Figure 3.22.ESI-mass spectrum of **5**

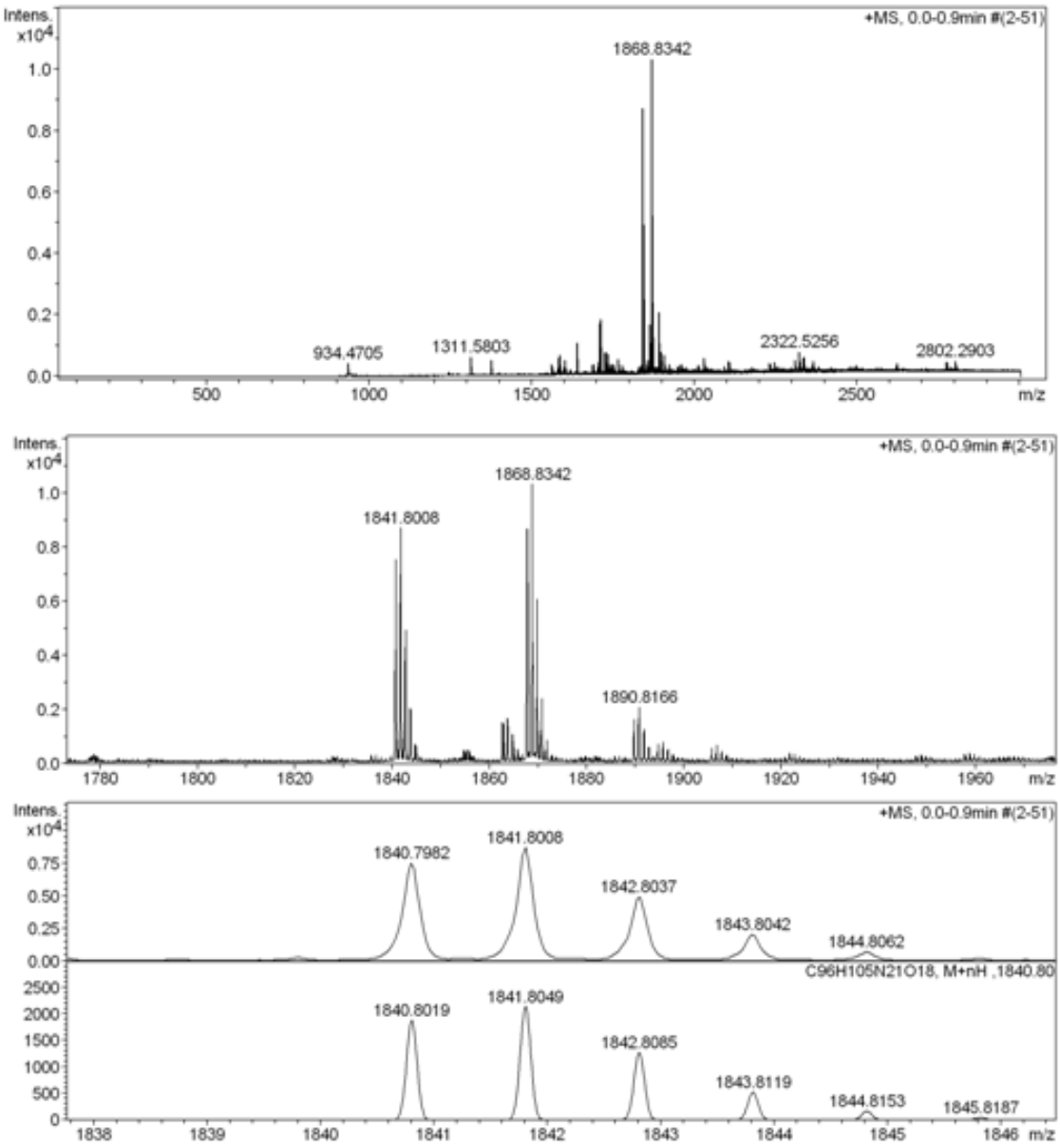


Figure 3.23.HRMS (ESI) spectrum of the capsule **1**

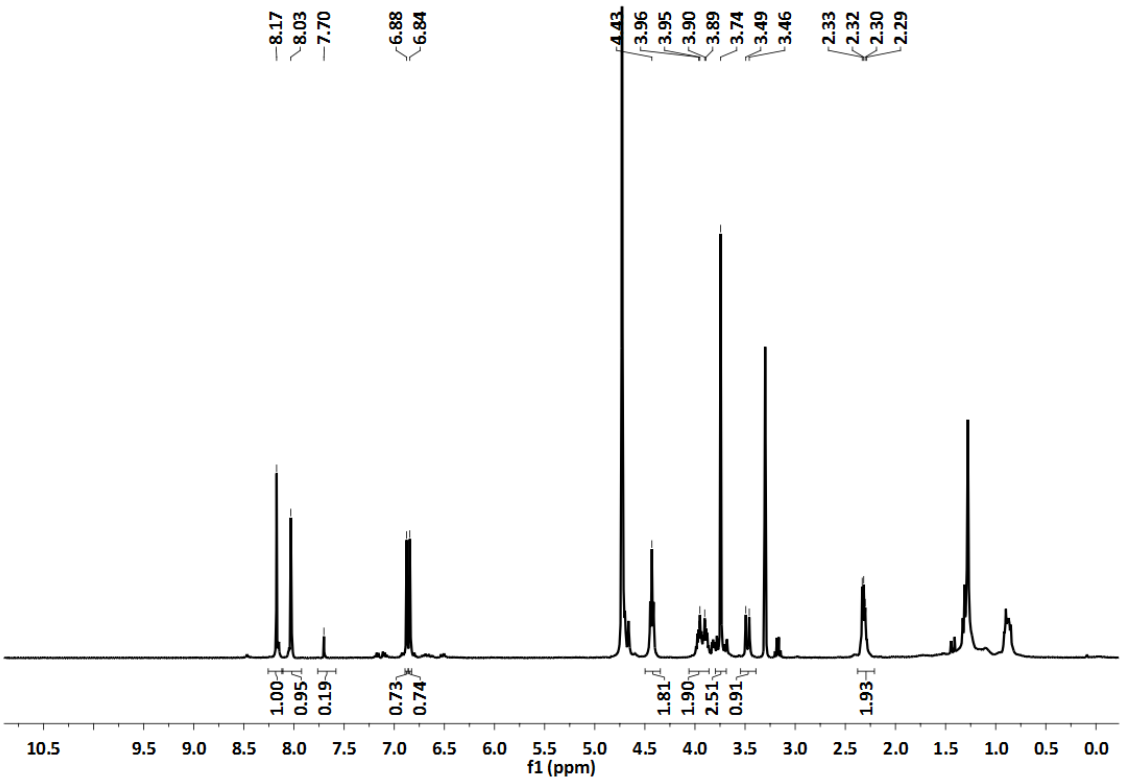


Figure 3.24.NMR Spectra of CTG-AD in CCl4+MeOH (1:1; v/v) at 298K

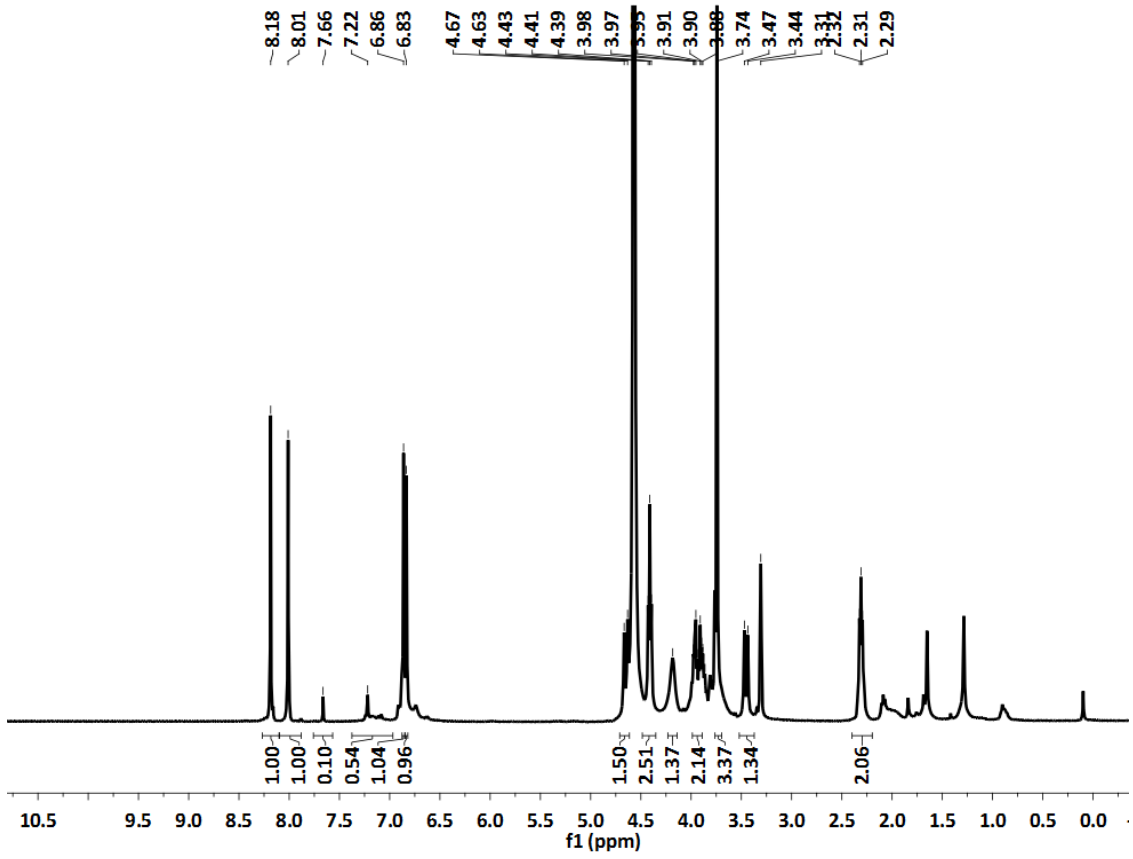


Figure 3.25.^{1}H NMR spectra of CTG-AT (capsule) in CCl_4 + CD_3OD at 298K

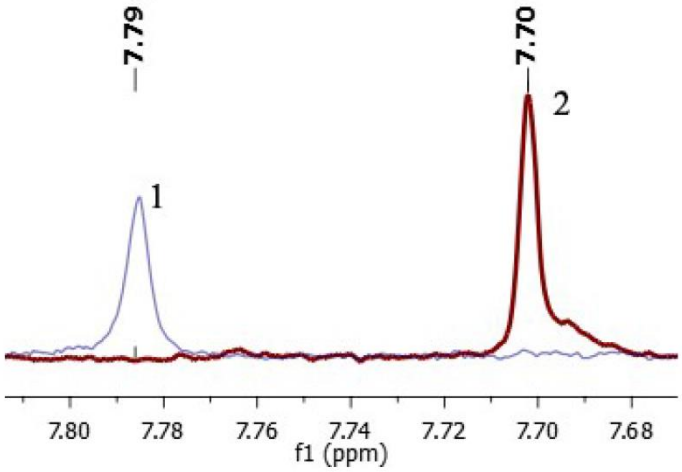
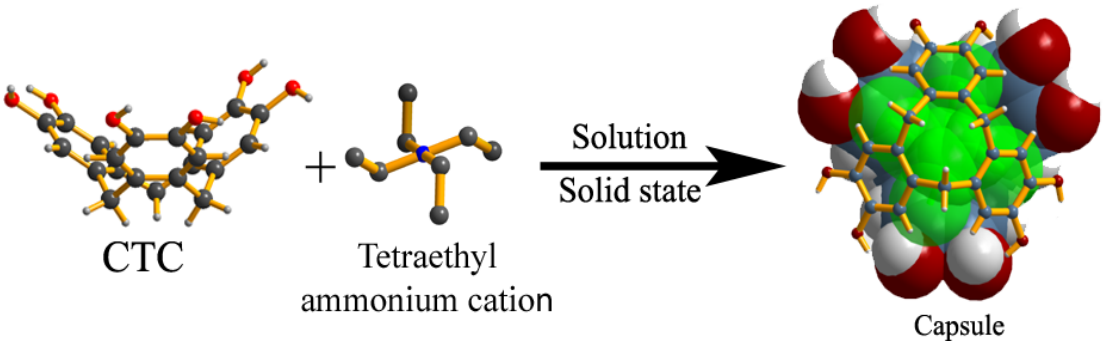


Figure 3.26. Comparison of amine peak in 1 and 2 (Expanded and superimposed)

CHAPTER 4

Guest induced, self assembled molecular capsule

4.1ABSTRACT:



Molecular capsules form due to various interactions between molecules. Cyclotricatechylene (CTC) is a poly-phenolic macrocycle that has been shown to form capsule under highly basic conditions. Here, we describe the formation of a molecular capsule under ambient conditions, from CTC by addition of a guest molecule. The capsule formation most probably is through pure electrostatic interaction between the guest and CTC. Confirmation of the capsule formation has been obtained using solution studies such as NMR and Mass spectroscopy. The solid state structure obtained by single crystal X-ray diffraction, corroborates well with these findings. Anions do not contribute to the capsule formation. By increasing size of the guest molecule the capsular structure has been disrupted and resulted in supramolecular assemblies. Cyclotricatechylene (CTC) is forming hydrogen bonding with halide anions Cl^-,Br^-, which are characterized by single crystal X ray-diffraction

4.2 Introduction:

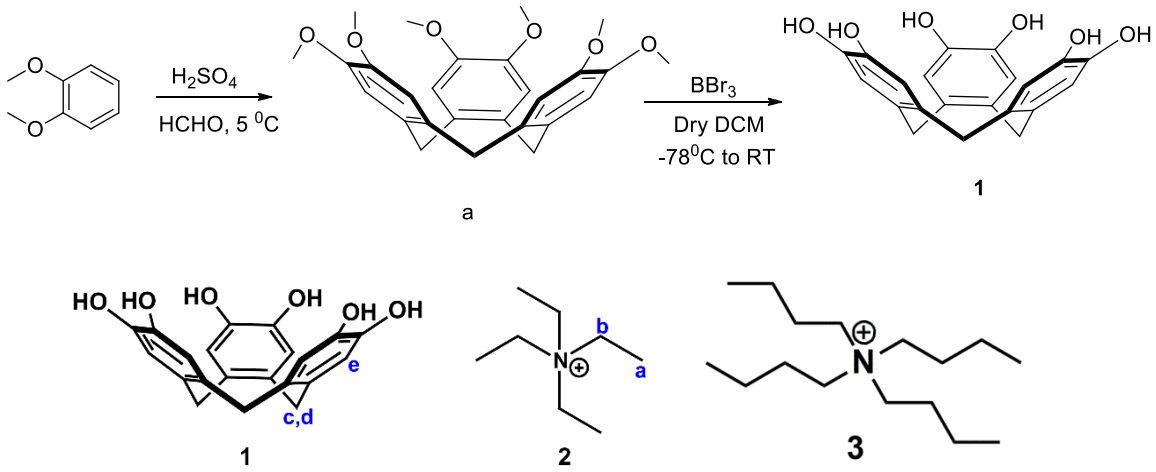
Molecular capsules, also called molecular flasks, are macro-molecules or supra-molecules, which have space inside to conceal other molecules as guests. Some molecules such as cryptands and enzymes, which inherently contain cavity, are also termed as molecular capsule.[1,2] They have recently emerged as a subject of great interest due to their possible applications in various fields. For example, they can accelerate the reaction speed as compared to in the bulk solvent environment when used as reaction vessels,[3-6] help in formation of different regioselective product as compared to products in bulk solvent environment,[6] stabilize unstable molecules and even reaction intermediate inside the cavity,[3-5,7,8] and selectively sense molecules and ions.[9] Molecular capsules may also be used as drug delivery vehicle for their ability to carry guest molecules, and release them under mild change in condition.[10] Suitable molecules may interact by hydrogen bonding,[3,4,11-13] ionic interactions,[14] metal ligand coordination,[15-17] hydrophobic effects,[18] or combination of them[19] to form molecular capsule. Reports from Sherman and co-workers suggest that guest molecules might also act as template to form different covalent cages viz. Hemicarceplex, Carceplex, tris-carceplex capsules.[20-24] There are however few reports where the guest entrapment is believed to be the primary cause of capsule formation.[25,26]

Such capsules which form due to the presence of a guest, may be compared with enzymes that change their three dimensional structure to accommodate its substrate.[27] Although several capsules have been synthesized and utilized for various functions, the major challenge that still remains is to design a capsule with predefined shape and size to target a specific molecule.[28] It would be an added advantage if the capsules form only when a specific target reaches them.

The macrocyclic molecule Cyclotriveratrylene (CTV) and its derivatives have been shown to form clathrate, entrapping different molecules owingto its shallow molecular cavity.[29-33] The de-methylated derivative of CTC, a poly-phenolic macrocycle, is known as cyclotricatechylene (CTC, **1,** Scheme 1). **1** has previously been studied for self-assembly into molecular capsule. Yuji et al. synthesized a hetero-dimeric capsule that they studied in solution phase. They utilized a boronic acid-appended hexahomo-trioxacalix-[3]arene along with **1** to form a heterodimeric capsule which hosts an Et_4N^+ inside the cavity.[34] Robson and co-workers showed that **1**, under basic condition can act like a clam, which captures alkali metals ions such as Rb^+ and Cs^+, but opens up when cations such as NMe_4^+ and NEt_4^+ are captured as guest.[35] The opening up of the capsule may be attributed to the size of the cations which large enough to be encapsulated

Abrahams and coworkers reported capsule formation by CTC, when metal ion coordinates phenolic oxygen atoms. This cage encapsulates alkali metals.[36] Same group, utilizing a similar strategy synthesized a highly symmetrical cage by metalation with Cu^{2+}.[37] Recently, our group has demonstrated that **1**, with suitable hydrogen bond acceptors such as phenanthroline or bipyridines can form molecular capsule through hydrogen bonding and π–π stacking.[38,39] In most of these efforts, the capsules are synthesized by applying harsh conditions and are studied in solid-state using X-ray analysis. Although the earlier reports shows the formation of capsule based on resorcin[4]arene which entrapps guest moleucle(NEt_4^+) inside of the cavity, the forces governing the formation are hydrogen bonding with the solvent molecule or anion.[40-43] Herein we are reporting a capsule fomration induced only by guest moleucle where in, there is niether intermoleuclar forces found between the two units of CTC nor with any solvent. There were no such capsule exists where only guest moleucle inducing formation, with out any intermoleuclar forces among them up to our knoweldge.

Although solid-state analysis provides important insights into the mechanism of capsule formation and the interaction between host and guest, solution studies are invaluable in many cases. For instance, solution studies are indispensable, when designing a capsule as a drug delivery vehicle, where the entire process happens in solution phase. Therefore, a system that forms and allows study in both solution and solid phases at ambient conditions would have many added advantages over those, which could be studied only in solid state. In continuation to our work on **1** and its derivative, herein we report the capsule formation by **1** in methanol under normal conditions and studies both in solution and solid states. It is further established that this capsule formation is triggered only by the guest molecule tetraethylammoniumcation, Et_4N^+(**2**)and neither intermoleuclar forces between the two units of CTC nor the solvent is responsiblefor the formation.



Scheme1: Synthetic strategy for synthesizing **1,** and guest molecules used for capsule formation, assemblies (**2**&**3**)

4.3 Synthesis

4.3.1 Synthesis of CTC: CTV&CTC has been synthesized using a reported procedure and characterized by spectroscopically.[44,45]

4.3.2Synthesis Of complex 1: 5mg (1.36 mmol) of CTC (1) was dissolved in methanol, to this solution 1 equivalent of **2**.PF_6 (3.75mg) was added, sonicated for 15 min, filtered and kept undisturbed for crystallization. Brown colored crystals suitable for X ray diffraction was found after a week.

Synthesis of complex 2: Synthesized in a similar manner to complex **1** by replacing the salt anion with **2**+Br^-.

Synthesis of complex 3: 5mg (1.36m.mol) of CTC (**1**) was dissolved in methanol to this solution 1 equivalent of **3**+Br^- (4.4mg) was added, sonicated for 15 min, filtered and kept undisturbed for crystallization;reddish brown colored crystals suitable for X ray diffraction was found after 15 days.

Synthesis of complex 4: 5mg (1.36 mmol) of CTC (**1**) was dissolved in methanol to this solution 1 equivalent of **3**.Cl (3.8mg) was added, sonicated for 15 min and filtered kept undisturbed for crystallization, reddish brown colored crystals suitable for X ray diffraction was found after 15 days.

4.3.3Physical Measurements: NMR was recorded at Bruker 400MHz instrument. Single crystals X-ray diffraction studies were done on a Bruker APEX-II diffractometer equipped with a CCD detector, the X-ray source being Mo K_α (wave length 0.71073 Å). Data collection was monitored with Apex II software and preprocessing was done with SADBS integrated with Apex II. The data was solved by SIR2002,[46]and expanded using Fourier technique. In case of capsule (1+ 2.PF6) disordered solvent molecules were

present. Hkl without disordered solvent was generated using SQUEEZE command in PLATON.[47] All these software were integrated in Wingx package.[48] Hydrogen atoms were not added to the disordered guest (**2**) in all the cases.

4.4 Results and Discussion:

We noticed that the solubility of **1** is enhanced by addition of **2**-PF_6 , indicating that some kind of interaction exists between them. To investigate further, we recorded ambient temperature ^{1}H NMR of the mixture and **2** alone in CD_3OD. The methyl protons resonate at 1.25ppm whereas the methylene protons come at 3.25ppm with respect to residual CHD_2OD for **2**. The NMR spectrum of the mixture showed that these signals are shifted to 0.86 and 2.5ppm, respectively, showing an appreciable increase in diamagnetic shielding (Figure 4.1.). Interestingly, the shift depends on the concentration ratio of **1**and **2**. Such large increase in shielding could only be explained by the strong ring currents produced by **1** is affecting the signals of **2**. In other words, the shift hinted toward a possible capsule formation by **1** with **2** being encapsulated therein. However, these signals are not as highly shielded as reported in literature, where the signals for encapsulated **2**shifted to 0.3 and -0.039ppm, respectively.[34] Moreover, it was observed that the peaks of **2** shift towards higher field till 1:3 equivalents of **1** and **2**. Any excess of **2** in the solution mixture does not further shift the signal. Also, at no concentration ratio any new peak could be observed. For a stable complex where the exchange of guest is slower or comparable to NMR time scale, 1D ^{1}H spectrum of the capsule consists two sets of signal, one for free guest and other for encapsulated guest, provided excess of guest is added in the solution. The fact that the shifts we observed were lower than those reported earlier with the same guest molecule, the shifts were dependent on the relative concentrations of **1**and the **2**-PF_6, and separate peaks for free and encapsulated **2**-PF_6 were not observed suggest that the guest molecule possibly remains in a dynamic

equilibrium between the free and encapsulated states. Therefore, the shifts observed are dynamic averages of the free and encapsulated chemical shifts of **2**.

At this point we asked ourselves three questions. First, if there really is a capsule formation and encapsulation of **2**. Second, in case of an encapsulation, why the shift is not as large as reported in the literature? And third, whether the capsule is stable enough in solution to be detected somehow.

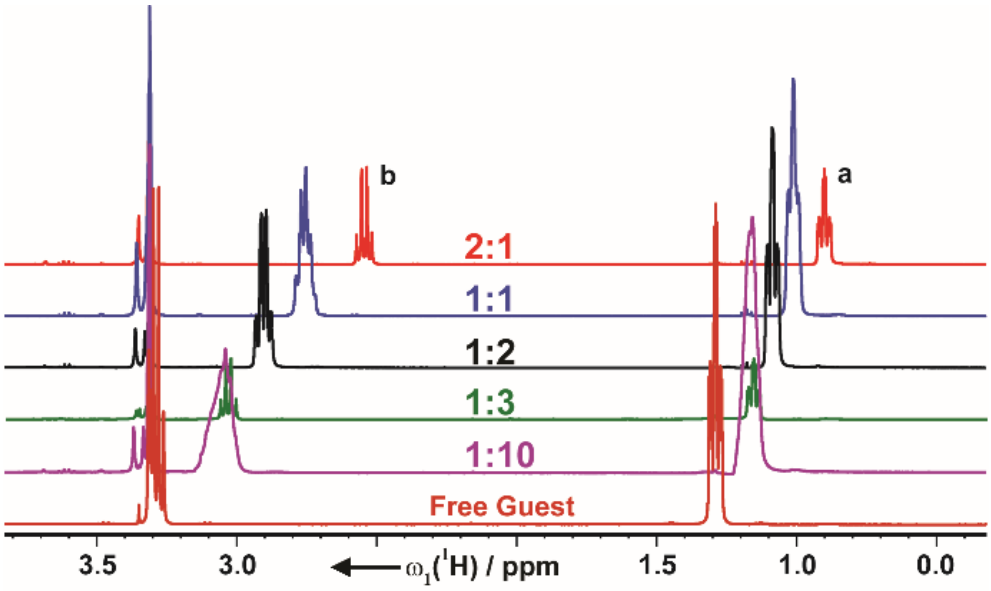


Figure 4.1. Stacked plot of ^{1}H NMR spectra at different host:guest ratio with an expansion between -0.2 and 3.8 ppm, highlighting the resonances a and b (see Scheme 1) of **2**-PF_6 The progressive high field shift indicates encapsulation of guest molecule

Encapsulation is a self-assembly process that can be verified in solution state by a NMR method namely DOSY.[49] It involves measurement of translational self-diffusion coefficient (**D**), a measure of how efficiently a molecule diffuses in solution. **D** increases with increase in solvent temperature, with decrease in solvent viscosity and hydrodynamic radius of the molecule. If a molecule is approximated as a sphere of uniform density, the mass of the molecule becomes proportional to the third power of the hydrodynamic radius. Under this approximation, **D** becomes inversely proportional to the

one-third power of molecular mass, provided all other experimental conditions remain unaltered. As a result, when a self-assembled capsule forms and remains stable in NMR time scale, the change in D values of the molecules before and after the assembly indicates the formation. The translational diffusion coefficients were measured using the standard Pulsed field Gradient Stimulated Echo (PGSE) experiment using bipolar z-gradients on a 400 MHz Avance III nanobay spectrometer. In this experiment diffusion induced attenuation of a NMR resonance signal is measured as a function of gradient strength for a fixed diffusion delay. The peak intensity (I) for a given gradient strength (g), normalized with respect to the non-attenuated intensity (I_0) follows a relationship $\log(I/I_0)=-\mathbf{D}\zeta g^2$, known as the Stejkal and Tanner equation.[50] ζ is a constant that depends on the gyromagnetic ratio of the spins under investigation, the diffusion delay and few other experimental parameters and can readily be calculated. The negative of slope of the curve of $\log(I/I_0)$ as a function of g^2 gives $D\zeta$, wherefrom D is calculated.

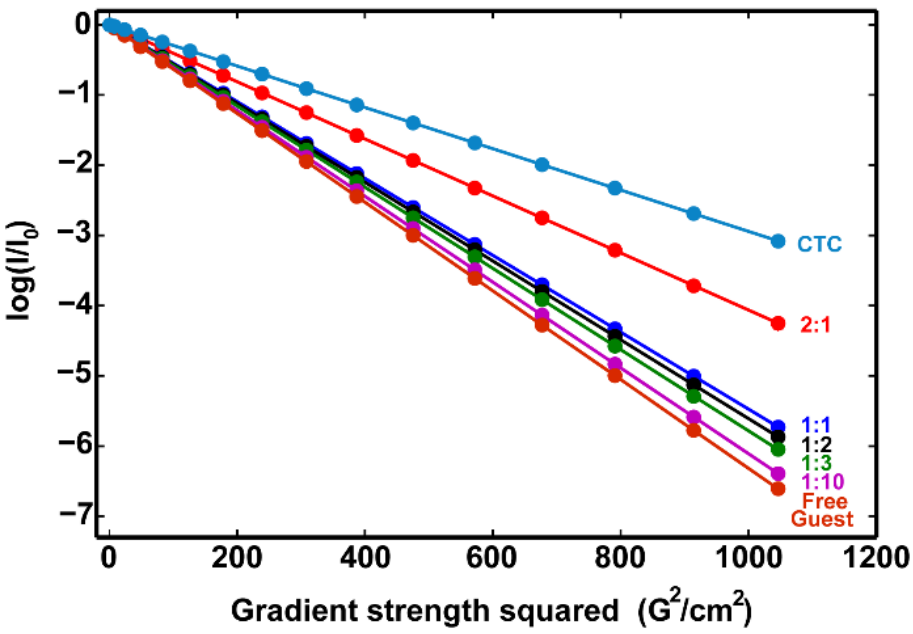


Figure 4.2. Logarithmic normalized peak intensity as a function of squared gradient strength obtained during the self-diffusion measurement of the guest molecule for different host:guest concentration ratio. A larger slope indicates higher translational

diffusion rate. For CTC, the aromatic peak at 6.8 ppm and for the guest the peaks around 1 ppm have been used for all calculations. Progressive decrease in guest diffusion rate indicates encapsulation of **2** within the slow diffusing capsule made of two CTC (**1**) molecules

We measured D for both host (**1)** and guest (**2)** for different host:guest concentration ratio in order to explain the observed NMR shifts of the guest molecule. **D** was also measured for **1** in absence of **2**-PF_6 (free CTC) and **2**-PF_6 in absence of **1 (**free Guest). Figure 4.2.shows the corresponding $\log(I/I_0)$ vs. g^2 plots. All experiments were performed at 27ºC. The free guest quite expectedly moves the fastest ($D=10\times10^{-10}$ m^2/s) while the free CTC was found to be the slowest ($D=4.6\times10^{-10}$ m^2/s). Interestingly, D for **1** does not change appreciably in presence of **2**. D for **1** ranges between 4.15×10^{-10} m^2/sand 4.77×10^{-10} m^2/s for different concentration ratios Table4.6.5. This indicates that **1** possibly is forming dimers in absence of the guest as well. However, it could not be ascertained at this point if the dimer is of the form of a capsule or otherwise. Presence of slow diffusing host molecules reduces the diffusion rate of the guest confirming their association. Diffusion coefficient for the guest molecule was found to be consistently decreased as the concentration of the guest was reduced with respect to the host. This is expected, as with lower relative concentration, each guest molecule spends longer time in captivity. At the preferred ratio of 2:1 (host: guest) for capsule formation, **D** for **2** becomes the minimum. However, D of **2** never becomes equal to that of the host, which is expected for a stable capsule of **1** with encapsulated**2**. The capsules form and open up continuously, maintaining a dynamic equilibrium.

To verify if the encapsulation is stable enough so that dipolar interaction between the host and the guest is detected using two dimensional NMR, we recorded a Rotating-frame nuclear Overhauser Effect SpectroscopY (ROESY) spectrum. Any cross peak

between the guest and the host protons would then confirm the existence of the capsule. The ROESY spectrum (Figure 4.3.) indeed shows cross peaks between aromatic protons of **1** and both methyl and methylene peaks of **2**. This clearly shows that the capsule is stable enough in the NMR relaxation time scale.

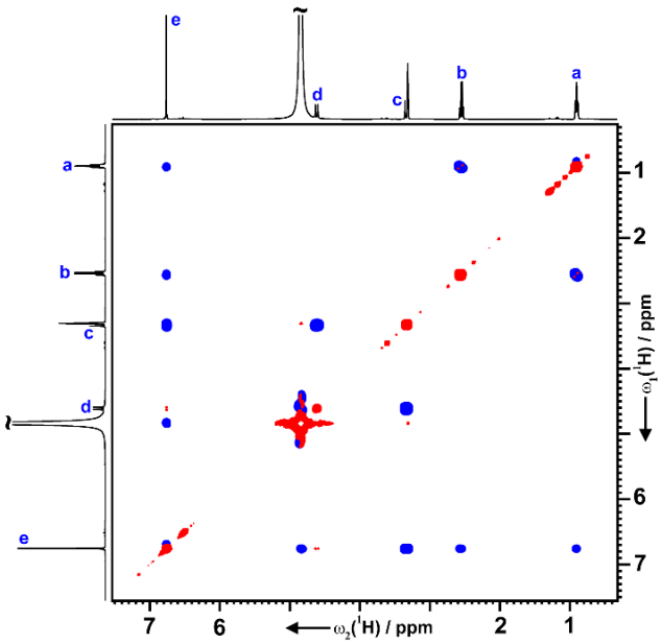


Figure 4.3. 2D ROESY spectrum of host-guest mixture at the relative concentration ratio of 2:1. The negative (shown in blue) cross peaks between guest peaks (a and b) and aromatic peak of the host (e) indicates formation of the capsule with encapsulated guest.

The spectrum was recorded with 700 ms mixing time and with 2048 direct and 256 indirect time domain complex data points. Peak assignments are according to Scheme 1.Absence of any such cross peak in a correlation spectroscopy (COSY Figure 4.4.) spectrum further confirms that **1** and **2** are not interacting covalently.

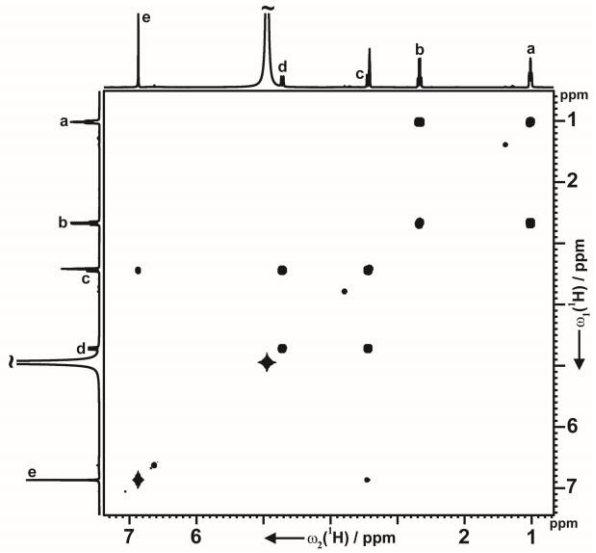


Figure 4.4.COSY Spectra recorded at 2:1 (host:guest) ratio in CD3OD

Another evidence of the stability of the capsule in solution came from the mass spectral data. We recorded mass spectrum of **1** along with 1 equivalent of 2.PF6. As per expectation, a clear peak at m/z 860(Figure 4.5.) reconfirms the presence of the capsule in solution. **1** also forms a dimer in solution as evident of the m/z peak at 731 as predicted by NMR

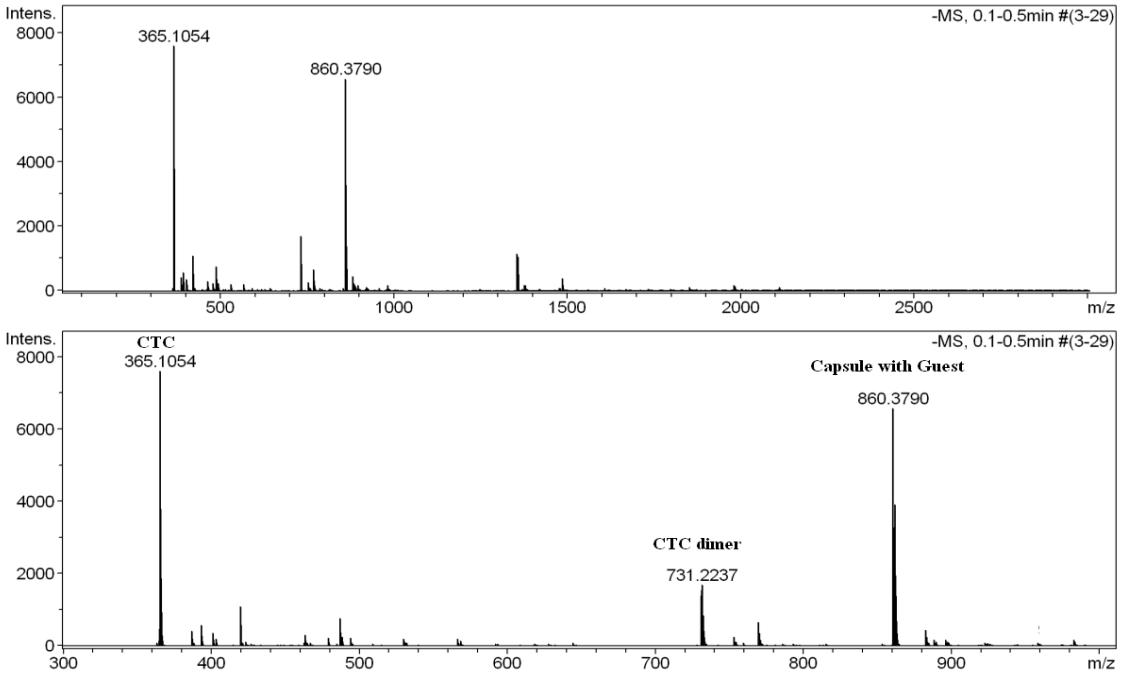


Figure 4.5.ESI-Mass Spectra of (-ve Mode) CTC with 2.PF6 in Methanol

The final evidence of the capsule formation and that the capsule only forms in presence of guest comes from the solid state X-ray data analysis. The crystal structure of **1**, was published earlier. The crystal was grown in DMSO due to its poor solubility in many organic solvents.[51] Thus, it might be irrelevant to compare them to the present study. We grew the crystals in methanol to compare it with the other experimental results. The crystals were grown by dissolving **1** in a mixture of MeOH and acetonitrile. Few drops of acetonitrile were added to improve the solubility

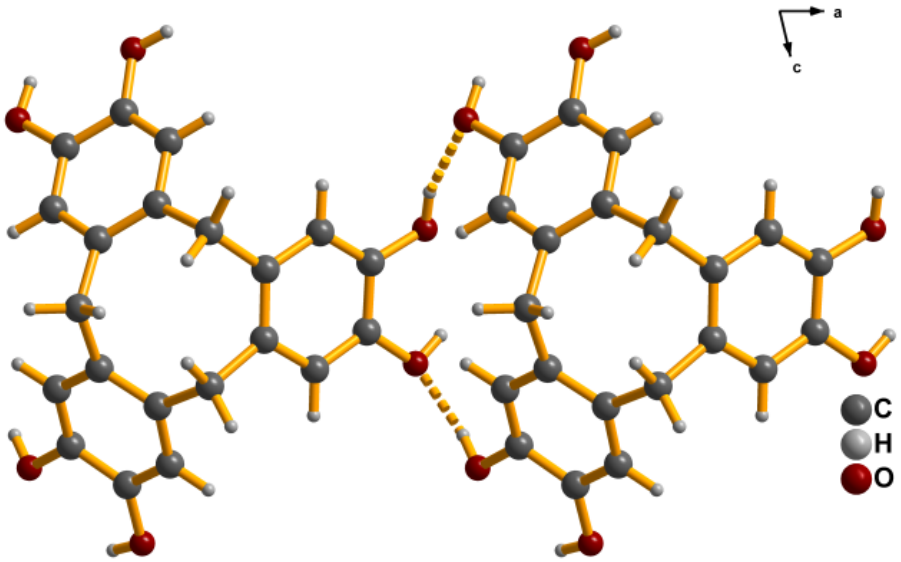


Figure 4.6. Dimer formation in crystal structure of **1,** projected alongcrystallographic b-axis. Other hydrogen bonds are not shown for clarity

It crystallized in $P\bar{1}$ space group (No. 2) in triclinic crystal system. Two methanol molecules as solvent of crystallization were also found in the unit cell. Upon analyzing, it could be seen that each molecule is surrounded by four others by hydrogen bonding and two methanol molecules by hydrogen bonding. (Figure 4.7) **1** forms a 2D polymeric structure but does not form any capsular structure as seen clearly in Figure 4.6.

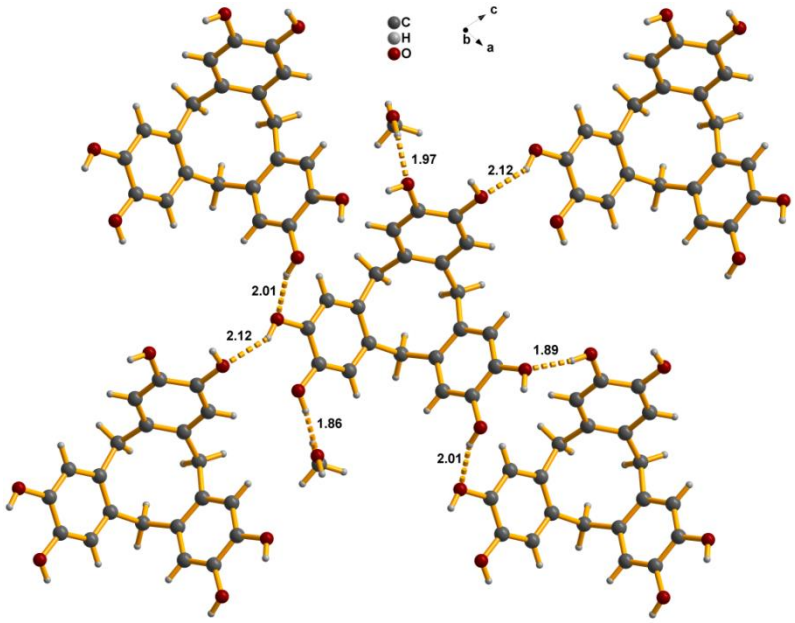


Figure 4.7. Hydrogen bonding between CTC molecules and with methanol in 1. The numbers indicate the distances in Angstrom.

Encouraged by the solution studies, we co-crystallized **1** and **2**-PF_6 by dissolving them (1:1 ratio)in methanol with few drops of acetonitrile. The crystals suitable for structure determination came in few days(capsule-**1**). It was found that capsule-1 crystallized in the $P1^{-}$space group (No. 2), similar to**1** itself. The capsular structure could immediately be visualized in the crystal structure (Figure 4.8.).

2 was found inside two molecules of 1, equidistance (5.22Å) from the planes constructed by joining C7, C14 and C21 (Figure 4.9. a). As a marked difference to an earlier report,[35] there exists no hydrogen bond between two CTC units. Rather the capsular units get engaged in hydrogen bonding among themselves and with the anion (PF_6^-) to form a chain of capsules (Figure4.9.b and 4.10.). This removes all possibilities for the solvent molecules to interact with the CTC units and thereby their contribution to the capsule formation. This is quite unlike the earlier reports of capsule formation due to hydrogen bonding with the solvent molecules or the anion.[40-43]

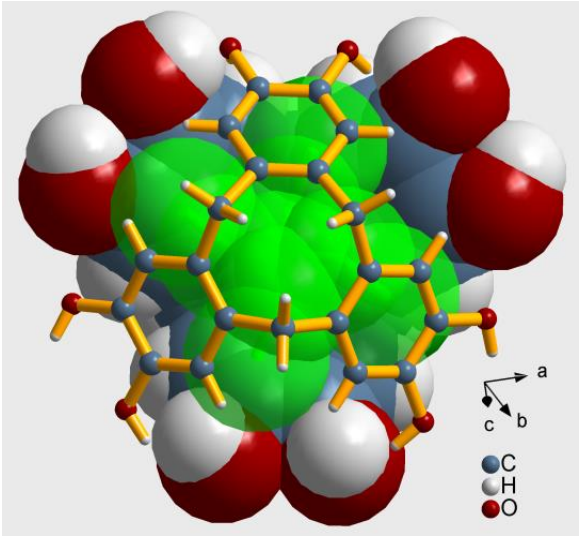


Figure 4.8. Crystal structure of **capsule-1** with encapsulation of **2**. One molecule of **1**(backside) and the guest are shown as space filling model. Guest (**2**) is shown in different colour for clear visibility

a) **b)**

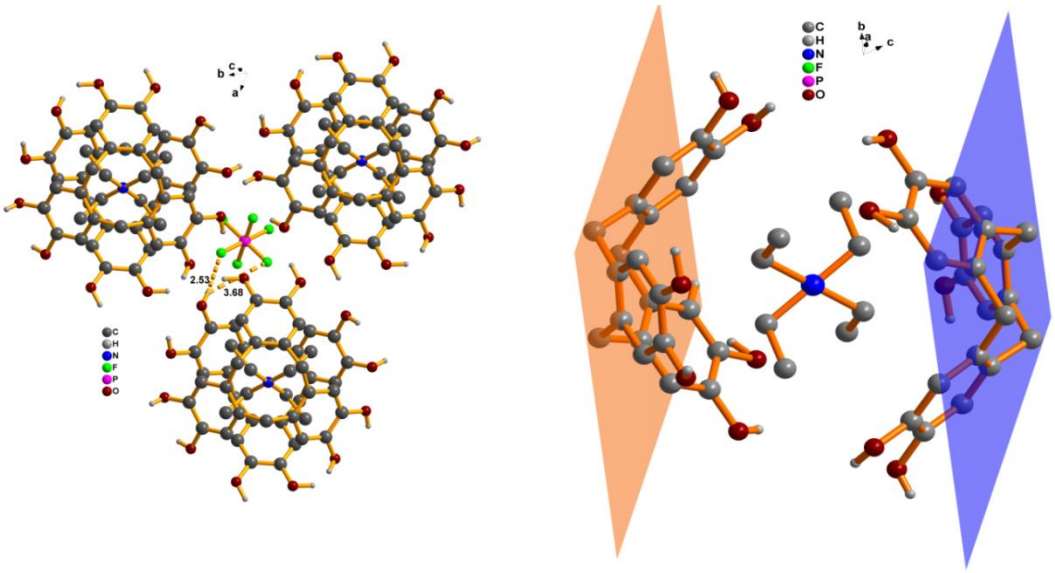


Figure 4.9. a)View of guest from side of CTC in Capsule-**1**. Guest (2) equally from both the planes constructed through C7, C14, C21. b) Hydrogen bonding of anion PF_6 with **1** phenolic hydrogen atoms in **Capsule-1**

It may be noted that these reported capsules were based on resorcin[4]arene and entrapped the same guest molecule (**2**) inside the cavity.The distances among the hetero atoms are 4.80Å (O1-O4#2), 5.10Å (O2-O5#2) and 5.24Å (O3-O6#2).[52] This suggests that the capsule is forming solely due to the entrapment of the guest. Due to very similar environment in either side, the guest is having a positional disordered at methylene carbon. It is interesting to note that the distance between aromatic protonsof the host and the guest protons are well within the limit of 5Å for obtaining cross peaks in a 2D ROESY spectrum.

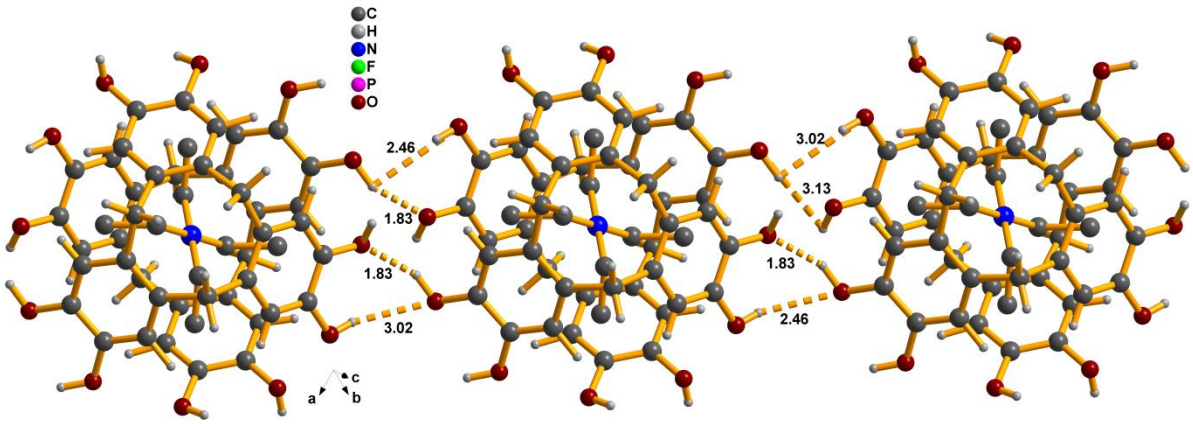
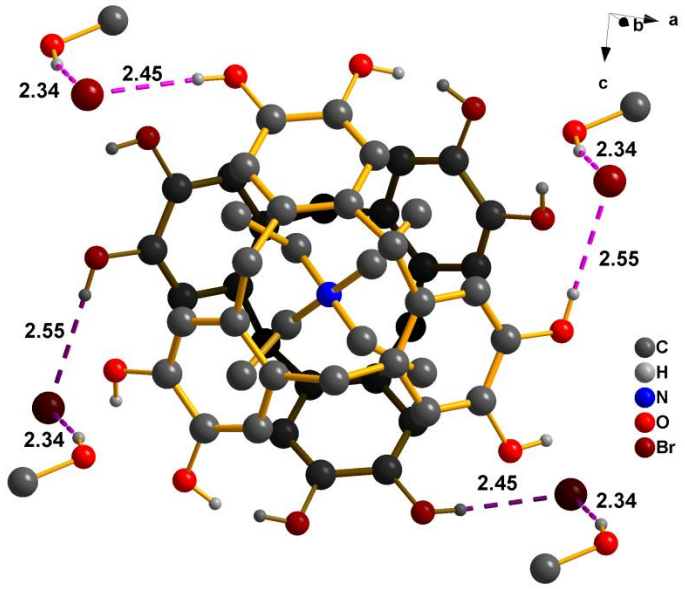


Figure 4.10. Arrangement of capsules due to hydrogen bonding among themselves in Capsule-**1**. Anion is omitted for clarity.

To study if anion plays any role in capsule formation, we recorded ^{1}H NMR of **2** with different anions such as Br^- and BF_4^-. It was found that the chemical shifts for **2**is similar for all the anions, thereby suggesting that anions might not have any role to play in the encapsulation process. This is further proved by solid-state structure of CTC with 2.Br grown in methanol(capsule-**2**). These crystals were also having similar encapsulated **2**(Figure 4.11.a) with no hydrogen bonding between two halves of the capsule or solvent molecules. The solvent molecules are forming hydrogen bonds with the anion (Br^-).

a)



b)

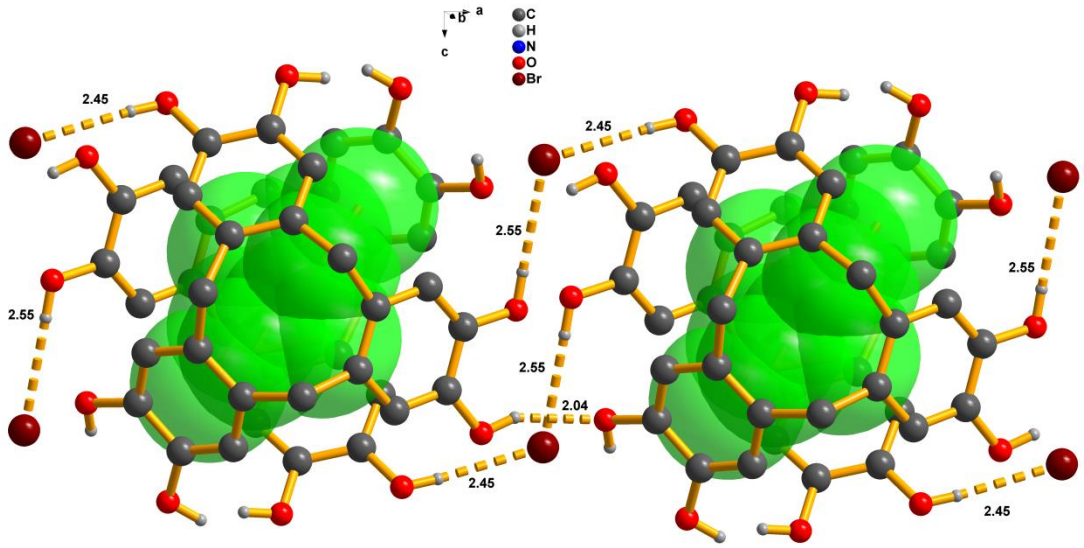


Figure 4.11. a) Hydrogen bonding in **Capsule-2**. Numbers shown are distances for the broken bonds b) The hydrogen bonding of Br- between the **Capsule-2**. Guest (**2**) is shown in space filling model

We further studied the cation dependence by changing the size of the guest molecule to tetrabutyl group in place of tetra ethyl. To our surprise no peak shift (Figure 4.26.) was noticed in ^{1}H NMR after mixing (1:0.5 eq of **1** and **3**). Further confirmation was obtained by single crystal analysis where, in the crystal structure of the complex, no capsular

arrangement could be ascertained. Co crystallization of CTC and TBABr was done in the same way for the capsule-**1**, by replacing tetra ethyl ammonium to tetrabutyl ammonium salt were resulted in deep red coloured crystals which were found suitable for single crystal analysis. The complex crystallized in cubic (P-43n) space group with a=19.257(4) Å, each unit cell contains eight CTC units and twelve bromide anions, two CTC molecules is sharing 3 bromide ions. Each CTC molecule is hydrogen bonded with three bromide ions. The bromide anions are residing equal distance from all the neighbour CTC units with a bond distance of 2.5254(4) Å. The bond distance, bond angle between O-H and Br- indicates a strong hydrogen bonding between CTC and bromide ions see in bond distance Table **4.6.3**

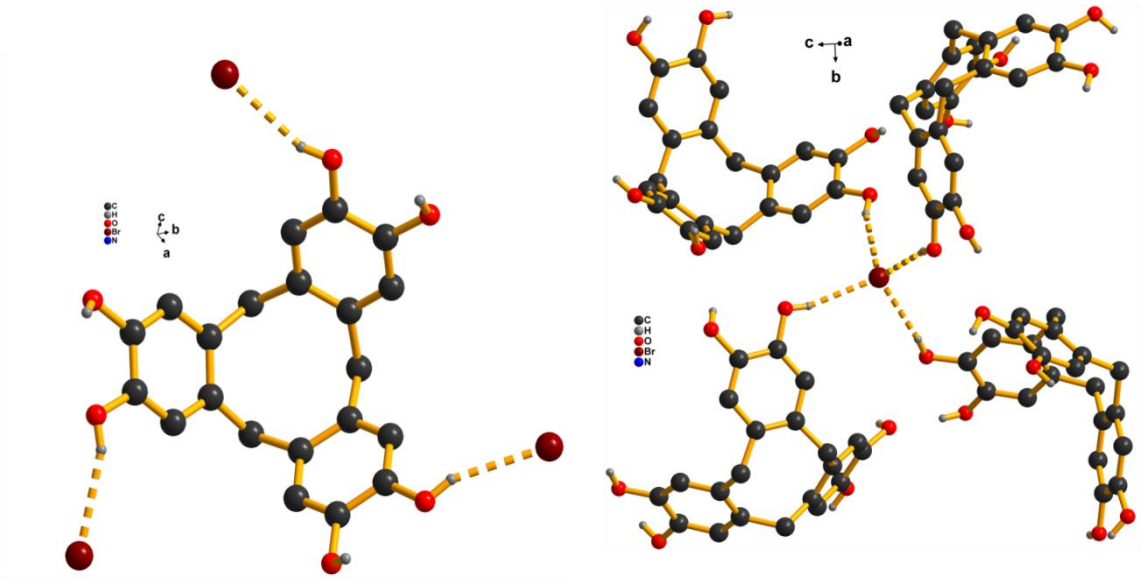


Figure 4.12. Hydrogen bonding distance and environment around CTC units. Bromide ion is shown in wine red color, hydrogen atoms which are not involved in hydrogen bonding, tetrabutyl groups are omitted for clarity.

One bromide ion is in between the centre of four CTC molecules with equivalent bond distance. The continuations of these interactions lead the assembly to channels which are shown in (Figure 4.12.)The bromide ions shown in wine red colour. The two CTC units

were not perfectly staggered face to face but they stacked each other with an angle of 54.05^{O}. The tetrabutyl ammonium which are counter cations were found in between the voids of unit cell but in between the two CTC units, which would have been resulted in a much ordered assembly like a capsule.

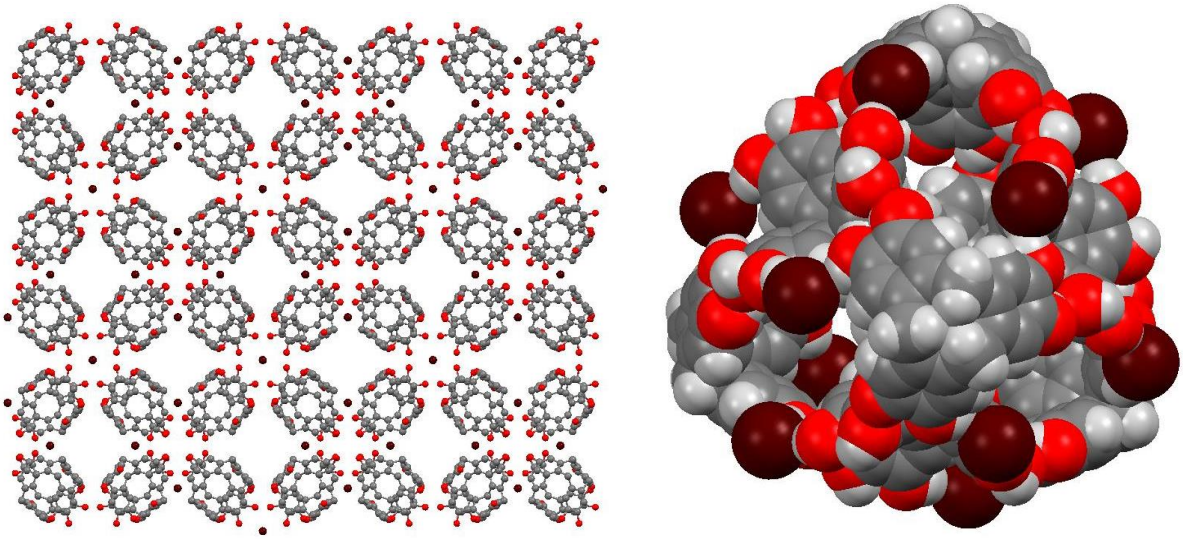


Figure 4.13. Packing diagram of **4** and space filling model

Co-crystallization of CTC and TBACl were resulted in deep red colored crystals, which were grown in similar manner to CTC-TBABr crystals. The complex crystallized in cubic (p-43n) space group with a=18.912(4) Å, each unit cell contains eight CTC units and twelve chloride anions, two CTC molecules is sharing 3 chloride ions(Figure 4.14.). Each CTC molecule is hydrogen bonded with three chloride ions. The chloride anions are residing equal distance from all the neighbor CTC units with a equivalent bond distance of 2.344(4) Å. The bond distance, bond angle between O-H and Cl- indicates a strong hydrogen bonding between CTC and chloride ions see in bond distance Table**4.6.4**. One chloride ion is in between the centre of four CTC molecules with equivalent bond distance.May be the bulkiness of tetrabutyl groups would have been restricted to the two CTC molecules allign face to face inturn not forming the capsule.

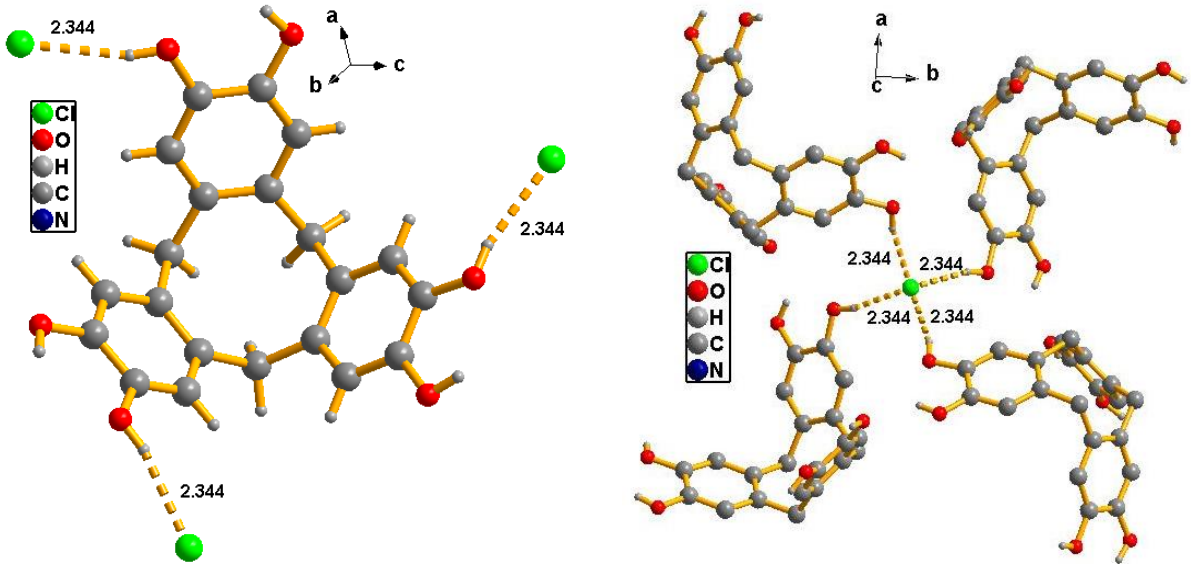


Figure 4.14. Hydrogen bonding distance and environment around CTC units. Chloride ion is shown in wine green color, tetra butyl groups, hydrogen atoms which are not involved in hydrogen bonding are omitted for clarity

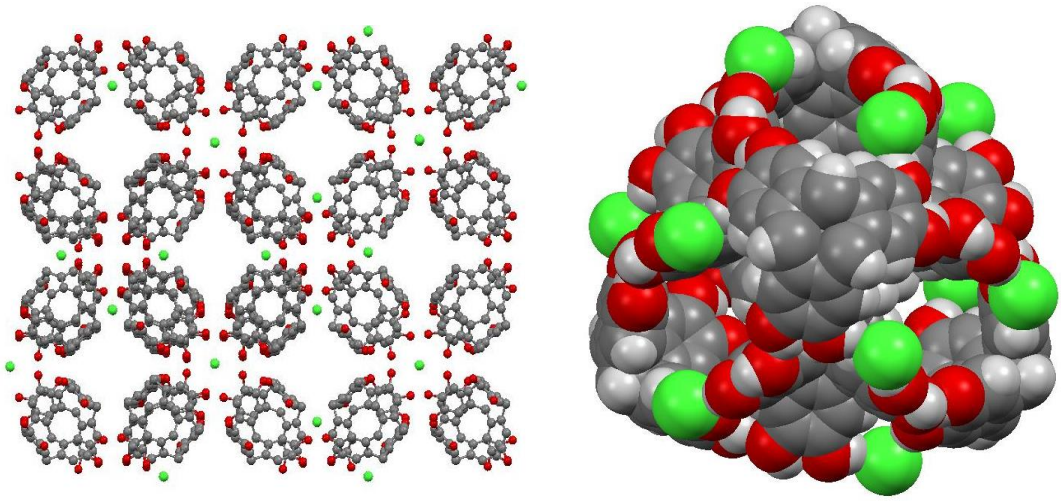


Figure 4.15. Space filling diagram of the molecular channels, hydrogen atoms which are not involved in hydrogen bonding, tetra butyl groups are omitted for clarity

4.5 Conclusions

In summary, we have synthesized and characterized a molecular capsule made of a bowl shaped CTC molecule. It is thoroughly characterized both in solution and solid states. In solution the encapsulation is dynamic in nature. It is also proved beyond doubt that the capsule formation is induced by the guest. The driving force is probably the electrostatic and hydrophobic interactions. The anion plays no role in the encapsulation process but helps the encapsulated units to assemble in the crystal lattice through hydrogen bonding. The guest role has been further studied by increasing it's size which resulted in discreate assembly over capsule. Other aspects of the encapsulation, such as guest selectivity by further modification of **1** are currently being investigated in our laboratory.

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(52) *#2 represent symmetrically grown atoms withsymmetry operation -x, 2-y, 2-z.*

Compound	**1**	**Capsule.1(2)**	**Capsule.2**	**4**	**5**
Empirical formula	$C_{23}H_{26}O_8$	$C_{25}H_{18}F_3N_{0.5}O_6P_{0.5}$	$C_{57}H_{48}Br_1N_1O_{15}$	$C_{11}H_{15}Br_{0.25}N_{0.25}O_2$	$C_{144}H_{168}Cl_3N_3\ O_{24}$
Formula weight	430.44	493.88	1066.87	202.71	2431.16
Temperature	296(2)K	296(2)K	100K	296(2) K	296(2) K
Wavelength	0.71073	0.71073	0.71073	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Triclinic	Triclinic	Cubic	Cubic
Space group	P-1	P-1	P-1	P-43n	P-43n
a (Å)	9.3096(3)	11.438(5),	11.1004(3)	19.257(4)	18.912(4)
b (Å)	10.4365(3)	11.458(5),	13.0392(4)	19.257(4)	18.912(4)
c (Å)	11.3393(3)	12.628(6)	19.5899(5)	19.257(4)	18.912(4)
α (deg)	85.047°(2)	65.406°(3)	71.377°(2)	90.000	90.000
β (deg)	75.659°(2)	89.780°(3)	86.738°(2)	90.000	90.000
γ(deg)	72.743°(2)	60.944°(2),	66.075°(2)	90.000	90.00
Volume ($Å^3$)	1019.24(5)	1273.9(9)	2447.47(12)	7141(3)	6764(3)
Z	2	2	2	24	2
Density (calculated)	1.403 Mg/mm^3	1.288Mg/mm^3	1.4488Mg/mm^3	1.131Mg/mm^3	1.194 Mg/mm^3
Absorption coefficient	0.106 mm^{-1}	0.135 mm^{-1}	0.915 mm^{-1}	0.909mm^{-1}	0.137 mm^{-1}
F(000)	456	508	1104	2580	2592
θ_{max}	30.58°	25.50	25.50	25.79°	30.55°
Reflections collected	17346	14179	30949	74313	63561
Independent reflections	6226	4720	9005	2294	2103
GOOF	1.060	1.086	1.080	0.968	1.117
Final R indices [I>2σ(I)]	R1= .0545, wR2= 0.1391	R1 = 0.0690, wR2 = 0.2069	R1 = 0.0599, wR2 = 0.1673	R1 = 0.0706, wR2 = 0.1824	R1 = 0.0765, wR2 = 0.2044
R indices (all data)	R1=0.0815 wR2= 0.1550	R1 = 0.0865, wR2 = 0.2215	R1 = 0.0795, wR2 = 0.1804	R1 = 0.0863, wR2 = 0.1965	R1 = 0.0857, wR2 = 0.2192

Table 4.1: Crystal data of 1, Capsule-1&2, complexes 4&5

Table 4.2: Hydrogen bond distances in **CTC.**

`Donor---H….Acceptor	ARU	D-H	H…A	D…A	D-H…A
O(1)—H(1)..O(6)		0.82	2.33	2.761 (2)	114
O(1)—H(1)..O(7)	2557.02	0.82	1.90	2.636(3)	148
O(2)—H(2)..O(102)		0.82	1.86	2.678 (2)	172
O(2)—H(2)..O(14)	1554.01	0.82	2.12	2.864(4)	150
O(3)—H(3)..O(2)		0.82	2.32	2.749(5)	114
O(4)—H(4)..O(3)	1655.01	0.82	2.01	2. 799(7)	161
O(5)—H(5)..O(4)		0.82	2.27	2.708 (1)	114
O(5)—H(5)..O(1)	2657.01	0.82	2.31	2.883(2)	128
O(5)—H(5)..O(2)	2656.01	0.82	2.39	2.971 (7)	128
O(6)—H(6)..O(5)	1455.01	0.82	1.90	2.710(9)	171
O (102)—H(102)..O(6)	1654.01	0.82	1.97	2.781(2)	168

Table 4.3: Hydrogen bonding distances in capsule-1

`Donor---H….Acceptor	ARU	D-H	H…A	D…A	D-H…A
O(1)—H(1)..O(1)		0.82	2.24	2.703(5)	116
O(1)—H(1)..O(4)	1645.01	0.82	2.46	3.222 (5)	154
O(4)—H(4)..O(1)	1465.01	0.94	1.83	2.721(5)	156
O(5)—H(5)..O(2)	1565.01	0.78	2.05	2.748(5)	148
O(6)—H(6A)..O(5)	17455.04	0.83	2.34	2.753(5)	112
O(3)—H(33)..O(4)		0.94	2.37	2.698(5)	100
O(3)—H(33)..O(6)	1455.01	0.94	1.84	2.746(5)	163

Table 4.4: Hydrogen bonding distances in capsule-2(**3**) & complexes **4**&**5**.

Donor---H….Acceptor	ARU	D-H	H…A	D…A	D-H…A
O(1)—H(1)..O(11)	1455.02	0.82	2.11	2.835(5)	148
O(2)—H(2)..Br(1)		0.82	2.45	3.271(4)	176
O(3)—H(3)..O(4)		0.82	2.32	2.733(5)	112
O(2)—H(2)..O(14)	2665.06	0.82	2.01	2.779(4)	156
O(4)—H(4)..O(13)	2565.05	0.82	1.91	2.725(5)	173
O(3)—H(5)..O(3)	1455.01	0.82	2.04	2. 803(5)	154
O(3)—H(5)..O(6)		0.82	2.32	2.742 (4)	113
O(3)—H(6A)..Br(1)	1455.08	0.82	2.55	3.364(3)	171
O(7)—H(7)..O(5)	1656.01	0.82	2.11	2.872 (4)	154
O(7)—H(7)..O(8)		0.82	2.27	2.710(5)	114
O (8)—H(8)..O(4)	1556.01	0.82	2.09	2.829(5)	149
O(9)—H(9..O(16)		0.82	1.91	2.725(5)	171
O(10)—H(10A)..O(1)		0.82	2.56	2.983 (5)	113
O(10)—H(10A)..O(2)		0.82	2.02	2.836(4)	175
O (11)—H(11)..O(14)		0.82	1.92	2.736(5)	177
O(12)—H(12)..O(9)	1655.02	0.82	1.97	2.789(5)	174
O(12)—H(12)..O(10)	1655.02	0.82	2.59	2.043(5)	116
O(13)—H(13A)..O(12)	1455.02	0.82	1.99	2.803(5)	171
O(14)—H(14)..Br(1)		0.84	2.35	3.163(5)	165
O(16)—H(16)..O(13)	2566.05	0.82	1.96	2.774(5)	170
Hydrogen bonding distances in **4**					
`Donor---H….Acceptor	ARU	D-H	H…A	D…A	D-H…A
O(1) --H(1) ..O(2)		0.82	2.42	2.716(6)	102
O(1) --H(1) ..O(1)	14554.01	0.82	2.17	2.723(6)	125
O(2) --H(2) ..Br(1)	2555.03	0.82	2.53	3.303(4)	159
Hydrogen bonding distances in **5**					
`Donor---H….Acceptor	ARU	D-H	H…A	D…A	D-H…A
O(1) --H(1) ..Cl(1)		0.82	2.35	3.140(2)	161
O(2) --H(2) ..O(1)		0.82	2.26	2.702(4)	114
O(2) --H(2) ..O(2)	19555.02	0.82	2.07	2.650(4)	128

Table 4.5: Self diffusion coefficient of host (1) and guest (2) at different host:guest ratio

Host:Guest	D of host (in 10^{-10} m^2/s)	D of guest (in 10^{-10} m^2/s)
Free Host	4.6	---
2:1	4.15	6.4
1:1	5.06	8.58
1:2	4.77	8.75
1:3	4.62	9.17
1:10	4.6	9.5
Free Guest	---	10

4.7 Spectral Data

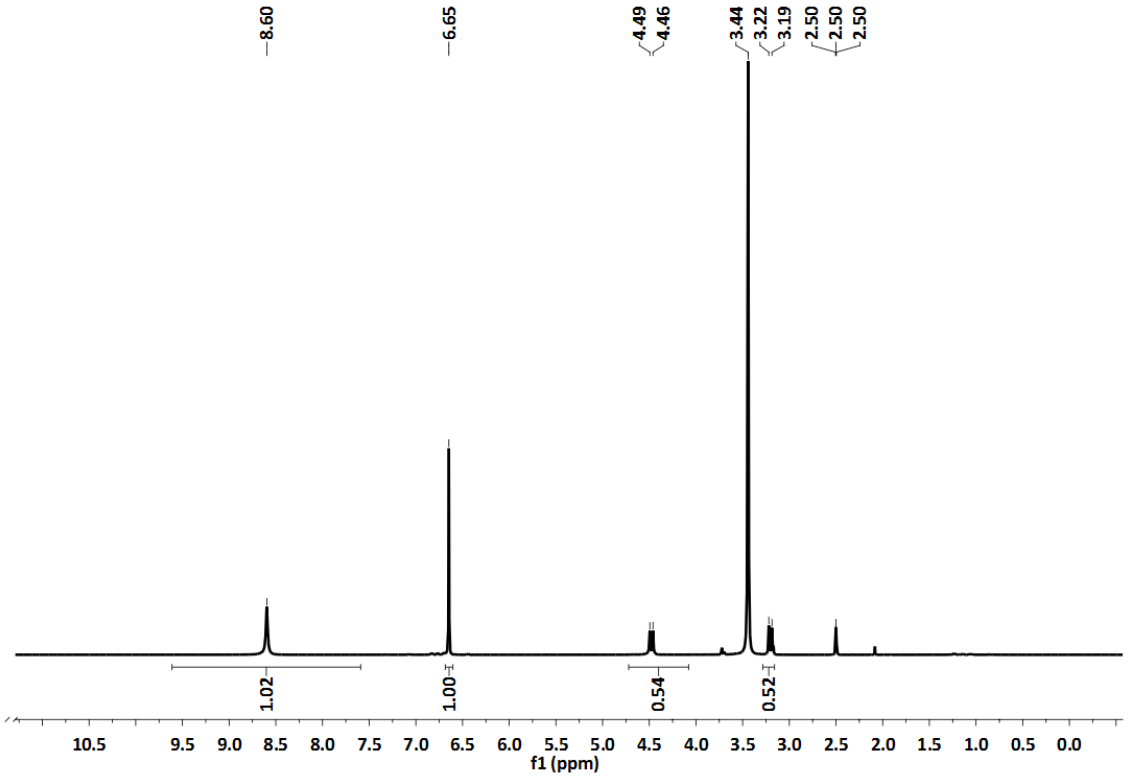


Figure 4.16. ^{1}H NMR spectra of CTC in DMSO-d_6

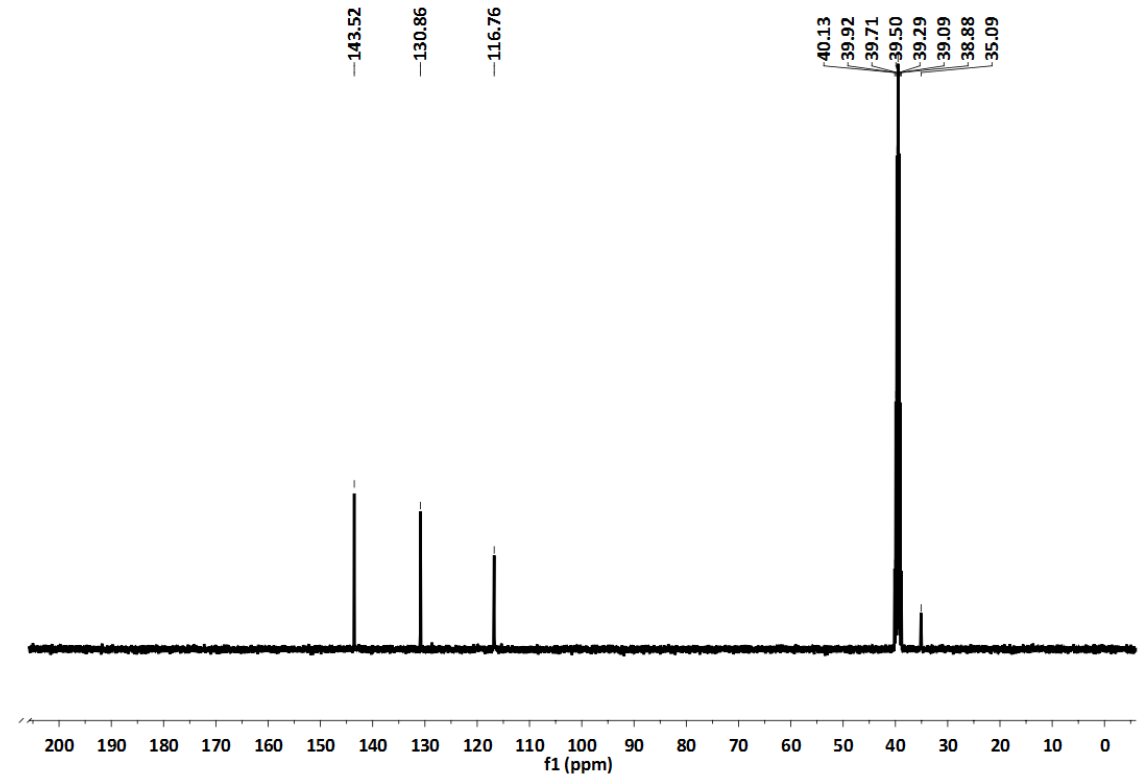


Figure 4.17. ^{13}C NMR spectra of CTC in DMSO-d_6

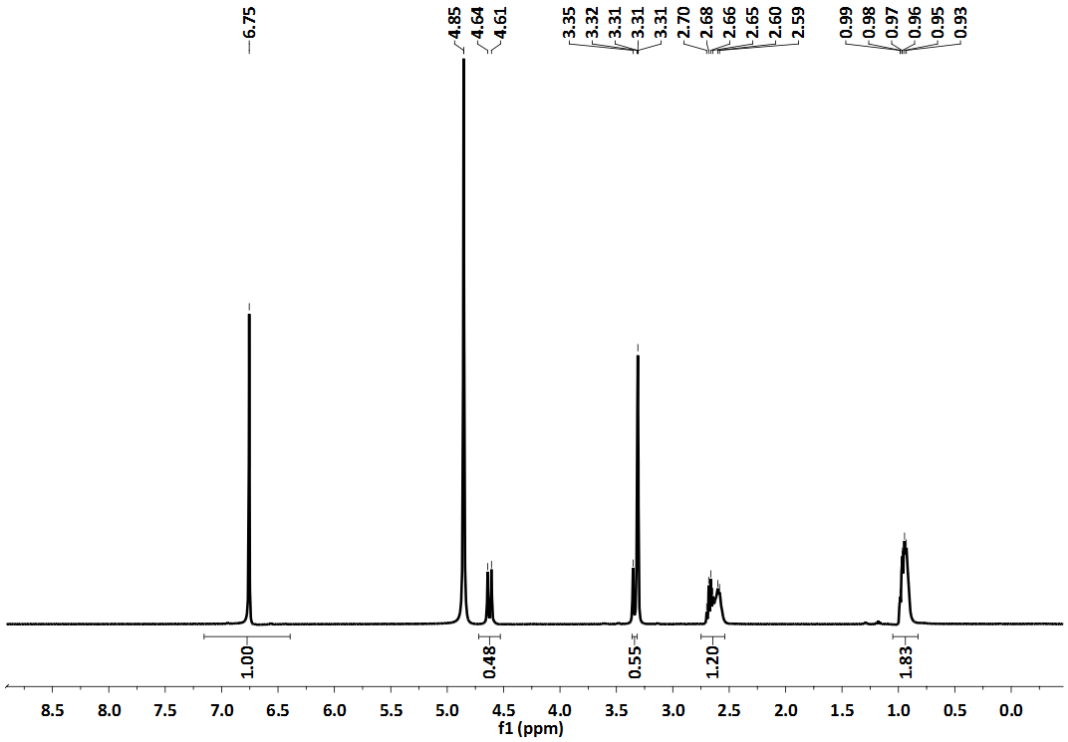


Figure 4.18. ^{1}H NMR Spectra of 1and **2**.Br in CD_3OD, star peak indicates H_2O in CD_3OD

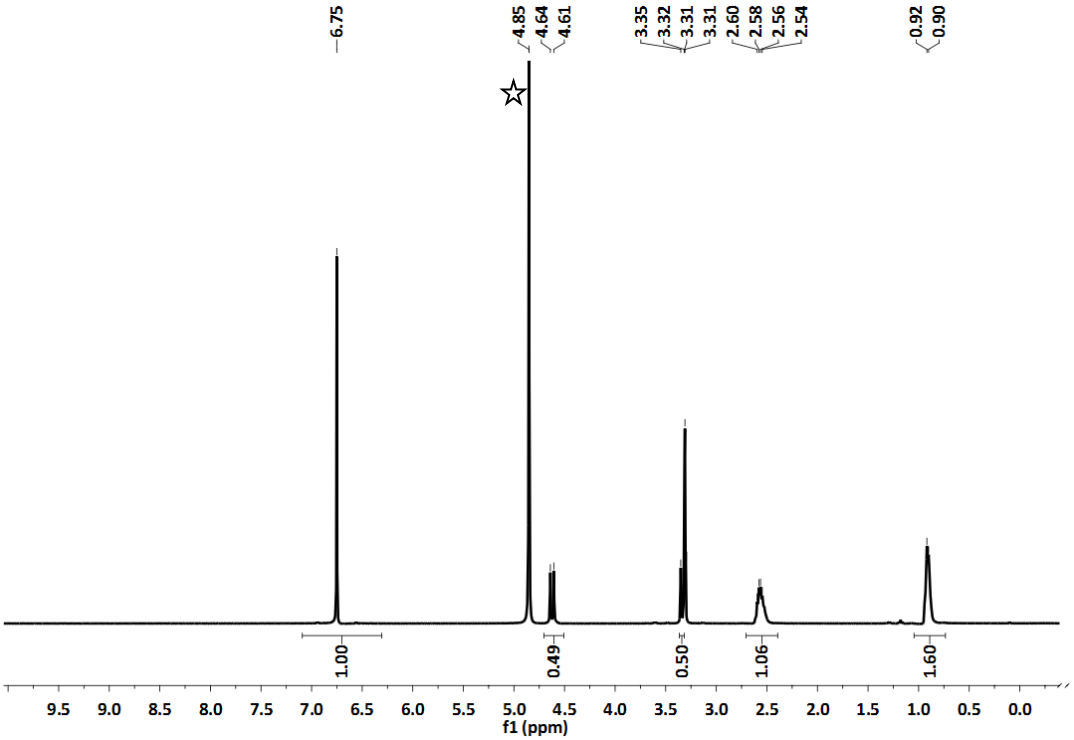


Figure 4.19.^{1}H NMR Spectra of 1and **2**.BF_4 in CD_3OD, star peak indicates H_2O in CD_3OD

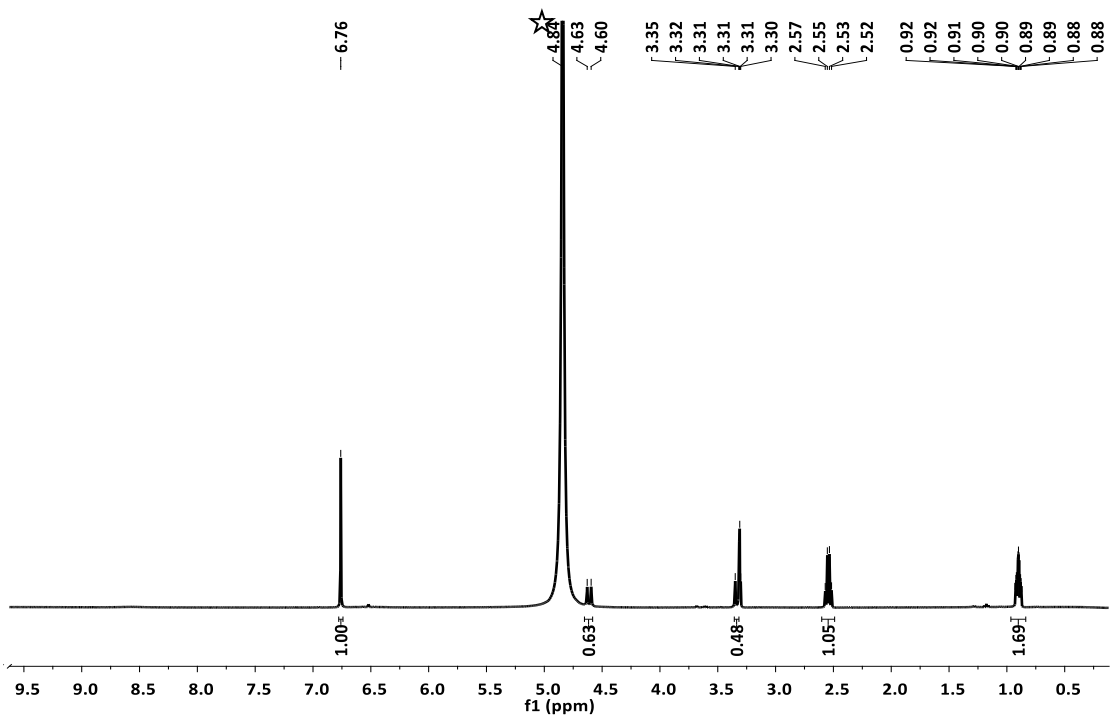


Figure 4.20.[1]H NMR Spectra of 1and **2**.PF_6 in CD_3OD, star peak indicates H_2O in CD_3OD

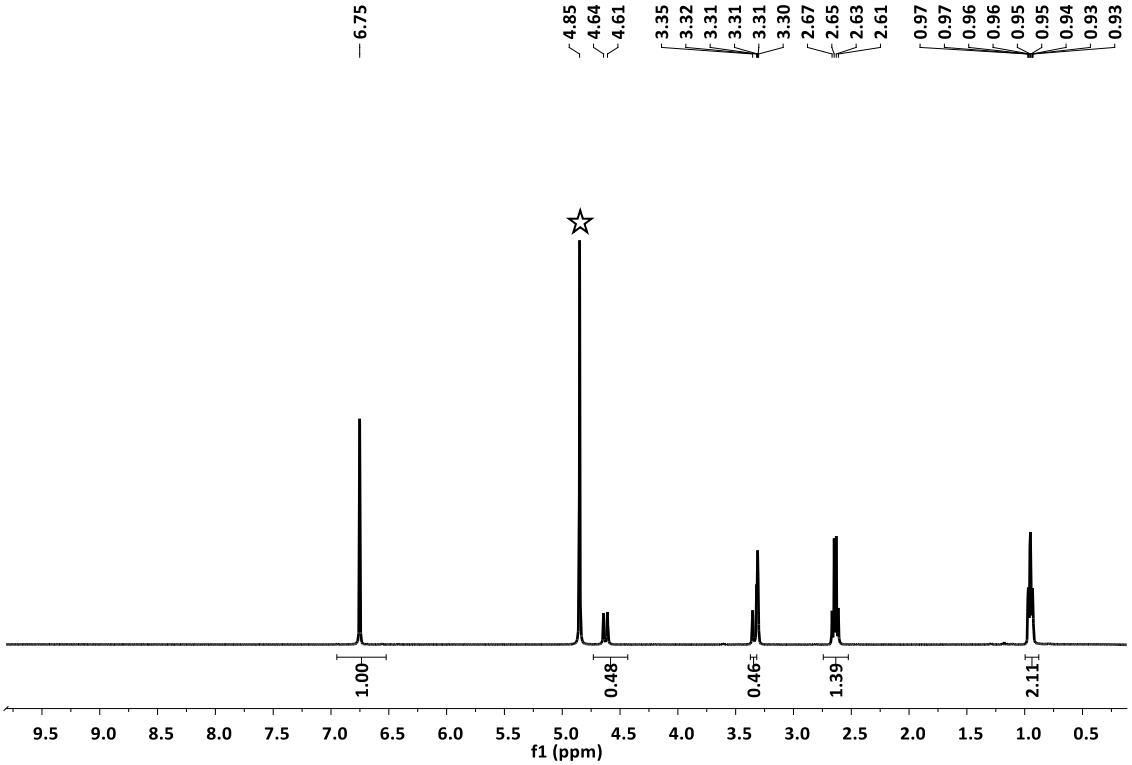


Figure 4.21.[1]H NMR Spectra of 1and **2**.PF_6 (1:1) in CD_3OD, star peak indicates H_2O in CD_3OD

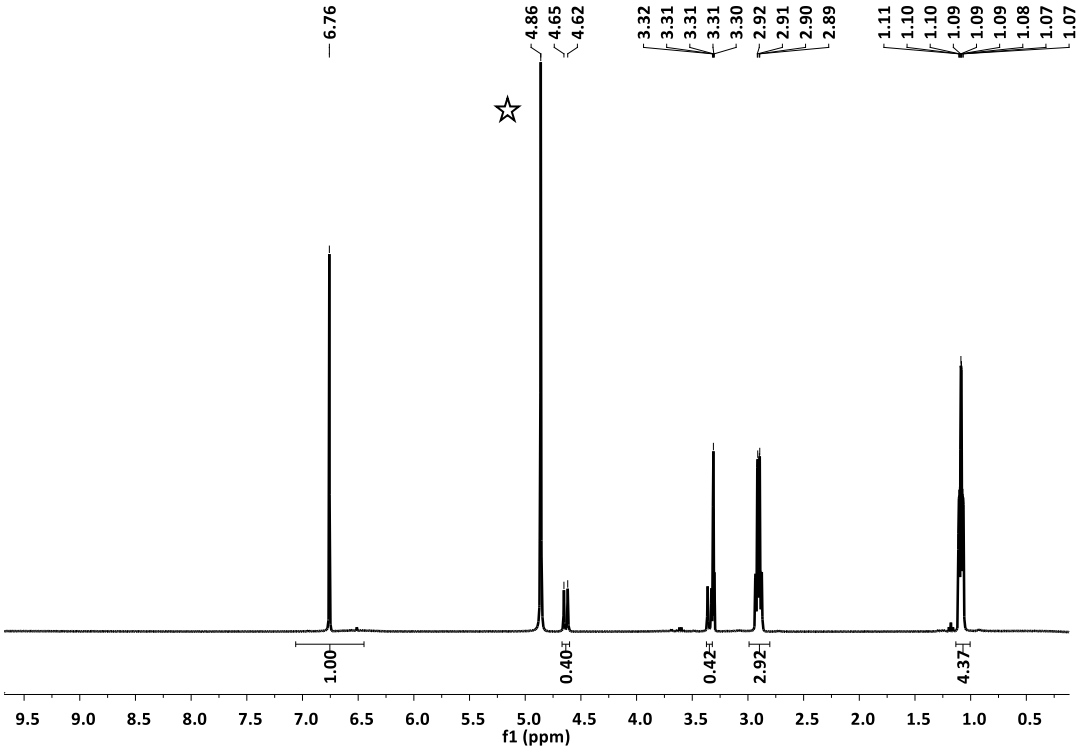


Figure 4.22.^{1}H NMR Spectra of 1and **2**.PF_6 (1:2) in CD_3OD, star peak indicates H_2O in CD_3OD

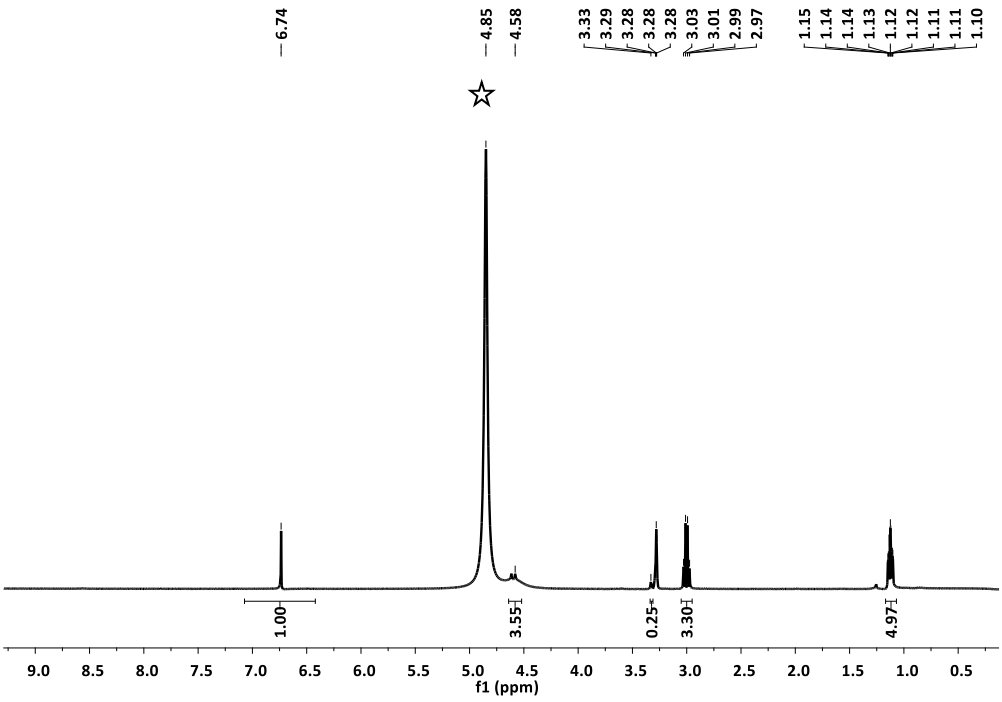


Figure 4.23.^{1}H NMR Spectra of 1and **2**.PF_6 (1:3) in CD_3OD, star peak indicates H_2O in CD_3OD

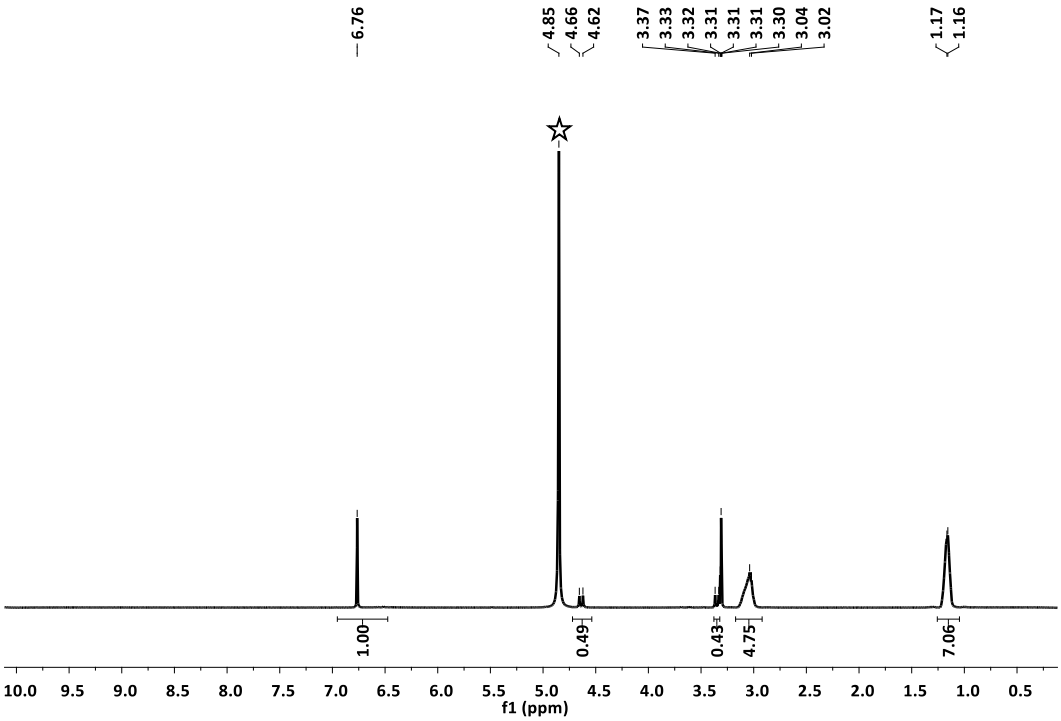


Figure 4.24. ^{1}H NMR Spectra of 1and **2**.PF_6 (1:10) in CD_3OD, star peak indicates H_2O in CD_3OD

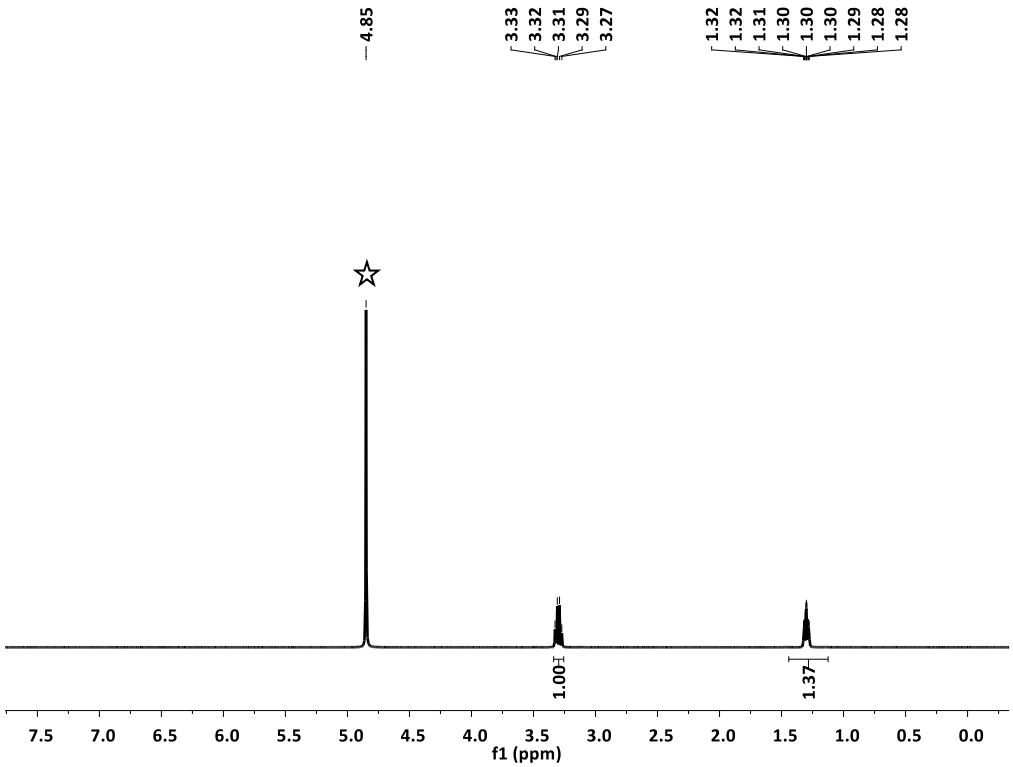


Figure 4.25. ^{1}H NMR Spectra of **2**.PF_6 in CD_3OD, star peak indicates H_2O in CD_3OD

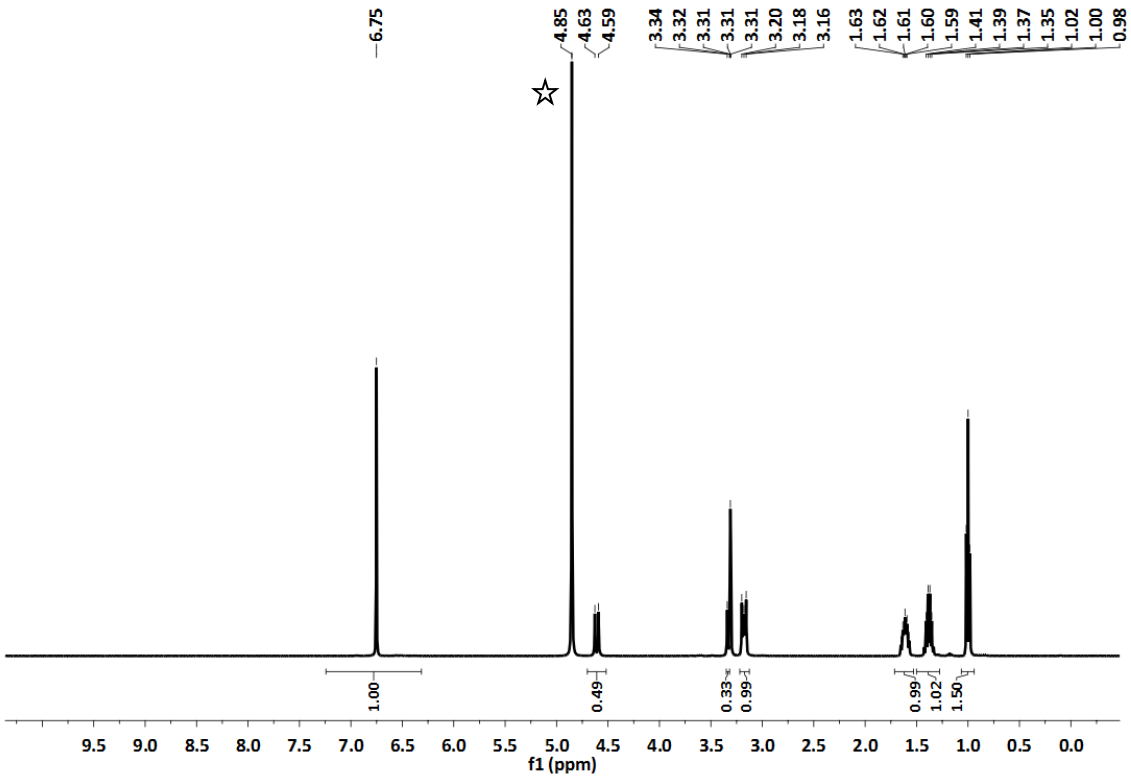


Figure 4.26.[1]H NMR Spectra of**1**and **3**.Br in CD_3OD, star peak indicates H_2O in CD_3OD

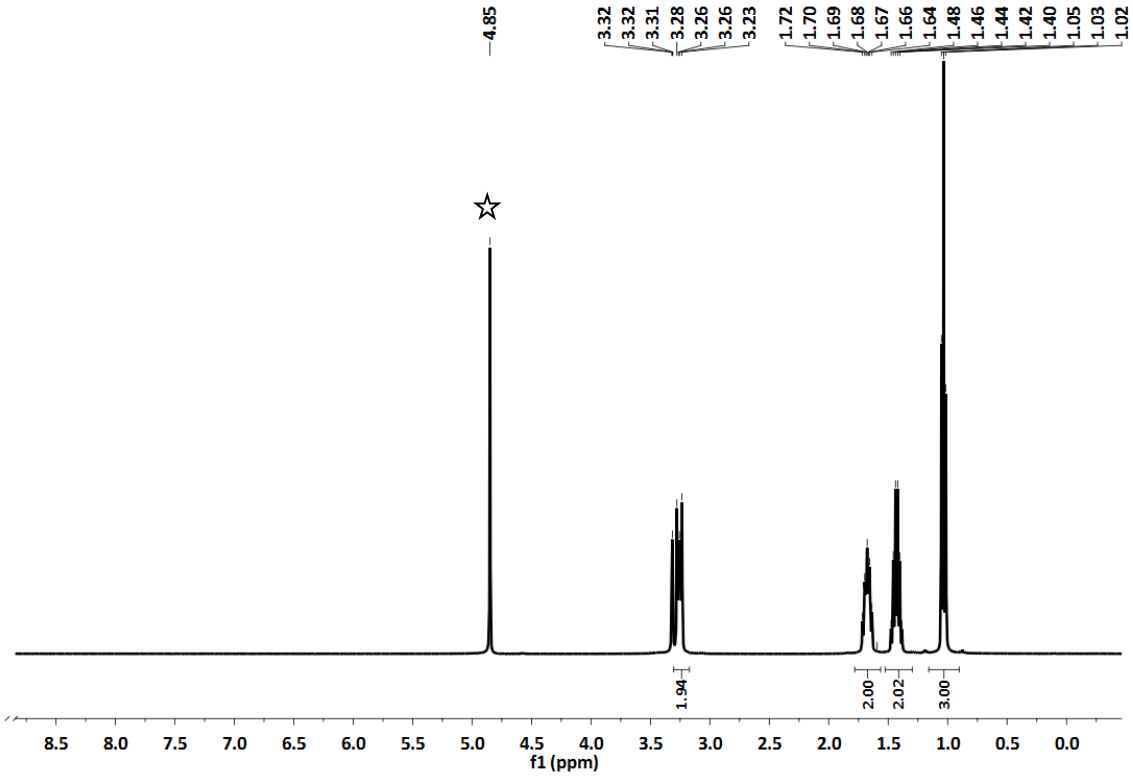


Figure 4.27. [1]H NMR Spectra of **3**.Br in CD_3OD, star peak indicates H_2O in CD_3OD

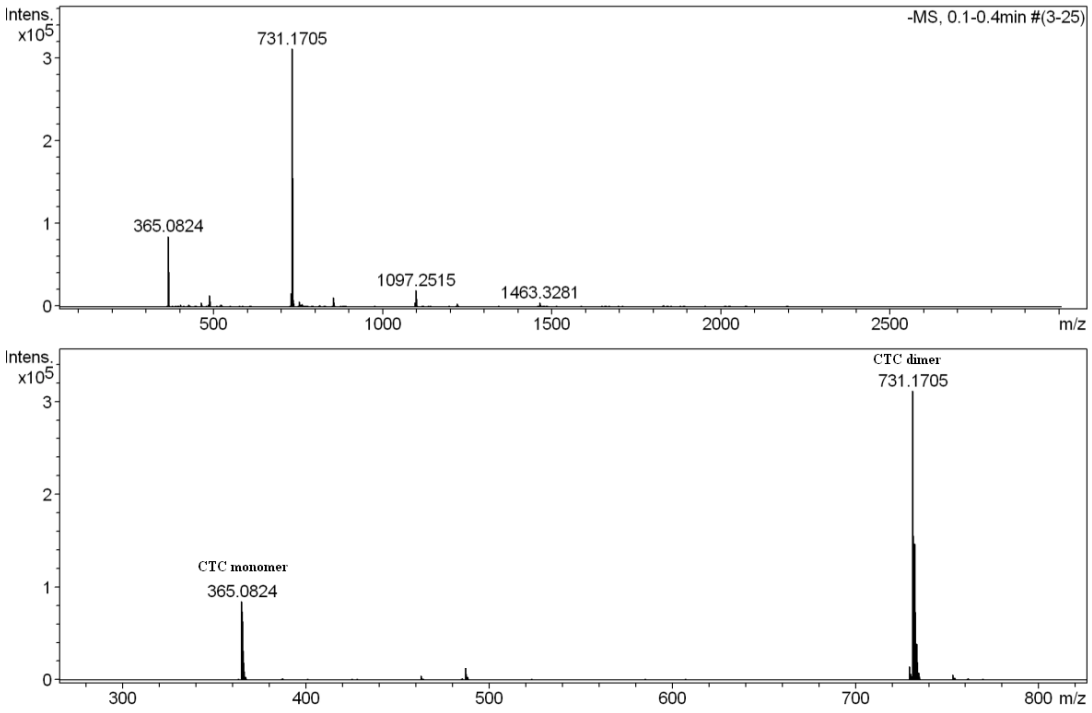


Figure 4.28. ESI-Mass Spectra of (-ve Mode) CTC in Methanol

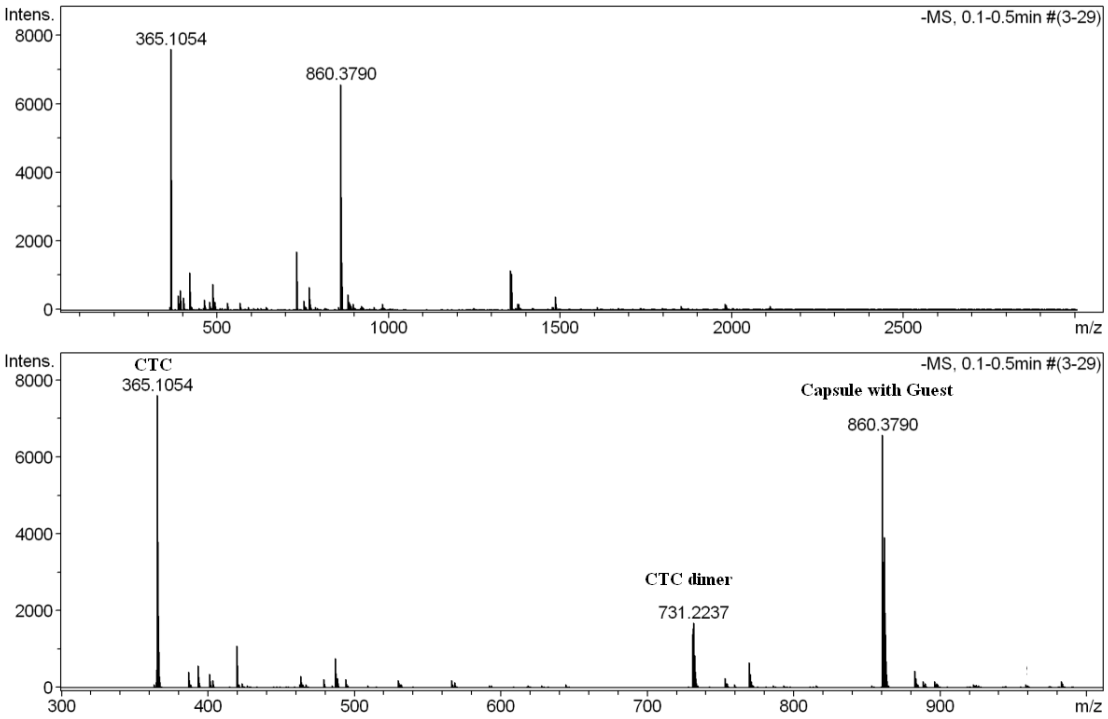
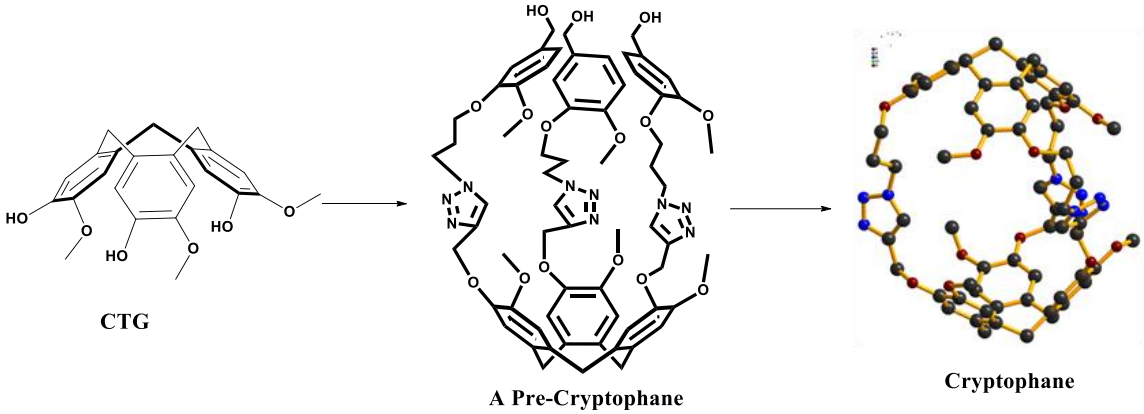


Figure 4.29. ESI-Mass Spectra of (-ve Mode) CTC with **2**.PF_6 in Methanol

CHAPTER 5

A Triazole bridged Cryptophane

5.1 ABSTRACT:

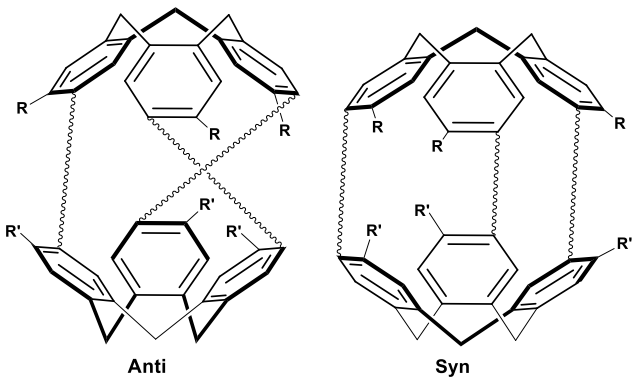


Cyclotriguaiacylene(CTG), a derivative of CTV, has three methoxy and three phenolic oxygen atoms, the phenol groups can be easily modified for preparing molecular cryptophanes. Many reports describe two units CTG to form cryptophanes with suitable spacer between them. Cryptophanes were used for different applications such as entrapping small organic, inorganic molecules as guests. The ability of cryptophanes to bind noble gas Xe as guest makes it important for biomedical applications. Two different methodologies, direct method and template method are used to synthesize cryptophanes. We used the later strategy by attaching azide functionality to Propargyl-CTG unit which leads to, three triazole bridged rings attached to CTG. This molecule is cyclised using a lewis acid, $BF_3.(OEt_2)$ forming of two diastereomeric cryptophanes. This chapter describes in detail the synthesis of the above said bridged cryptophanes with the aid of click reaction.

5.2 Introduction:

Supramolecular capsules connected via covalent bonds having enclosed cavities, that can entrap smaller molecules or ions is a fascinating area of research.[1-3] This cavity is different from bulk solvent and behave differently towards reactions. Complexes that permanently imprisoned guests are called carcerands and those which let the guest out under suitable condition are called hemicarcerands. These are briefly discussed widely in chapter **1.2.1.** In chapter **1.2.2** we already introduced the cryptophanes, a covalently linked molecular capsules. In this chapter, synthesis of cryptophanes by different methods and their applications in various field will be discussed.

The cyclotriveratrylene scaffold is one of the fundamental building blocks for molecular capsules besides calixarene, Resorcinarene, Pyrogallarene. The cyclotriveratrylene and its demthylated analogue are shown to form different molecular capsules with different non-covalent binding forces which has been discussed in chapters**2-4**. Two cyclotriveratrylene or modified cyclotriveratrylene, joined in face to face manner with suitable bridges between them are called cryptophanes. Different cryptophanes has been synthesized by varying the functional groups, bridging length and the bridging groups.If three bridges between the CTV units are same and R=R' then cryptophanes may have either syn or anti conformations shown in (**Scheme 5.1.**)

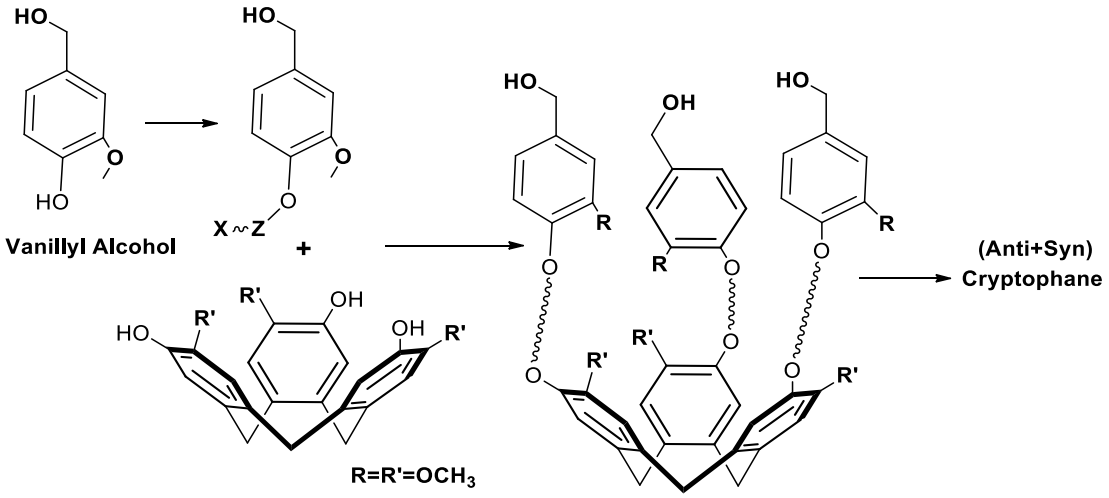


Scheme 5.1. The Syn and Anti isomers of cryptophane

5.2.1Nomenclature of Cryptophanes

All the cryptophanes that have been described to date are relatively simple, they can be represented with a general formula O-(Z)-O represents the identical bridges. Z may be any functional group viz. (CH_2,), CH,-CH=CHXH, or CH,-C=C-CH,);in most of them, R = R', and the anti and syn isomers have been identified; there also exists one pair of C3-anti and C3-syn isomers, with R and R' are different. For the designation of these compounds, researchers have provisionally adopted a system based principally on the chronology of their description. For example the first member of the family was thus named cryptophane-A, followed by B, C etc. Stereo chemical description can be added to the generic name wherever necessary for example D3-cryptophane-E, where D3 represents the symmetry.[4]

5.2.2 Synthetic methods used for cryptophanes

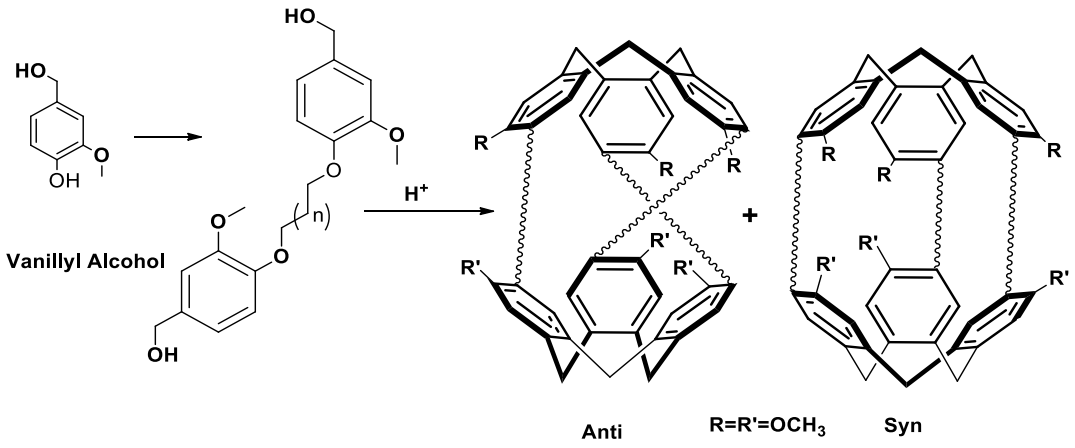


Scheme 5.2. Template directed approach for synthesizingCryptophanes

Two synthetic methodologies have been proposed for synthesis of cryptophanes. Template directed approach and direct approach. Among them, the direct approach requires less number of steps. In both of the approaches vanillyl alcohol is the starting material. In template directed approach (**Scheme5.2.)** vanillyl alcohol is converted into

cyclotriveratrylene(CTV), to which three more vanillyl alcohol units are attached. This on cyclization under suitable acidic conditions, leads to cryptophanes with D_3, C_{3h}, orC_3 conformations. In the initial stage of the cryptophanes research, researchers used mineral acids for cyclization but later different methods have been invented. Acids such as acetic acid, formic acid, $HClO_4$ were used. In recent times Lewis acids viz. P_2O_5, $Sc(OTf)_3$and ionic liquids was also shown to be efficient in cyclising.[5-9]

The anti/syn ratio in this method depends on the length and structure of the bridges. Even number of bridges preferentially cyclise to the anti-isomer, odd number of bridges preferentially cyclise to the syn-isomer. In direct method, vanillyl alcohol is dimerised into Bis(vanillyl alcohol), which is then trimerized intermolecularly. This results in cryptophanes with D3 and C3h conformations (**Scheme5.3.)**. In this method stereochemical outcome of the cryptophanesis reverse to that of previous method i.e. even number of bridges preferentially cyclise to the synisomer, odd number of bridges preferentially cyclise to the antiisomer.



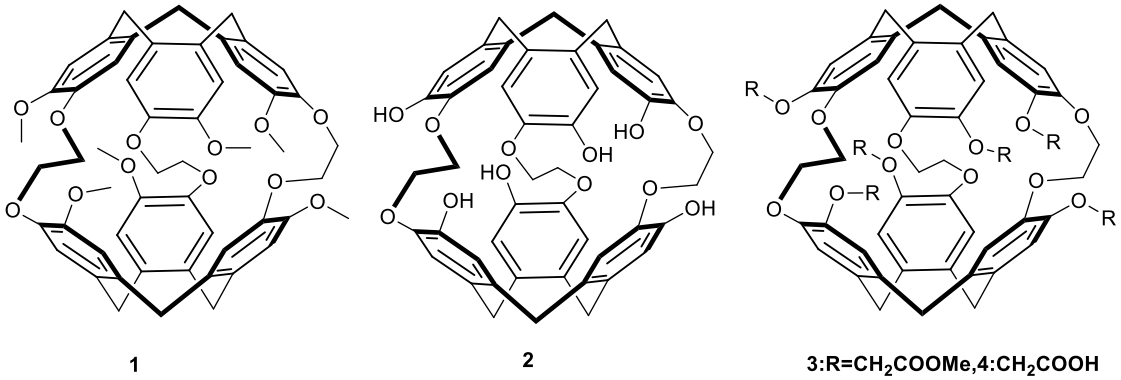
Scheme 5.3. Two step approach for synthesizingCryptophanes

5.2.3Literature survey of cryptophanes

The first synthesis of cryptophanes was done by A. Collet and co-workers in early 1980's.They reported cryptophanes of various lengths,[8] and tested for

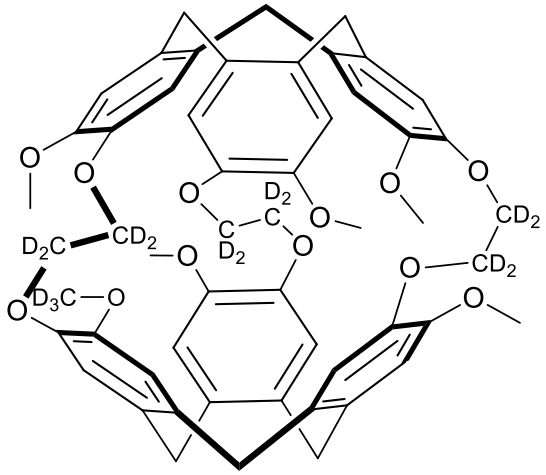
differentapplications.[10,11,12] Complexing with the solvent molecules, and with different small molecules like CHFClBr, and for chiral resolution were reported.

By replacing the peripheral substituent's in the cryptophane (**1**)different functional transformations were reported by Andre Collet and co-workers. Demthylating methoxy groups resulted in a hexaphenol cryptophane-A(**2**).The hexaphenol has been treated with methylbromoacetate resulting hexaester (**3**)and hydrolyzed to the hexaacidcryptophane-A(**4**)which is the first water-soluble(**Scheme 5.4.**)cryptophane.[13]



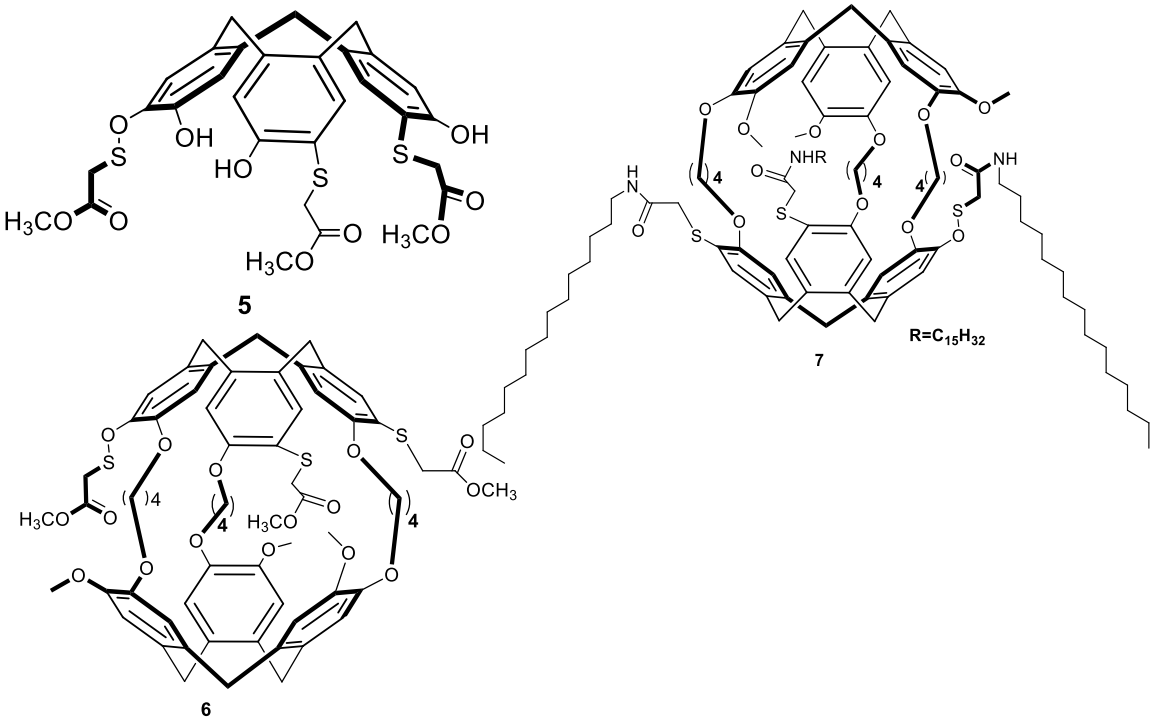
Scheme5.4. Functional group transformations for obtaining first water soluble cryptophane

Sulphur containing cryptophanes have been reported by Garciaet al. where the six OMe groups have been replaced with six SMe. They are called thio-cryptophanes which has shown the similar binding properties that was reported with cryptopahnes. [14]Brotin and co-workers have synthesized deuterium labelled cryptophanes(**Scheme 5.5.)** by template method for studying the environmental effects on Xenon chemical shift using ^{129}Xe NMR spectroscopy. [15]



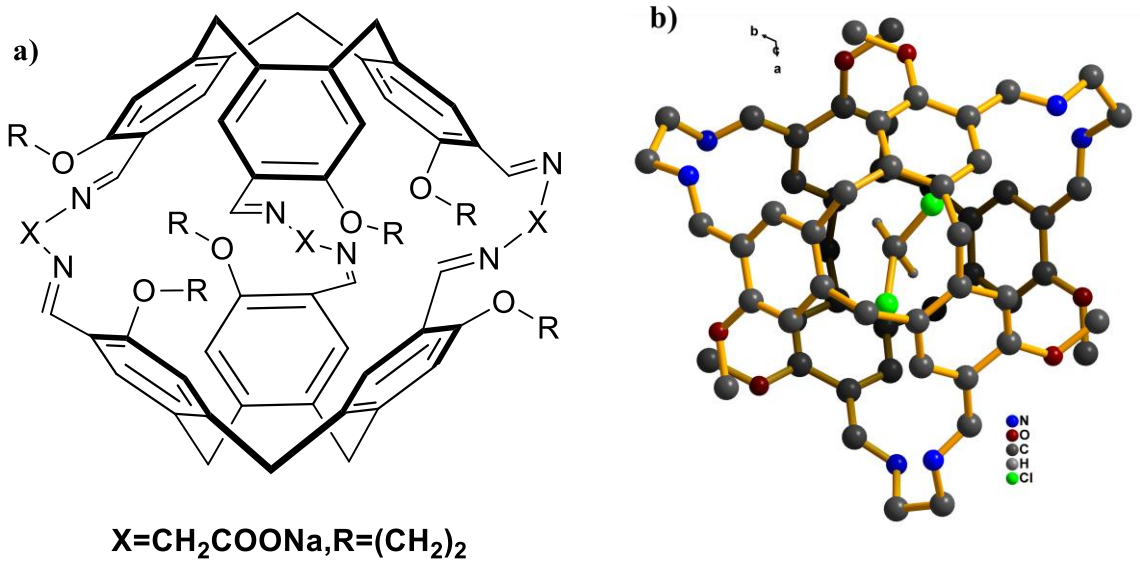
Scheme 5.5. Schematic representation ofDeuteratedCryptophane

Amphiphilic cryptophanes have been synthesized by importing long alkyl chains to the periphery of these bowl-shaped molecules.[16] In 2005,Jean-Pierre Dutasta and co-workers have reported anamphiphilic cryptophane which forms thin films in gas-liquid interface.[17] They have synthesized a tris-thioester substituted cyclotriveratrylene(**5**) which in turn cyclised to a cryptophane (**6**), on attachment of long alkyl chains by replacing ester groups gave an amphiphilic cryptophane(**7**), shown in (**Scheme 5.6.**)



Scheme 5.6. Precursors used for synthesizingAmphiphiliccryptophanes (**5&6**)and target Amphiphiliccryptophane(**7**)

In 2011 Ralf Warmuth group synthesized a dynamic hexaimine cryptophane which is soluble in water. In this template synthesis, two triformylcyclotribenzylenes and three diamino linkers in the presence of a suitable template formed a cryptophane and found $CHCl_3$to be the best template for a series.[18] They further increased the size of the cryptophane by increasing the bridge length to 1,4-diaminobutane(**Scheme5.7.),**p-xylylenediamine between the two cyclotribenzylenes and they further found that norbornene, cycloheptene act as templates and are encapsulated inside.



Scheme5.7.a) Schematic representation of water soluble cryptophanes**b)** Crystal structure of cryptophane when $X=CH_2CH_2$ $R=CH_3$

When the bridging chain length ($O-CH_2-O$) between the two CTV units contains more than 5 methylene groups, inversion of one of the CTV unit occurs. This gives inverted in-outcryptophane. In other words an imploded cryptophane has been reported by Holman and co-workers.[19] They successfully isolated the imploded cryptophane by vacating the

guest molecule from the cryptophanes cavity. In this form, one CTV of the ring was in the cone facing towards outside and the other CTV ring adopted a flexible saddle conformation which was confirmed by ^{1}H NMR spectroscopy. The in-out conformation and out-out conformation was noted to be in reversible condition without guest molecule and with guest molecule respectively(**Figure.5.1.**).

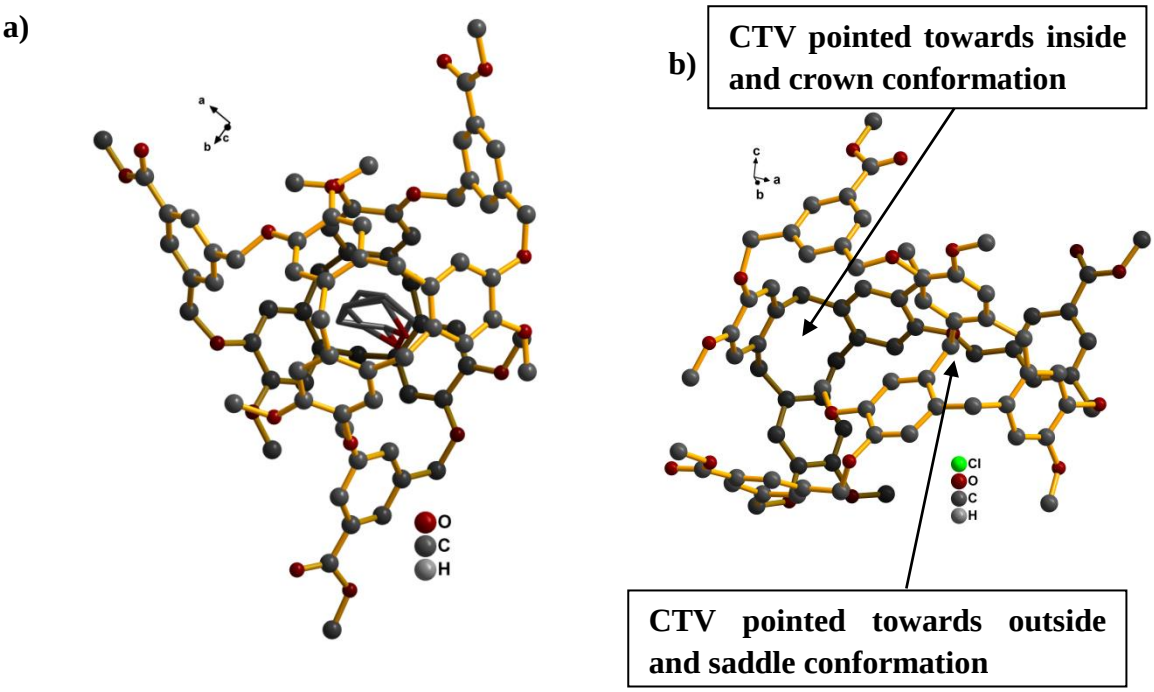
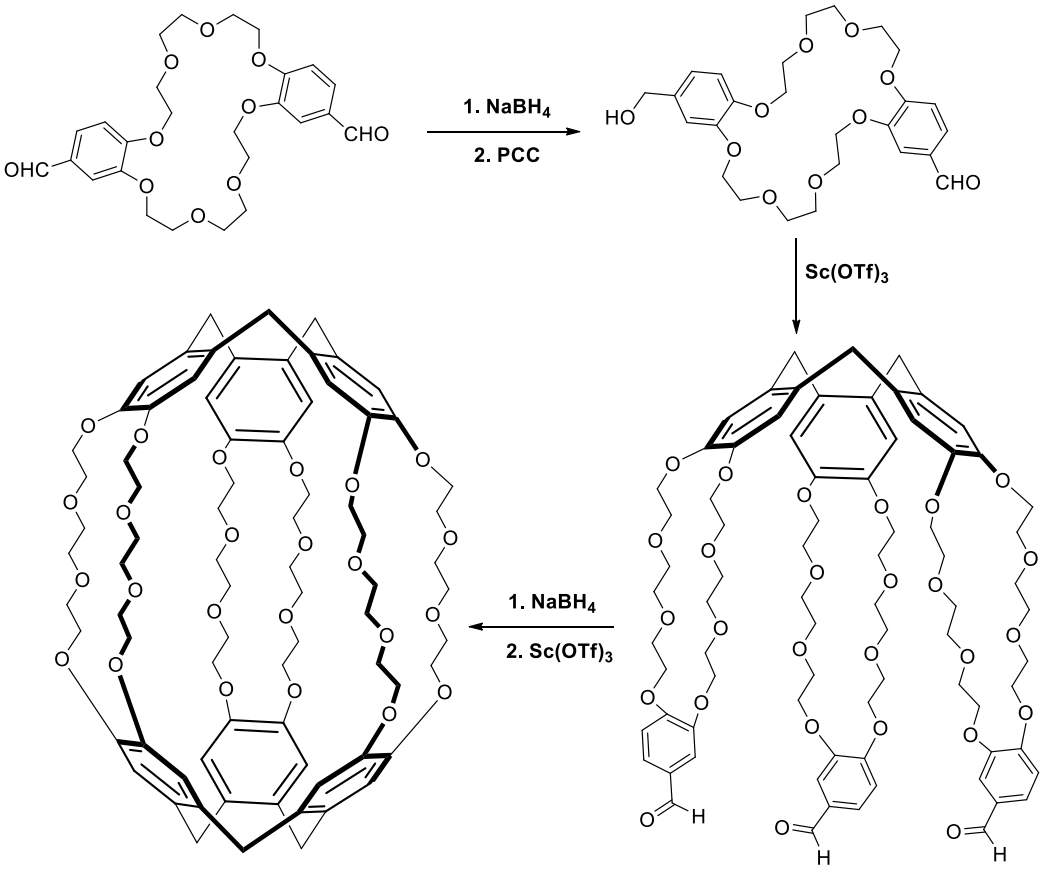


Figure.5.1.a) Crystal structure of the cryptophane, THF molecule is shown in wire frame b) Imploded cryptophane, solvent molecules and hydrogen atoms are removed for clarity

5.2.4 Hemicarceplex formation by cyclotriveratrylene

All the cryptophanes which were reported in the previous section are based on partially demethylated version of CTV called as cyclotriguaiacylene (CTG) where in three methoxy groups are readily open for the guest moleucle movement. In this section we will discuss cyclotriveratrylene-based molecular cages consctucted by covalent linkage.In these cases, guest moleucles are confined more strongly than in the traditional cryptophanes.In 2009,Sheng-Hsien Chiu and co-workers have reported a cyclotriveratrylene based hemicarceplex, wherein they synthesized a molecular container



Scheme5.8. Synthetic scheme applied to for the CTV-based molecular container.

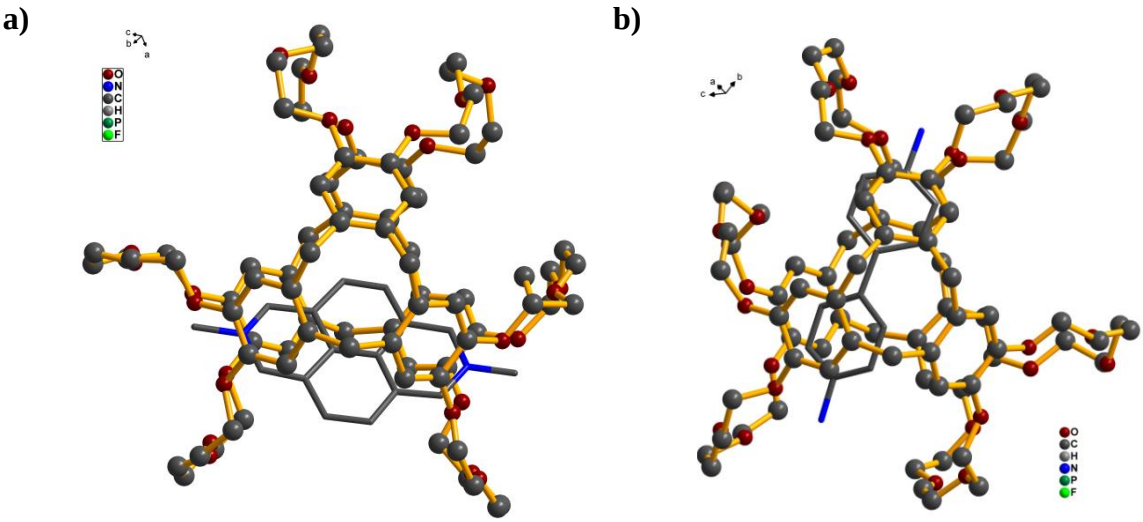


Figure5.2. Crystal structure showing different binding modes of guest molecules a)DMDAP b) BPBD

with CTV, by attaching ethylene glycol chains to CTV by templating method **(Scheme5.8.)** and cyclising it using $Sc(OTf)_3$.[20] They further proved that two different

guest molecules (DMDAP=Dimethyl diazopyrenium,BPBD = 4, 4'-biphenylbisdiazonium) were binding in the confined space with different binding modes (**Figure5.2.)**.

The same group synthesized a hemicarceplex by replacing the ethylene glycol units with long alkyl chains (n=6, 8), by implementing the similar strategy which they reported earlier (**Scheme 5.8.)**. The hemicarceplex used as chromatography tool by separating 99% pure C_{70} from the fullerene extracts(**Figure5.3.**) characterized by HPLC.[21]

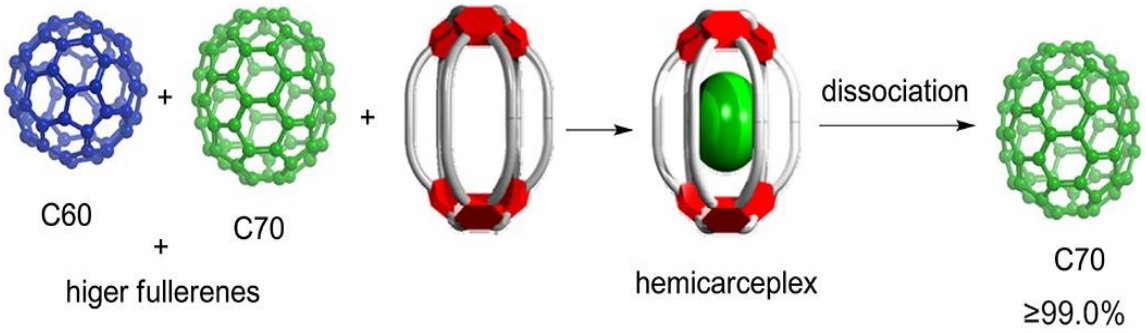
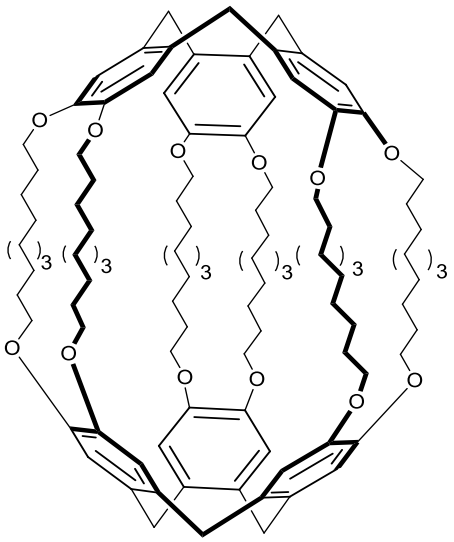


Figure5.3. Schematic representation of separating C_{70} from mixture of fullerenes using a hemicarceplex

Their report of a hemicarceplex in 2014, with reduced number of bridging alkyl chains couldincarcerate C_{60}. Partly modified the hemicarceplex by adding $[(\eta^5\text{-}C_5Me_5)Ru^{III}]$ which has shown increment in solubility of fullerene(**Figure5.4.**) in polar solvents and increment in reduction potentials.[22]



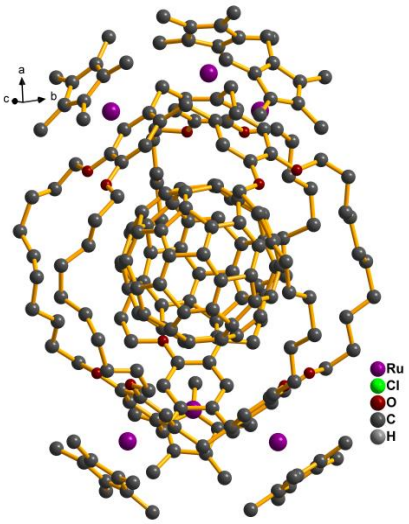
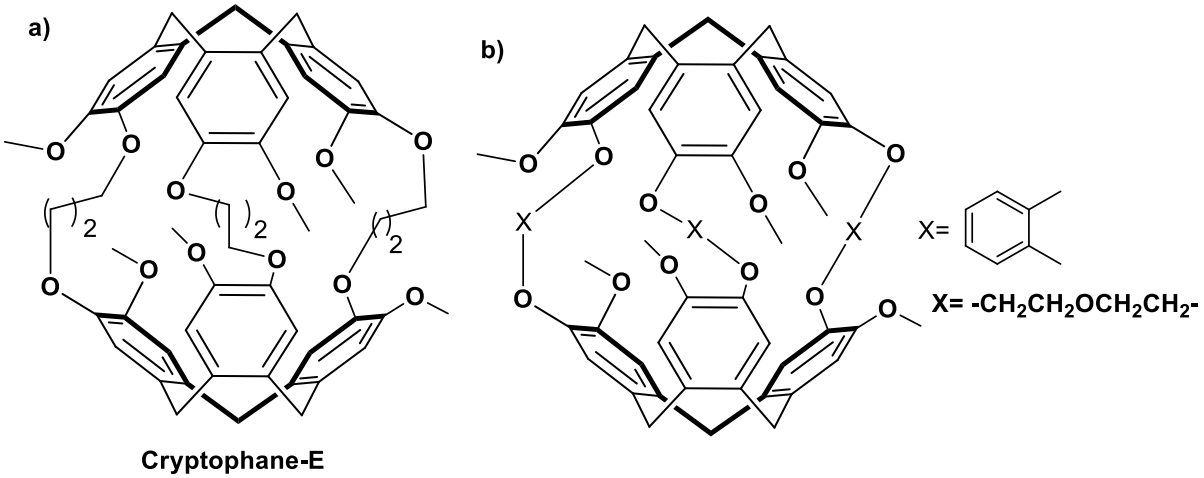


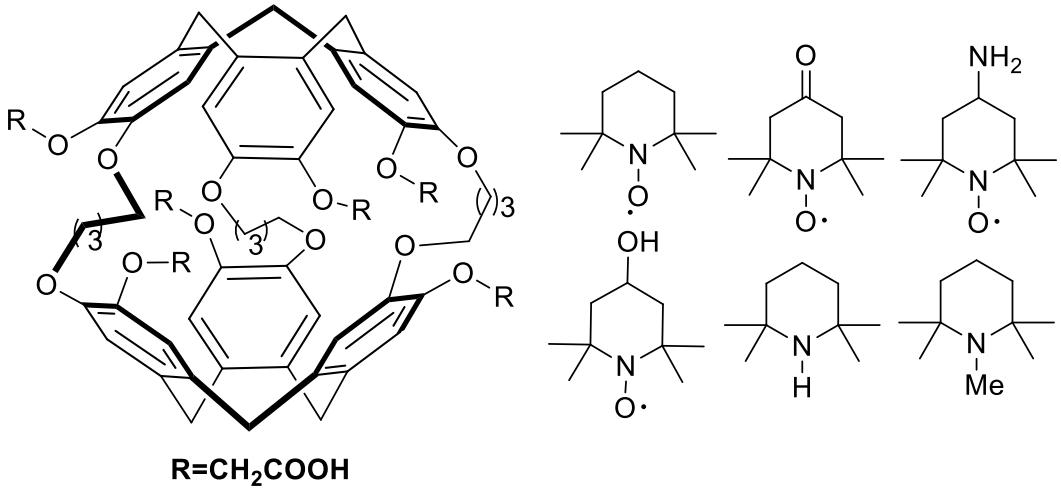
Figure5.4. Chemical structure of hemicarceplex which binds $C_{60}$and crystal structure of entrapment of C_{60} in modified hemicarceplex hydrogen atoms, bonds between Ru-C are removed for clarity.

5.2.5 Applications of cryptophanes: The first ever reported applications of the cryptophanes are in binding of small molecules, the capability of the guest depends on the size of the guest molecule and portals from which guest molecule enters and leaves.[12] The guest to cavity size ratiodecides the effectiveness of binding.[23] Andre Collet and co-workers have investigated guest molecules (CH_2Cl_2, $CHCl_3$, and CCl_4) in the cavity of cryptophane-E (**Scheme 5.9.**)by molecular dynamics and free-energy perturbation simulationsin the gas phase and in chloroform solution, and found that $CHCl_3$ is best fit for cryptophane-E among all.[24] Akabori and co-workers showed that the syn and anti isomers of xylene-bridged cryptophane can discriminate between the guest molecules (2,2-dimethylbutane, 3-methylpentane, 3,3-di- methylpentane and 3-ethylpentane) where syn isomer can bind the guest but not the anti one. On the other hand both syn and anti isomers of diethyleneoxy-bridged cryptophane can bind the guest molecules.[25]

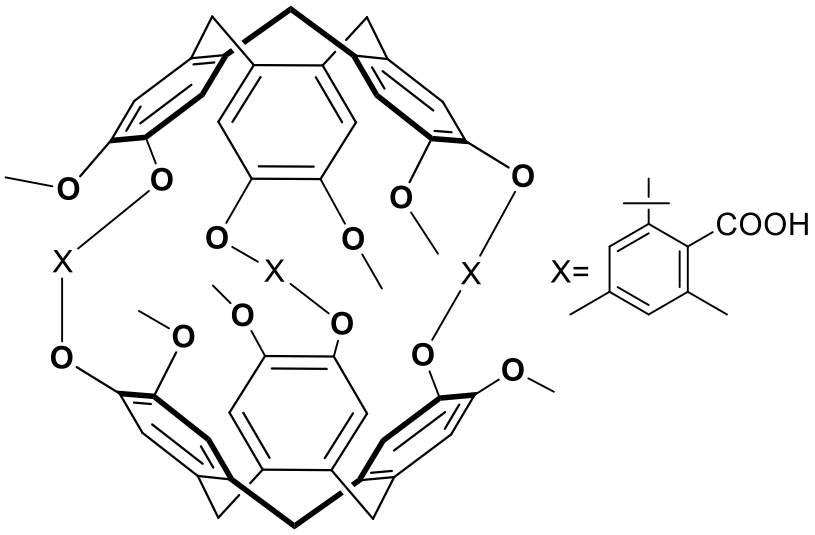


Scheme 5.9.a) Schematic representation of cryptophane-E **b)**Xylyl bridged cryptophane, diethyleneoxy-brdigedcryptophane.

Garel and co-workers reported synthesized cryptophane**123**shown inScheme 5.10., and showed that it can bind reversibly the aminoxy radicals in water which was studied by EPR.[26]Akabori and co-workers showed that cryptophane(**Scheme5.9.b**)when $X=CH_2CH_2OCH_2CH_2$, can bind to different alkali cations and alkyl ammonium cations. They further proved that cryptophane can be used to extract $(CH3)4N^+$ from water solution, the extraction efficiency of the cryptophane towards different cations follows the order $(CH_4)N^+ > (CH_3)_3NH^+ > (CH_3)_2NH^+ > CH_3NH_3^+ > NH_4^+$.[27]



Scheme 5.10. Chemical structure of cryptophane**123** and the radicals studied for the inclusion complexes.



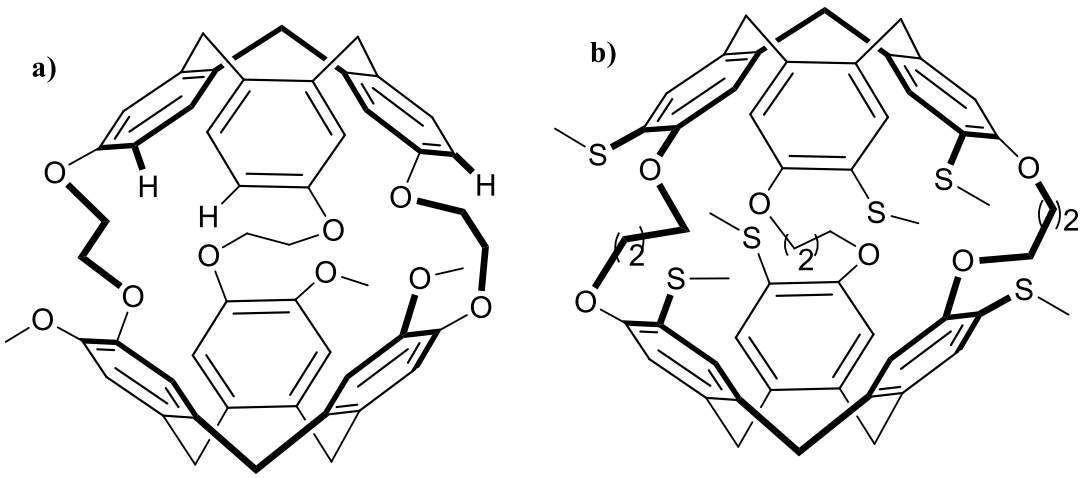
Scheme 5.11. Chemical structure of cryptophane that used for liquid-liquid extraction of the cations.

In 2006, Weber and co-workers reported a cryptophane with endo-carboxylic acid functional groups which binds to the Ca^{+2}, Sr^{+2} the extraction order is following Ca^{2+}~ Sr^{2+} >Mg^{2+}> Ba^{2+}> Cs^{+}> Na^{+}. Because of the strong attraction forces between carboxylic anion and Ca^{2+} the affinity of the cryptophane(**Scheme 5.11.**) for Ca^{2+} is more.[28] They further proved that lanthanide ions, Yb^{3+} and Eu^{3+}, are also efficiently extractedby cryptophane. The pre-organized structure of the endo-carboxylic acid in the cryptophane attributed to the high binding efficiency of the cations.

5.2.6 Cryptophanes for chiral resolution

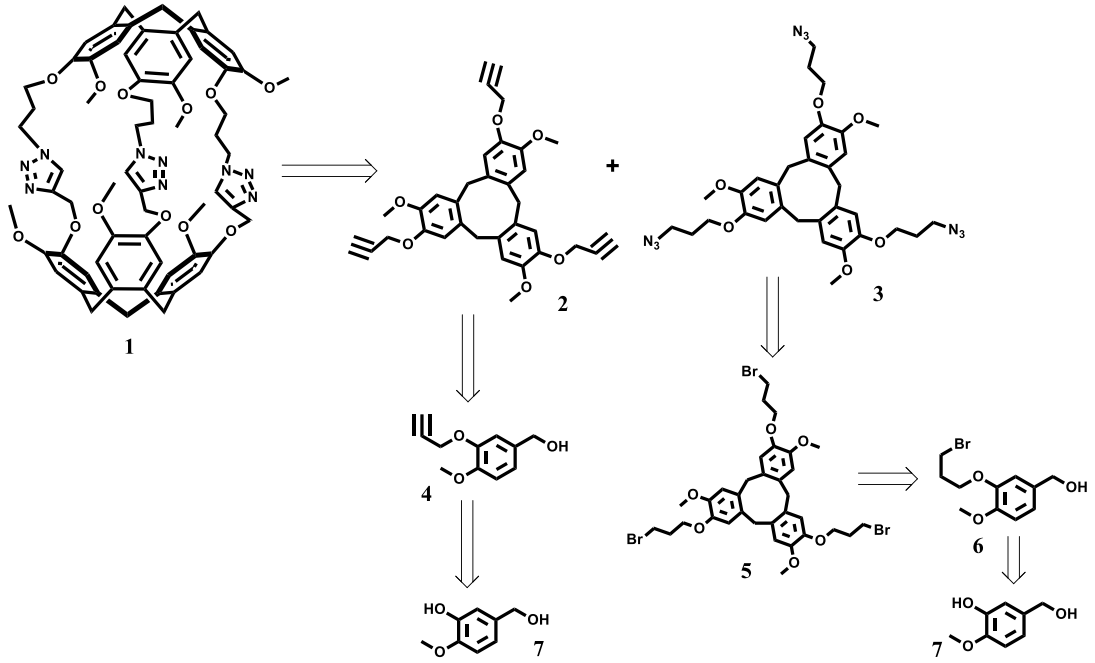
Cryptophanes were first designed for chiral resolution of racemic molecules; a chiral version of cryptophane**(Scheme5.12.a)** has been synthesized by Collet and co-workers in 1985to separate the two enantiomers of small chiral molecule CHFClBr.[29] From then on different chiral cryptophanes have been synthesized depends upon on the chiral guest molecule size, the enantio-enrichedcryptophane(**Scheme5.12.b)** was used to measure the enantio purity of CHFClI.[30]

In 2011, Thierry Brotin and co-workers reported chiral propylene oxide complexation enantio-selectively in enantio-pure water soluble cryptophane.[31] Cryptophanes being chiral, because of the axial and equatorial bridged hydrogen's, this can separate as enantiopure compounds. Each enantiomer will have different binding capacity for different guest molecules, because of the orientation. This is how cryptopahnes are used for chiral resolution. Because of the increasing demand for the chiral cryptophanes different methods have been developed by the researchers to synthesize optically active cryptophanes.[32-37]



Scheme5.12. Chemical structure of enantio purecryptophane that used for chiral discrimination

5.3Results and discussions

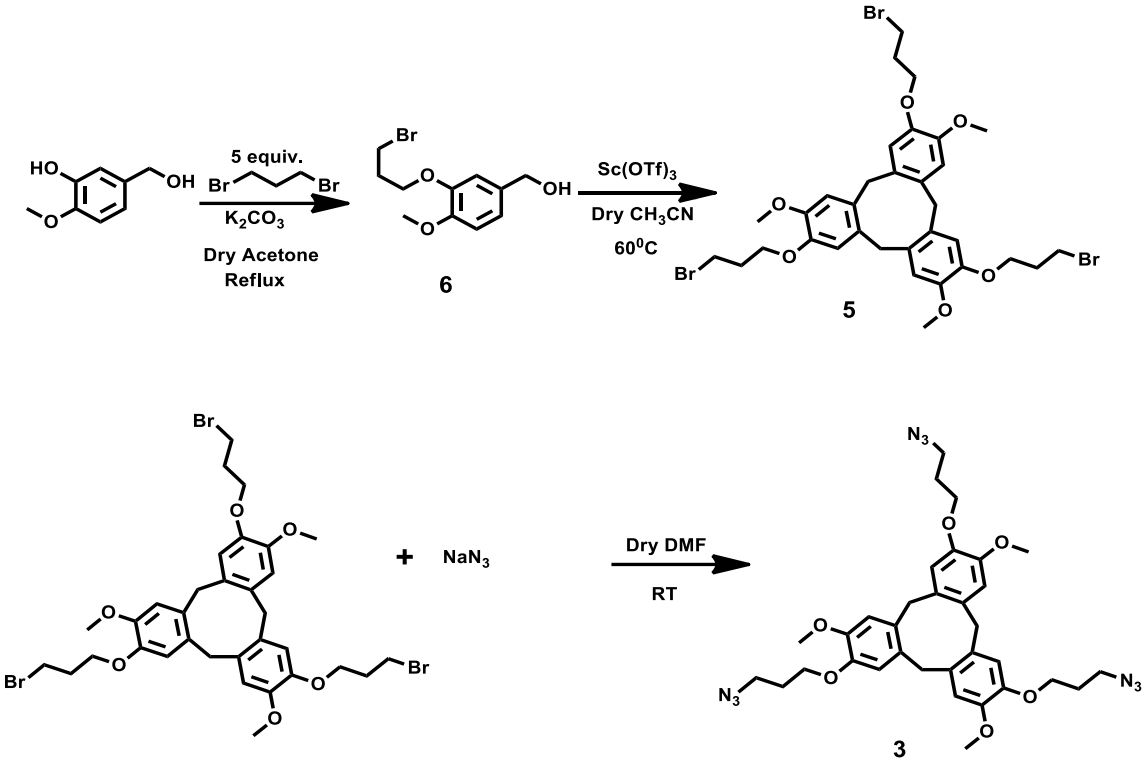


Scheme 5.13. Retrosynthetic analysis of the target moleucle

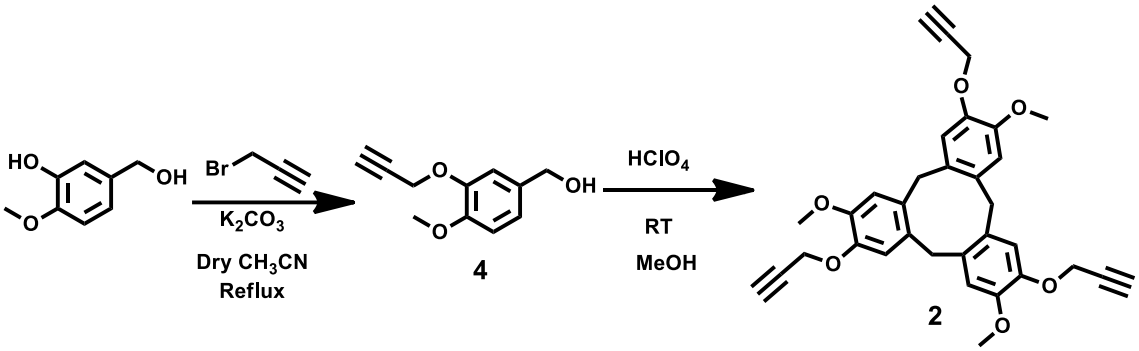
5.3.1 Direct method

The aim of this project is to synthesize a triazole bridged covalent capsule in otherwords called as triazole bridged-cryptophane. To synthesize our target molecule we choose the route, which is shown in the retrosynthetic analysis(**Scheme 5.13.**).As shown in the scheme, to synthesize a triazole cryptophane we thought of using the well known Click reaction. To construct triazole cryptophane, we need cyclotriguaiacylenedecorated withrigid propargyl units (**2**) on one side, on the other side we need the complementary azide groups stitched to Cyclotriguaiacylene(**3**).

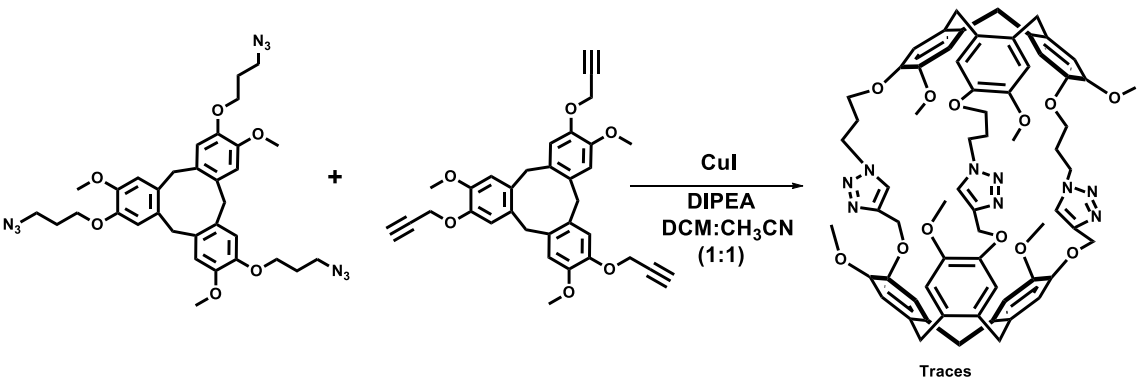
The propargyl chains can be tailored to cyclotriguaiacylene by two step synthesis starting from commercially available vanillyl alcohol (**7**).Vanillyl alcohol was alkylatedwith propargyl bromide by S_N2 reaction resulting in propargyl vanillyl alcohol(**4**). The alkylated vanillyl alcohol **4**was trimerized in acid catalyzed condensation reaction(**Scheme 5.14.a**) which forms cyclotriguaiacylene with rigid propargyl units at the end (**2**). Azide groups were attached to cyclotriguaiacylene in three step syntheses starting from vanillyl alcohol (**7**).We alkylated vanillyl alcohol with 1,3 dibromo propane by replacing selectively only one bromide, obtained bromo propyl vanillyl alcohol(**6**). Bromo propyl vanillyl alcohol was then trimerised using a mild Lewis acid, Scandium triflate, forming cyclotriguaiacylene with bromopropyl chains (**5**). The bromide in cyclotriguaiacylene bromopropyl chain was replaced by azide,using sodium azide in DMF, forming azido propyl cyclotriguaiacylene (**3**)as shown in scheme 5.14**.**



Scheme 5.14. Synthetic scheme for synthesing precursors (**3**)needed for cryptophane

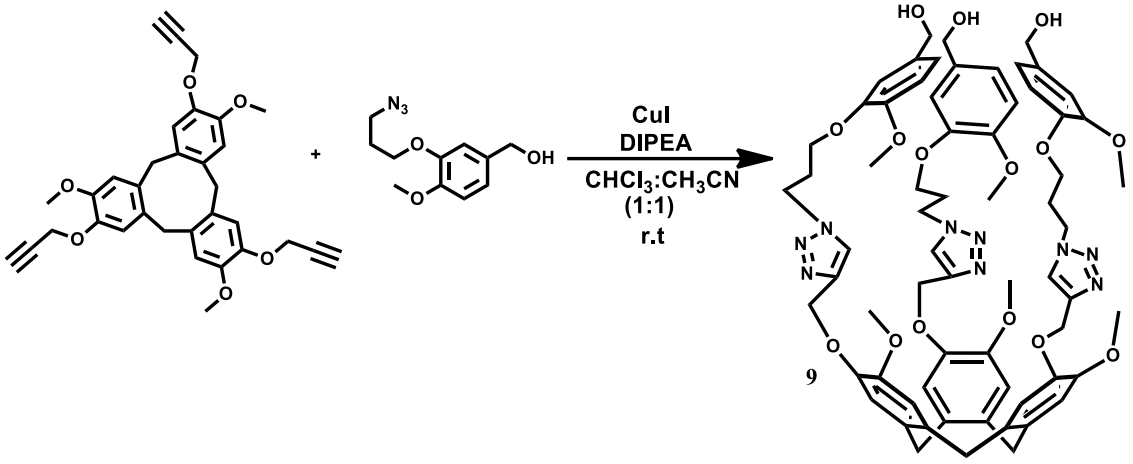


Scheme 5.14.a Synthetic scheme for synthesing precursors (**2**) needed for cryptophane

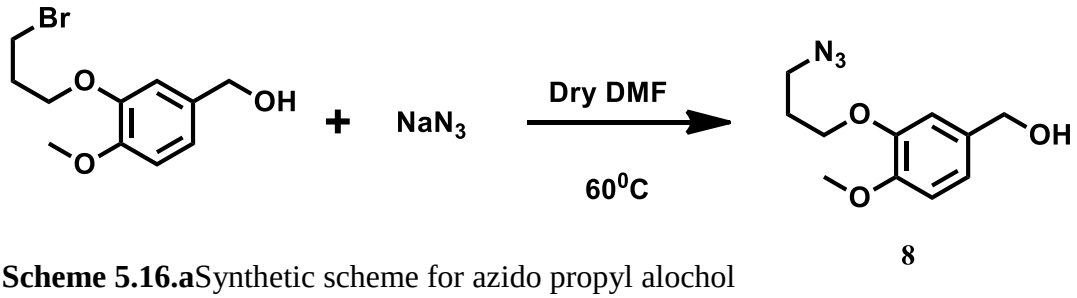


Scheme 5.15. Synthetic scheme for click reaction

After synthesizing the precursors, we utilised them to form a triazole bridged cryptophane under general click reaction conditions (**Scheme 5.15.**).The end product was a white solid, that was practically insoluble in common organic solvents. However, we could confirm the existence of product by ESI-mass spectroscopy ($[M+H]^+$ = 1180) in a mixture of acetonitrile and chloroform (1:1). The insoluble solid could be attributed to polymer formation. But pure product could not be isolated in this case.



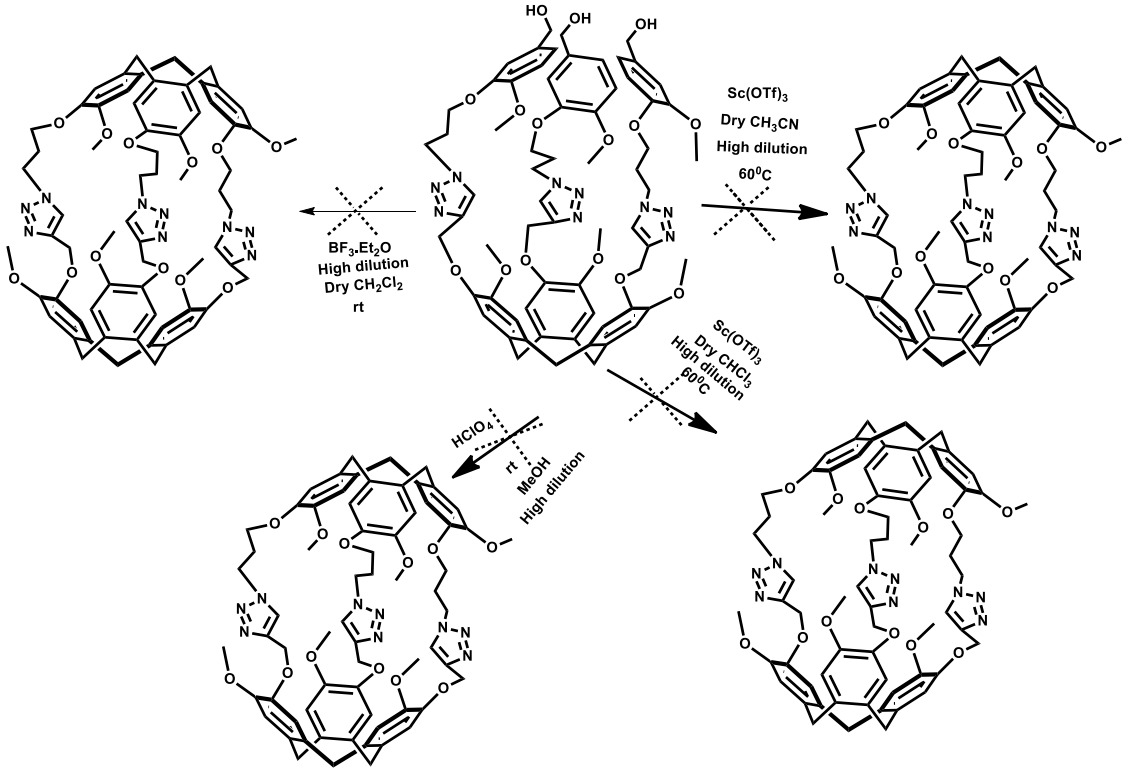
Scheme 5.16. Strategy applied for synthesis of a pre-cryptophane



Scheme 5.16.a Synthetic scheme for azido propyl alochol

5.3.2Template method: As discussed in section 5.2.2, there are two major routes for synthesis of cryptophanes. We failed to synthesize desired cryptophane using the direct method as describe in the previous section. Therefore, we turned to template method, where click reaction between propargyl cyclotriguaiacylene and azido propyl vanillyl alcohol could result in formation of a pre-cryptophane (**Scheme 5.16.)**. The precursor molecule for the template azido propyl vanillylalcohol (**8**) has been synthesized from bromopropylvanillyl alcohol (**6**) by replacing bromide with azide as shown in

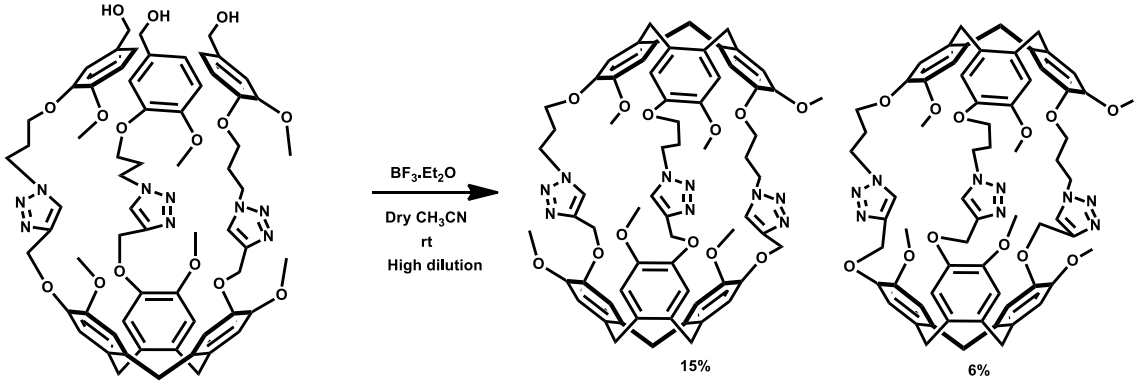
(**Scheme5.16.a).**The pre-cryptophane molecule after cyclisation should yield a triazole bridged cryptophane.



Scheme 5.17 Strategies applied to cyclise precryptophane

As discussed in section **5.2.2,** there are some known reagents which have been proven to cyclise the pre-cryptophanes. We tested all the known reagents in different conditions as showed in **Scheme 5.17,** but failed to get the desired cryptophane. While trying to alter the reaction condition, to our delight, $BF_3.Et_2O$in CH_3CN as solvent, we could successfully cyclise the pre-cryptophane to target cryptophane as shown by ESI MS. However, there were two close spots in TLC which gave same mass spectra,but their NMR spectra were different. These productswere there after isolated by repeated column chromatography (2% MeOHin $CHCl_3$) and analysed spectroscopically. The two close spot could be assigned to two diastereomers formed in the cyclisation step. This agrees

well with earlier reports. We were able to separate the two diastereomers and one of them;namely the anti-isomer was characterized using single crystal analysis.



Scheme 5.18. Strategy applied for synthesis of cryptophane and the two isolated diastereomers

5.3.3 Single crystal analysis of the anti-cryptophane

The single crystals suitable for X-ray diffraction were grown by dissolving 5mg of the compound in 10 mL $CHCl_3$ and was then heated to $60^{O}C$ for 30 min. It was then kept undisturbed. Crystals suitable for X-ray analysis could be found in few days.

Important Crystal parameter for **1**: $C_{69}H_{72}Cl_9N_9O_{12}$, Crystal dimensions : 0.18x 0.14 x 0.09, *M*= 1538.41, Triclinic with space group P-1, *a*=14.277(11), *b*=14.907(11), *c*= 20.490(16), α= 103.517° (2), β=98.159°(2),γ= 110.901(2)°, *V*=3837(2)Å^3,*Z*=2, $2\theta_{max=}$ 51.86, ρ_{calcd}=1.331 mg/m^3,T=100K,μ-($Mo_{k\alpha}$)=0.71073,min/max transmission factors= 0.6173/ 0.7456, 44804 Reflections collected, 14215 unique (*R*1= 0.0429) ,*WR2* =0.2463 (all data). Residual electron density max/min=1.146 /-0.995e.Å^{-3}. Table **5.1** contains the other parameters for this crystal.

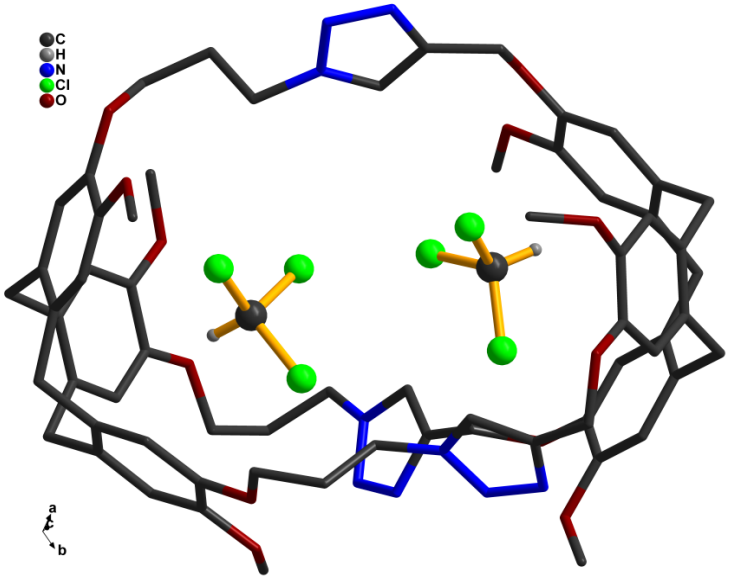


Figure5.5. Crystal structure of the anti-cryptophane showing two $CHCl_3$molecules inside the cavity, hydrogen atoms are omitted for clarity

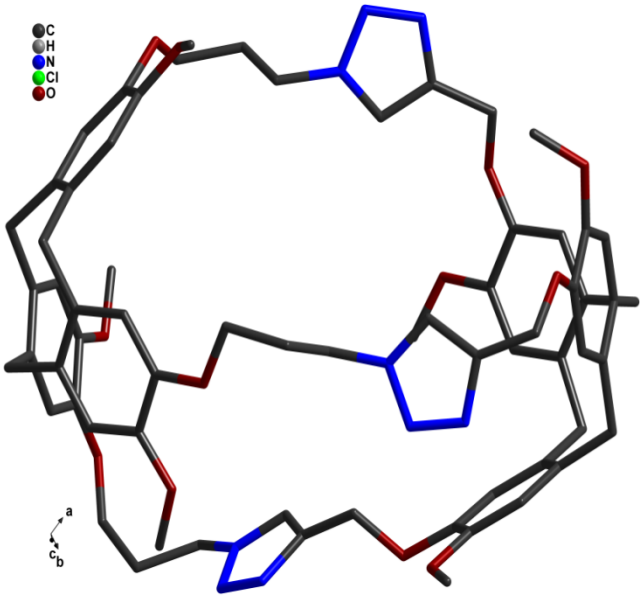


Figure5.6. Crystal structure of the anti-cryptophane showing the methoxy groups are on the opposite side of the each benzene ring confirms the conformation, hydrogen atoms, solvent molecules are omitted for clarity

The compound crystallized in Triclinic with space group P-1 where two cryptophanes were found in each unit cell and three chloroform molecules were found in the unit cell

out of them two are confined inside the cryptophane.Figure 5.5 & 5.6 shows the binding of $CHCl_3$ and conformation of the cryptophane respectively

5.4. Experimental Section

Materials: Reagent grade and metal salts were acquired from Aldrich and used as received. All solvents, were procured from Merck Chemicals, India. Solvents were purified prior to use following standard procedures.

Physical Measurements: NMR was recorded at Bruker 400MHz instrument. Single crystals X-ray diffraction studies were done on a Bruker APEX-II diffractometer equipped with a CCD detector, the X-ray source being Mo K_α (wave length 0.71073 Å) at room temperature. Data collection was monitor with Apex II software and preprocessing was done with SADBS integrated with Apex II.[38] The data was solved by SIR2002,[39] and expanded using Fourier technique. In case of **1** and **4**, disordered solvent molecules were present which were taken out using SQUEEZE command in PLATON.[40] All these software were integrated in wingx package.[41]

5.4.1 Synthesis of the compounds

(3-(3-bromopropoxy)-4-ethoxyphenyl)methanol(6): Vanillylalcohol(5 g, 32.45 m.mol) was dissolved in 30 mL of dry acetone and anhydrous K_2CO_3 (5.4 g, 38.94 mmol) was added under N_2 atmosphere, to this solution 1, 3 dibromopropane (30.485g, 162.25 m.mol) was added and refluxed overnight. The reaction mixture was filtered and solvent was evaporated under reduced pressure. To this diethyl ether was added most of the di-alkylated product was precipitated and filtered.The diethyl ether layer was washed with water and ether layer was evaporated under reduced pressure and purified by column chromatography using (silica 100-200), (20%Hexane+80%EtOAc) as eluant, resulted in a white coloured solid (6.7g, 74%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.27-2.38, m, 2H),

(3.61, t, 2H), (3.86, s, 3H), (4.13, t, 2H, *J=12Hz*), (4.61, s, 1H), (6.85-6.94, m, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.27, 32.49, 56.05, 65.35, 67.00, 111.16, 113.80, 119.56, 134.33, 147.84, 149.87). m/z calculated for $C_{11}H_{14}BrO_2$ (tropylium cation) is 257.0206, found 257.0172.

2,7,12-tris(3-bromopropoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene(CTG-Br(5)):

CTG-Br was prepared according to a reported procedure.[9] The alkylated vanillyl alcohol (5) (6.6g, 23.98m.mol) was dissolved in dry acetonitrile (15 mL) under N_2 atmosphere, to this solution $Sc(OTf)_3$(118mg, 0.239m.mol) was added and kept at 70^0C for overnight. The solution was evaporated under reduced pressure to this DCM was added and washed with water, the DCM layer was dried under anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product purified by column chromatography (silica 100-200) DCM as eluant yielded a white coloured solid (3.5g, 19%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.29-2.37, m, 2H), (3.54, d, *J=16Hz*, 2H), (3.59-3.64, m, 2H), (3.83, s, 3H), (4.09-4.17, m, 2H), (4.74, d, *J=16Hz*, 2H), (6.85, s, 1H), (6.91, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.45, 32.28, 36.46, 56.24, 67.08, 113.70, 115.88, 131.84, 132.66, 146.85, 148.47). ESI-Solid state mass m/z calculated for $C_{33}H_{39}Br_3O_6$ (M+2) is 770.0021 found 770.0273

2,7,12-tris(3-azidopropoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene(CTG-Azide(3)): Compound **2**(1.5g, 1.95 m.mol) was dissolved in dry DMF (10 mL) under N_2 atmosphere, to this solution NaN_3 (1.26g, 19.5m.mol) was added and stirred at RT for 12 hours. The solvent was evaporated under reduced pressure and dissolved in DCM, washed with water. The organic layer was evaporated under reduced pressure and the crude product was purified by column

chromatography (silica 100-200) (98% DCM +2%MeOH) as eluant yielded a white coloured solid (0.8g, 62.3%). ^{1}HNMR (400MHz, $CDCl_3$) δ: (2.03, t, 3H), (3.49-3.56, m,2H), (3.82,d, *J=16Hz*, 2H), (3.83, s, 3H), (4.09-4.17, m, 2H), (4.73-4.77, d, *J=16Hz*, 2H), (6.84, s, 1H), (6.87, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ:(28.86, 36.46, 48.27, 56.15, 66.32, 113.78, 116.02, 131.88, 132.74, 146.85, 148.52).

(3-(3-azidopropoxy)-4-methoxyphenyl)methanol(8): Bromo propyl Vanillyl alcohol **1** (2g, 7.269 m.mol) was dissolved in dry DMF 10 mL under N_2 atmosphere, to this solution NaN_3 (2.36g, 36.34m.mol) was added and heated at 60^{O} C for 12 hours. The solvent was evaporated under reduced pressure and dissolved in DCM, washed with water. The organic layer was evoparated under reduced pressure and the crude product was purified by column chromatography (silica 100-200) (30%Hexane+70%EtOAc) as eluant yielded a colourless oil (1.5g, 98.1%); ^{1}HNMR (400MHz, $CDCl_3$) δ: (2.05, t, 2H), (3.52, *J=8Hz,* d,2H),(3.86, s, 3H), (4.07, t, *J=12Hz*, 2H), (4.61, s, 2H), (6.86, s, 1H), (6.92, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ:(28.80, 48.27, 55.91, 65.22, 66.02, 111.01, 113.59, 119.42, 134.33, 147.68, 149.75).

(4-methoxy-3-(prop-2-yn-1-yloxy)phenyl)methanol(4): Vanillyl alcohol (5g, 32.45m.mol) was dissolved in 30 mL of dry CH_3CN and anhydrous K_2CO_3 (5.4g, 38.94mmol) was added under N_2 atmosphere, to this solution propargyl bromide (4.24g, 35.69m.mol) was added and refluxed overnight. The reaction mixture was filtered and solvent was evaporated under reduced pressure. The compound was dissolved in dichloromethane and washed with water; the organic layer was dried under anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography by using DCM/MeOH(99:1) as eluant, pure compound was obtained as colourless oil (4.5g, 72.6%).^{1}HNMR (400MHz, $CDCl_3$) δ:

(2.48, t, 1H), (3.81, s, 3H), (4.55, s, 2H), (4.70, s, 2H), (6.84-6.96, m, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (55.83, 56.82, 64.92, 75.85, 78.60, 110.88, 114.36, 119.10, 135.17,146.11,149.74).

2,7,12-trimethoxy-3,8,13-tris(prop-2-yn-1-yloxy)-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene(2): Compound **1**(4.5g, 23.56 m.mol) was dissolved in 20 mL of dry MeOH, to this $HClO_4$(22 mL) was added drop wise at 0^{O}C in an ice bath. The reaction was kept at room temperature overnight. The precipitate was re dissolved in DCM and the organic layer was washed with water, 1N NaOH solution. The organic layer was dried under anhydrous Na_2SO_4; the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography using DCM/MeOH(98:2) as eluant, pure compound was obtained as white coloured solid (3.5g, 28.4%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.46, t, 1H), (3.56, d, *J=12Hz*, 1H), (3.81, s, 2H), (4.71, d, *J=4Hz*, 2H), (4.75, d, *J=12Hz*, 1H), (6.88, s, 1H), (7.02, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (29.70, 36.53, 56.17,56.99, 75.71, 79.02, 113.89,116.54, 131.59, 133.38,148.43, 148.50).

((((4,4'-(((7-((1-(3-(4-(hydroxymethyl)-2-methoxyphenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,8,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,13-diyl)bis(oxy))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(propane-3,1-diyl))bis(oxy))bis(4-methoxy-3,1-phenylene))dimethanol (Pre-cryptophane (9))

Compound **6** (1.46 g, 2.80m.mol) was dissolved in 100 ml of solvent (40ml CH_3CN+60 ml CH_2Cl_2), then DIPEA (N,N-Diisopropylethylamine) was added under N_2 and kept at RT with stirring. To this CuI was added, after that azido propyl vanillylalcohol **8** (2g, 8.42m.mol) by dissolving in 30 ml of CH_2Cl_2, was added and kept at RT for 12 hours. Aqueous ammonia was added to quench the reaction and extracted to CH_2Cl_2three times (3*60ml), the DCM layer was washed with water and dried under anhydrous $Na_2SO_4$and

evaporated under reduced pressure. The crude compound was purified by column chromatography by using DCM/MeOH[pack the column with (98:2)] keep increasing the polarity up to 94:6; at this polarity product started coming, the solvent was evaporated under reduced pressure yielded the title compound as white coloured solid(3.0 g, 86.8% yield). ^{1}HNMR (400MHz, $CDCl_3$) δ: (2.25, t, 2H), (3.46, d, 1H, *J=16Hz*), (3.67, s, 3H), (3.78, s, 3H),(3.81, s, 2H),(4.47, t, 2H), (4.55, s, 2H), (4.65, d, 1H, *J=12Hz*), (5.21, s, 2H), (6.61, d, 1H, *J=8Hz*), (6.69, d, 1H, *J=8Hz*), (6.78, s, 1H),(6.85, s, 1H), (6.99, s, 1H),(7.56, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (29.76, 36.43, 47.00, 55.60, 56.27, 63.18, 64.83, 65.44,110.88, 113.62, 114.01, 115.84, 119.34, 123.78, 131.64, 132.91, 135.01, 144.29, 146.10,147.07,148.21,149.64). ESI-HRMS: m/z calculated for $C_{66}H_{75}N_9O_{15}$ ($M+H^+$) is 1234.5455, found 1234.5477

Cryptophane(1)

Compound **9**(1.5g, 1.21m.mol) was dissolved in 100 ml of CH_3CN solvent stirred at 0^{O}C to this $BF_3.Et_2O$ was added after that the reaction was kept at RT with stirring. After 6 hours the solvent was evaporated under reduced pressure, the solid was re-dissolved in CH_2Cl_2, washed with water and brine solution. The organic layer was separated, dried under anhydrous $Na_2SO_4$and evaporated under reduced pressure. The crude compound was purified by column chromatography by using DCM/MeOH [pack the column with (99:1);silica gel 230-400 mesh] keep increasing the polarity up to(97.5:2.5) at this polarity product started coming (the syn isomer ;180 mg, 12.6% yield), on increasing the polarity to 3% MeOH the anti isomer was obtained. The solvent was evaporated under reduced pressure yielded the title compound as white coloured solid (80mg, 5.6% yield). ^{1}HNMR of the syn isomer (400MHz, $CD_3C(O)CD_3$) δ: (2.23, t, 2H, *J=12Hz*), (3.51, d, 2H, *J=12Hz*), (3.68, s, 3H), (3.69, s, 3H), (3.72, m, 2H), (4.39, m, 2H), (4.72, d, 2H, *J=12Hz*), (5.02, dd, 2H), (6.97, s, 1H), (7.01, s, 1H)), (7.07, s, 1H), (7.16, s, 1H), (7.79,

s, 1H); ^{13}CNMR (100MHz, $CD_3C(O)CD_3$) δ: (35.45, 35.62, 46.44, 54.06, 55.56, 55.66, 63.33, 66.07, 114.03, 114.19, 116.20, 116.68, 123.71, 131.92, 132.13, 133.00, 133.16, 144.19, 146.71, 146.83,148.61,148.73. ESI-HRMS for the syn isomer: m/z calculated for $C_{66}H_{69}N_9O_{12}$ ($M+H^+$) is 1180.5138, found 1180.5139

^{1}HNMR of the anti isomer (400MHz, $CD_3S(O)CD_3$) δ: (2.08, m, 2H), (3.43, d, 2H, *J=12Hz*), (3.58, s, 3H), (3.63, s, 3H), (3.82, m, 2H), (4.88, m, 2H), (4.07, m, 2H, *J=12Hz*), (5.05, s, 2H), (6.91, s, 1H), (7.00, s, 1H)), (7.06, s, 1H), (7.08, s, 1H), (7.89, s, 1H); ^{13}CNMR (100MHz, $CD_3C(O)CD_3$) δ: (30.21, 35.39, 35.56, 47.11, 56.27, 56.55, 62.95, 66.75, 114.54, 114.68, 116.59, 116.97, 124.26, 132.20, 132.48, 133.32, 133.39, 144.06, 146.27, 146.62,148.33,148.53 ESI-HRMS for the syn isomer: m/z calculated for $C_{66}H_{69}N_9O_{12}$ ($M+H^+$) is 1180.5138, found 1180.5100

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5.5 Spectral data

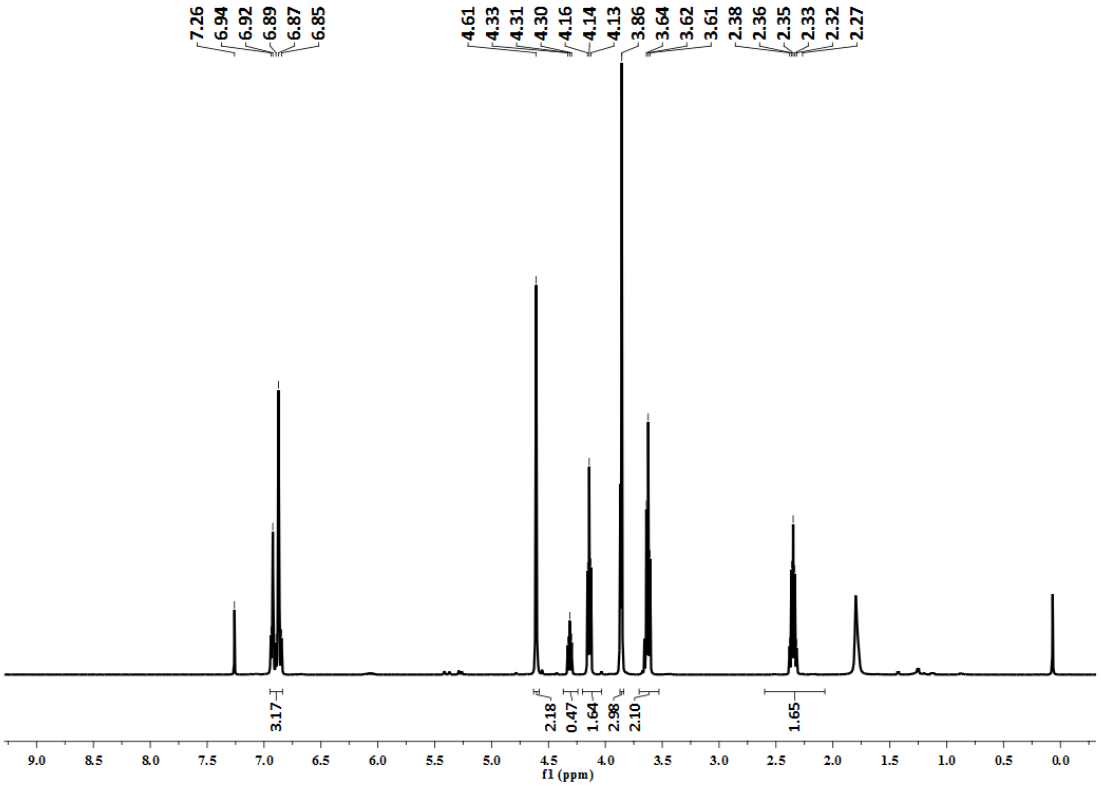


Figure5.7.[1]H NMR spectra of Bromo propyl vanillyl alcohol in $CDCl_3$

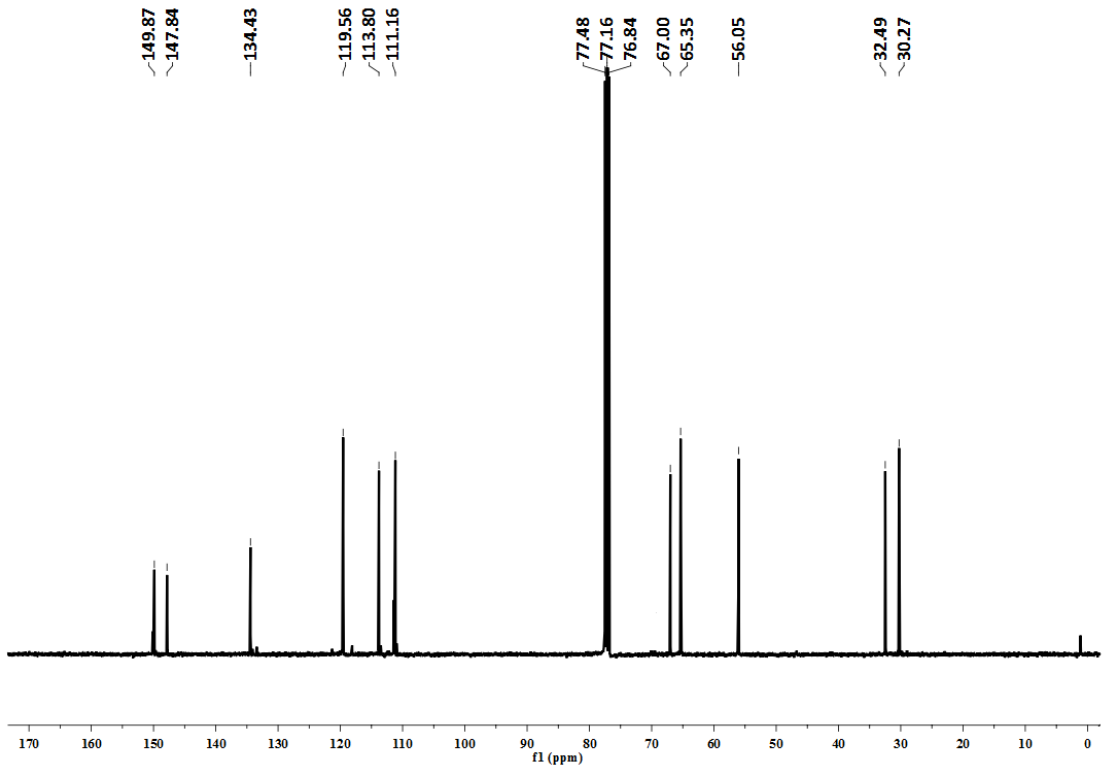


Figure5.8.[13]C NMR of Bromo propyl vanillyl alcohol in $CDCl_3$

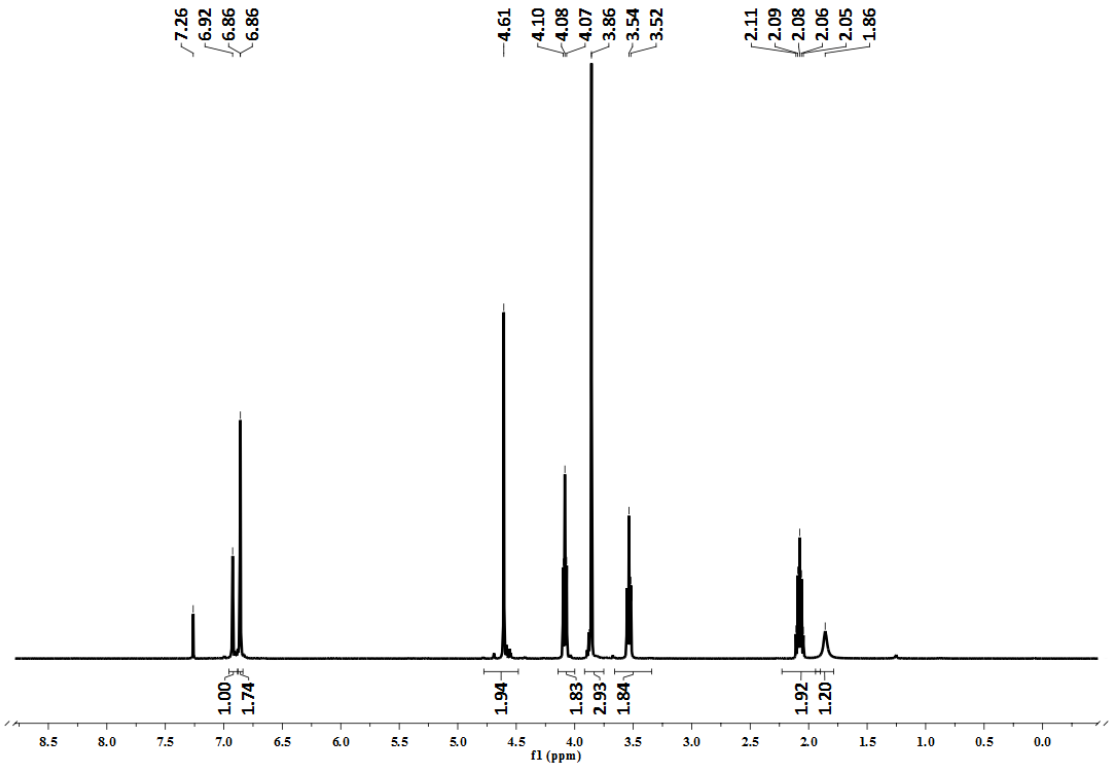


Figure5.9.[1]H NMR spectra of CTG-Br in $CDCl_3$

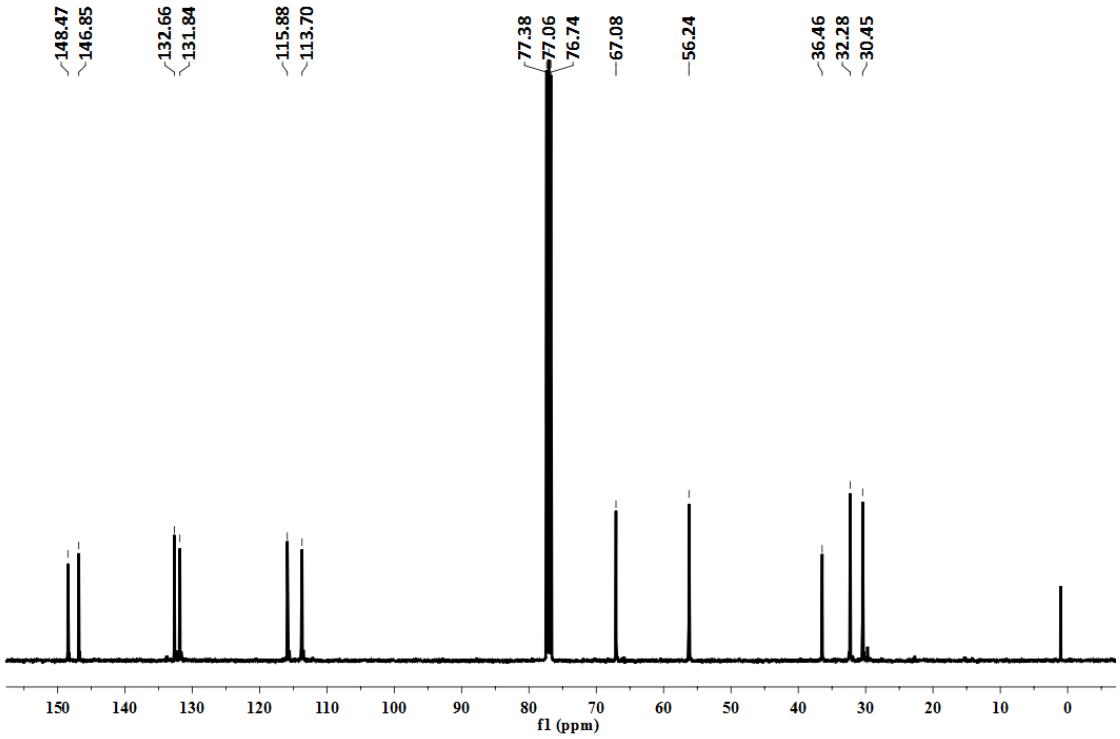


Figure5.10.[13]C NMR spectra of compound CTG-Br in $CDCl_3$

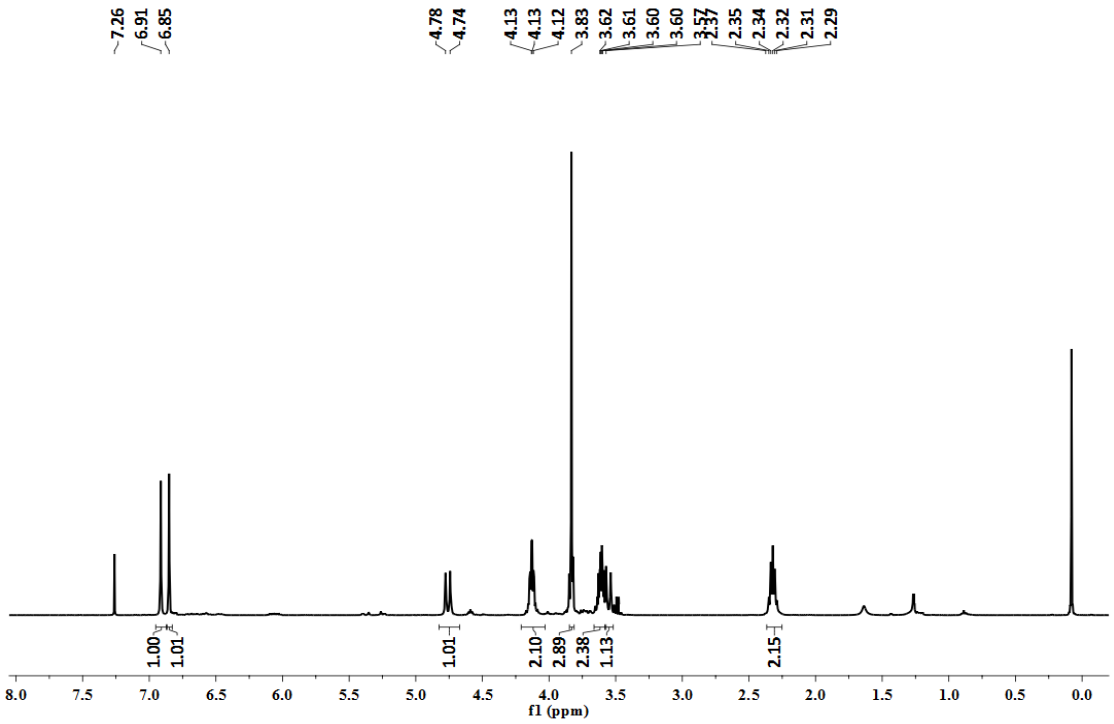


Figure5.11.[1]H NMR Spectra of vanillyl alcohol azide in $CDCl_3$

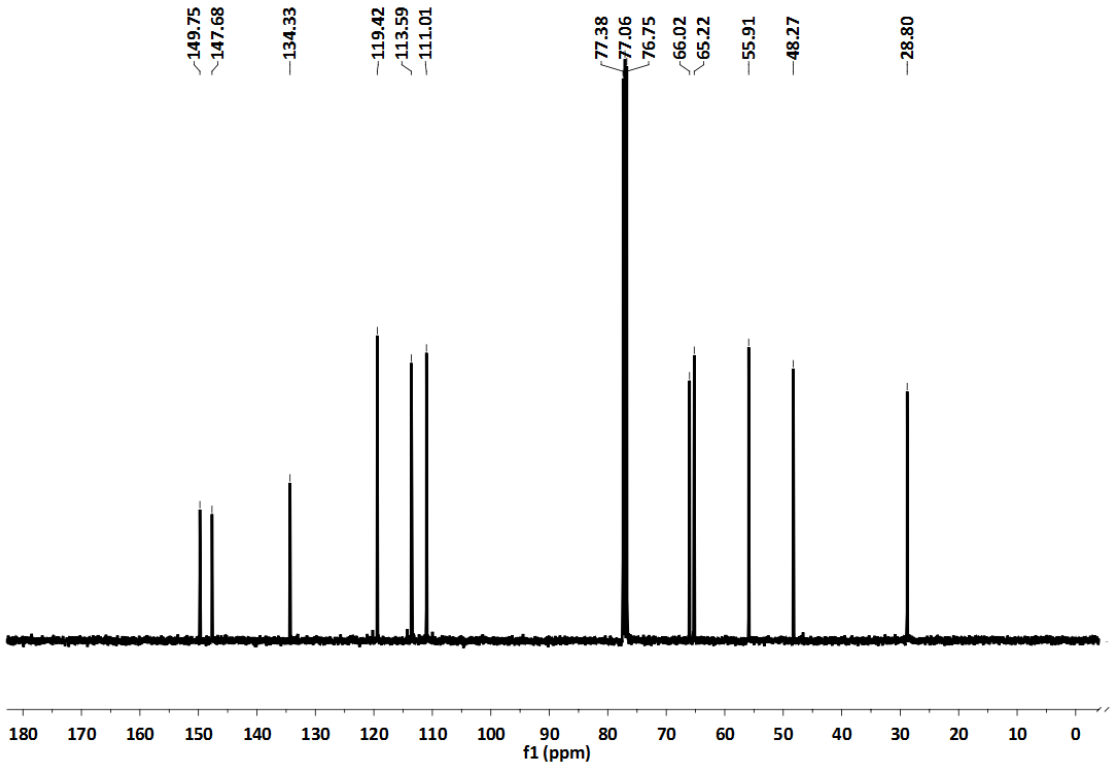


Figure5.12.[13]C NMR Spectra of vanillyl alcohol azide in $CDCl_3$

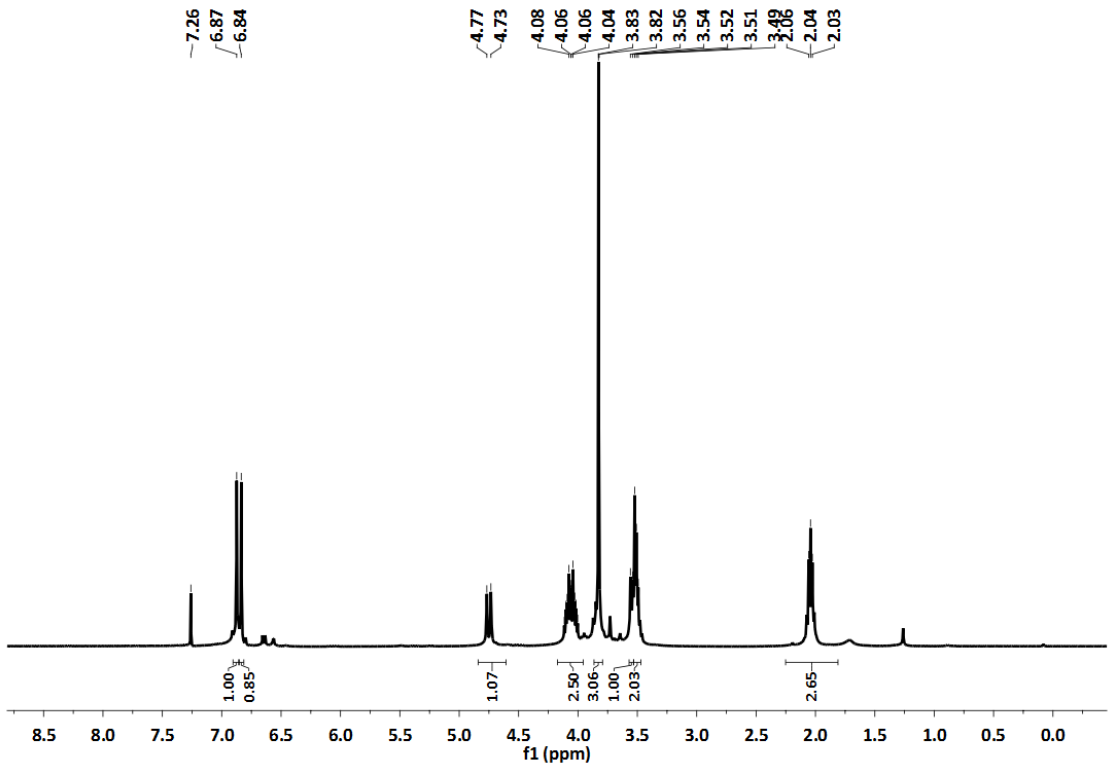


Figure5.13.^{1}H NMR spectra of CTG-azide in $CDCl_3$

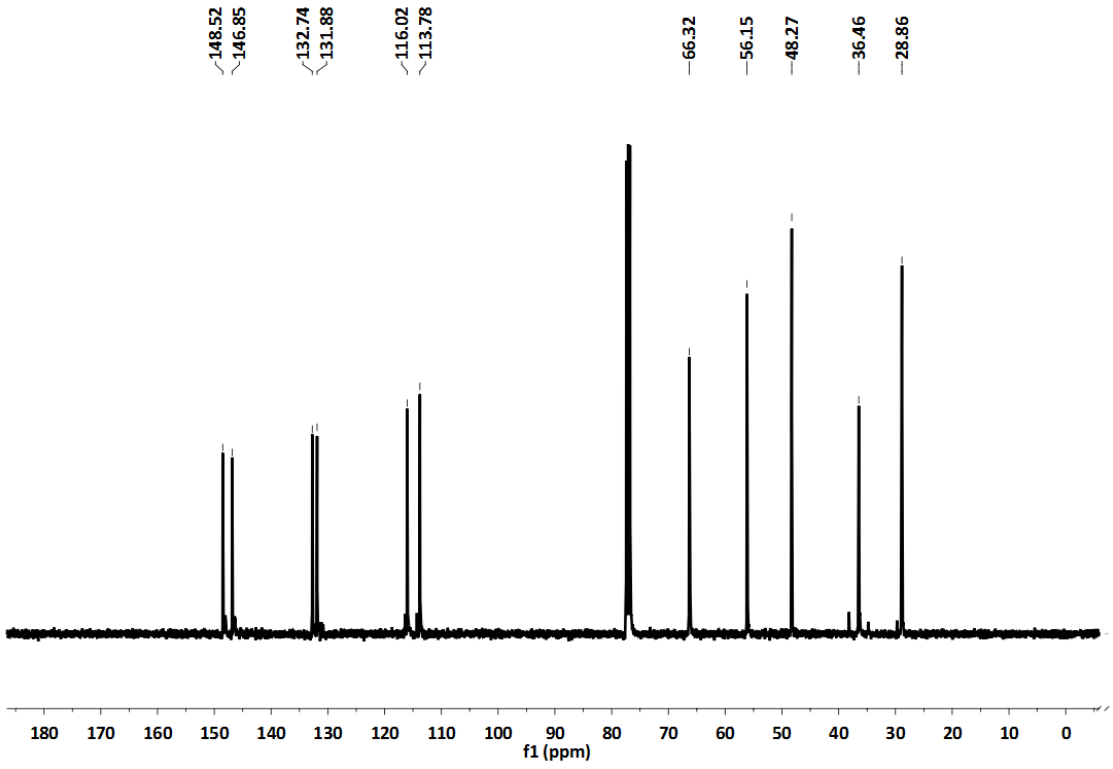


Figure5.14.^{13}C NMR spectra of CTG-azide in $CDCl_3$

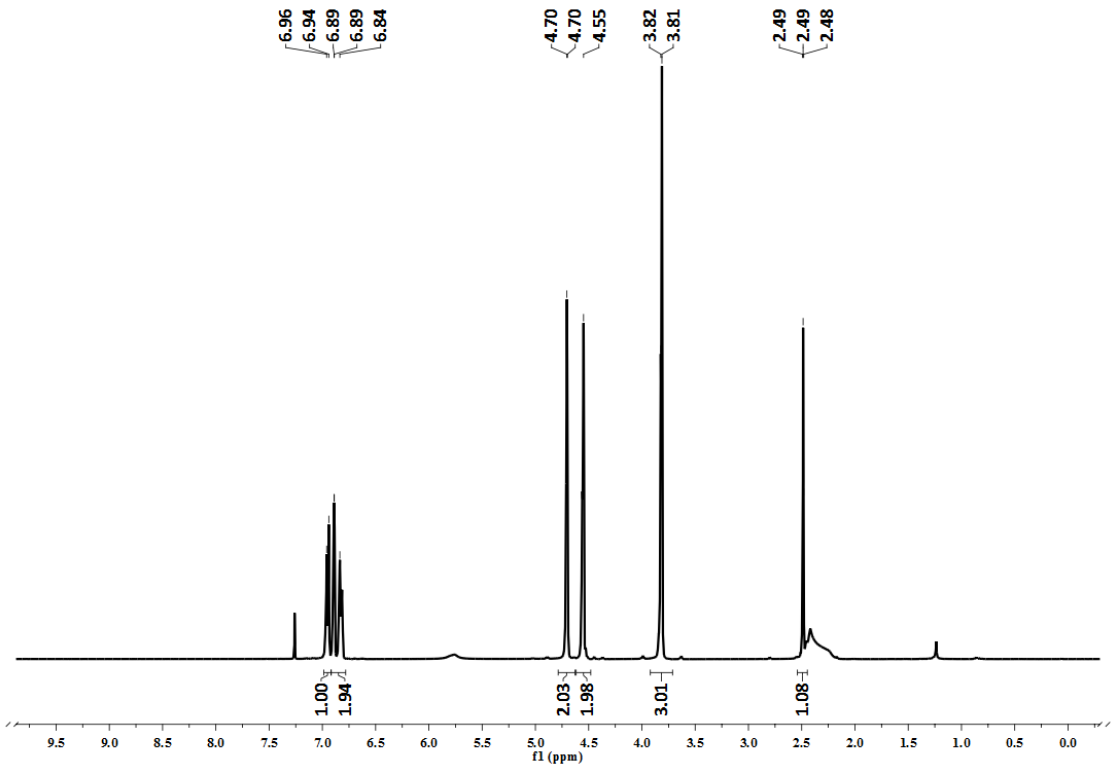


Figure5.15.[1]H NMR of PropargylVanillyl alcohol in $CDCl_3$

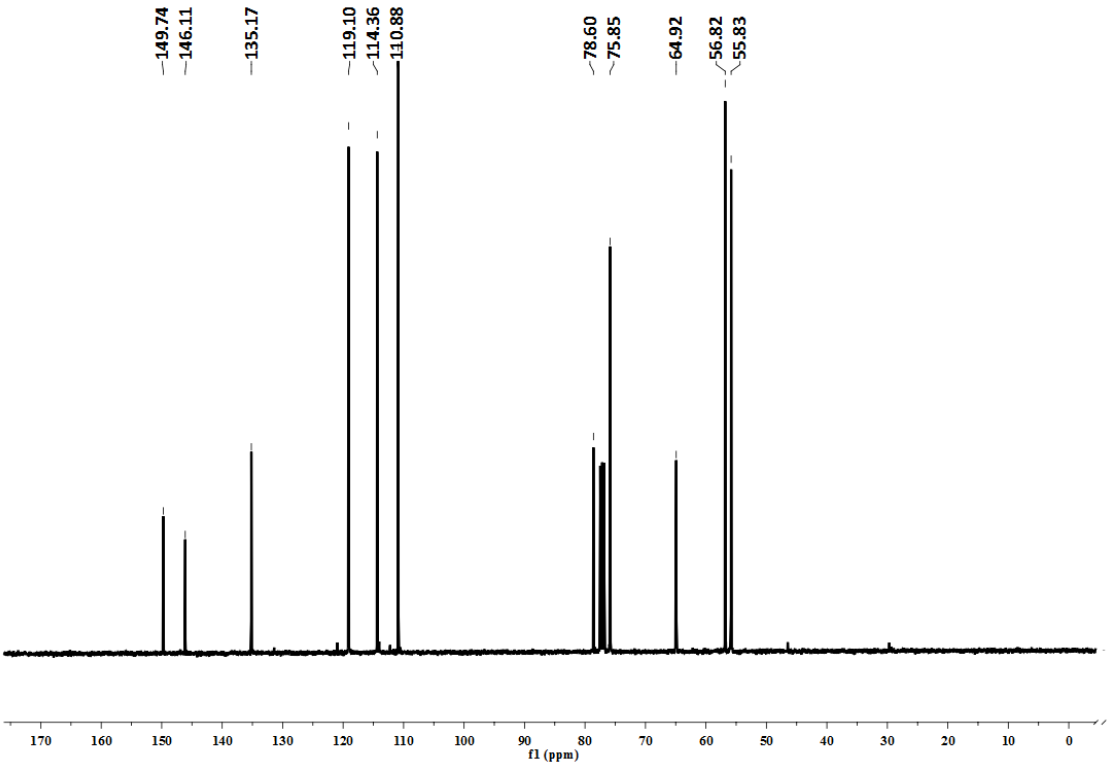


Figure5.16.[13]C NMR of PropargylVanillyl alcohol in $CDCl_3$

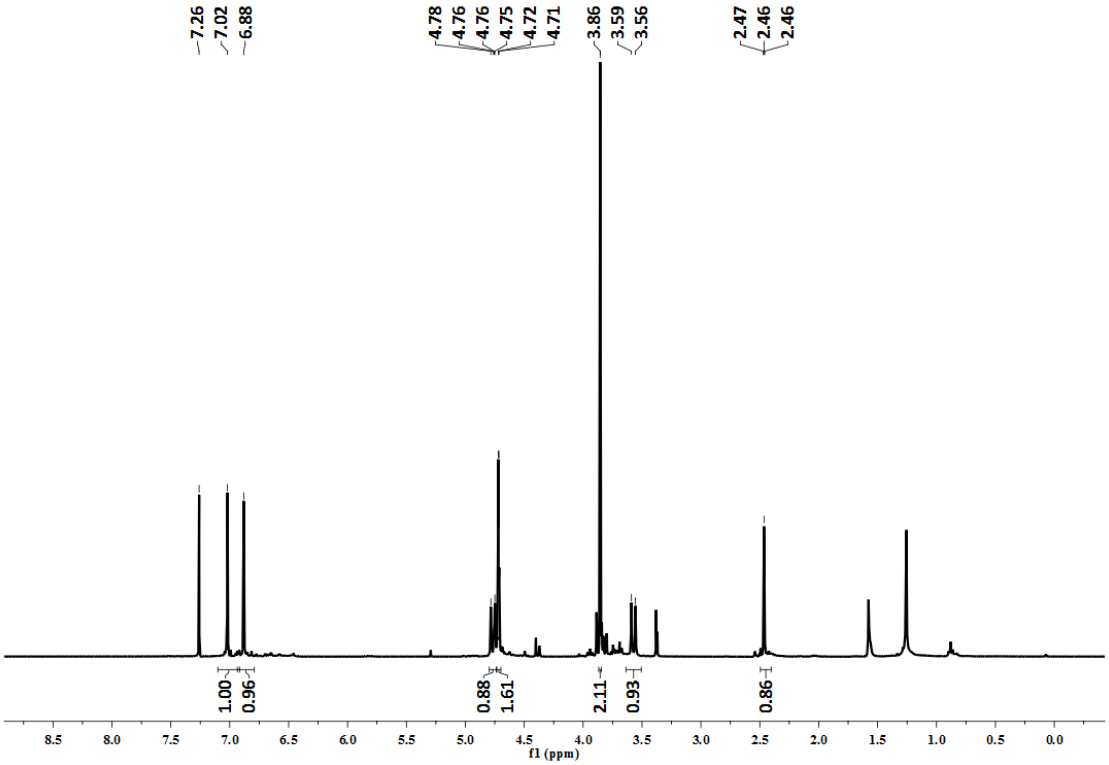


Figure5.17.^{1}H NMR spectra of compound CTG-Propargyl in $CDCl_3$

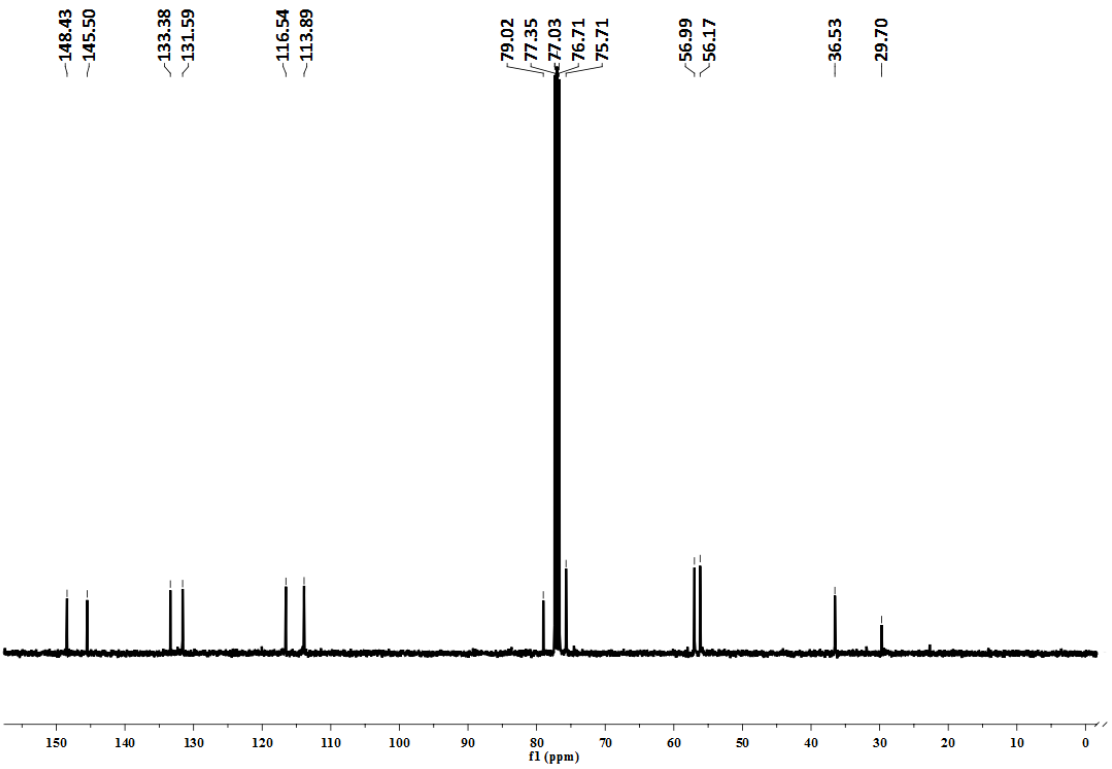


Figure5.18.^{13}CNMR spectra of CTG-Propargyl in $CDCl_3$

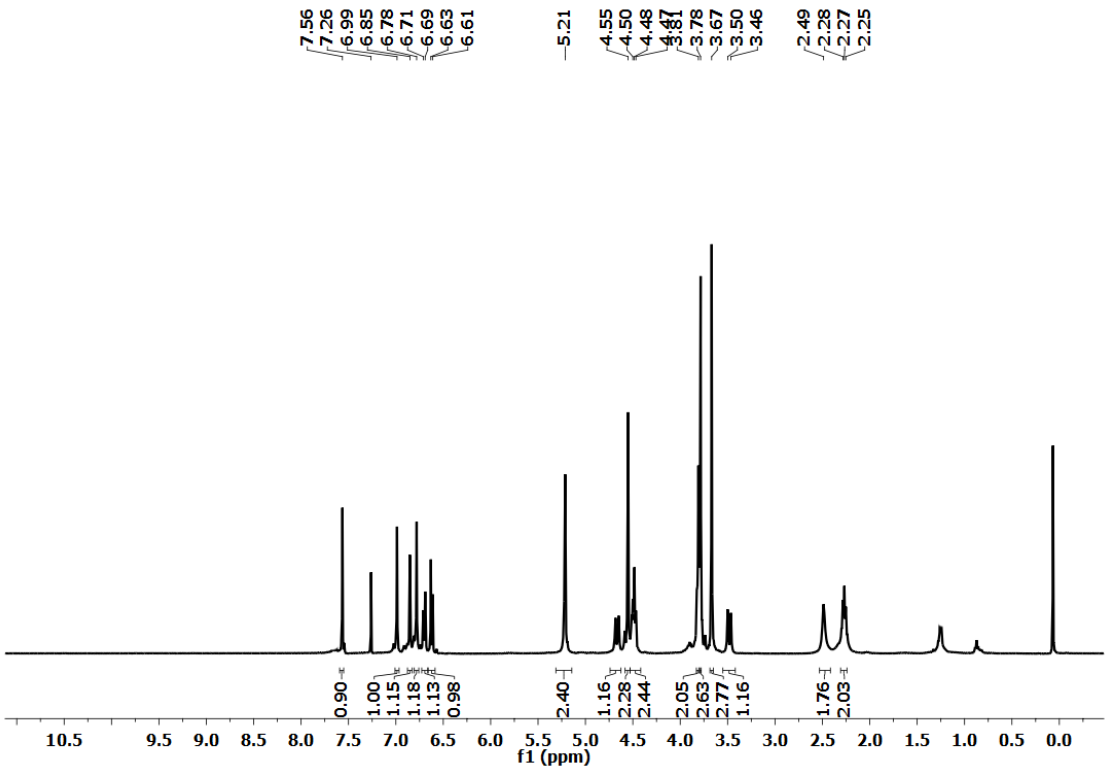


Figure5.19.[1]H NMR spectra of Pre-cryptophane in $CDCl_3$

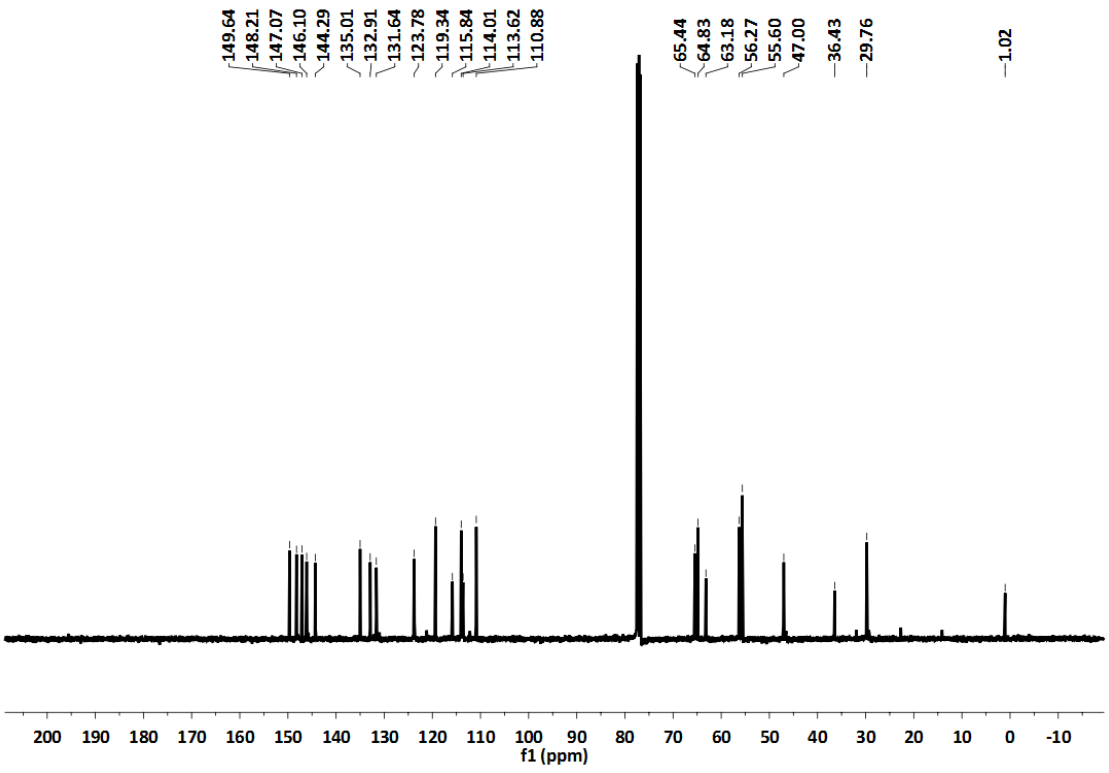


Figure5.20.[13]C NMR spectra of Pre-cryptophane in $CDCl_3$

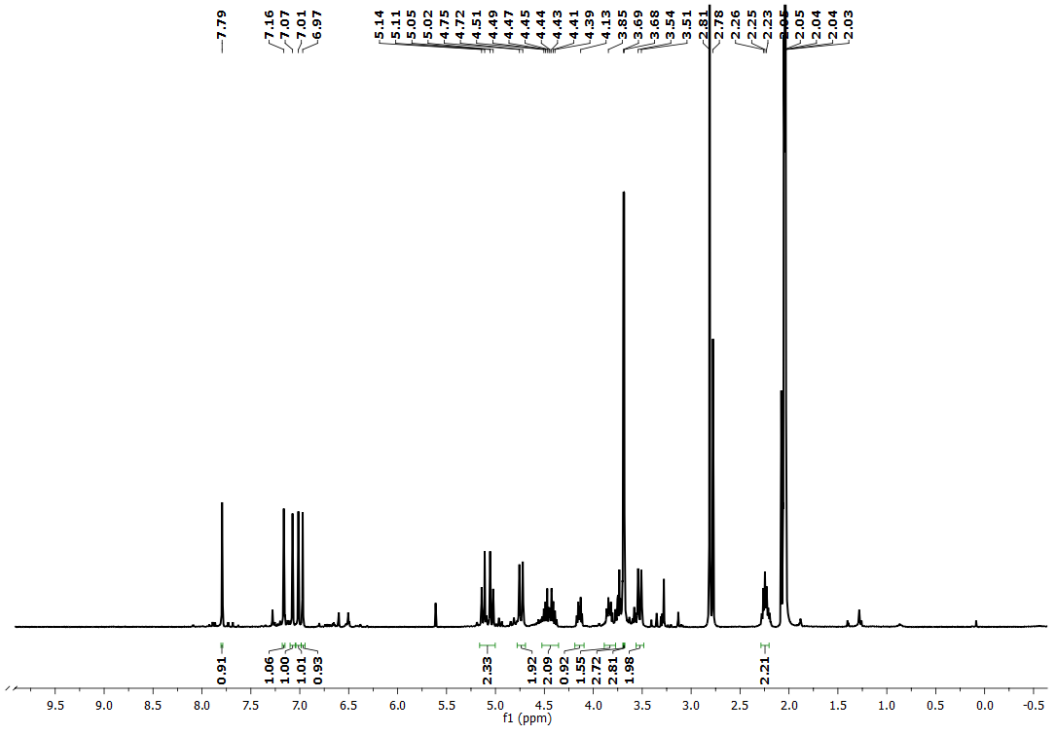


Figure5.21.[1]H NMR spectra of cryptophane (Syn isomer) in Acetone-d_6

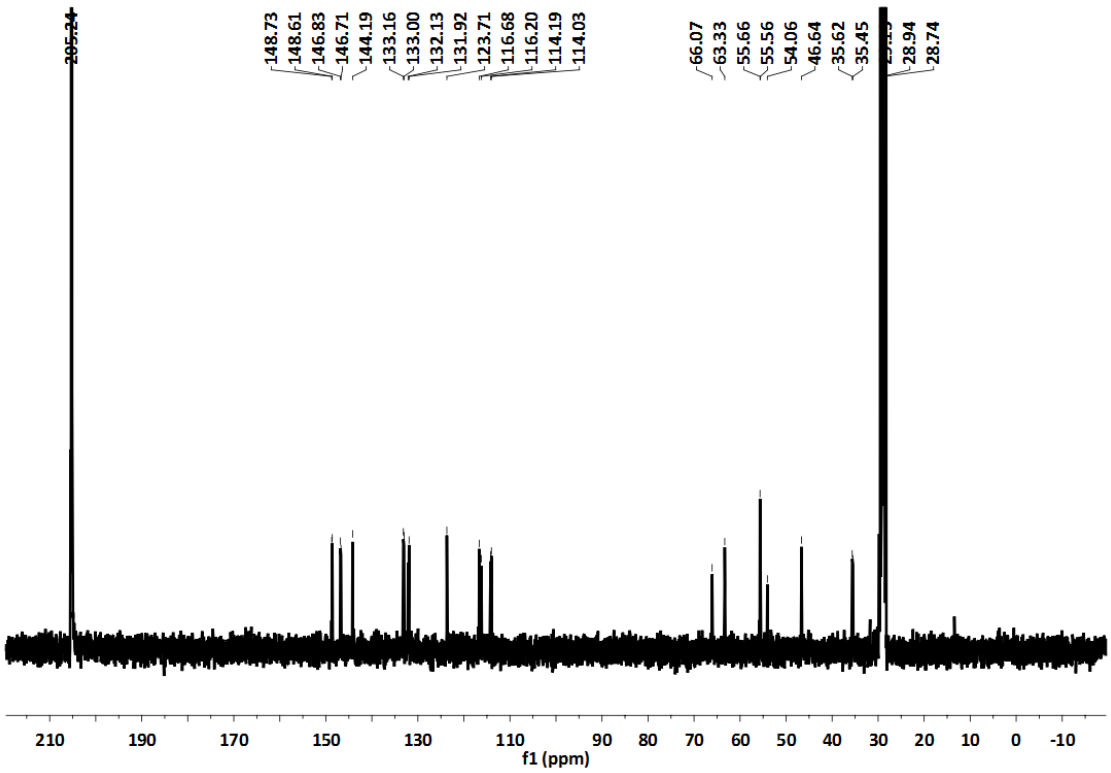


Figure5.22.[13]C NMR spectra of cryptophane (Syn isomer) in Acetone-d_6

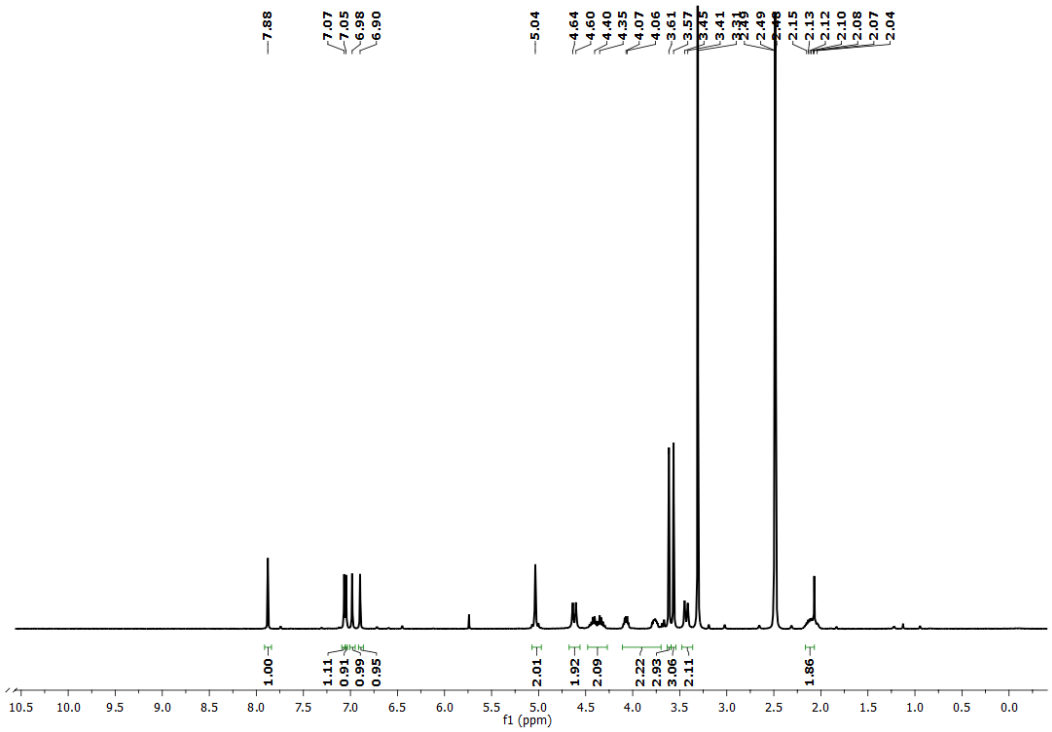


Figure5.23. ^{1}H NMR spectra of cryptophane (Anti isomer) in DMSO-d_6

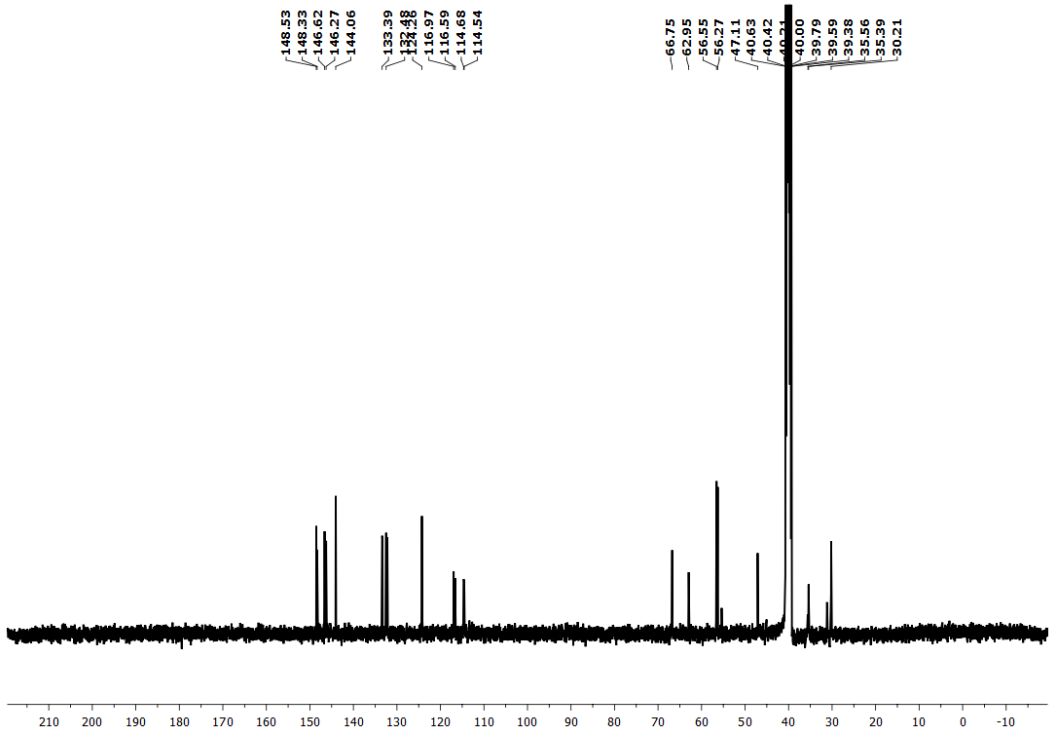


Figure5.24. ^{13}C NMR spectra of cryptophane (Anti isomer) in DMSO-d_6

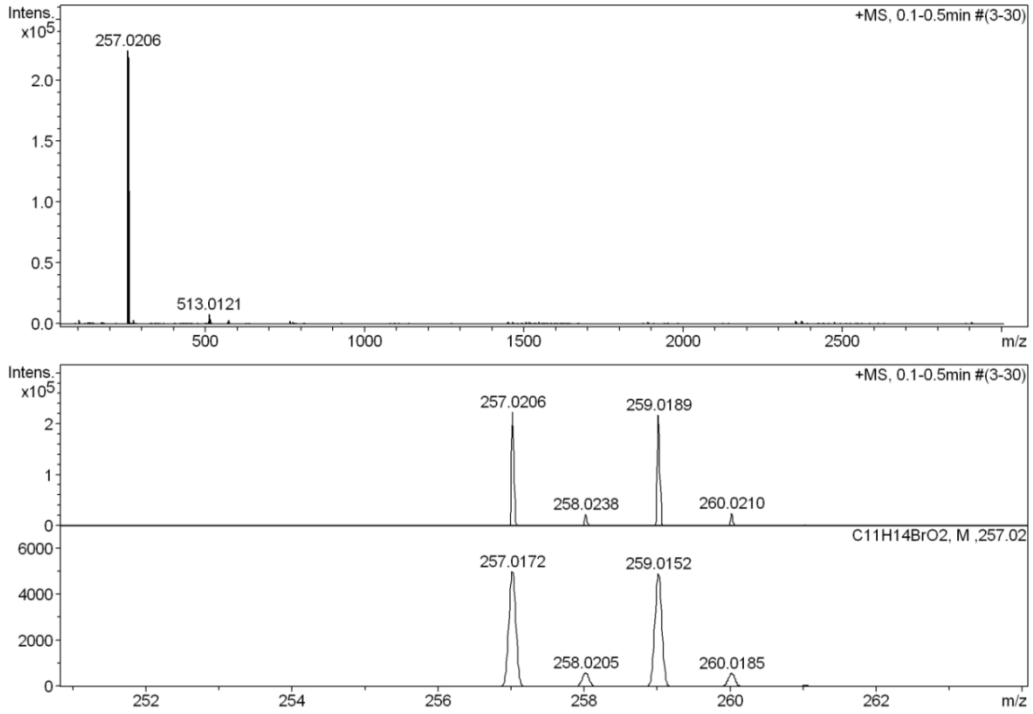


Figure5.25.ESI-Mass Spectra of Bromo propyl vanillyl alcohol (corresponding tropyliumcation)

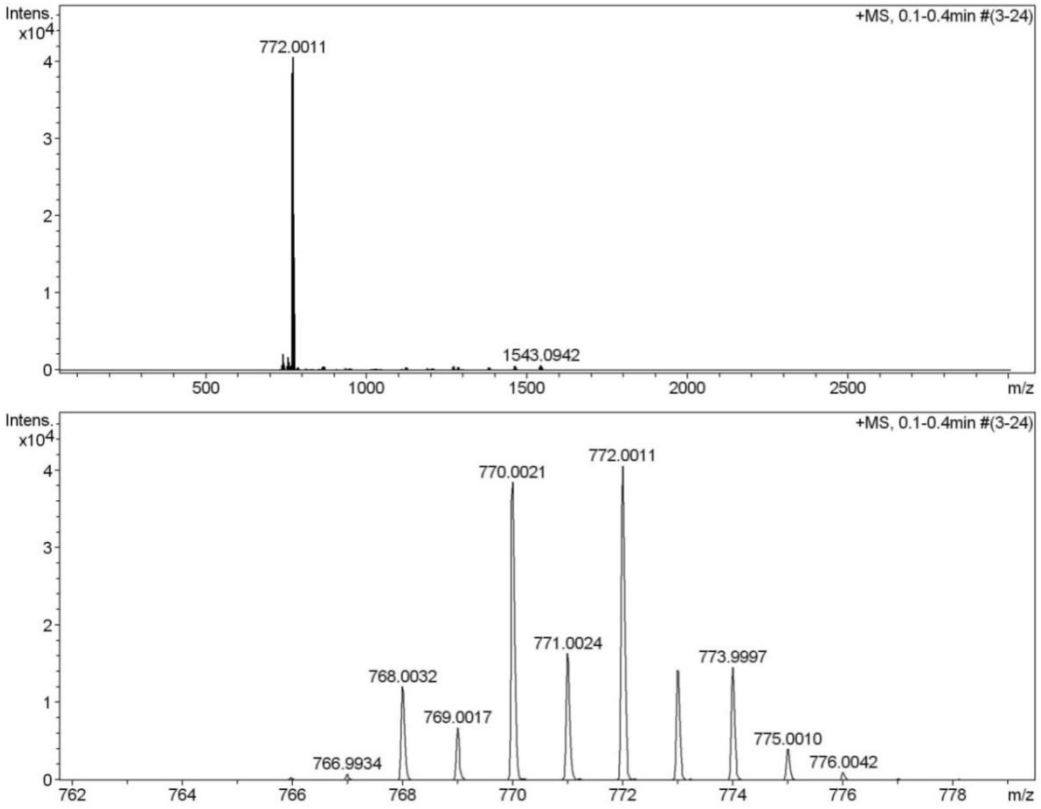


Figure5.26.ESI-Mass Spectra of CTG-Br

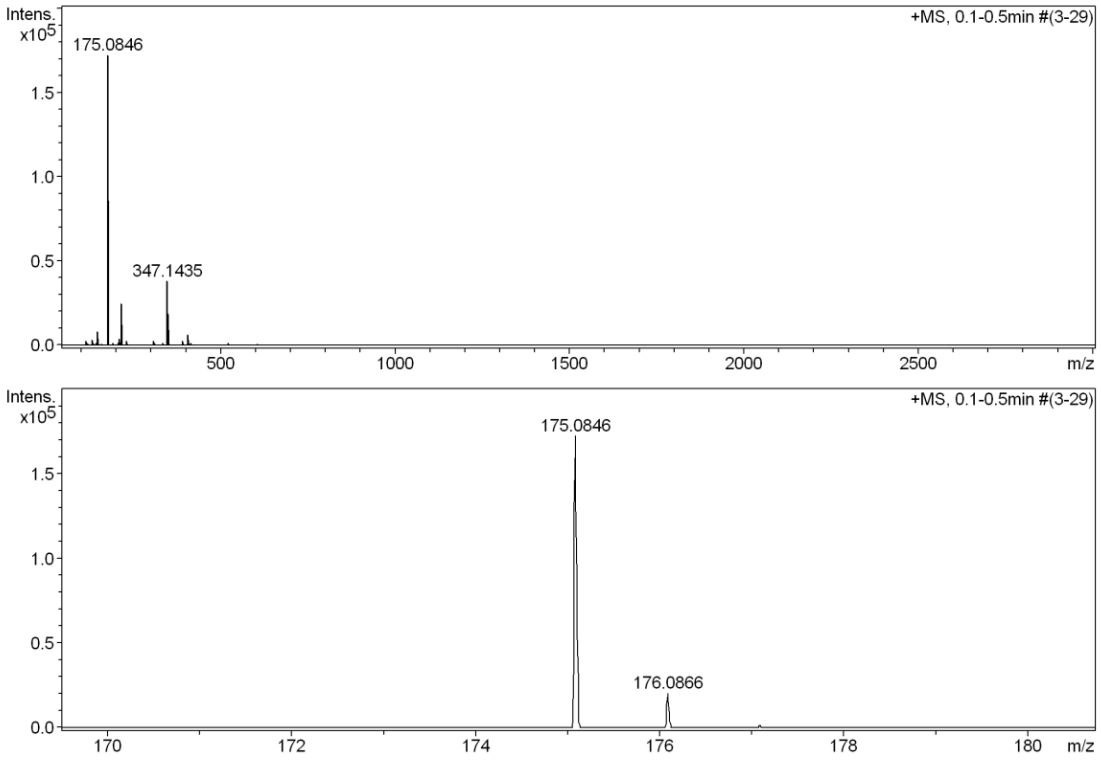


Figure5.27.ESI-Mass Spectra of Propargylvanillyl alcohol (corresponding tropyliumcation)

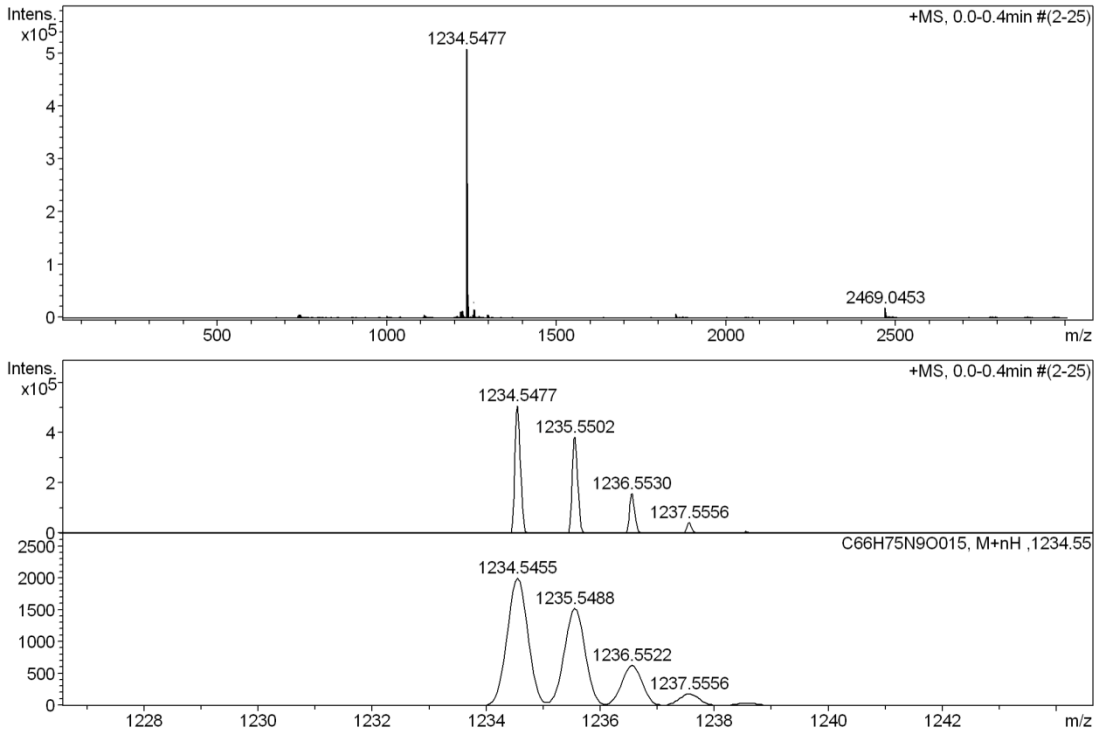


Figure5.28.ESI-Mass (HRMS) Spectra of pre-cryptophane

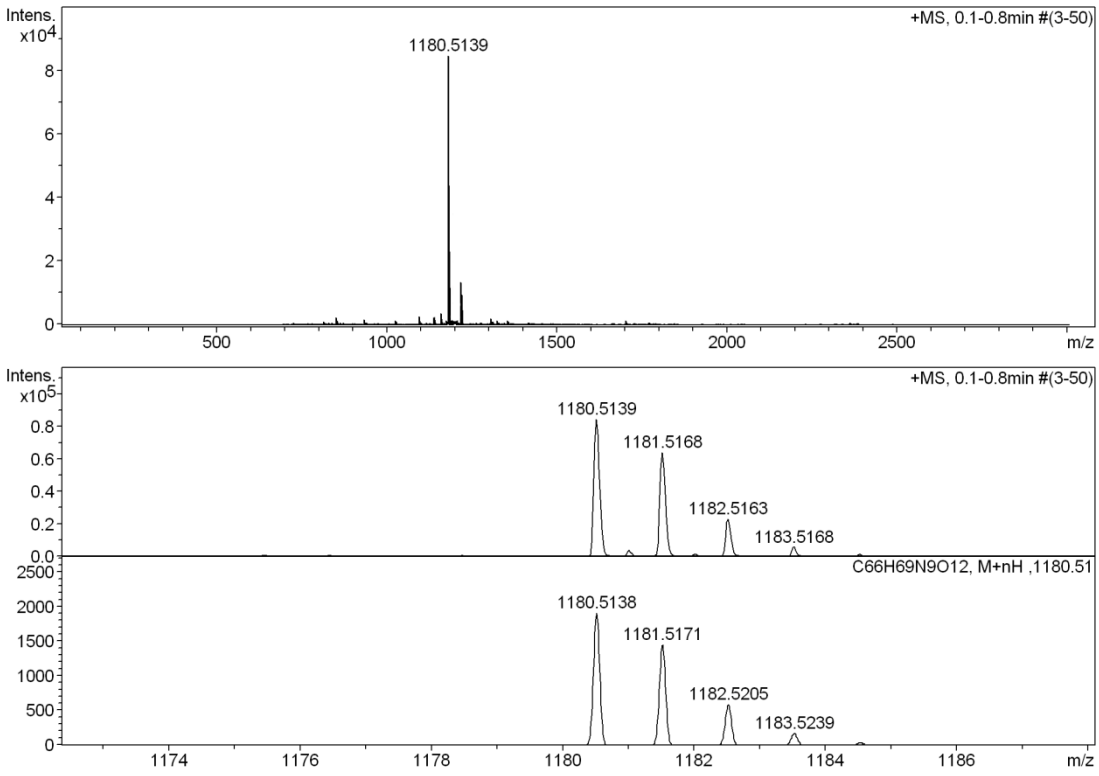


Figure5.29.ESI-Mass (HRMS) Spectra of cryptophane-1 (Syn isomer)

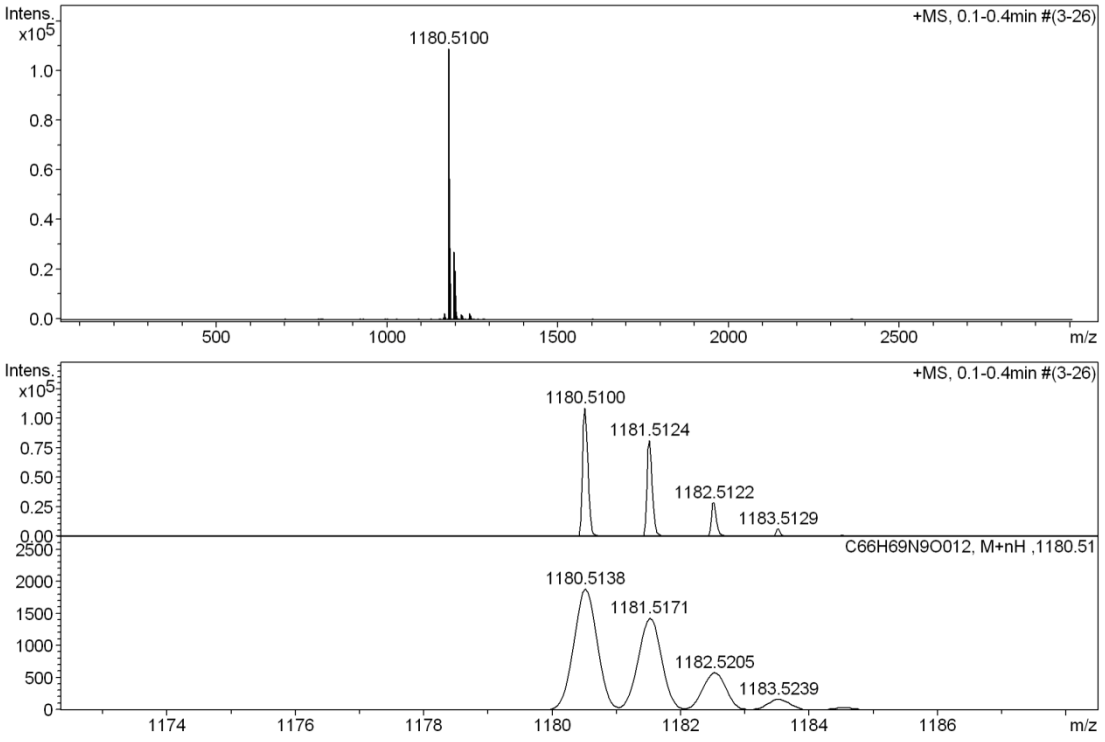
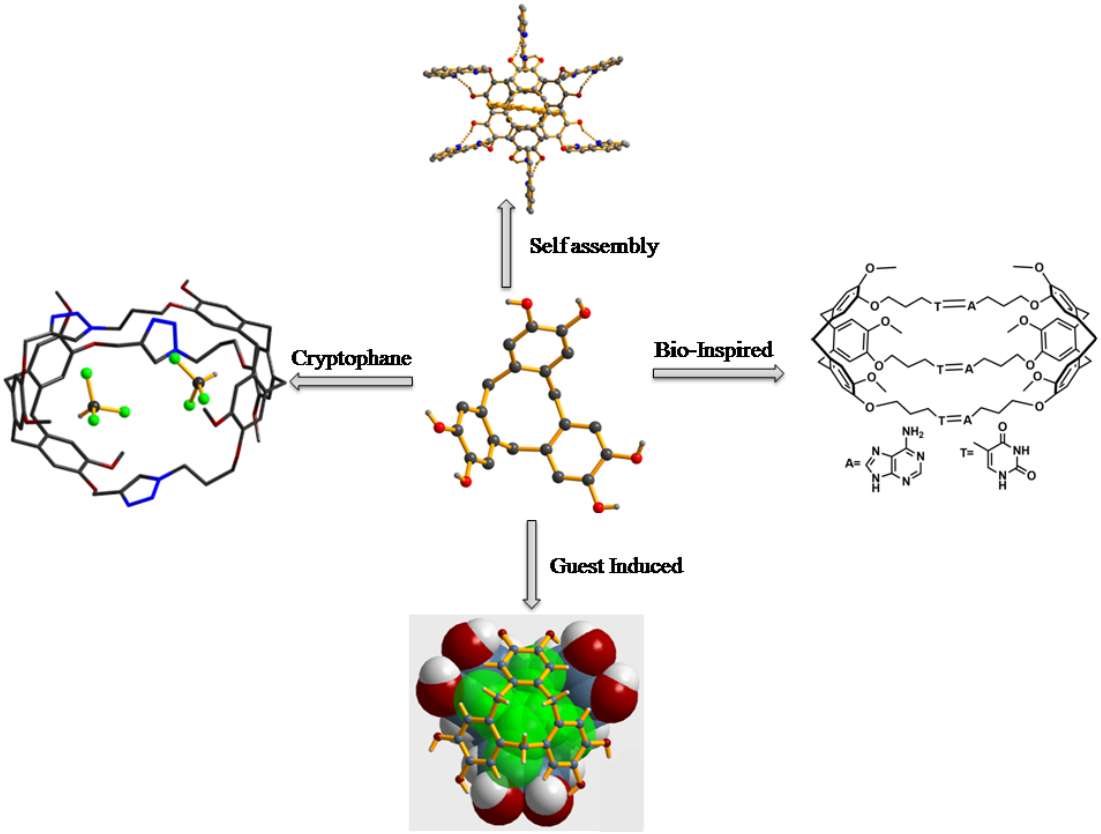


Figure5.30.ESI-Mass (HRMS) Spectra of cryptophane-1 (Anti isomer)

Compound	**1(Cryptophane-syn)**
Empirical formula	$C_{69}\ H_{72}\ N_9\ O_{12}\ Cl_9$
Formula weight	1538.41
Temperature	100 K
Wavelength	0.71073 A°
Crystal system	Triclinic
Space group	P-1
a (Å)	14.277(11)
b (Å)	14.907(11)
c (Å)	20.490(16)
α (deg)	103.517(2)
β (deg)	98.159(2)
γ (deg)	110.901(2)
Volume ($Å^3$)	3837(2)
Z	2
Density (calculated)	1.331
Absorption coefficient	0.391
F(000)	1596
θ max	25.50
Reflections collected	44804
Independent reflections	14215
GOOF	1.049
Final R indices [I>2σ(I)]	R1 = 0.0774, wR2 = 0.2279
R indices (all data)	R1 = 0.1025,wR2 = 0.2463

Table5.1: Crystal data of Anti-Cryptophane(**1**)

Summary



Future directions

This thesis contains construction of molecular capsules with different binding forces such as, hydrogen bonding, guest induced and covalent bonding. We have now standard protocols to synthesize the capsules discuss in this thesis. Additional advantage will be the formation in neutral medium. However, the functional aspects of these capsules are not investigated thoroughly. To use them as container molecules, increment in the volume of the capsule is desired. One of the future direction would be to synthesize capsules with larger volume utilizing similar protocol used in this thesis. This would require suitable modification of functional group, so that they form a suitable assembly that have enough space inside. For functional application such as drug delivery would require water solubility of these capsules. These changes required a suitable functional group that can be modified. Phenolic group present in these molecules can help for easy manipulation of the capsules studied.