Course Name: **Supramolecular & Photoinorganic Chemistry**
Paper Number: **101**
Section: **B**
Course Instructor: **Prof. Rajeev Gupta**
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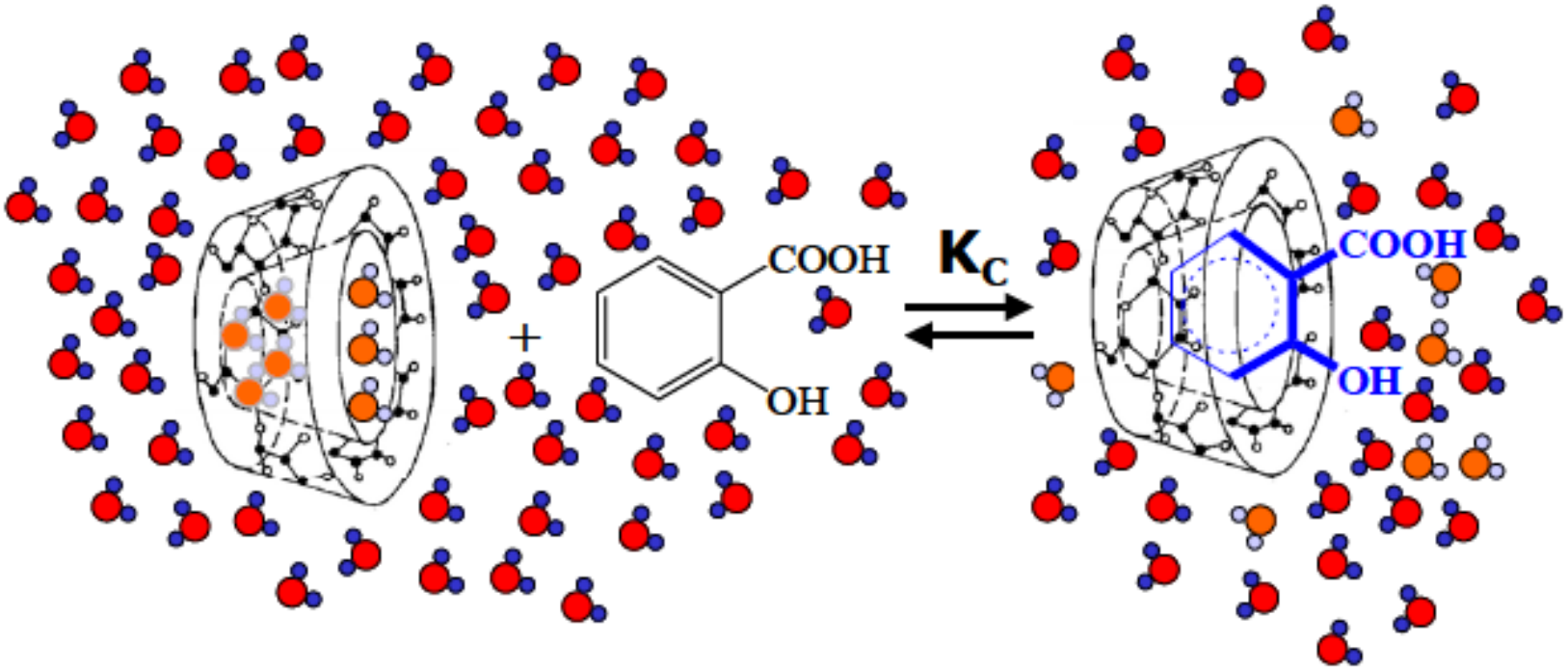
Part – 3

PART-III: BINDING OF NEUTRAL MOLECULES



Source / Materials:

1. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry, Second Edition*, John Wiley & Sons, Ltd: West Sussex, U.K., **2009**.
2. Steed, J. W.; Turner, D. R.; Wallace, K. J. *Core Concepts in Supramolecular Chemistry and Nanochemistry*, John Wiley & Sons: West Sussex, U.K., **2007**.
3. Cragg, P. J. *Supramolecular Chemistry: From Biological Inspiration to Biomedical Applications*, Springer: Dordrecht, **2010**.
4. Lehn, J. -M. *Supramolecular Chemistry: Concepts & Perspectives*, Wiley-VCH: Weinheim, **1995**.
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BINDING OF NEUTRAL MOLECULES

- The host-guest binding of a neutral (usually organic) molecule may occur *via* its physical imprisonment either as part of a solid-state network, forming a solid-state inclusion compound (clathrate), or a metal-organic framework complex or within the cavity of a solution species such as a ***cavitand*** (a molecule such as a calixarene possessing a permanent and intrinsic guest-binding cavity).
- In general, the binding of neutral, non-polar organic molecules in non-polar solvents by the majority of cavitands is relatively weak because there is no significant enthalpic gain from strong host–guest interactions.
- Solid-state complexes are widespread, however, because of the need to pack efficiently in the crystal lattice – unfilled holes are relatively unstable and hence very uncommon because there is a loss of stabilization from the van der Waals interactions between all molecules.
- In solution, interactions between the guest and the host may be either very limited (*e.g.* van der Waals interactions) or of significant stability (*e.g.* hydrogen bonds). Significant binding of polar or charged molecular guests is observed in many hosts, with binding of alkyl ammonium cations being particularly common.
- In non-polar solvents such binding often takes the form of specific host-guest dipole–dipole or hydrogen-bond interactions, often with charge assistance (*i.e.* the interaction is strengthened by ion–dipole interactions). Hydrophobic portions of the guest are sequestered within hydrophobic portions of the host.

TYPES OF INTERACTIONS IN MOLECULAR HOST-GUEST COMPLEXES

- **Hydrophobic binding.** The hydrophobic effect can have both enthalpic and entropic components, although the classical hydrophobic effect is entropic only. Studies on the associations between planar aromatic molecules show an approximately linear relationship between the interaction energy and their mutual contact surface area with slope 64 dyn cm^{-1}, very close to the macroscopic surface tension of water (72 dyn cm^{-1}). Hence, in the absence of specific host or guest interactions with the solvent the hydrophobic effect can be calculated solely from the energy required to create a free surface of 1 $Å^2$ which amounts to 7.2×10^{-12} J or 0.43 $kJÅ^{-2}$ mol^{-1}.

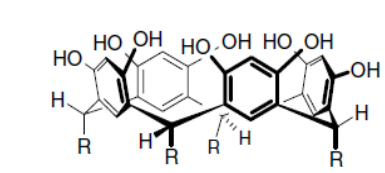
- **Induced dipolar interactions.** The electron clouds in many (especially large) organic molecules are readily polarised resulting in the formation of induced dipoles that can interact, resulting in complex stabilization. Both cations and anions can induce dipoles in aromatic molecules, for example.

- **π-π Interactions and charge transfer.** Stacking interactions between an electron poor and electron rich partner can result in the transfer of electron density from the HOMO of the donor to the low-lying LUMO of the acceptor. The viologens (*N*,*N*′-disubstituted-4,4′-bipyridyl derivatives) for example are particularly electron-poor and form charge transfer complexes on complexation with the host.

- **Hydrogen bonding.** Hydrogen bonding in neutral molecule complexes is most significant in non-polar solvents where the polar hydrogen bonding donor and acceptor groups are relatively unsolvated.

CAVITANDS

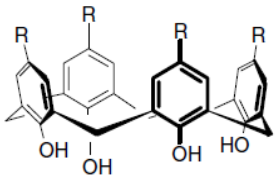
- Individual host molecules possessing an intrinsic cavity that is present in both the solid state and in solution are termed ***cavitands***. A cavitand is defined as a molecular container with an enforced, concave surface. The molecular cavity is generally open at one end. Inclusion of guest species within a cavitand results in a ***cavitate*** (or caviplex).
- Molecules or fragments that possesses intrinsic curvature (*i.e.* are structurally bent or curved) may be used to bind guest molecules in both solution as well as the solid state since dissolution of the host does not result in disappearance of the cavity. A range of examples of synthetically accessible cavitands and curved precursors that have been used to host molecular guests are shown below.



[4]resorcarene

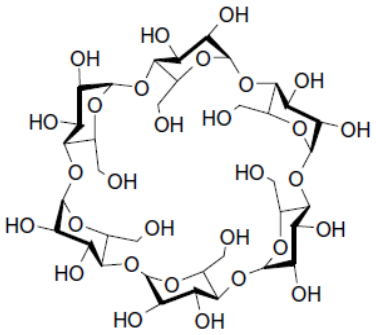
6.3

R = CH_3, CH_2CH_2Ph *etc.*



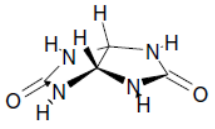
calix[4]arene R = H, CH_3, t-Bu

3.118



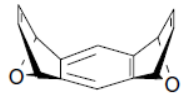
α-cyclodextrin

6.7



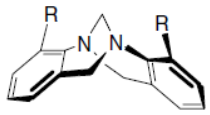
Glycoluril

6.4



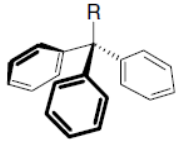
Kohnkene precursor

6.5



Tröger's base

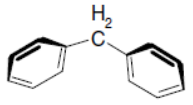
6.6



triphenylmethane

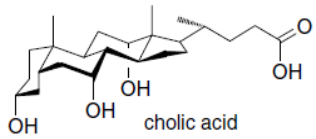
R = H, Me

6.8



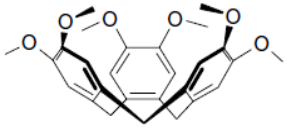
diphenylmethane

6.9



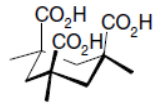
cholic acid

6.11



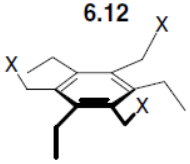
CTV

6.10



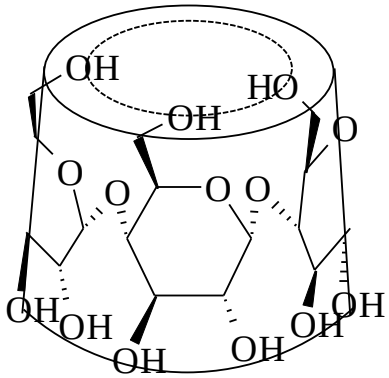
Kemp's triacid

6.12

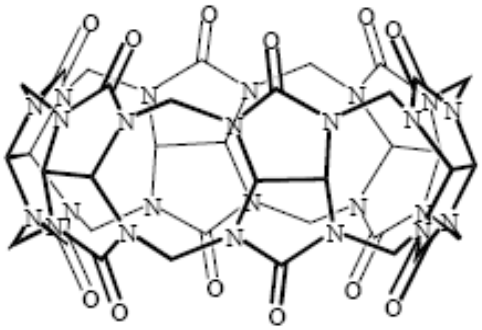


MACROCYCLIC RECEPTORS

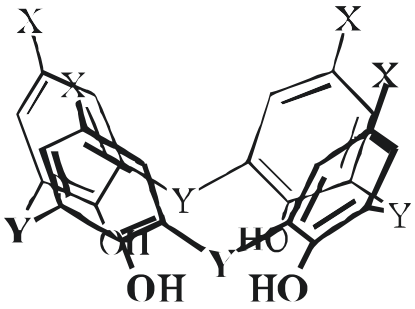
Cyclodextrins

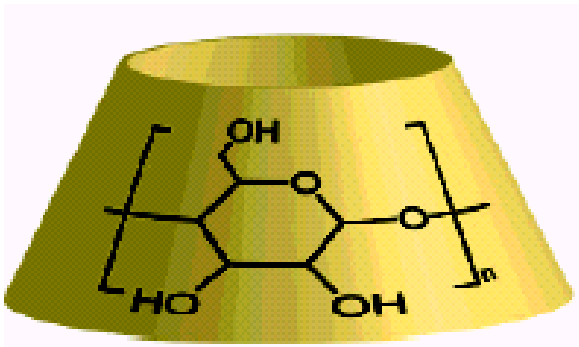


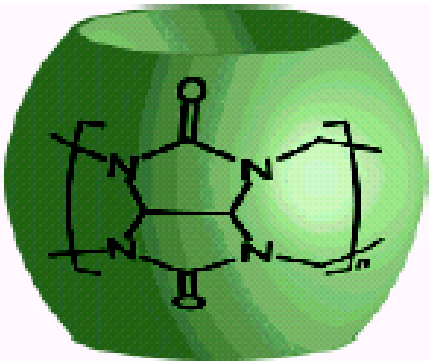
Cucurbiturils

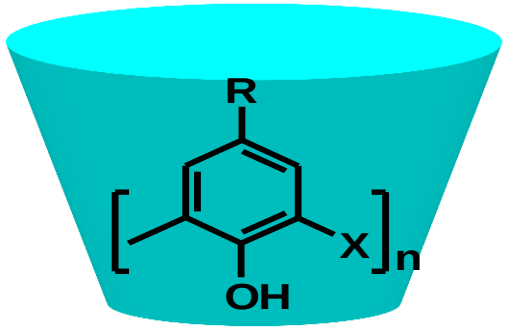


Calixarenes

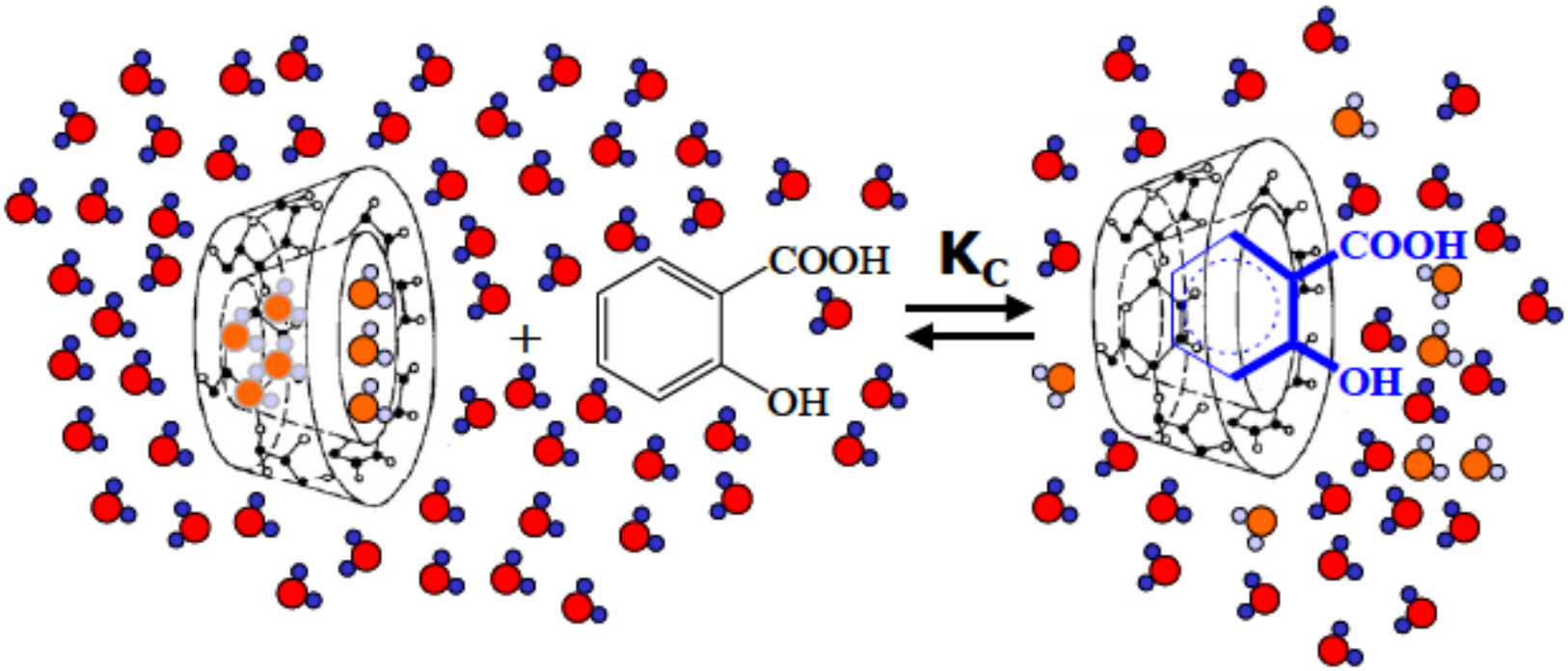








CYCLODEXTRINS

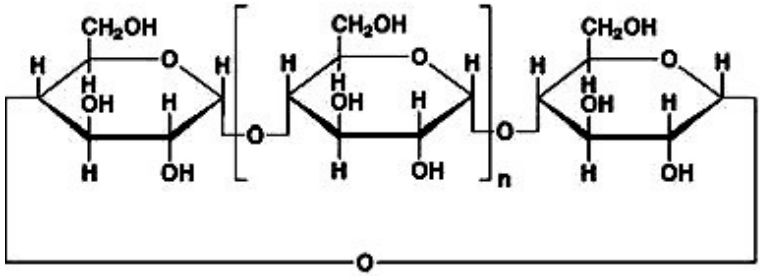


HISTORY OF CYCLODEXTRINS

- Cyclodextrins, as they are known today, were called "cellulosine" when first described by A. Villiers in 1891. Soon after, F. Schardinger identified the three naturally occurring cyclodextrins -α, -β, and -γ. These compounds were therefore referred to as "Schardinger sugars".
- For 25 years, between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrating that cyclodextrins formed stable aqueous complexes with many other chemicals.
- By the mid- 1970s, each of the natural cyclodextrins had been structurally and chemically characterized and many more complexes had been studied. Since the 1970s, extensive work has been conducted by Szejtli and others exploring encapsulation by cyclodextrins and their derivatives for industrial and pharmacologic applications.

CYCLODEXTRINS

- Cyclodextrins are formed by the action of cyclodextrin glucosyltransferase enzyme (CGTase) on the medium containing starch.
- Cyclodextrins are macrocyclic oligosaccharides containing at least six D-(+)- glucopyranose units attached by α (1-4) bonds.
- One of the important feature of cyclodextrins is their ability to form inclusion complexes with a variety of compounds, by entrapping their molecules inside the cyclodextrin cavity, which act as a host.



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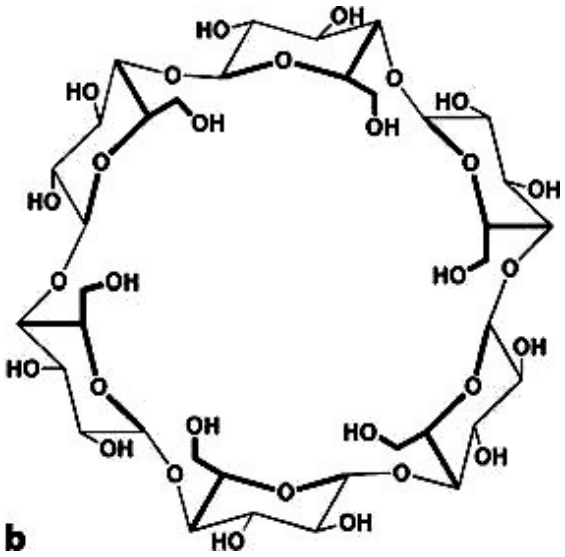

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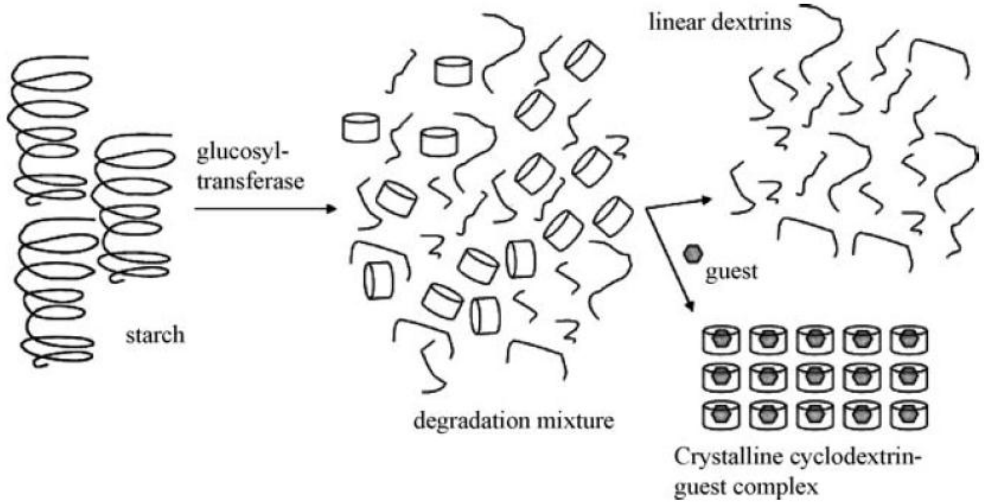
CYCLODEXTRINS

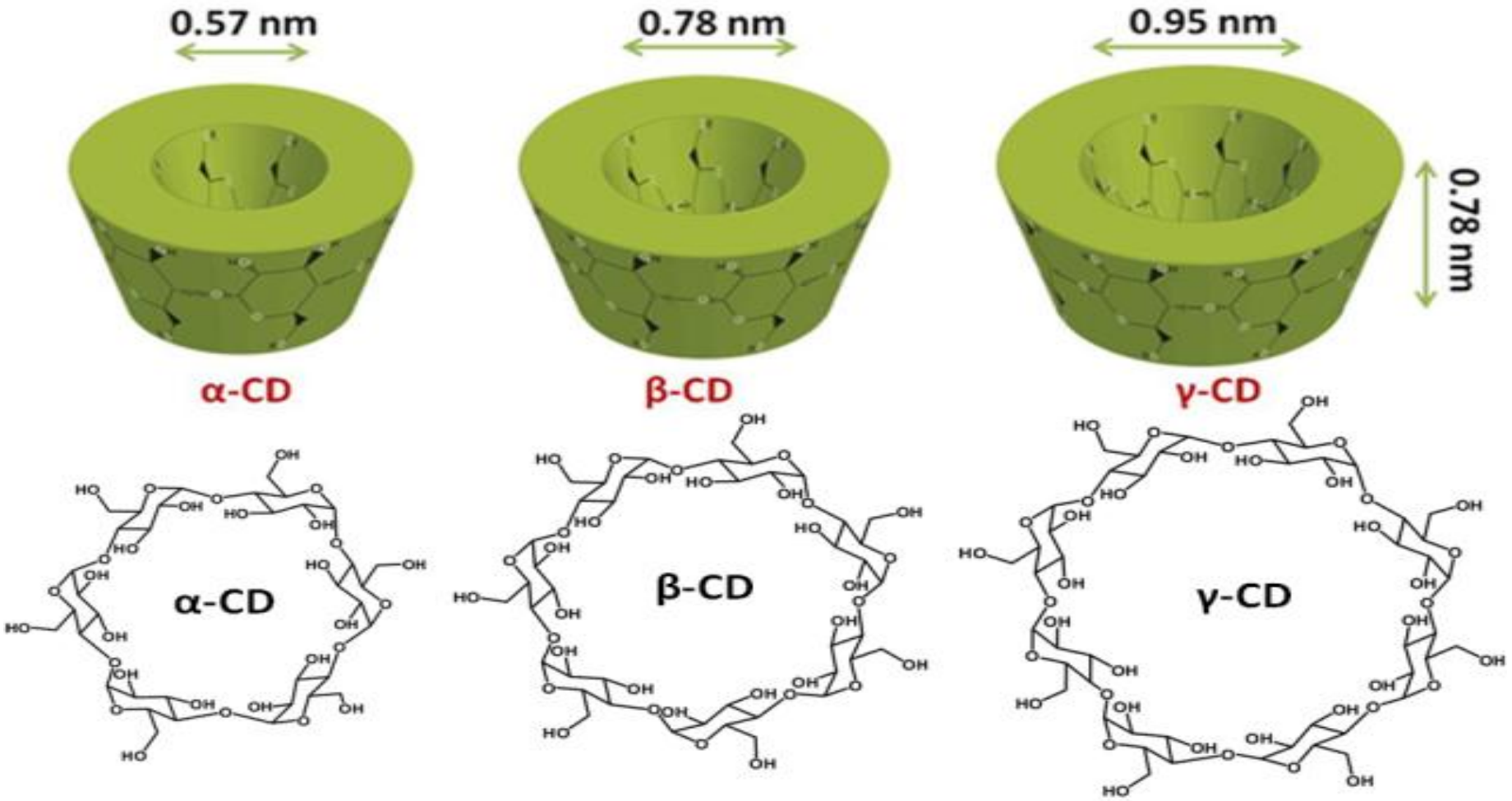
- It is a Complexing agent.
- Synonym: cavitron, cycloamyloses, cycloglucan, cyclic oligosaccharide.
- Cyclodextrins (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides).
- Cyclodextrins are non- reducing, crystalline , water soluble, cyclic, oligosaccharides.
- Cyclodextrins consist of glucose monomers arranged in a donut shape ring.
- It is a important for increasing the solubility of poorly water soluble drugs.
- Cyclodextrins are produced from starch by means of enzymatic conversion.
- They are used in food, pharmaceutical, drug delivery, and chemical industries, as well as agriculture and environmental engineering.
- Cyclodextrins are composed of 5 or more α-D glucopyranoside units linked 1>4, as in amylose linkage.

SYNTHESIS OF CYCLODEXTRINS

- The production of cyclodextrin is relatively simple and involves treatment of ordinary starch with a set of enzymes.
- Commonly cyclodextrin glucosyltransferase (CGTase) is employed along with α-amylase.
- First starch is liquefied either by heat treatment or using α-amylase, then CGTase is added for the enzymatic conversion.
- CGTases can synthesize all forms of cyclodextrins thus the product of the conversion results in a mixture of the three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used: each CGTase has its own characteristic α:β:γ synthesis ratio.

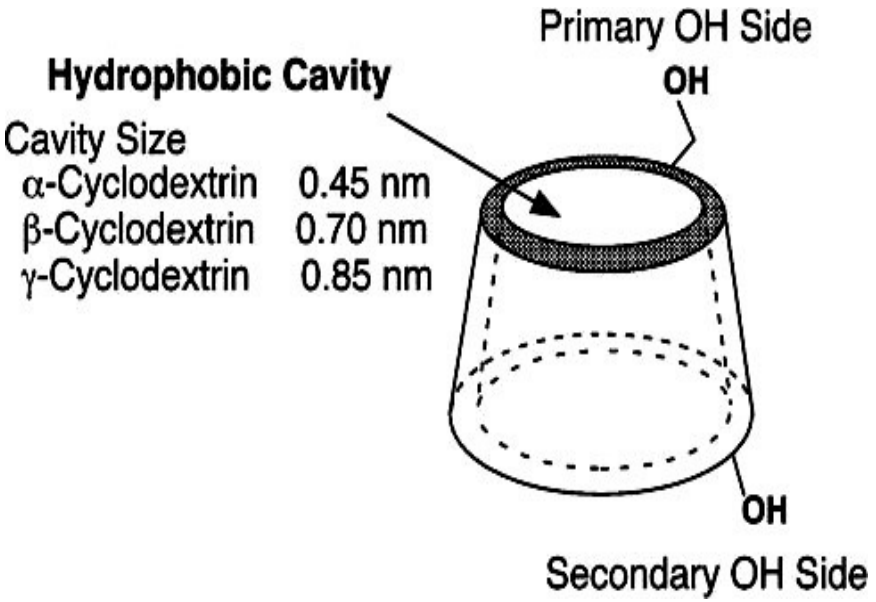


Cyclodextrins contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4- configuration to form rings of various diameters.



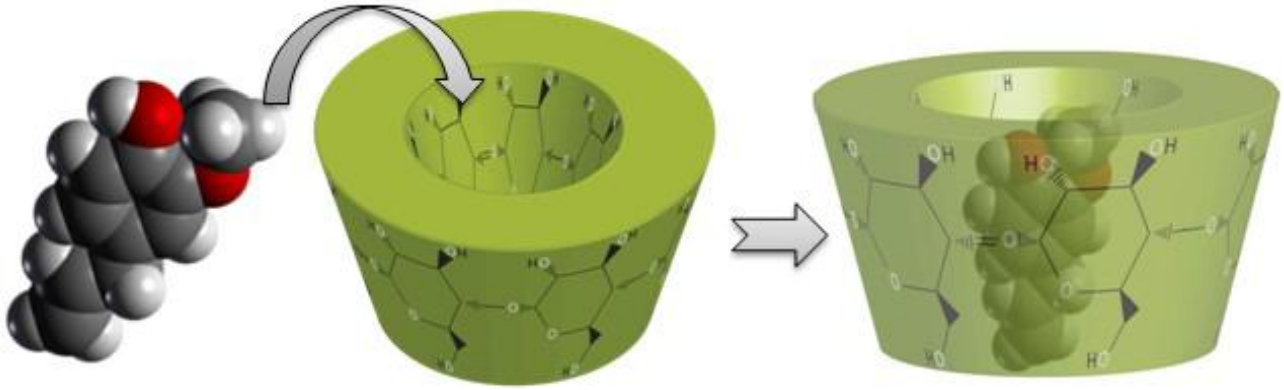
STRUCTURAL DESIGN

- These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface.
- Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders.
- Primary hydroxyl groups are located at the side of a narrow inlet, while secondary hydroxyl groups are found on the reverse side (at the side of a wide inlet).
- Therefore, no hydroxyl groups exist on the wall, and so the cavity of the cyclodextrin is hydrophobic.
- Cyclodextrins dissolved in an aqueous phase can accommodate hydrophobic guests such as aromatic hydrocarbons (benzene), inorganic ions & gas molecules in their cavities.

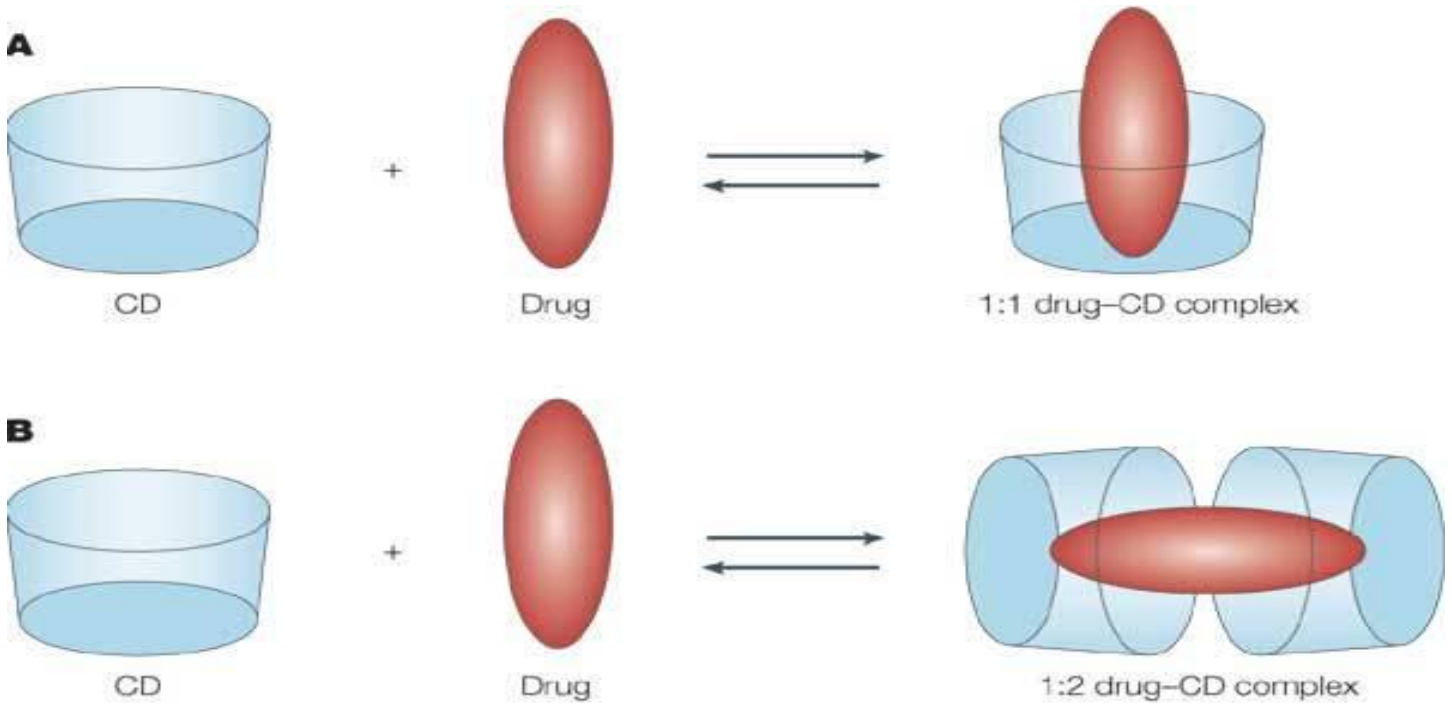


INCLUSION COMPLEX

- Internal hydrophobic cavity is the key feature for complex formation.
- The surface of the cyclodextrins molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized nonpolar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrins complex.
- The ring has a hydrophilic exterior and lipophilic(hydrophobic) core in which appropriately sized organic molecules can form non-covalent inclusion complexes.
- The complex formed results- Increased solubility, Increased dissolution rate, Increased stability, Decreased volatility.
- Complexation relies on relatively weak force such as **London forces, hydrogen bonding and hydrophobic interactions.**

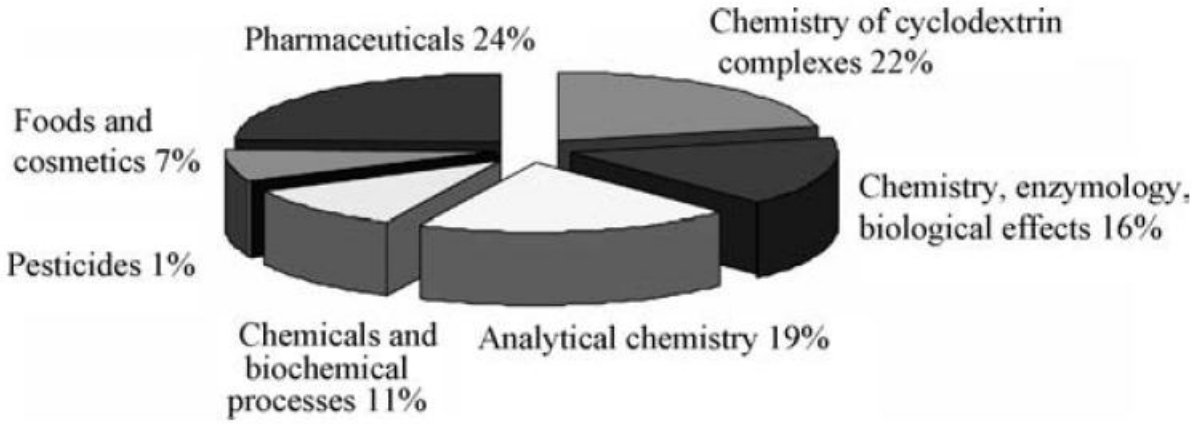


- The surface of the cyclodextrins molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized nonpolar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrins complex.
- Inclusion complexation with agents such as β-cyclodextrin (β-CD) is one method to **increase the aqueous solubility** of a poorly water-soluble drug and **thereby its stability and bioavailability**.



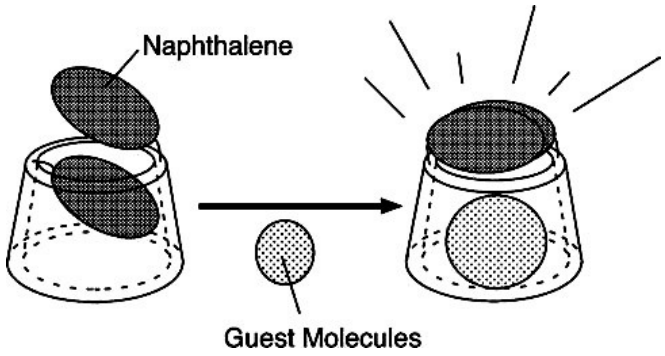
APPLICATIONS

- Because cyclodextrins are hydrophobic inside and hydrophilic outside, they can form complexes with hydrophobic compounds. Thus they can enhance the solubility and bioavailability of such compounds. This is of high interest for pharmaceutical as well as dietary supplement applications in which hydrophobic compounds shall be delivered. Alpha-, beta-, and gamma-cyclodextrin are all generally recognized as safe by the FDA.
- In the food industry, cyclodextrins are employed for the preparation of cholesterol free products: the bulky and hydrophobic cholesterol molecule is easily lodged inside cyclodextrin rings that are then removed.
- Due to its surface-active properties, α-cyclodextrin can also be used as emulsifying fiber, for example in mayonnaise as well as a whipping aid, for example in desserts and confectionary applications.

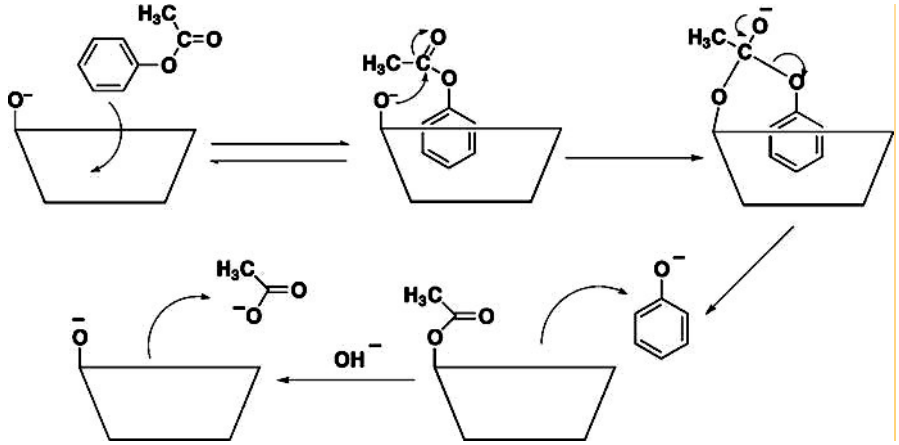


APPLICATIONS

1. Dimer naphthalene formation results in stronger emission Inclusion of a guest inside the cavity of a cyclodextrin induces light emission.



2. Hydrolysis of phenyl acetate by cyclodextrin to phenol & acetate by artificial enzyme, where a cyclodextrin cavity works as a hydrophobic binding site and hydroxyl groups play the role of a catalytic residue.



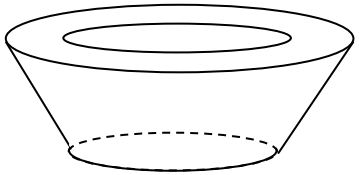
APPLICATIONS IN DRUG DELIVERY SYSTEM

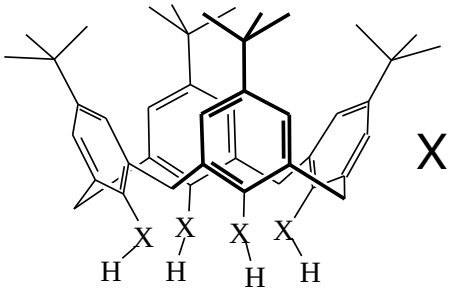
- Oral drug delivery
- Parenteral drug delivery
- Nasal drug delivery
- Rectal drug delivery
- Controlled drug delivery
- Peptide & protein delivery
- Dermal & transdermal delivery
- Liposomes
- Microcapsules
- Nanoparticles

CALIXARENES

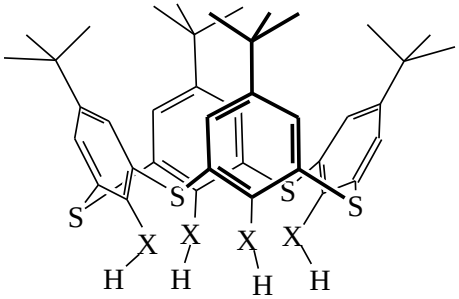
Calyx

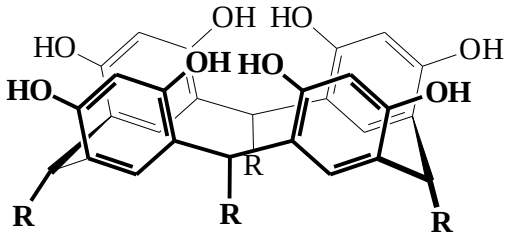
CPK-Model

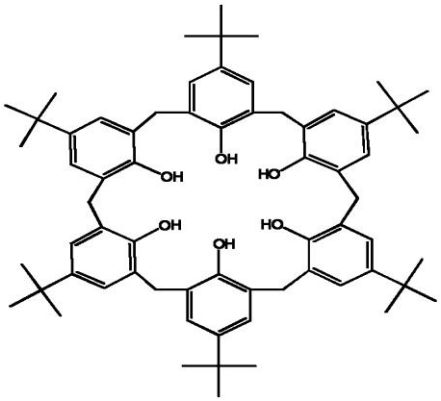


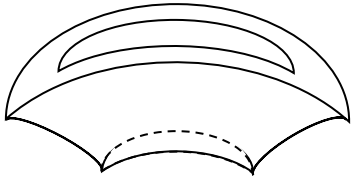


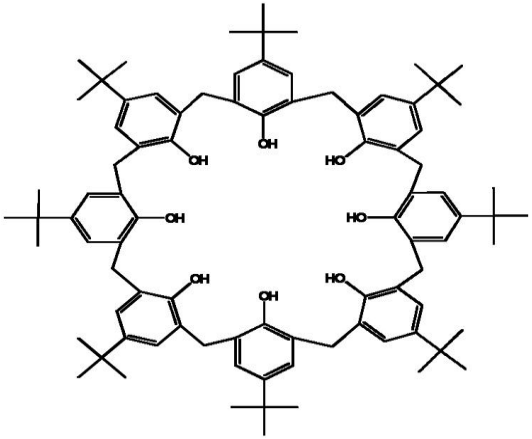
X=O, S, NH

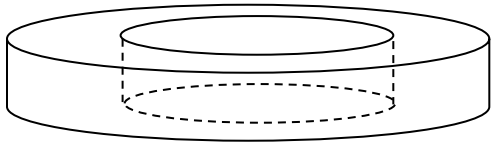






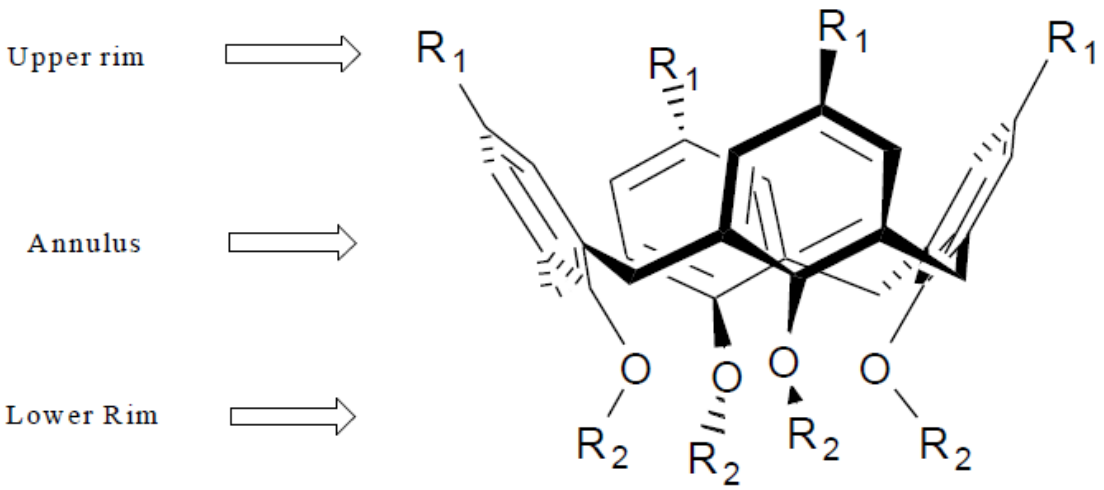




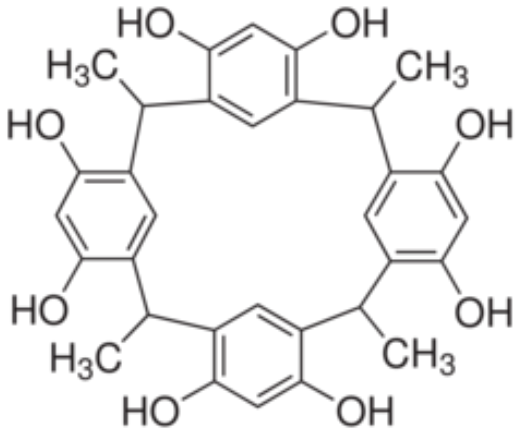


CALIXARENES

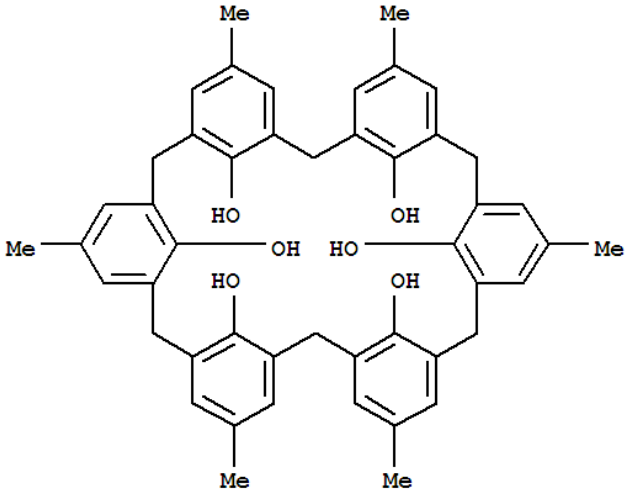
- The calixarenes are a class of cyclic oligomers formed via a phenol-formaldehyde condensation.
- They exist in a ‘cup’ like shape with a defined upper and lower rim and a central annulus.
- Their rigid conformation enables calixarenes to act as host molecules as a result of their preformed cavities. By functionally modifying either the upper and/or lower rims it is possible to prepare various derivatives with differing selectivity for various guest ions and small molecules.
- Calixarenes and its derivatives can be used to complex a range of cations, anions and neutral molecules.



- The word calixarene is derived from calix or chalice because this type of molecule resembles a vase and from the word arene that refers to the aromatic building block.
- Calixarenes have hydrophobic cavities that can hold smaller molecules or ions and belong to the class of cavitands known in Host-guest chemistry.
- Calixarene nomenclature is straightforward and involves counting the number of repeating units in the ring and include it in the name. A calix[4]arene has 4 units in the ring and a calix[6]arene has 6. A substituent in the meso position $\mathbf{R_b}$ is added to the name with a prefix C- as in C-methyl calix[6]arene.



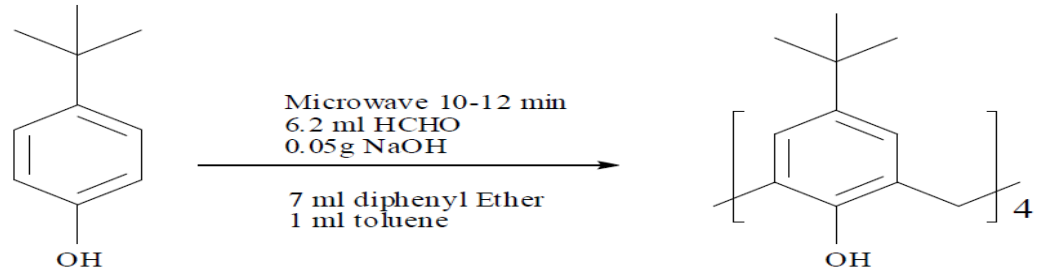
C-Methyl calix[4]resorcinarene



p-Methyl calix[6]arene

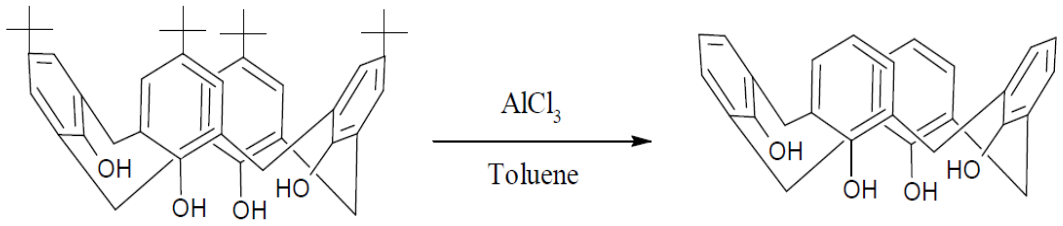
SYNTHESIS

- The synthesis of p-tertbutylcalix[4]arene were carried out for the first time by using base-catalysed condensation of p-substituted phenol and formaldehyde using microwave irradiation with an improvement of yield to 90-95%
- The aromatic components are derived from phenol, resorcinol or pyrogallol.
- For phenol, the aldehyde most often used is simply formaldehyde, while larger aldehydes (acetaldehyde, or larger) are generally required in condensation reactions with resorcinol and pyrogallol.
- The chemical reaction ranks under electrophilic aromatic substitutions followed by an elimination of water and then a second aromatic substitution.
- The reaction is acid catalyzed or base catalyzed.



p-tert butyl phenol

tert-butylcalix[4]arene

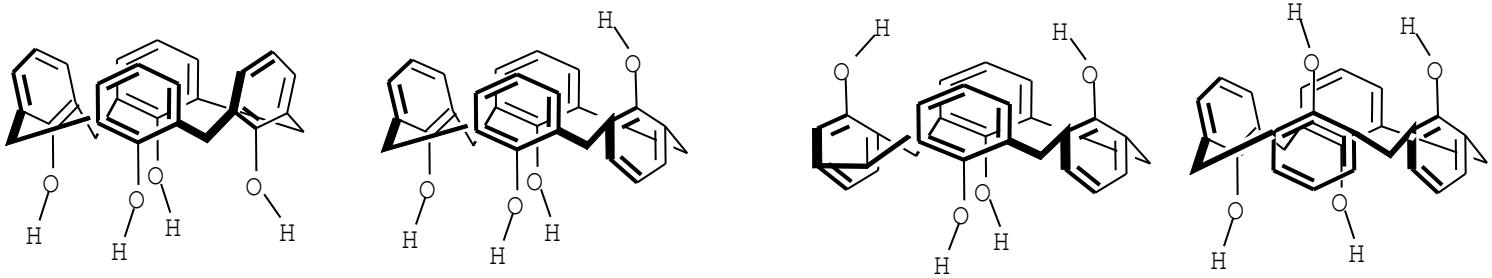


p-tert butyl calix[4]arene

Calix[4]arene

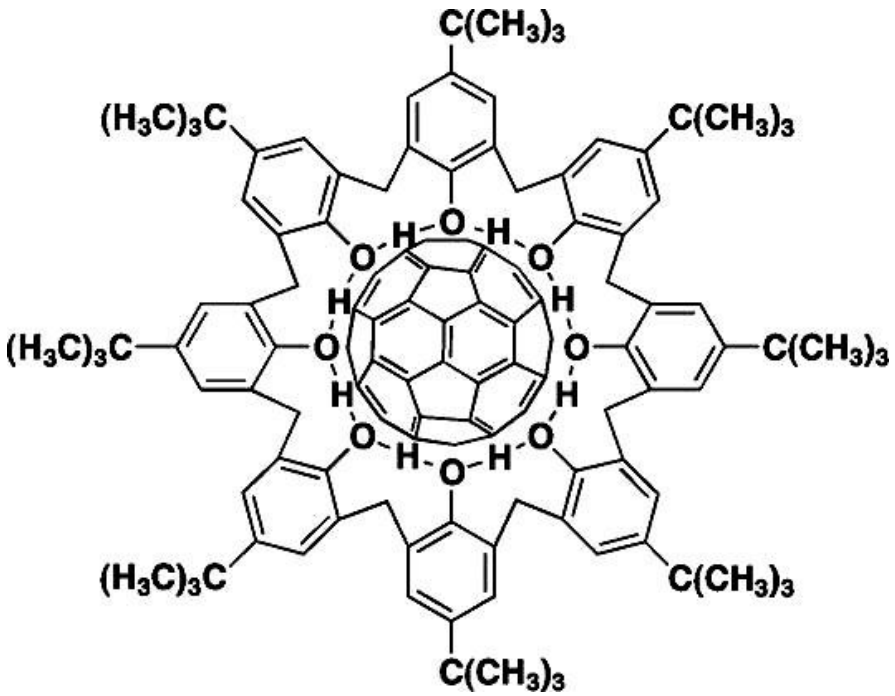
STRUCTURE

- Calixarenes are characterized by a three-dimensional basket, cup or bucket shape. Calixarenes are characterized by a wide upper rim and a narrow lower rim and a central annulus.
- With phenol as a starting material the 4 hydroxyl groups are intra annular on the lower rim. In a resorcin[4]arene 8 hydroxyl groups are placed extra annular on the upper ring.
- Calixarenes exist in different chemical conformations because rotation around the methylene bridge is not difficult.
- In calix[4]arene 4 up-down conformations exist: cone (point group C_{2v},C_{4v}), partial cone C_s, 1,2 alternate C_{2h} and 1,3 alternate D_{2d}. The 4 hydroxyl groups interact by hydrogen bonding and stabilize the cone conformation. This conformation is in dynamic equilibrium with the other conformations. Conformations can be locked in place with proper substituents replacing the hydroxyl groups which increase the rotational barrier. Alternatively placing a bulky substituent on the upper rim also locks a conformation.
- Out of these conformations, 'Cone' conformer is by far the most common and stable due to cyclic network of intramolecular hydrogen bonds between the -OH groups at the lower rim.



Cone ***Partial Cone*** ***1,3-Alternate*** ***1,2-Alternate***

The calix[8]arene depicted in Fig. can bind fullerenes



Binding of fullerene by Calix[8]arene

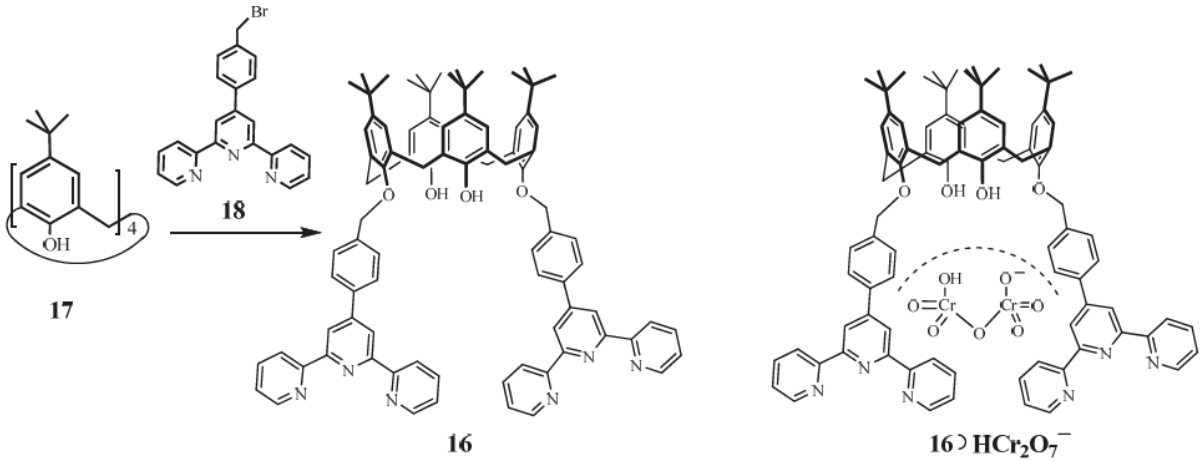
The calix[8]arene has a cavity with an inner diameter of ~1nm, which is therefore suitable for C60, since it has a diameter of ~0.7nm. So in the figure 10 we can see the fullerene “soccer ball” is trapped in the calix.

APPLICATIONS

- Calixarenes are applied in enzyme mimetics, ion sensitive electrodes or sensors, selective membranes, non-linear optics and in HPLC stationary phase. In addition, in nanotechnology calixarenes are used as negative resist for high-resolution electron beam lithography.
- Calixarenes are able to accelerate reactions taking place inside the concavity by a combination of local concentration effect and polar stabilization of the transition state. An extended resorcin[4]arene cavitand is found to accelerate the reaction rate of a Menshutkin reaction between quinuclidine and butyl bromide by a factor of 1600.
- Calixarenes are efficient sodium ionophores and are applied as such in chemical sensors. With the right chemistry these molecules exhibit great selectivity towards other cations.
- Calixarenes are used in commercial applications as sodium selective electrodes for the measurement of sodium levels in blood.
- Calixarenes also form complexes with cadmium, lead, lanthanides and actinides. Calix[5]arene and the C_{70} fullerene in p-xylene form a ball-and-socket supramolecular complex. calixarenes also form exo-calix ammonium salts with aliphatic amines such as piperidine.

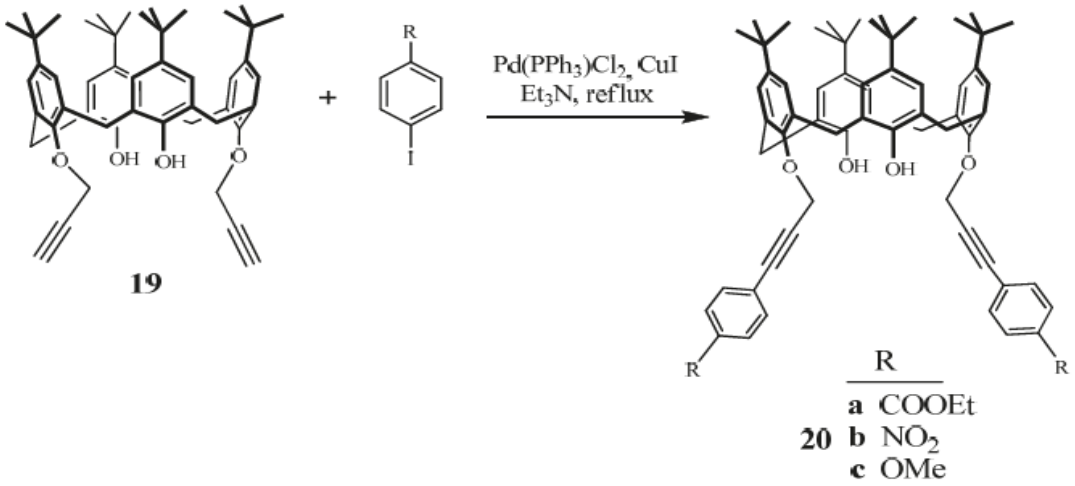
Sensing of $Cr_2O_7^{2-}$ and $HCr_2O_7^-$ ions

- It is known that dichromate oxo anions are highly toxic. Chromium and its derivatives are transmitted to groundwater in trivalent and hexavalent forms, and their influence on the environment is significant.
- In the experiments the anion extraction properties of “proton-switchable” calix[4]arene bearing terpyridine moieties have been investigated.Their luminescent properties allow the fluorescent recognition of a target.
- It was established that the complexation efficiency of dichromate anions depends on the hydrogen-binding ability and proton-switchable ability of calixarene.
- The obtained results have shown that **Calixarene** is promising for the removal of dichromate anions from environmental aqueous solutions.



SENSING OF *O*- AND *P*-NITROPHENOLS

- Palladium-catalyzed Sonogashira cross-coupling reactions are very important in syntheses of fluorescent calixarenes which combine properties of ionophores and fluorophores. This method was used for coupling of calixarene **19** with *para*-substituted iodobenzene, affording calixarene derivatives **20a-c**

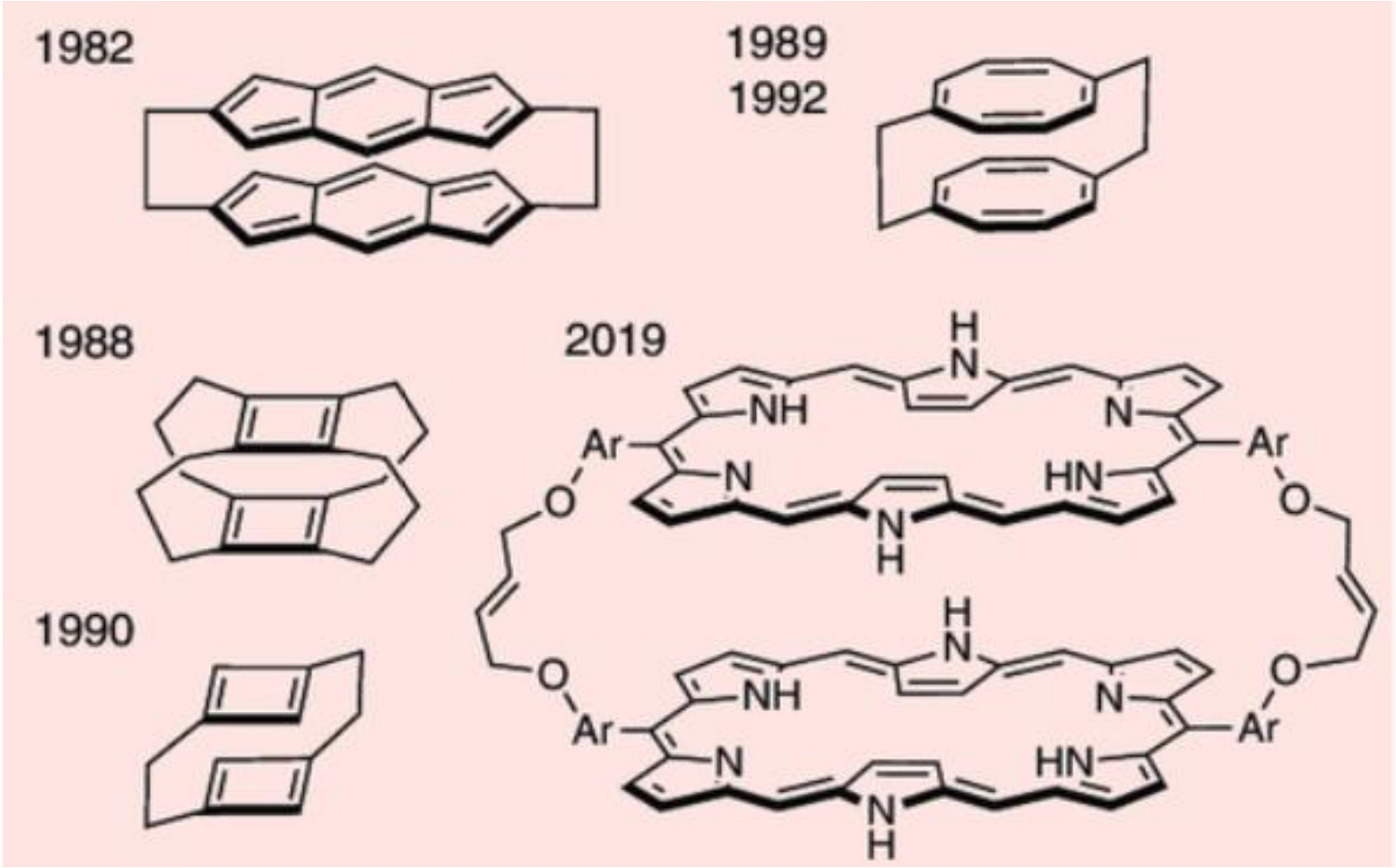


19

20

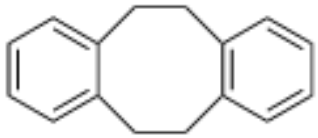
- It was observed that the calixarene **20c** has a high binding affinity to nitrophenols since its fluorescence is strongly quenched by *o*- and *p*-nitrophenols. The computational calculations of the complex of **20c** with *p*-nitrophenol have shown that the ∏-∏ stacking occurring between **20c** and *p*-nitrophenol forms a tweezer structure, which leads to electron transfer and results in the fluorescence quenching of **20c**

CYCLOPHANES

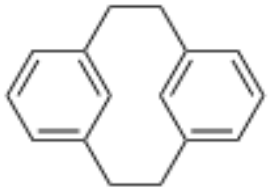


CYCLOPHANE– 3 DIMENSIONAL CAVITIED HOST

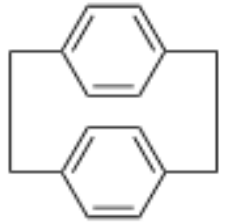
- Cyclophanes are strained organic molecules which contain aromatic ring(s) as well as aliphatic unit(s). Cyclophane means any organic molecule containing a bridged aromatic ring. The aromatic rings provide rigidity to their structure, whereas the aliphatic unit(s) form bridge(s) between the aromatic rings and also provide flexibility to the overall structure.
- Cyclophanes play an important role in "host–guest" chemistry and supramolecular assembly."Phane"-containing molecules show interactions with π-systems, and they can also bind to a large number of cations, anions, and neutral molecules. Cyclophanes are widely used in materials science and molecular recognition processes.
- A general classification of cyclophanes is as follows: [*n*]orthocyclophane, [*n*]metacyclophane, and [*n*]paracyclophane.



4
[2,2]orthocyclophane



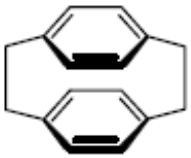
5
[2,2]metacyclophane



6
[2,2]paracyclophane

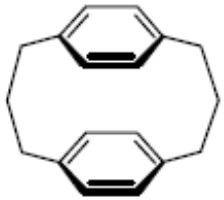
CYCLOPHANE NOMENCLATURE

- Cyclophane chemistry can be traced back at least as far as 1899 when Pellegrin prepared [2.2]metacyclophane. In general, any aromatic ring bridged by at least one aliphatic *n*-membered bridge with $n \geq 0$ is termed a cyclophane (a contraction of cyclo phenylene alkane). The number of atoms, *n*, in each bridge is denoted in square brackets in front of the name 'cyclophane', starting with the longest one along with a designator (ortho-, meta- or para- or numbers in brackets) indicating the substitution pattern of the aromatic ring(s).



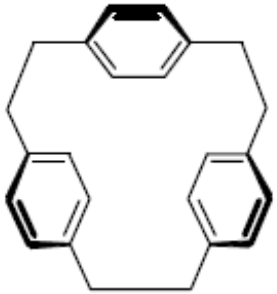
[2.2]paracyclophane

6.54



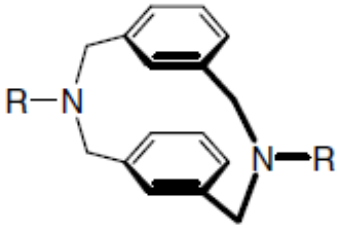
[3.3]paracyclophane

6.55



[2.2.2]paracyclophane

6.56

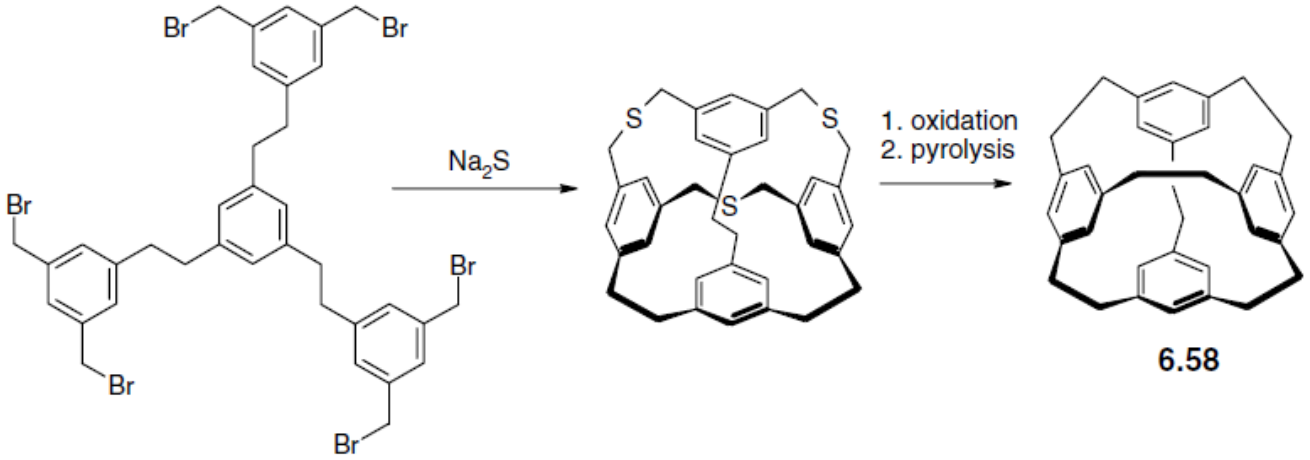


diaza[3.3]metacyclophane

6.57

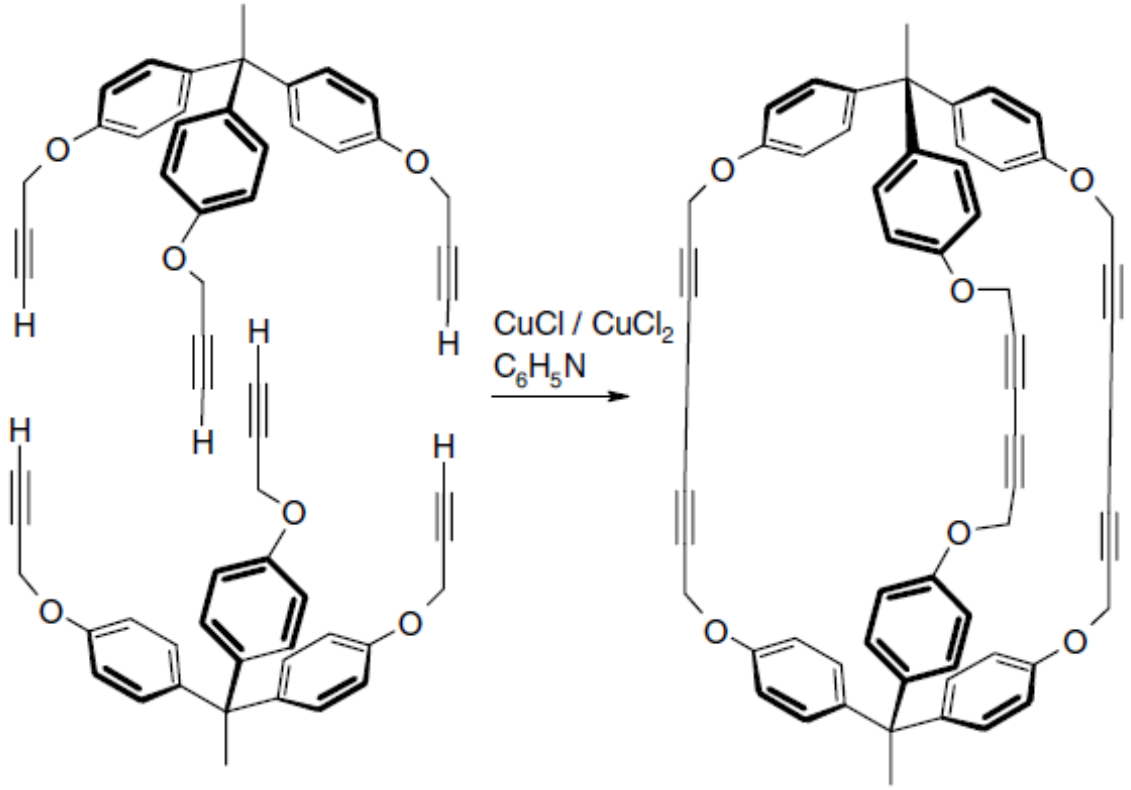
CYCLOPHANE SYNTHESIS

- Cyclophane synthesis necessarily involves the closure of medium - to large-sized rings and is therefore always problematic because of competing oligomerisation and polymerization reactions. Some common Techniques are listed below.
- Nucleophilic substitutions involving sulfur, and sulfur extrusion reactions. Sulfur is much more reactive than oxygen as a consequence of the greater acidity of the SH functionality. Intermediate thioethers may be oxidized to the corresponding SO or SO_2 derivatives, and pyrolysis results in sulfur extrusion to give the corresponding C-C bonded species.



6.58

- Copper-catalysed alkyne coupling.



IRON MAIDENS CYCLOPHANES

Highly sterically strained cyclophanes that exhibit bonding way outside the normal realm of chemistry.

- Deformation of the aryl rings as a consequence of steric strain with interesting consequences on its electronic structure.
- Cyclophane **3.93** is synthesised by sulfur extrusion from a larger precursor. This size reduction results in the *endo* CH bond becoming highly compressed because of a repulsive interaction with the aromatic ring. The CH bond is sterically crushed up against the arene and its IR frequency rises from a typical value of *ca.* 2900 cm^{-1} for aliphatic CH stretches to 3325 cm^{-1}.
- This means the bond is getting in effect stronger since IR frequency is related to the square root of the bond force constant. It is this 'crushing' that gives these kinds of compound their 'iron maiden' nickname

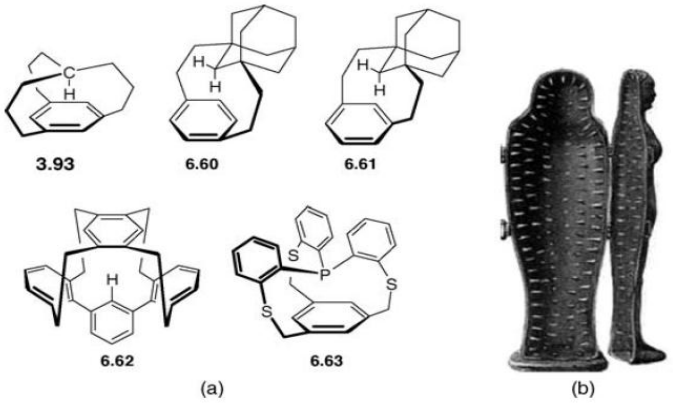
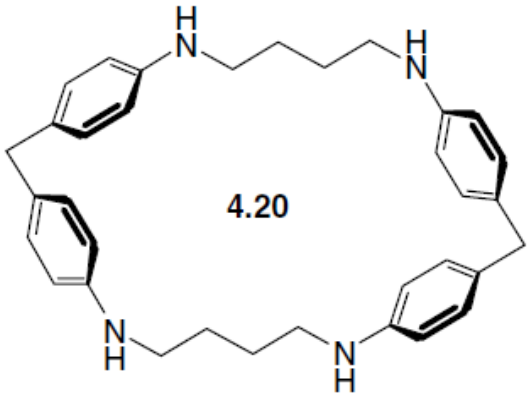
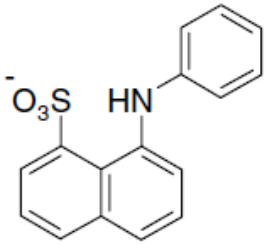


Figure 6.32 (a) 'iron maiden' cyclophanes exhibiting severe steric compression and (b) the real thing – a medieval iron maiden torture device.

CYCLOPHANE HOSTS

Macrocycle **4.20** binds anions such as 1-anilino-8-naphthalenesulfonate (ANS), which is used as a fluorescent probe in order to measure host–ANS affinity spectrophotometrically. Binding of ANS relies on hydrophobic and ∏–∏ stacking interactions, as well as electrostatic interactions and hydrogen bonds, since neutral molecules are also strongly bound.





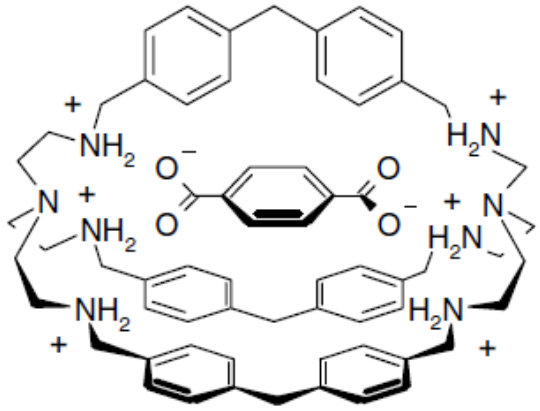
ANS

The diphenylmethane moiety is commonly used as a spacer in the construction of cyclophane hosts for both anions and neutral molecules in order to impart

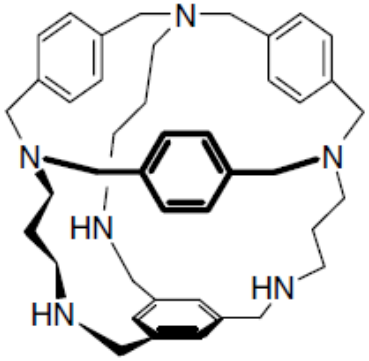
- ❑ curvature
- ❑ Rigidity
- ❑ Binding ability

CYCLOPHANE HOSTS

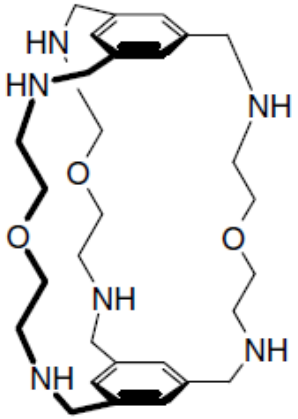
- Extending the host to three dimensions gives **4.21**, which is an effective host for terephthalate dianion.
- The X-ray crystal structure of the complex shows that the anion is encapsulated entirely by the bicyclic host system, held in place by N—H--O hydrogen bonds, hydrophobic and van der Waals interactions and ∏–∏ stacking.
- On terephthalate complexation, the two bridgehead nitrogen atoms move in towards the guest by some 1.8 Å, indicating some induced fit.
- The host also binds nucleosides with log *K* 4–5.



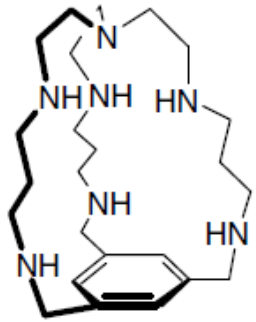
4.21.terephthalate^{2-}



4.22

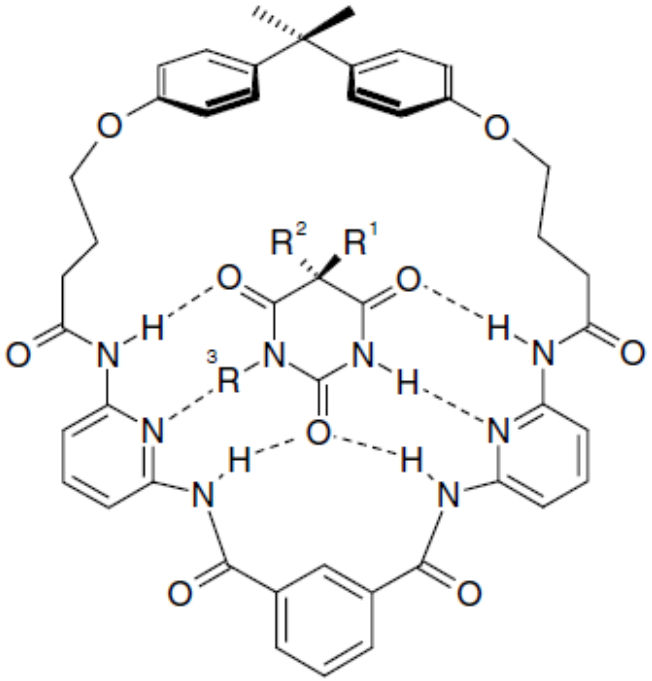


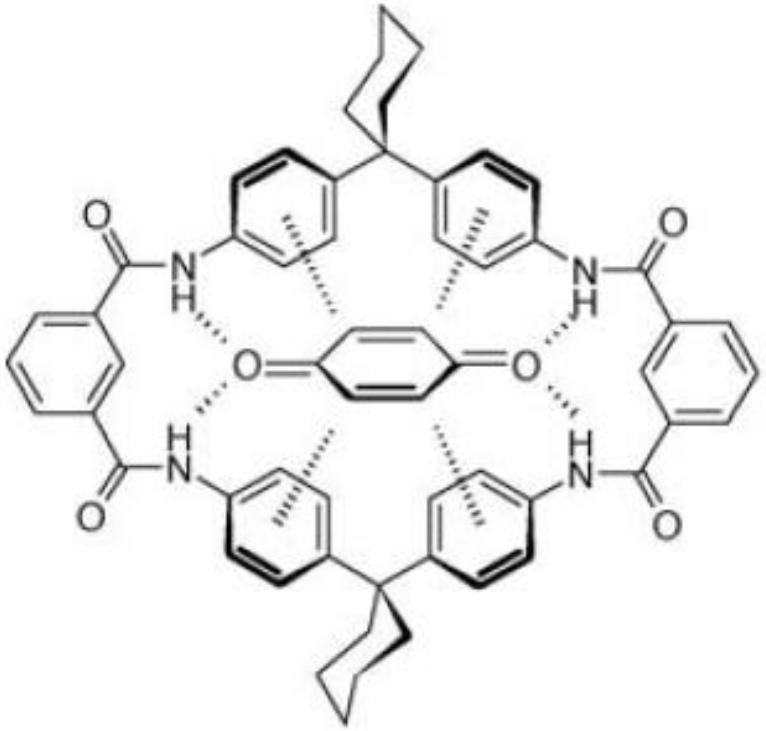
4.23



4.24

GUEST INCLUSION BY HYDROGEN BONDING





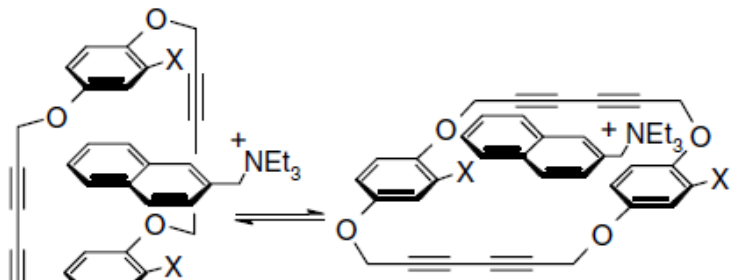
INTRACAVITY COMPLEXES-FROM TWEEZERS TO CYCLOPHANES

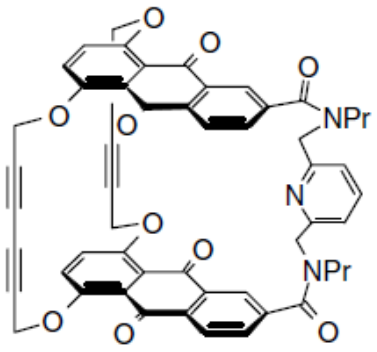
- The [8.8]para cyclophane **6.64** containing two hexadiyne bridges was prepared by Whitlock in 1980 by using Tweezer concept. Multipoint binding is incorporated by an ion-pairing interaction between the carboxylate anion and the positive charge of a 2-naphthylmethyltriethylammonium cation guest. The binding constant for this apparently complementary pair is only 55 M^{-1}, however.

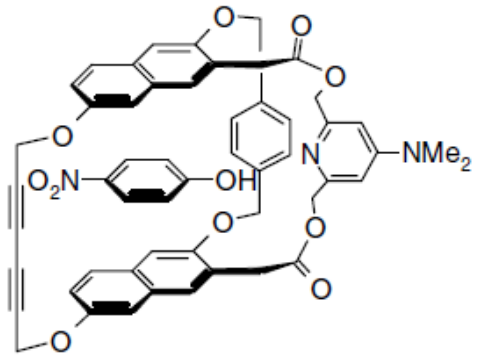
- Molecular modelling studies show that the cavity is too small for the guest and it simply does not fit within. Furthermore, an open conformation may be adopted that does not offer significant ∏–∏ stacking interactions. In response to this problem, a number of other hosts, such as **6.65**, were designed with larger cavities, which also incorporated additional preorganising bridges and hydrogen bond acceptor sites in some instances. Unfortunately, binding constants for **6.65** in $CHCl_3$ for a variety of guests were also low.

- In this case, the cavity is too large for effective guest binding, resulting in disruption of the double ∏–∏ stacking motif. It is through such apparent failures as these that Whitlock was able to recognise the importance of the key interactions of the system and the overall host–guest complementarity.

- As a compromise, host **6.66** was designed. This species uses a napthyl spacer and incorporates a hydrogen-bond accepting pyridyl moiety at the core of its bonding pocket. One of the hexadiyne bridges has also been replaced by a shorter *p*-xylyl spacer, which results in additional edge to-face ∏–∏ interactions. The association constant of this host for *p*-nitrophenol is much larger: 9.6×10^4 M^{-1} in CD_2Cl_2 solution.



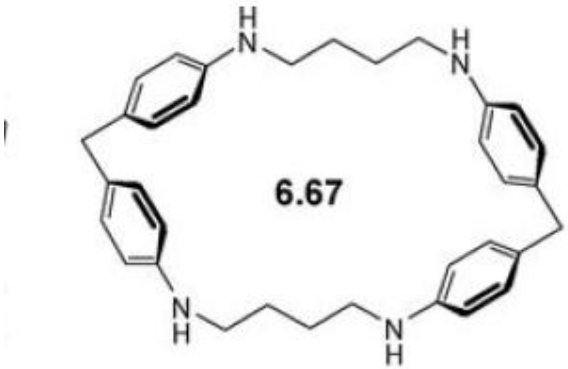


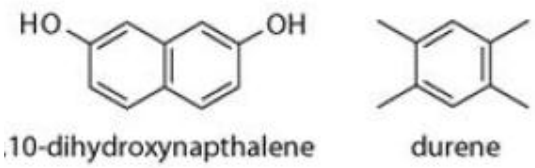


The effectiveness of the molecular tweezers may be linked to the enhancement of podand binding by the rigid end group which enhances preorganisation. Clearly, however, moving from podand-like tweezers to true cyclophanes, in which the binding pocket is part of an overall cyclic structure, should result in further binding enhancements by additional host preorganisation and entropic gains in binding affinity associated with the lowering of the degrees of host conformational freedom.

THE INTRACAVITY COMPLEXATION OF DURENE.

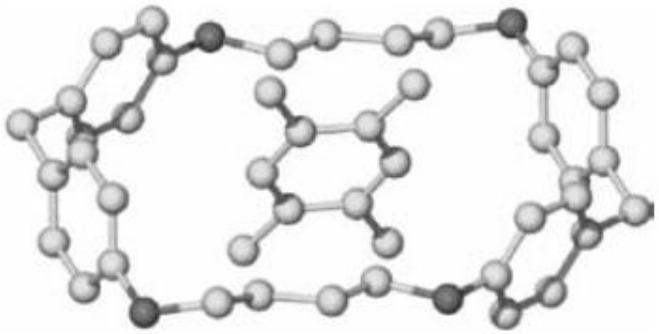
This structure provided the first definitive evidence of the inclusion of the organic guest in the centre of the macrocyclic cavity, just as suggested by simple model building. It was hence possible to design an entirely artificial cavity that could complex organic guests in water. The durene molecule is bound *via* both edge-to-face and offset face-to-face ∏–∏ stacking interactions, with the shortest C–C distance being 3.59 Å from a durene methyl group to a host aryl carbon atom.





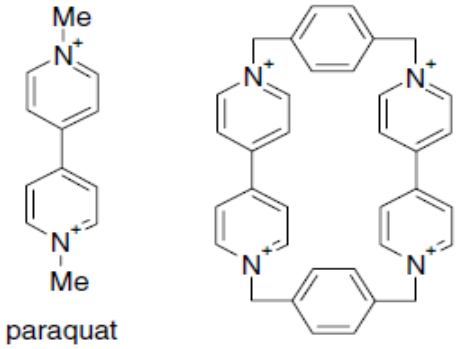
,10-dihydroxynapthalene

durene



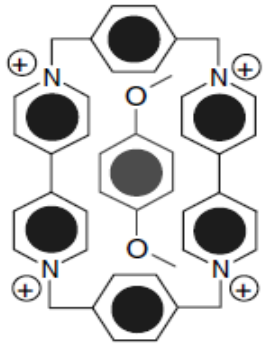
CHARGE-TRANSFER CYCLOPHANES

- In addition to cyclophane hosts based on hydrophobic and hydrogen bonding recognition, a wide range of cyclophanes and cages have been prepared based on charge-transfer interactions.
- electron-rich cyclophanes – benzo crown ether derivatives able to form attractively colored charge transfer complexes with the herbicide paraquat (*N,N´*-dimethyl-4,4´ -bipyridinium) and related electron deficient pyridinium type compounds.
- The host-guest interactions arise from face-to-face charge transfer $\prod$ -stacking and CH···O hydrogen bonding. We can readily turn the polarity of this interaction on its head to give an electron deficient paraquat-derived cyclophane **6.81** capable of binding electron rich aromatic guests such as derivatives of *p*-dimethoxybenzene.



paraquat

6.81



Stoddart representation:
"blue box" with included
p-dimethoxy benzene in red

APPLICATIONS

Chiral catalysis

- Despite the early discovery of the planar chirality of the **pCp**, its uses in catalysis were almost non-existent until 1990 with the work of Rossen, Pye *et al.* on the 4,12-bis(diphenylphosphino)-[2.2]- paracyclophane, also known as PHANEPHOS.
- Inspired by the good efficiency of the well known 2,2‟-bis(diphenylphosphino)-1,1‟-binaphtyle (BINAP) ligand, also planar chiral (Figure 13), they described this new ligand paracyclophane-based, suitable for Rhodium catalysed hydrogenations.
- The catalyst, synthesised from $Rh(COD)^{2+}OTf^{-}$ and PHANEPHOS, made possible the hydrogenation of dehydroamino acid methyl esters **14** at -45°C in methanol with very good enantiomeric excess (ee) up to 99% with complete conversion in less than 1 hour.

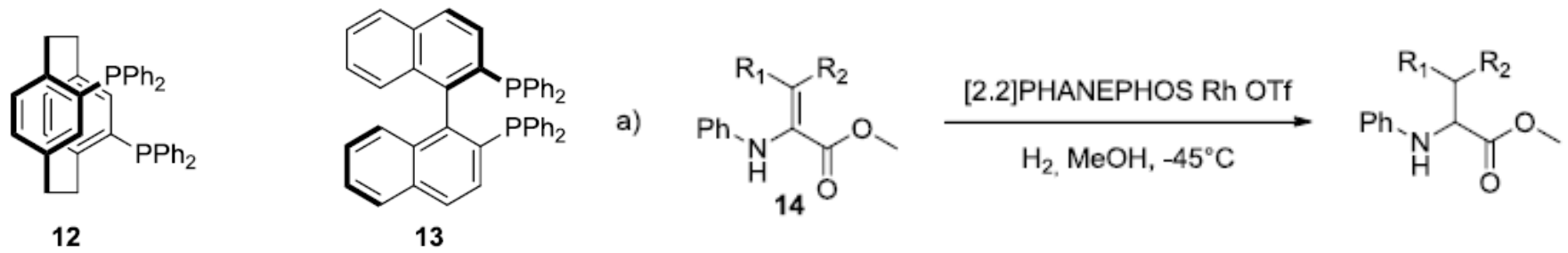
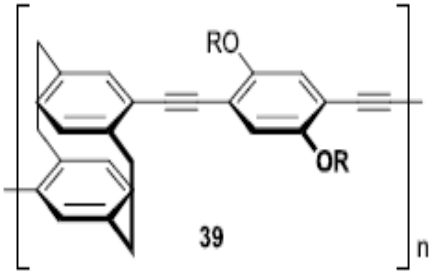


Figure 13: PHANEPHOS (**12**) and BINAP (**13**)

POLYMER MATERIALS

The first π-conjugated polymer containing [2.2]paracyclophane was synthesised by Morizaki *et al*.6 by Sonogashira coupling. Compared with the model compounds **40** and **41**, the optical properties of the polymer **39** have presented a red shift of the absorption band. These results indicated the extension of the π-delocalization length *via* the cyclophane through-space interactions.



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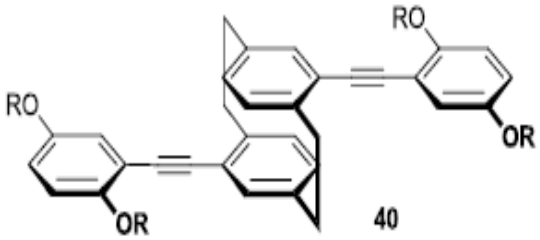

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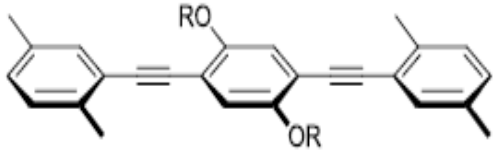

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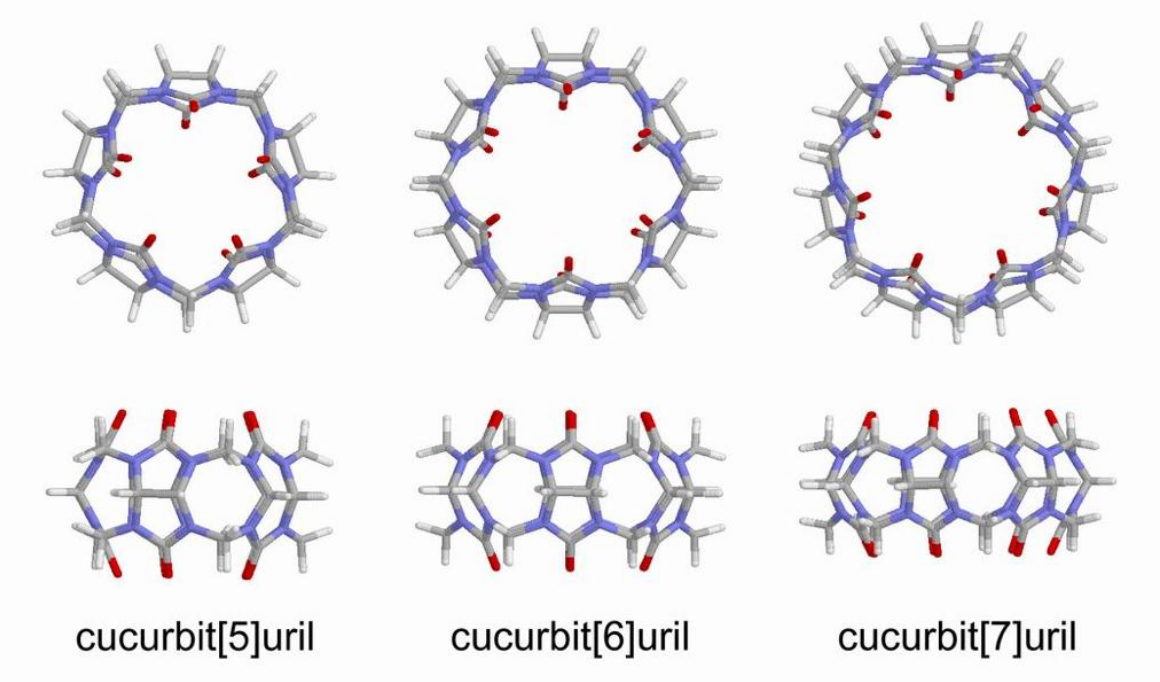
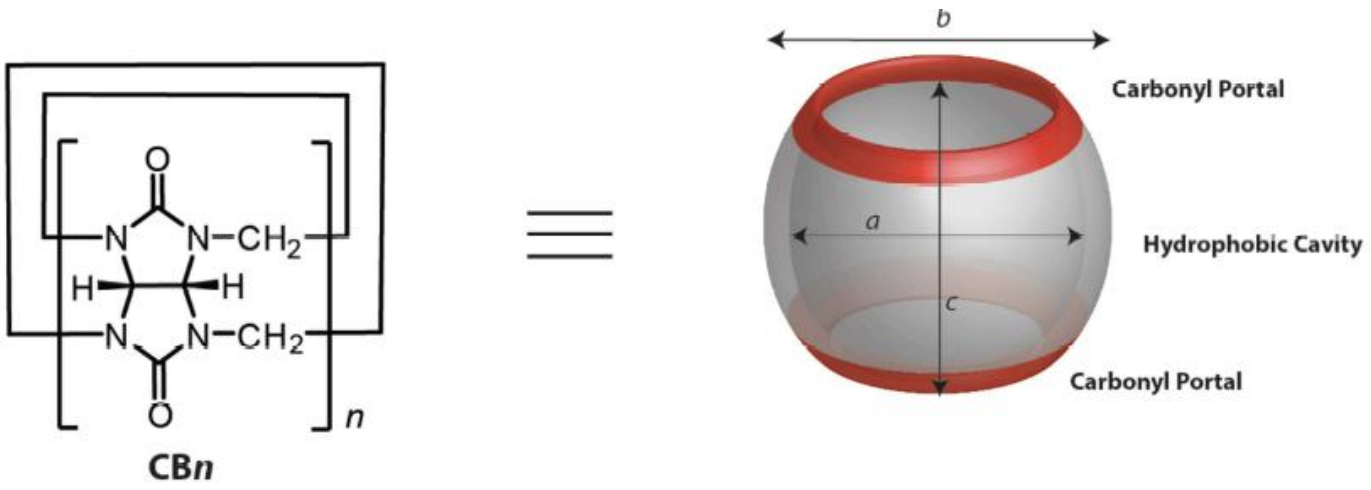
CUCURBITURILS

CUCURBITURIL

- **Cucurbiturils** are macrocyclic molecules consisting of glycoluril repeat units. These compounds are particularly interesting to chemists because they are molecular containers that are capable of binding other molecules within their cavity.
- The name is actually derived from the resemblance of this molecule with a pumpkin of the family of Cucurbitaceae. The cavity of cucurbit[6]uril has nanoscale dimensions with an approximate height of 9.1 Å, outer diameter 5.8 Å and inner diameter 3.9 Å.



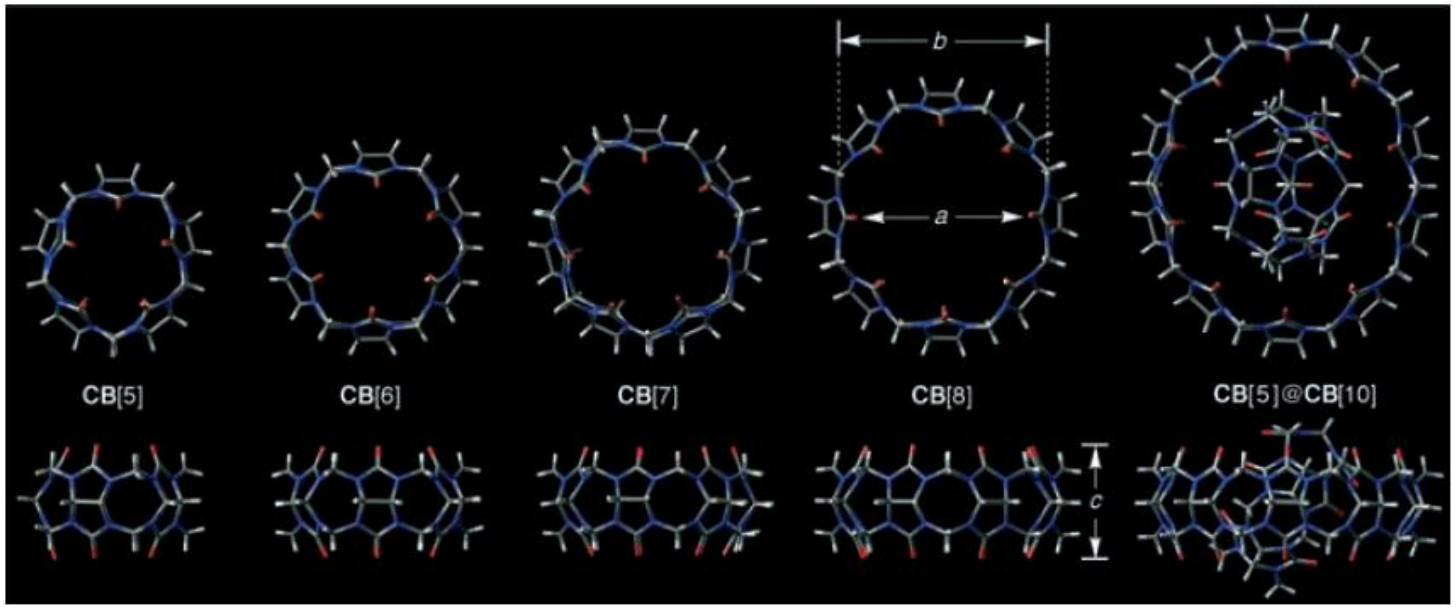
- CBs are well-known to bind a wide range of guest molecules, including small organic molecules, amino acids, peptides, and proteins. The association of guest molecules to CBs is generally driven by ion-dipole interactions, as well as the classical and non-classical hydrophobic effect.
- In recent years, CBs have come out as attractive macrocyclic hosts for applications in medicinal chemistry and chemical biology. The binding constants (Ka) of their host-guest complexes are several orders of magnitude higher than those of CDs in aqueous medium.
- Most importantly, CBs hold promise as being non-toxic and highly biocompatible.



CB*n*

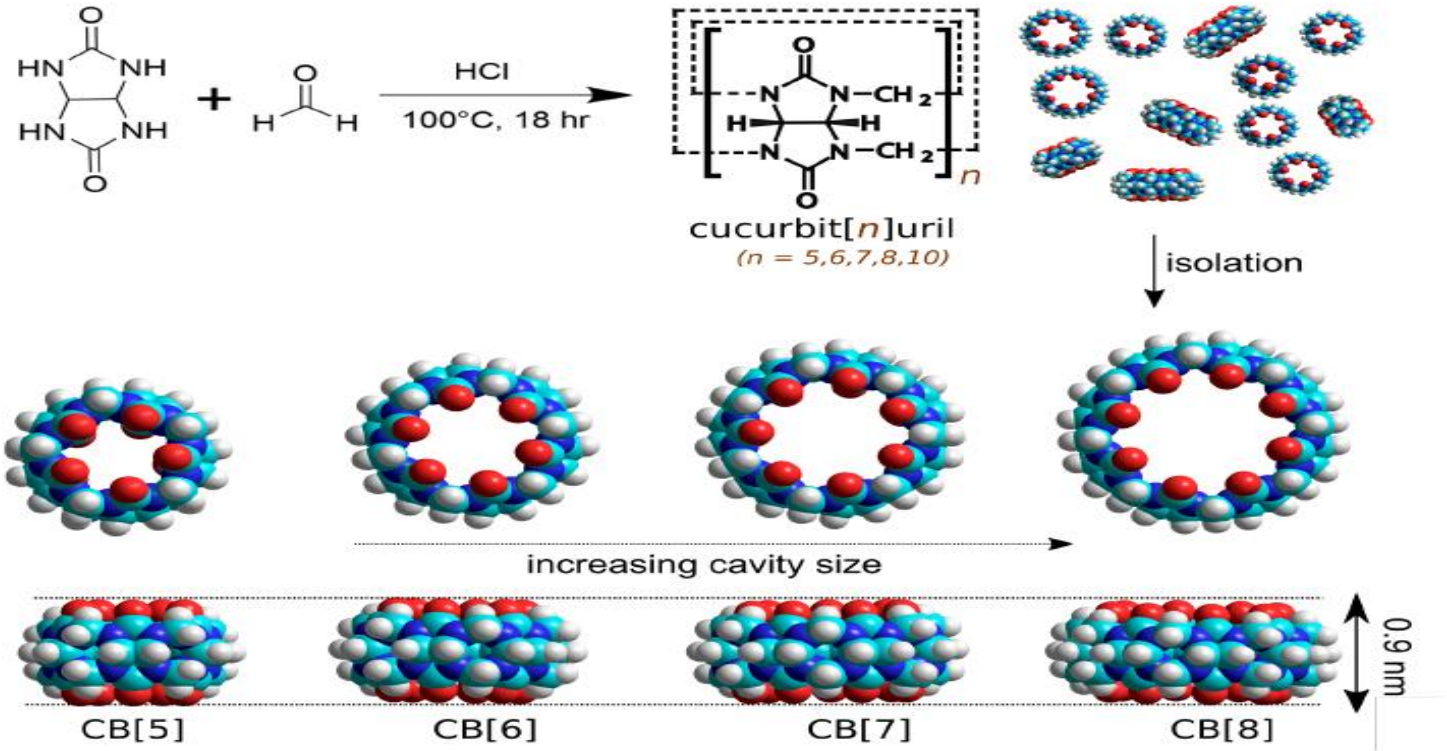
HISTORY

- The first synthesis of a cucurbituril was as early as 1905, when Behrend reported the formation of an insoluble polymer upon the condensation of glycoluril with formaldehyde in concentrated HCl. The structure of this residue was unknown.
- It wasn't until 1981 that the structure of Behrend's polymer became known, when Mock and coworkers were able to fully characterize this compound, and obtain its crystal structure. They found it to be a macrocycle, composed of glycoluril units held together with aminal linkages. Due to the general shape of this molecule, Mock named this compound cucurbituril, which is derived from the Latin word **cucurbitaceae**, for the pumpkin family.



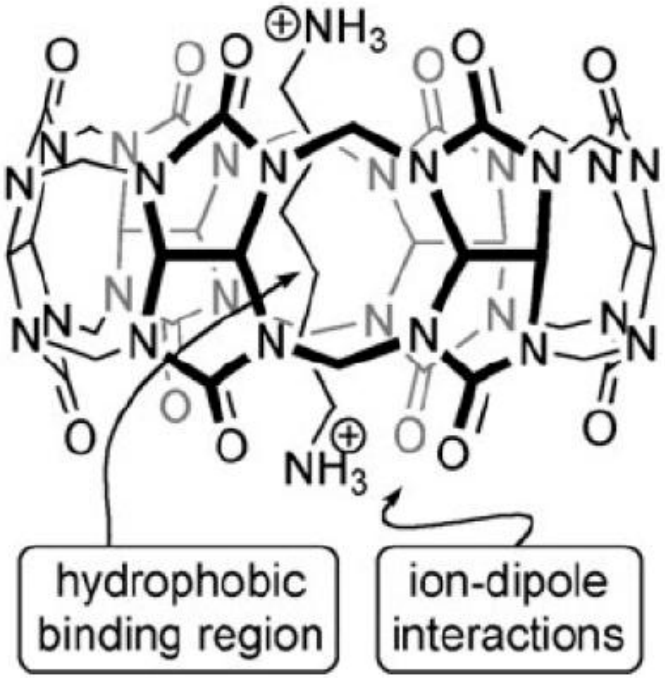
SYNTHESIS OF CB'S

- CBn (n = 5–10) are readily synthesized from the condensation of glycoluril and formaldehyde in strongly acidic media. Interestingly, though the synthesis was reported back in 1905 by **Behrend et al. (1905)** the determination of the chemical structure of CB6 took 70 years when Mock and coworkers refined it for the first time crystallographically **(Freeman et al., 1981).** CB9 is yet to be isolated, but other homologs of CBs (5–10) have in the meantime been purified.



STRUCTURE

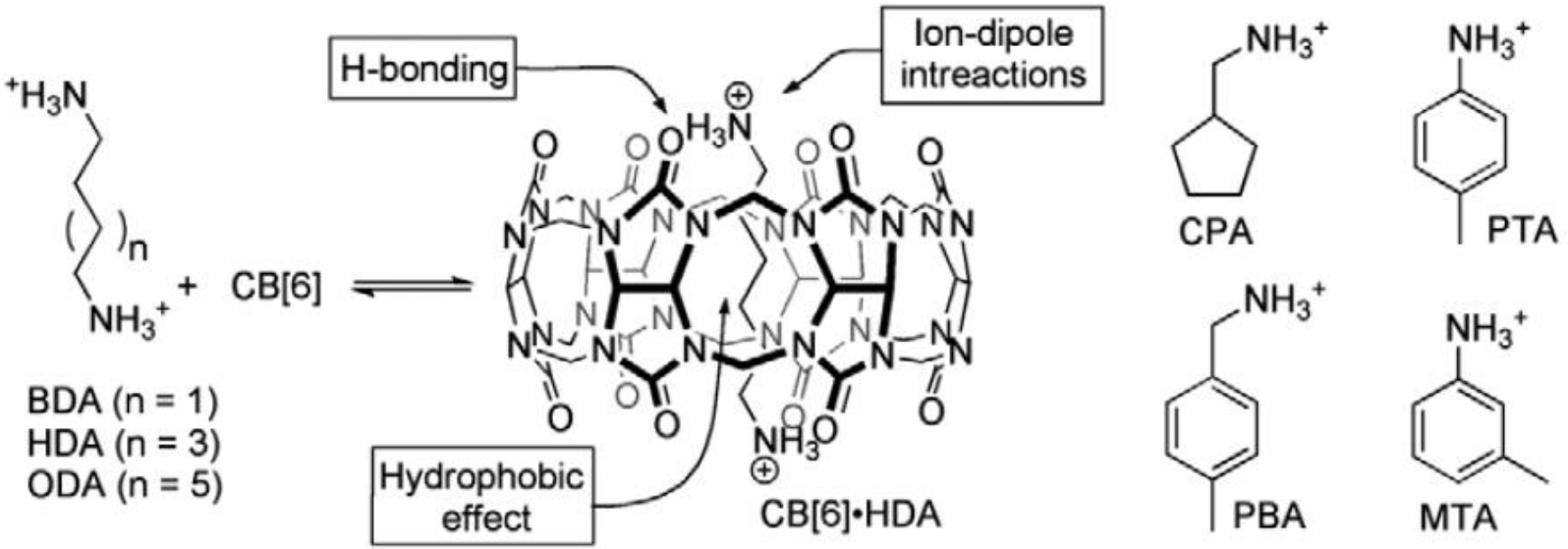
- Structural analysis of these analogs showed that CBs are macrocycles containing 5 to 10 glycoluril units connected by two methylene bridges on each side of the glycoluril segments. The cyclic structure, thus, creates two identical partially negatively charged hydrophilic carbonyl portals on each sides and a hydrophobic cavity with low polarity and polarizability.



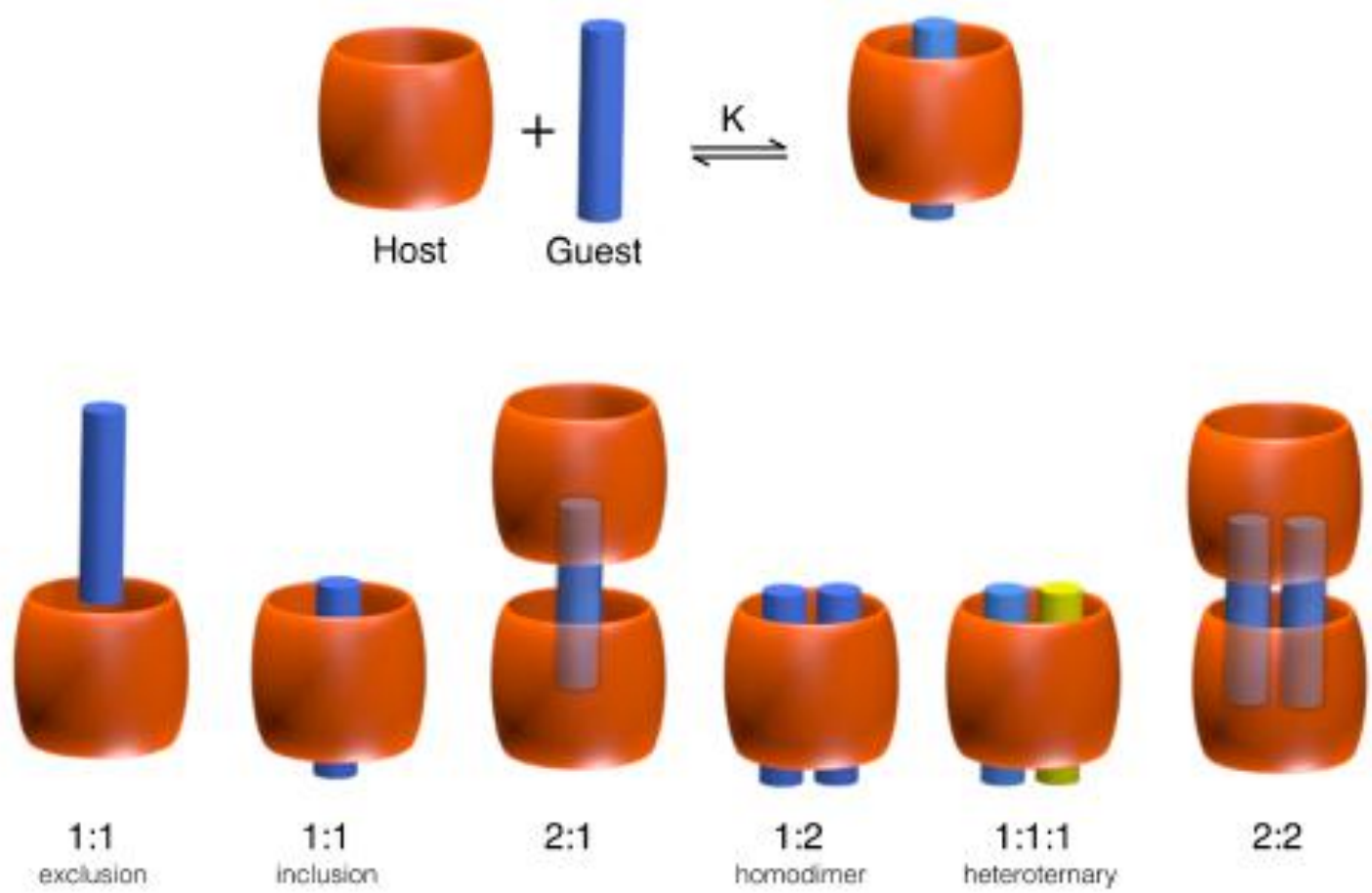
HOST-GUEST CHEMISTRY

- The cavity of the cucurbiturils hosts is nonpolar and is ideal for binding to hydrophobic guests. At the same time, the carbonyl-lined portals are electron rich and are suitable for binding to positively charged guests through electrostatic interactions.
- The CB cavity provides a hydrophobic void for the binding of neutral hydrophobic molecules, while the two identical carbonyl rims represent docking sites for positively charged groups, in most cases ammonium groups or other cations. The complexation of hydrophobic residues inside the cavity is associated with the release of high-energy water molecules from the CB cavity, which contributes to the high association constants. The size and shape of the guest molecules also modulate the binding process. An ideal binding is generally obtained when the guest volume is around 55% of that of the inner cavity of CBs.
- Among the CB homologs, CB7 can bind guest molecules with extremely high binding affinities, which exceed that of the biotin-avidin pair, the strongest non-covalent interaction between two partners found in nature. The highest binding affinity measured with CBs is 7.2×10^{17} M^{-1}, observed between CB7 and a diamantane diammonium guest molecule.

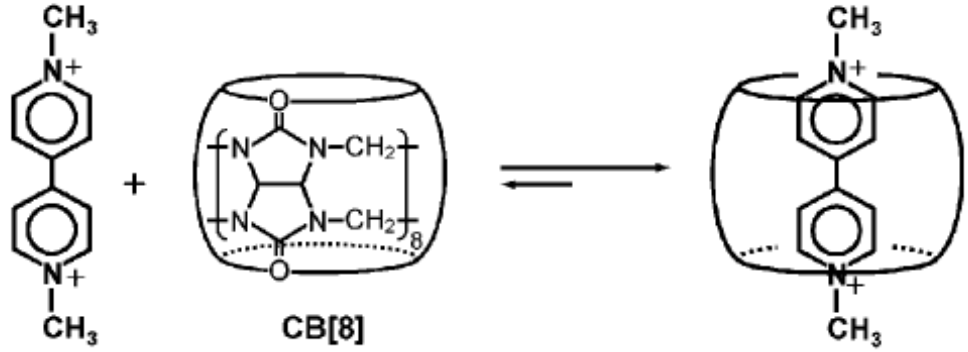
- Host guest interactions also significantly influence solubility behavior of cucurbiturils. Cucurbit[6]uril dissolves poorly in just about any solvent but solubility is greatly improved in a solution of potassium hydroxide or in an acidic solution. The cavitand forms a positively charged inclusion compound with a potassium ion or a hydronium ion respectively which have much greater solubility that the uncomplexed neutral molecule.



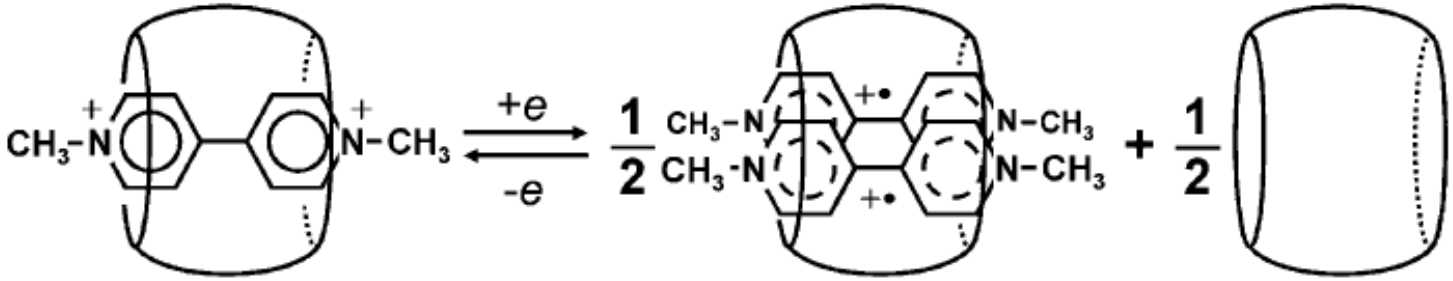
INCLUSION AND EXCLUSION COMPLEXES



INCLUSION COMPLEXES



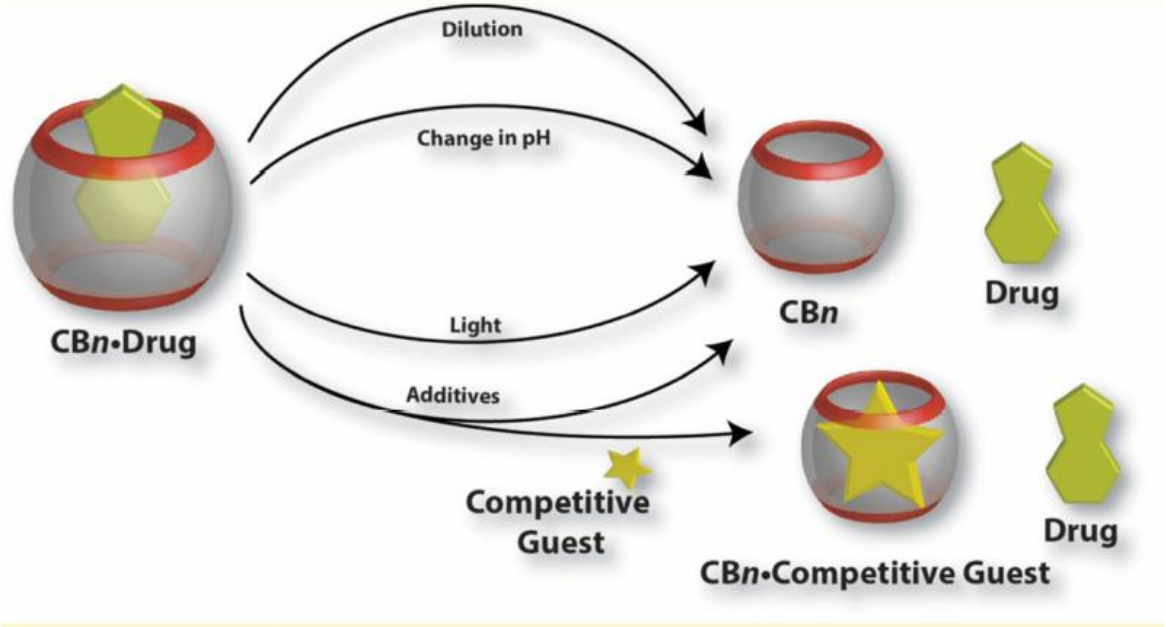
Scheme 1 Schematic illustration for the inclusion of MV^{2+} in CB[8].



Scheme 2

CB's IN DRUG DELIVERY

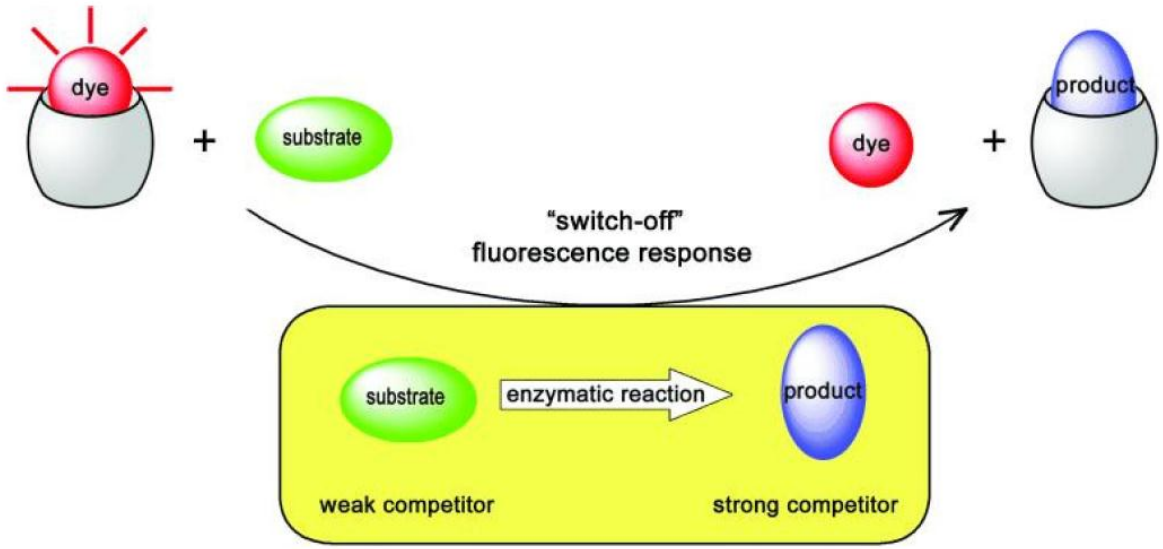
- Drug molecules that have been studied for their inclusion complexation with CBs to date include anti-neoplastic, antipathogenic, antagonist agents, vitamins and hormones, enzyme inhibitors, neurotransmitters, neuromuscular blockers, antituberculosis agents, local anesthetics, and others.
- The supramolecular complexation of benzimidazole-based drugs has been systematically studied by Nau and coworkers. CB7, in particular, is capable of encapsulating the benzimidazole derivatives albendazole, carbendazim, thiabendazole, and fuberidazole. These molecules possess very low water solubility in their neutral forms.



- The pKa values of this class of molecules are in the range of 3.5–4.8, and, therefore, they are neutral at physiological pH, which hinders their usability. The binding affinities of benzimidazole derivatives to CB7 in their neutral forms are in the millimolar range; these increase significantly for the protonated forms, reaching micromolar values.
- The preferential binding of the protonated forms increases the pKa values of the conjugate acids of these drug molecules by 2–5 units and, thereby, improves their solubilities by stabilizing the protonated forms at pH 7.2. For example, CB7 increased the aqueous solubility of albendazole by 2,000-fold.

DYE DISPLACEMENT

- Recently Nau and coworkers have developed a method for using CB[7] as part of a sensor in enzyme assays used to monitor amino acid decarboxylases, which can play important roles in tumor growth and inflammation.
- A fluorescent dye, Dapoxyl, was used as a competitor. This dye was chosen because it had a stronger binding affinity for the CB[7] than the amino acid substrates, but a lower binding constant than their products after cleavage of their carboxylates.



- Thus, once the amino acid, which was initially unable to displace the dye from the CB[7] cavity, had its carboxylate group cleaved by the enzyme (such as the conversion of lysine to cadaverine), the product was then able to displace the dye from the CB[7] cavity Because Dapoxyl's fluorescence signal differed significantly between its free form and its CB[7]-bound species, a change in the dye's fluorescence signal could be used to indicate that it was being displaced by the decarboxylated amino acid.

Scheme 2. Product-Selective Fluorescence Switch-Off Tandem Assay Using CB7 and AO as Reporter Pair[a]