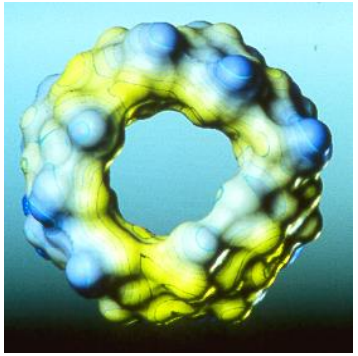
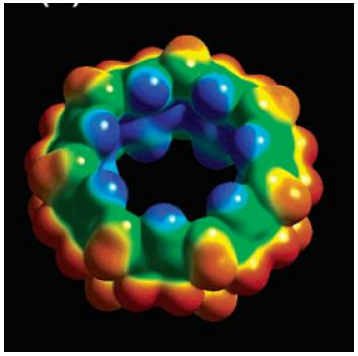
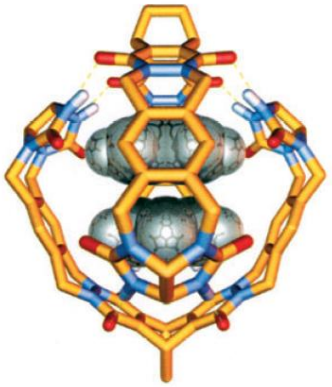
Neutral Molecule Receptors

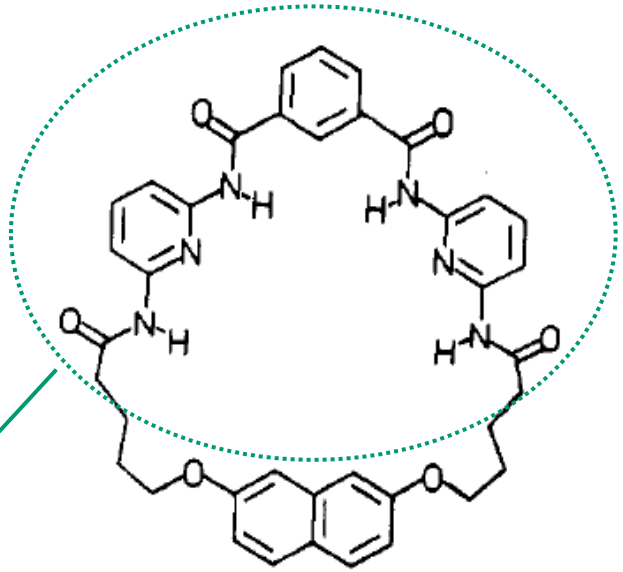
- Hydrogen-Bond Receptors
- Cyclodextrins
- Cyclophanes
- Calix[n]arenes
- Resorcin[n]arenes
- Cucurbiturils
- Molecular Tweezers and Clips
- Boronic Acid Receptors for Diols
- Covalent Container Molecules
- Container Molecules by Self-Assembly





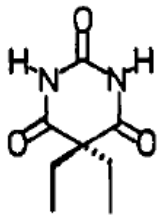


Hydrogen-Bond Receptors for Barbiturates

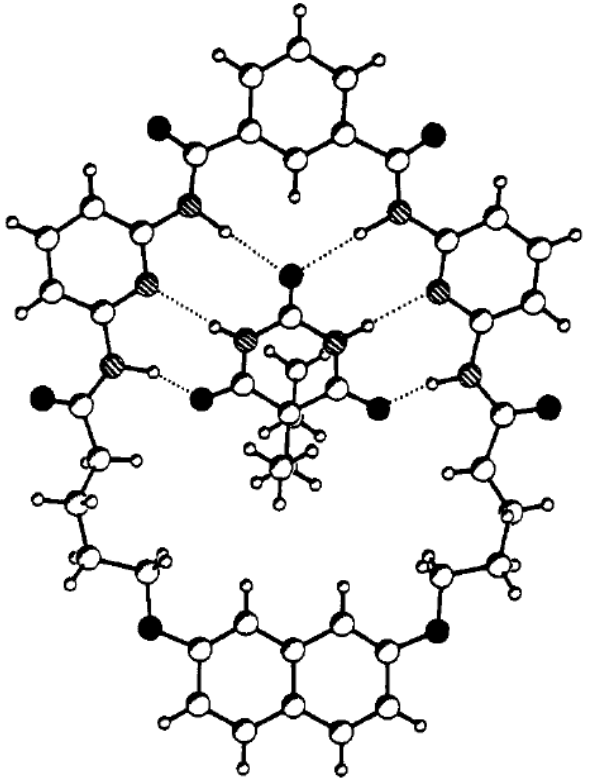


Structural motif known as ‘Hamilton receptor’

+



Barbiturate

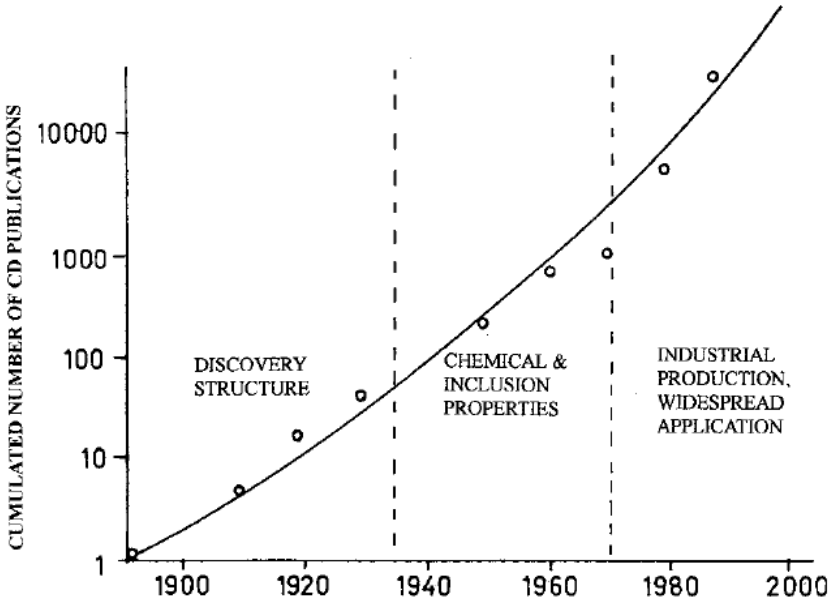


K = 2.5 x 10^5 M^{-1} (CH_2Cl_2)

A. Hamilton et al., *J. Am. Chem. Soc.* **1991**, *113*, 7640.

Cyclodextrins

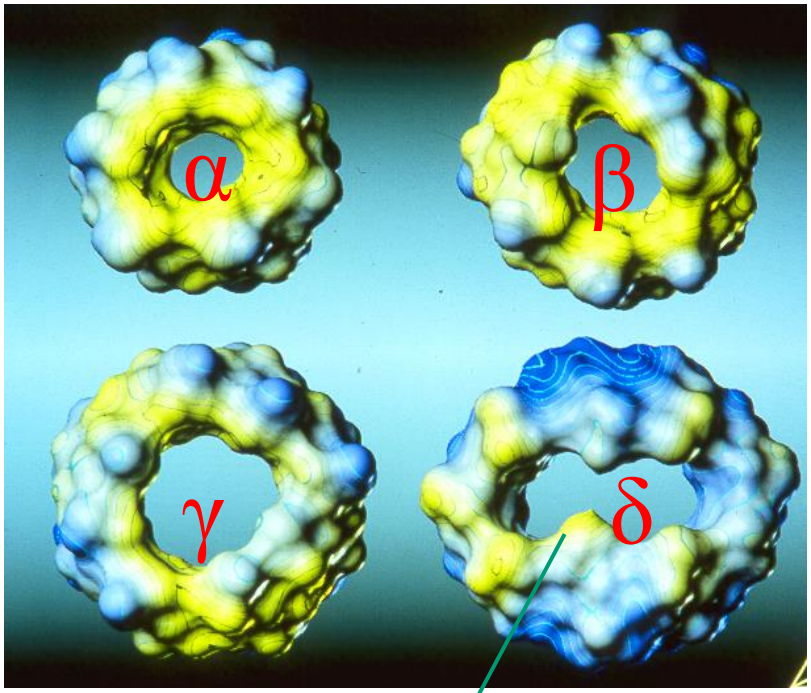
Cyclodextrins (CD's) are a group of naturally occurring cage molecules, which are built up from **α-D-glucose units**. Depending on the number of glucose moieties in the ring (6, 7 or 8) they are named **α-, β-, and γ-cyclodextrin**. CD's are produced by the enzyme glucosyl transferase enzyme (CGT-ase) which is found in a large number of microorganisms.



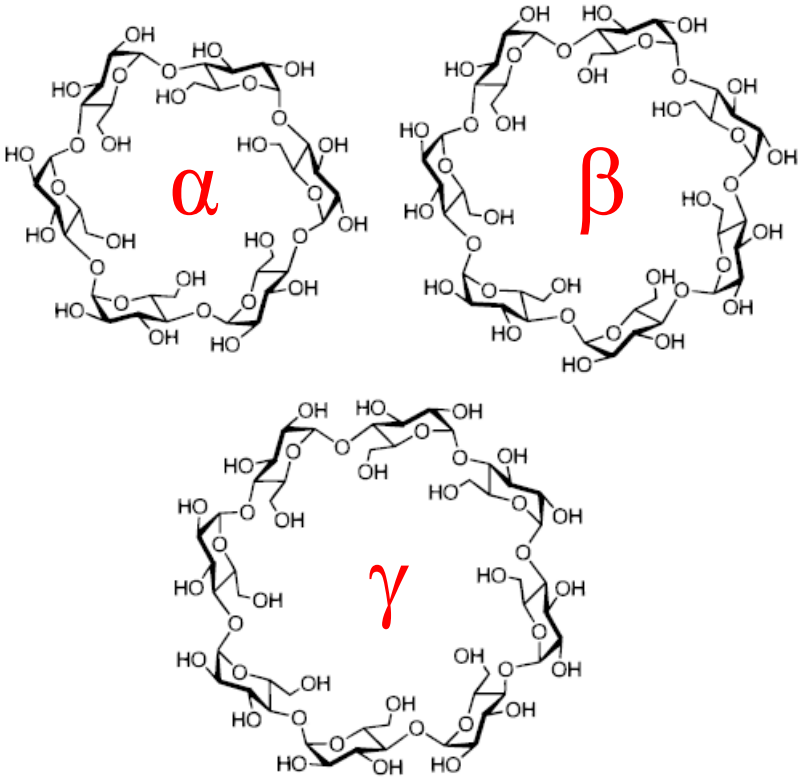
The three stages in development of CD technology. In the first 45 years about 50, in the second period (~35 years) about 2000, and in the third period (during the last 27 years) about 13 000 CD-related publications (papers, patents, conference abstracts) have been published

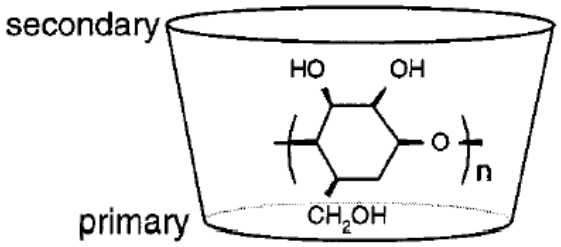
Chem. Rev. **1999**, *98*, Issue 5 (special issue on cyclodextrin chemistry)

The Structures of Cyclodextrins

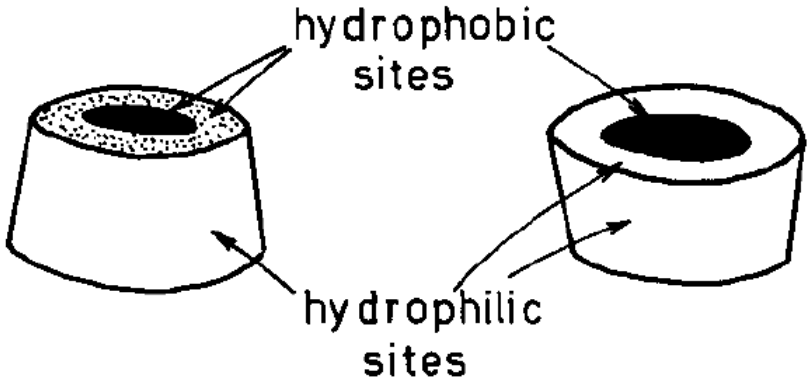


'collapsed cylinder' structure of δ-CD

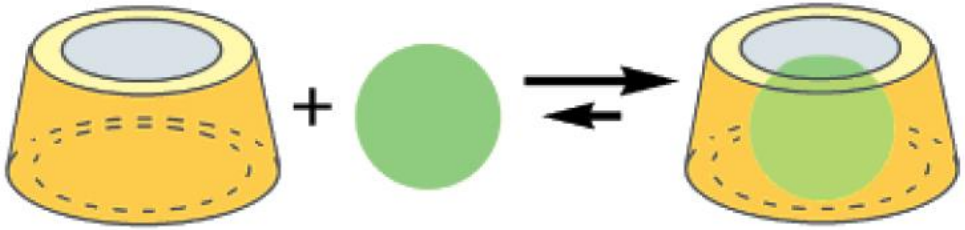




Host-Guest Chemistry of Cyclodextrins

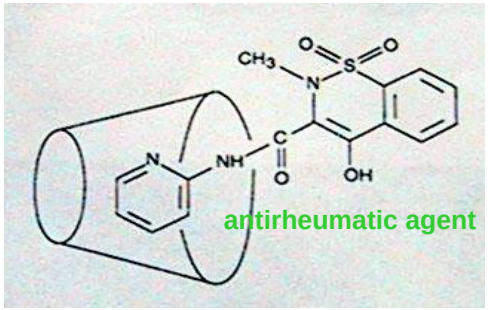


CD's can bind a variety of guests inside their apolar cavities in aqueous solution. The hydrophobic cyclodextrin cavity is occupied by water molecules which are energetically unfavored. The main driving force for this binding is the substitution of these high-enthalpy water molecules. The formed inclusion complexes can often be isolated as stable crystalline substances.



Hydrophobic guest

Cyclodextrins as Drugs

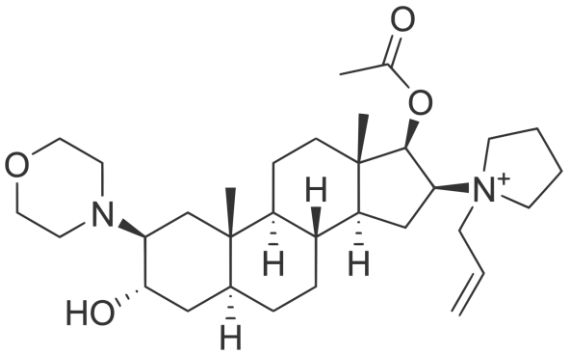


quicker response,
gastrointestinal tolerability

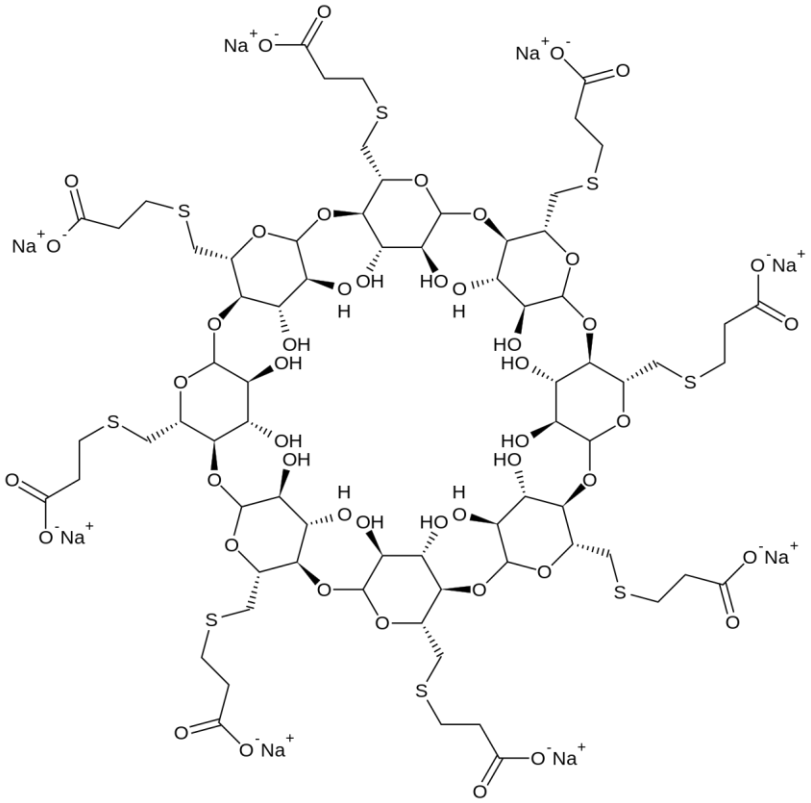
(special CD to increase the solubility)

Traditional formulation systems for very insoluble and/or unstable drugs have involved a combination of organic solvents, surfactants and extreme pH conditions. These formulations are often irritating to the patient and may cause adverse reactions. Using cyclodextrins, aqueous solubilities have increased by a factor of 10 to 50,000 depending on the compound.

Sugammadex



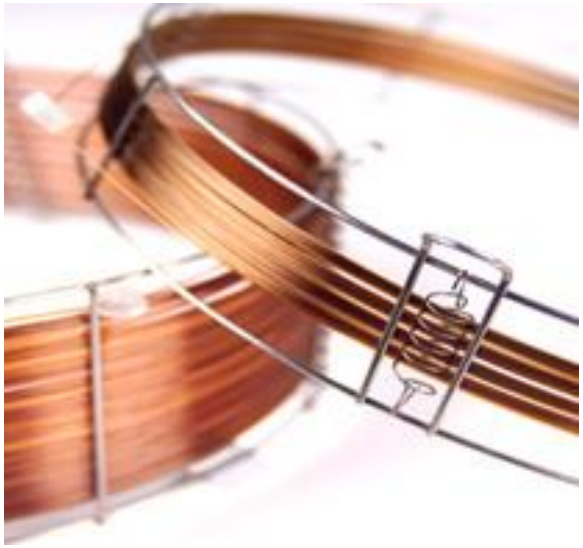
Rocuronium: a muscle relaxant used in modern anaesthesia to facilitate tracheal intubation.

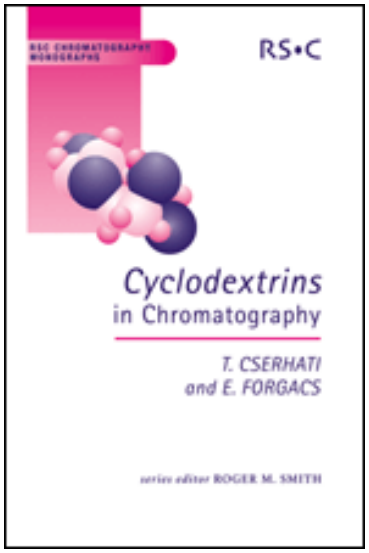


Sugammadex is a modified γ-cyclodextrin. It is indicated for the reversal of neuromuscular blockade induced by Rocuronium and related compounds

Sugammadex sales reached $1.5 billion globally in 2021 (sold by Merck).

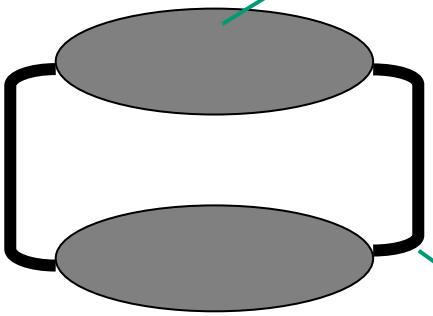
Cyclodextrins in Chromatography

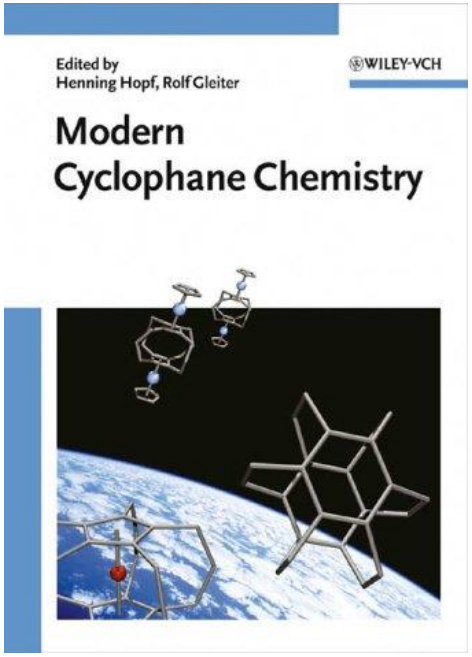




Incorporated into GC- or HPL columns, CD's display unprecedented potential for chiral separation of enantiomers.

Cyclophanes



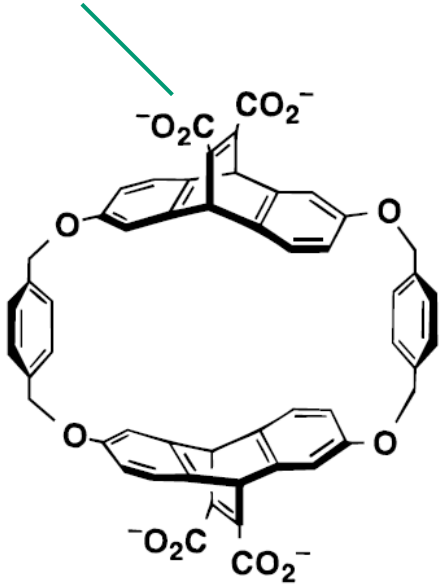


Published 2004

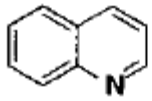
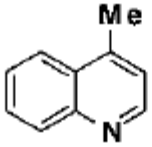
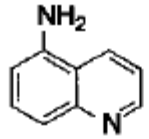
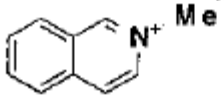
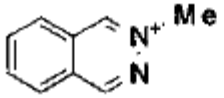
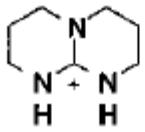
"*Cyclophanes represent* the *central class of synthetic receptors in molecular recognition. All types of substrates…have been complexed by tailor-made cyclophanes. In these association processes, all known modes of intermolecular binding interactions have been used.*" François Diederich in 1990

A Water-Soluble Cyclophane-Receptor

Solubilizing group



The cyclophane host presents a well-defined, hydrophobic binding site that can bind a wide range of guests with often very high affinity. Central to these binding events are **π-π** and **cation-π** interactions as well as the **hydrophobic effect** (reduced binding with CH_3CN!)

Guest	-Δ*G*° (kcal/mol)
	5.3
	5.9 [3.5]
	5.7
	7.2 [4.9]
	6.5
	5.0 [<3.5]

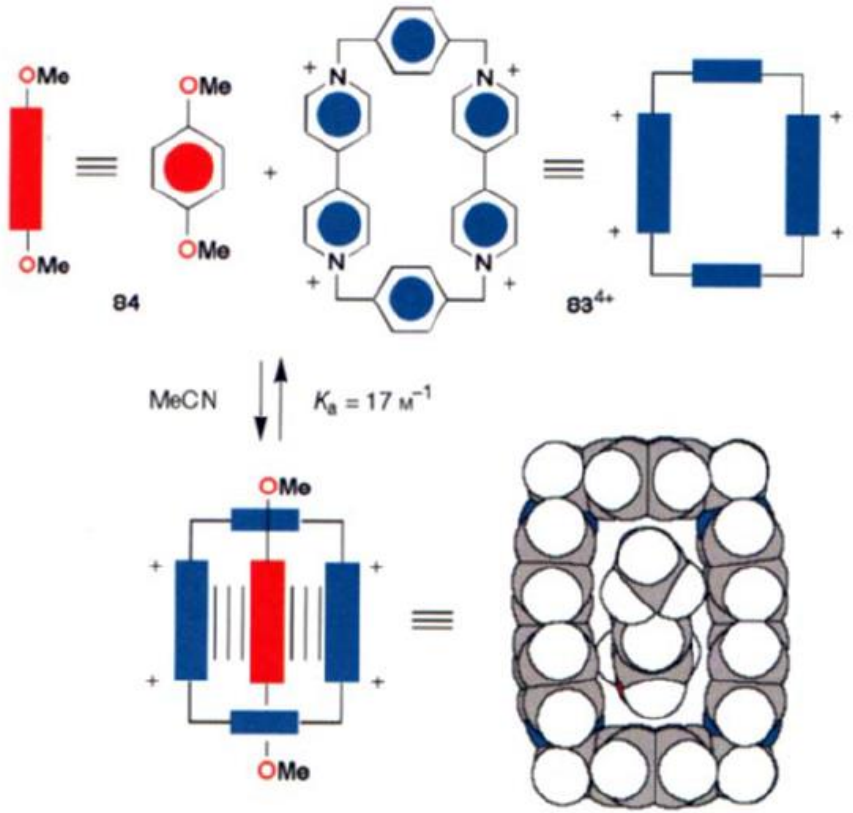
H_2O

+ 10 % CH_3CN

D. A Dougherty et al., *J. Am. Chem. Soc.* **1988**, *110*, 6825.

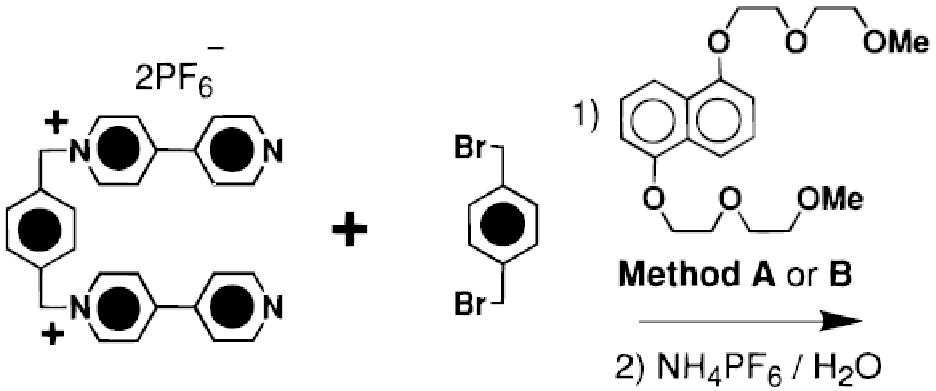
Stoddard's Cyclobis(paraquat-*p*-phenylene)

Since its synthesis was first reported in 1988, cyclobis(paraquat-*p*-phenylene) has turned out to be an excellent receptor for substrates containing π-electron rich aromatic rings, such as hydroquinone and resorcinol derivatives, biphenyl guests, aromatic amino acids in both organic and aqueous solutions. The tetracationic cyclophane has also been incorporated into a wide number of mechanically-interlocked molecular compounds, such as catenanes and rotaxanes (see later).

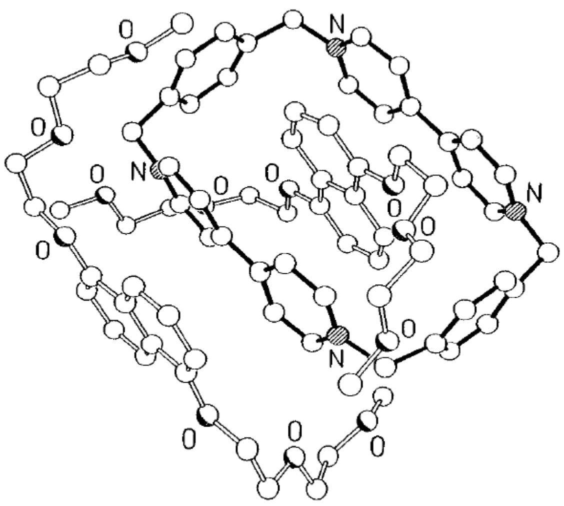


J. F. Stoddart et al., *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1547 .

Templated Synthesis of Cyclobis(paraquat-*p*-phenylene)



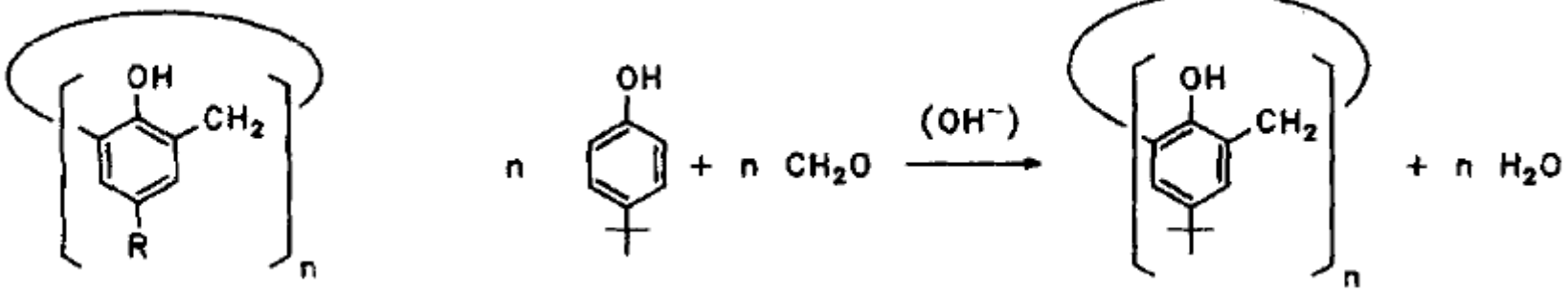
The use of a π-electron rich guest as a template resulted in an improvement of the yield up to a remarkable 81%.



(X-ray)

J. F. Stoddart et al., *J. Org. Chem.* **1996**, *61*, 9591.

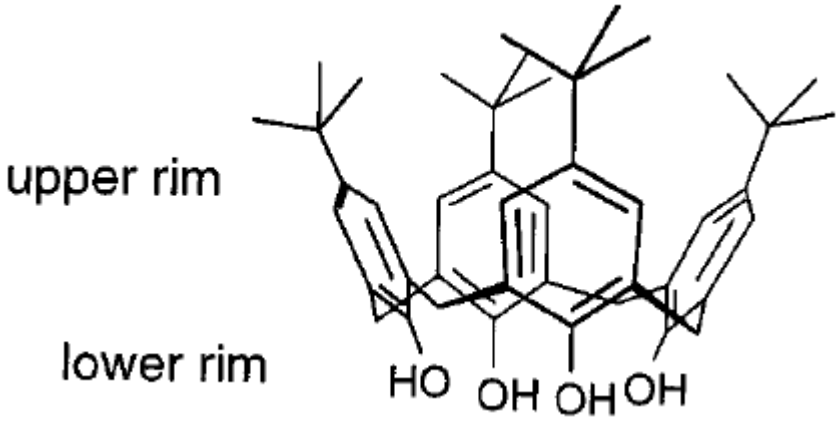
Calix[n]arenes

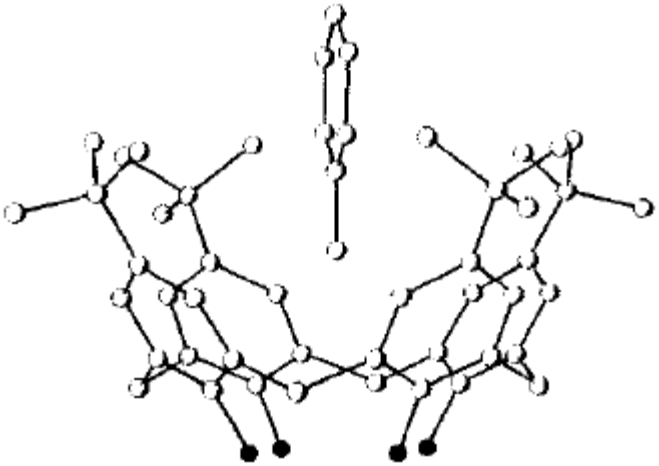


- Calix[n]arenes are made up of phenol and methylene units.
- Multigram amounts can be obtained in a (relatively) simple manner, in particular when *tert*-butylphenol is employed.
- Some are commercially available.

‘Calixarenes, Macrocycles with (Almost) Unlimited Possibilities’
V. Böhmer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713.

Calix[4]arenes

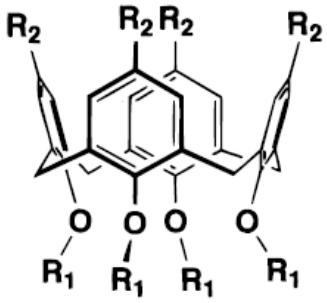




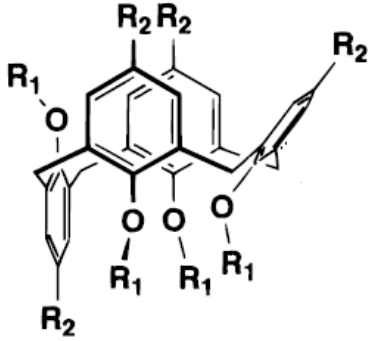
***p-tert*-butylcalix[4]arene**

Calix[4]arenes are cyclic tetramers. Although each phenol unit can rotate, they **favorably adopt a cone conformation** because of the stabilization by intramolecular hydrogen-bonding interactions among OH groups. Therefore, the *p-tert*-butylcalix[4]arene (**1**) adopts C_{4v} symmetry and has a **π-basic cavity in the upper rim**. In the crystalline state several kinds of solvent molecules are included in this cavity (toluene, acetonitrile, *etc*.).

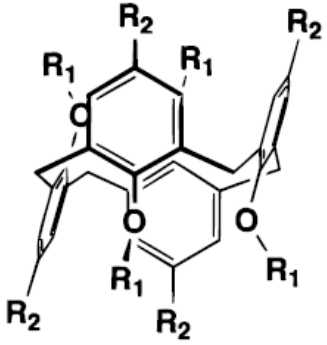
Structures of O-Alkylated Calix[4]arenes



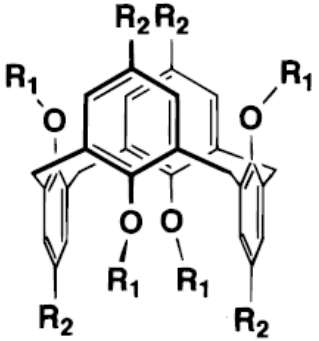
"Cone"



"Partial-cone"



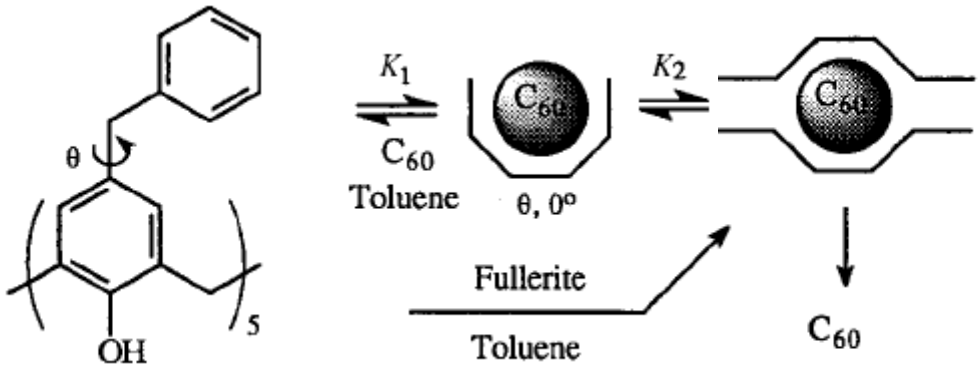
"1,2-Alternate"

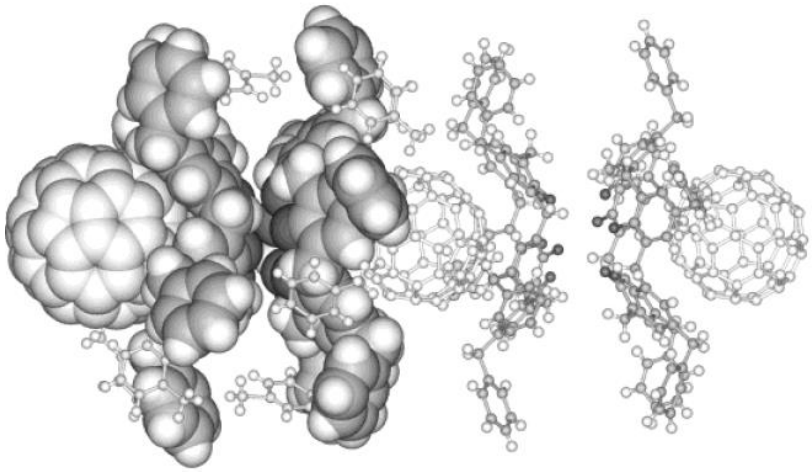


"1,3-Alternate"

In tetra-*O*-alkylated calix[4]arenes the cone conformation is not necessarily stabilized because of the absence of intramolecular hydrogen-bonding interactions. Thus, **four** different **conformational isomers** must be taken into account.

Fullerene Complexation by Calix[n]arenes





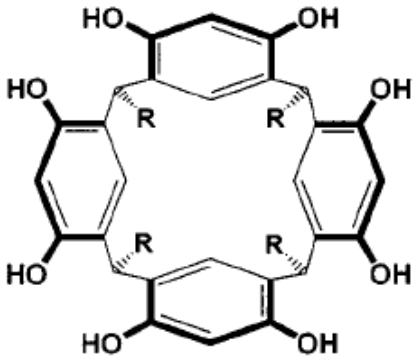
(X-ray)

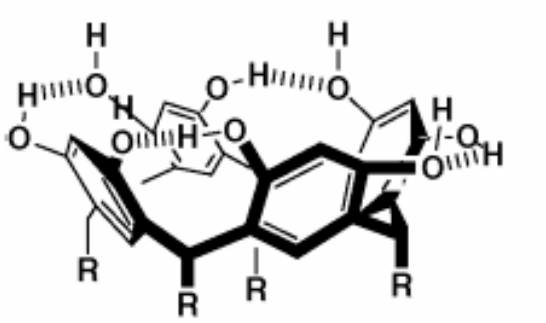
Several calix[n]arenes are known to bind C_{60} and/or C_{70}. This can be used to purify C_{60}. The stability of the complexes in solution is generally not very high.

J. L. Atwood et al., *Chem. Eur. J.* **1999**, *5*, 990.

Resorcin[n]arenes

Resorcin[n]arenes can be obtained by **condensation of resorcinol with aldehydes** in an acid-catalyzed reaction. Usually, the cyclotetramer crystallizes from the reaction mixture. Similar to Calix[n]arenes, they have shown to be **versatile building blocks** in supramolecular chemistry.



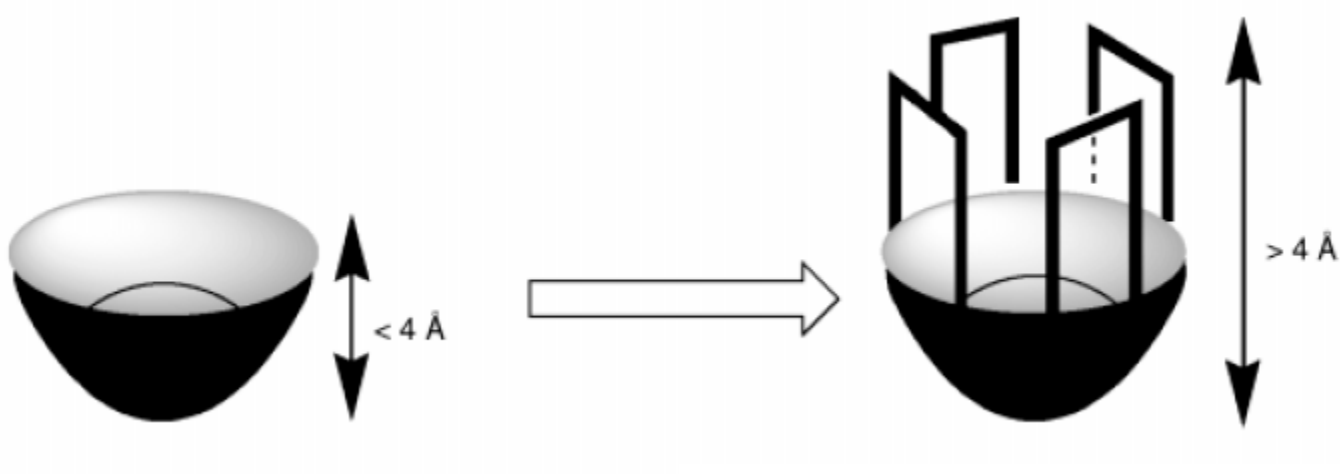


A bowl-shaped resorcin[4]arene

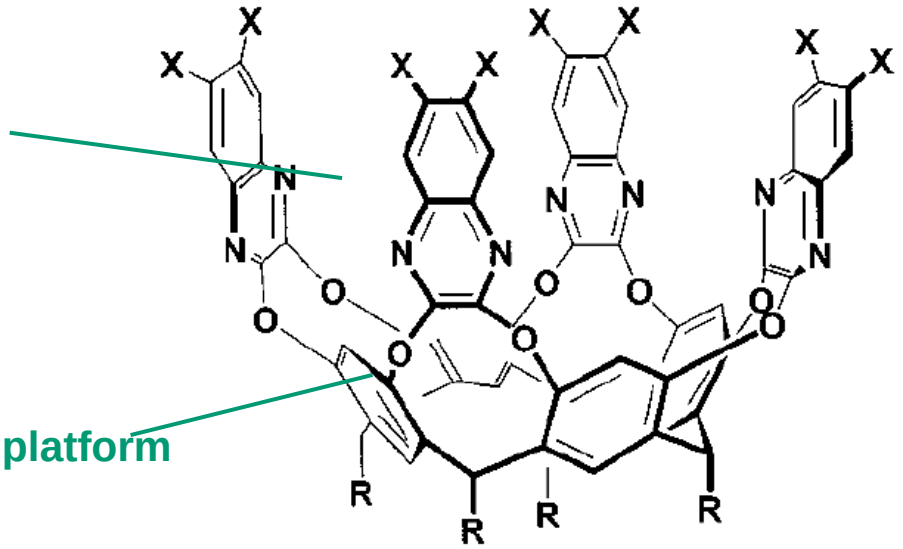
‘Resorcinarenes’

D. N. Reinhoudt et al., *Tetrahedron* **1996**, *52*, 2663.

From Resorcin[4]arenes to Cavitands

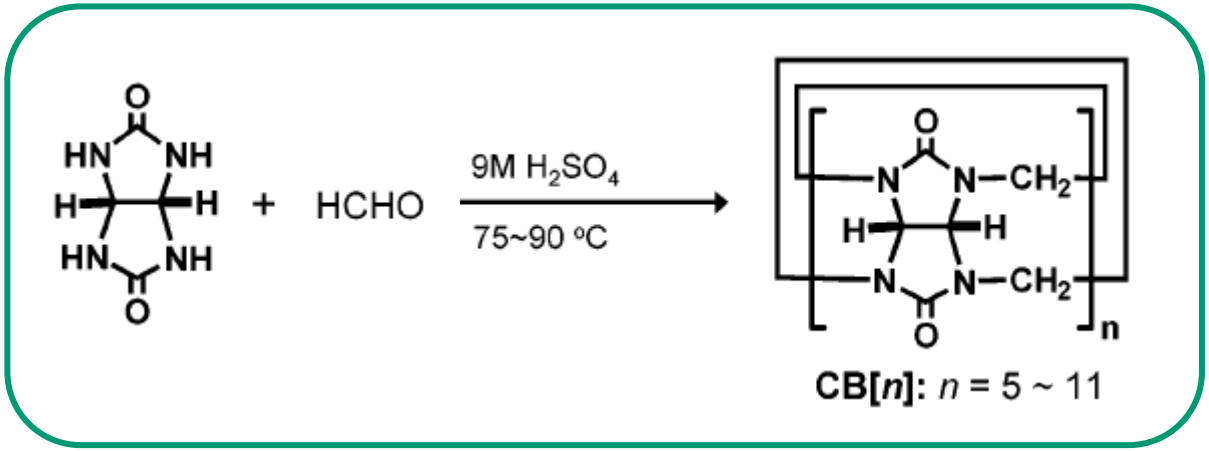


Lipophilic cavity with can accommodate aromatic molecules in solution and in the gas phase



Bowl-shaped resorcin[4]arene platform

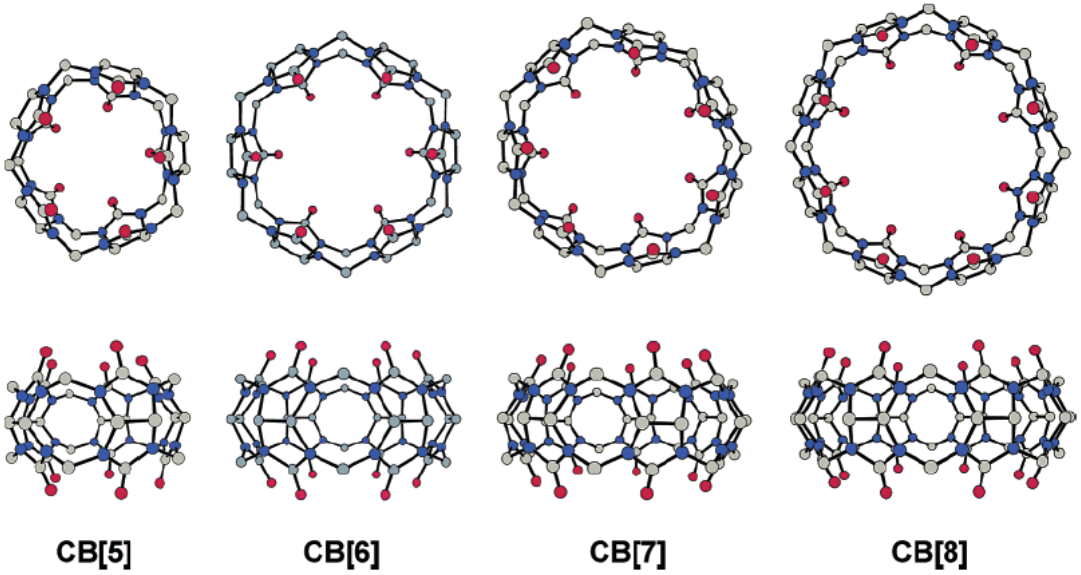
Cucurbiturils (CB[n])

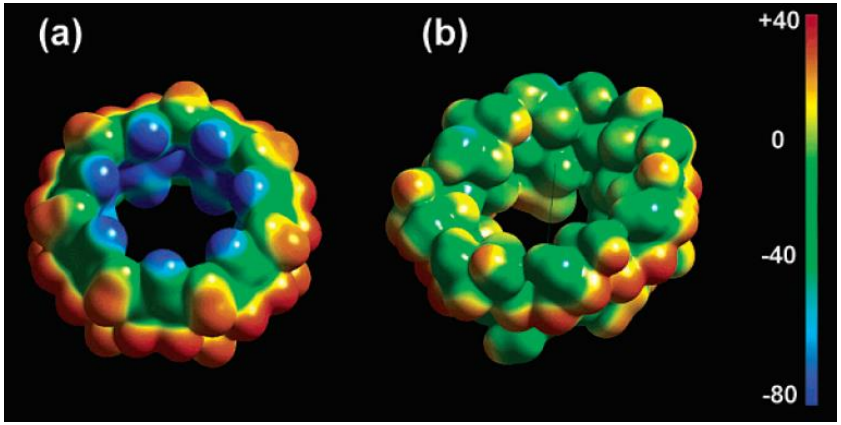


- Macrocyclic compounds formed in an acid-catalyzed condensation reaction of glycoluril and formaldehyde.
- The first synthesis in 1905 was limited to CB[6], which displays a very low solubility in water. In 2000, Kim reported the synthesis of other homologues. Since then, may applications have been described
- CB[5] and CB[7] have a moderate solubility in water (2-3 × 10^{-2} M), which is comparable to that of β-CD (1.6 × 10^{-2} M).

K. Kim et al., *Acc. Chem. Res.* **2003**, *36*, 621.

The Structures of Cucurbiturils

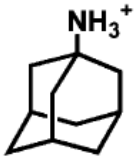
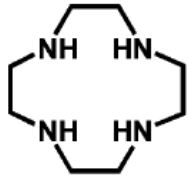
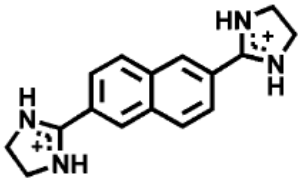
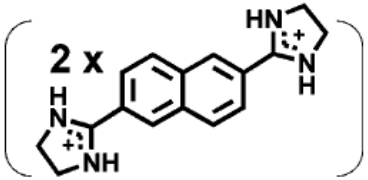
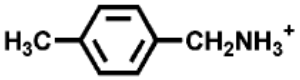
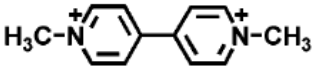
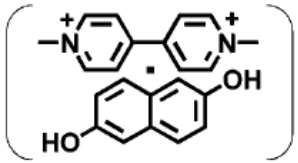




(blue = negative !)

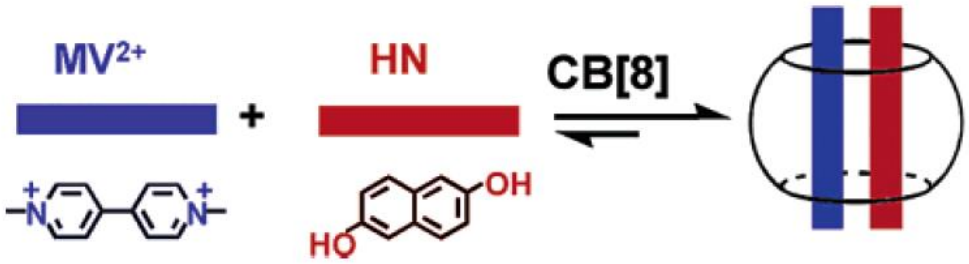
Electrostatic potential surfaces of:
(a) CB[7]
(b) β-CD

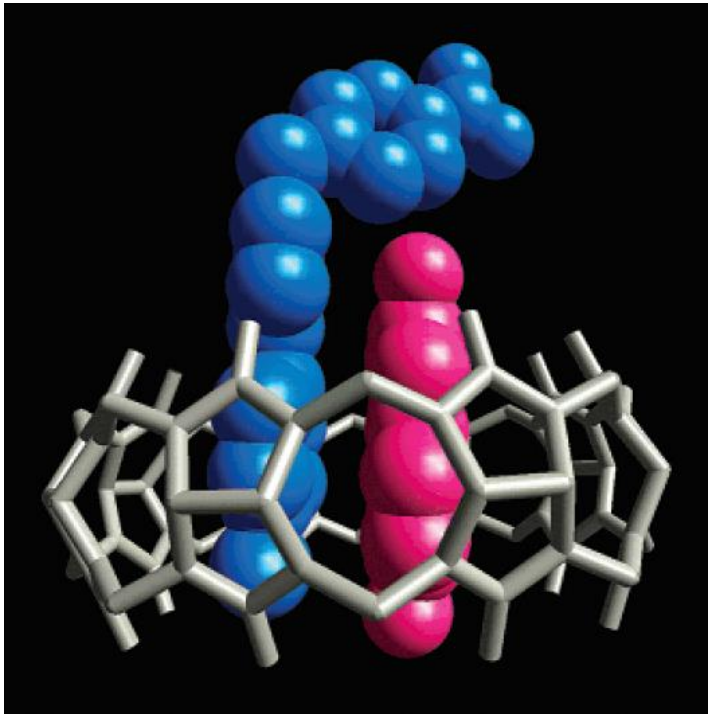
The Host-Guest Chemistry of Cucurbiturils

CB[5]	CB[6]	CB[7]	CB[8]
N_2, O_2, Ar	$^{+}NH_3(CH_2)_nNH_3^{+}$ (n = 4-7, $K_a > 10^5$)		
NH_4^+ alkali metal ions Pb^{2+}	THF, benzene		
binding to the carbonyl oxygens of the portals	 (K_a ~ 3 x 10^2)		
	o- and *m*-isomers are not included.		

CBs have a hydrophobic cavity, and polar carbonyl groups surrounding the portals. The carbonyl groups at the portals of CBs allow charge-dipole interaction as well as H-bonding with guests, and are capable of coordination to metal ions.

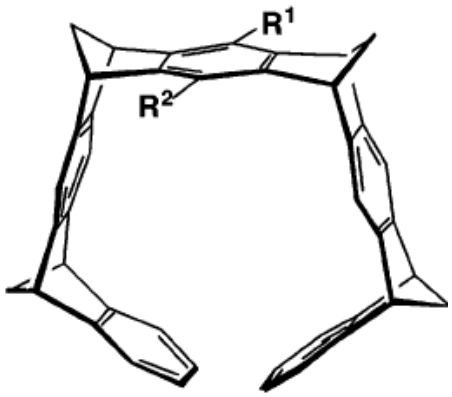
A Charge-Transfer Complex Stabilized by CB[8]

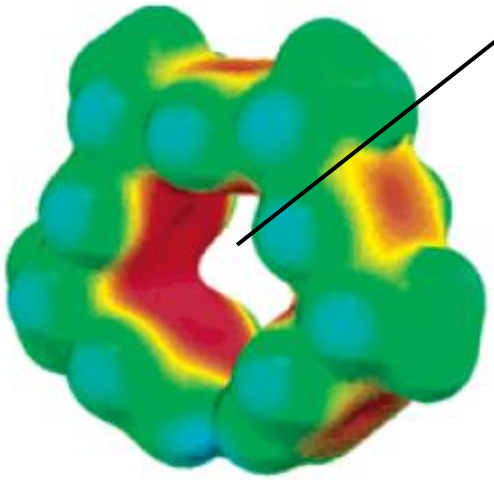




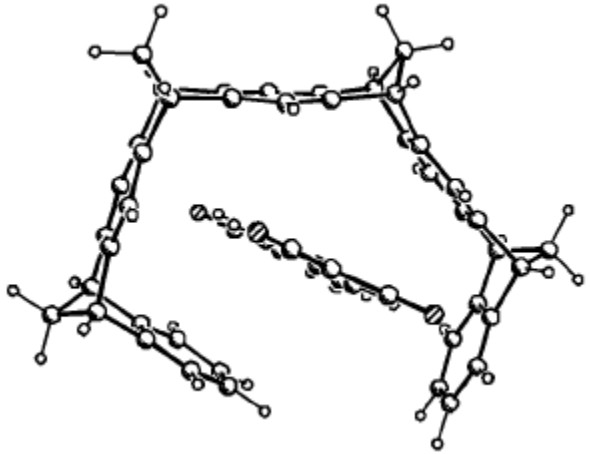
Instantaneous formation of an inclusion complex containing a hetero-guest pair is observed upon addition of 1 equiv of **HN** to the 1:1 complex of **MV**2+ and CB[8]. The ternary complex is also formed exclusively when their components are mixed in a 1:1:1 ratio. The major driving force for the ternary complex formation appears to be strong charge-transfer (CT) interaction between **HN** and **MV**2+ inside the host cavity.

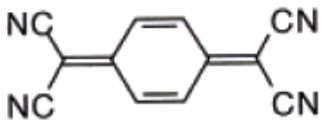
A Molecular Tweezers for Aromatic Guests

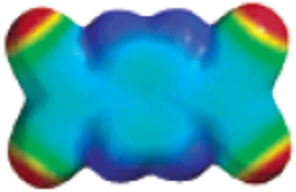




More negative inside than outside!



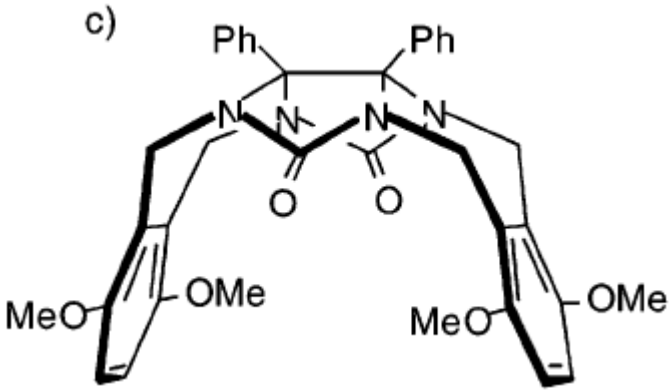


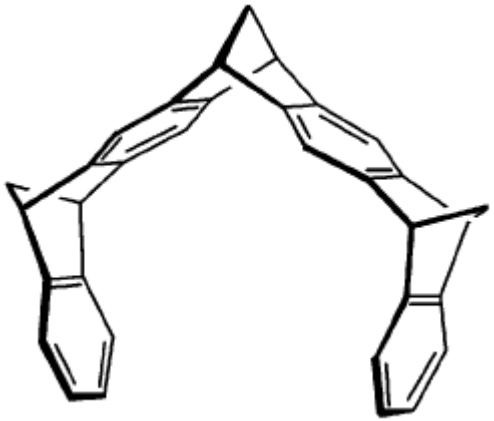


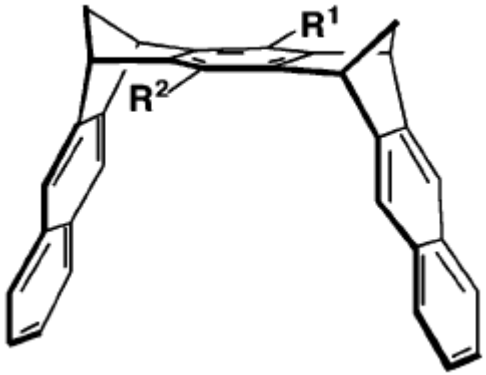
Attractive CH-π as well as π-π interactions contribute to the stability of the complex.

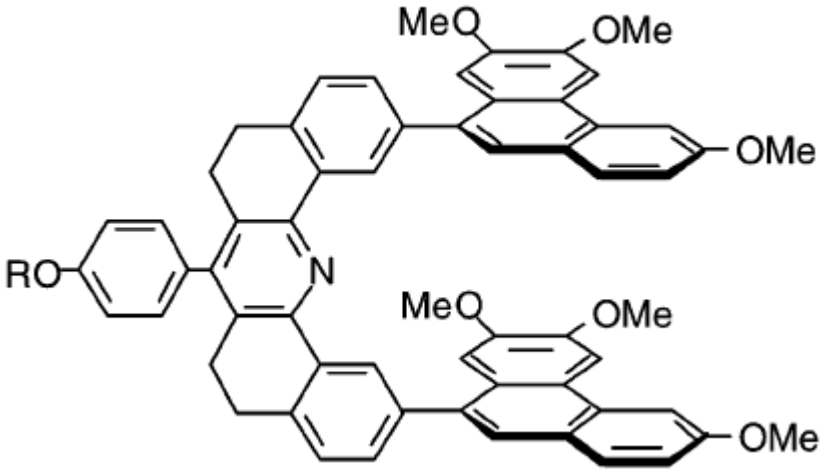
Electrostatic potential surface
(red = negative; blue = positive)

Other Molecular Tweezers and Clips



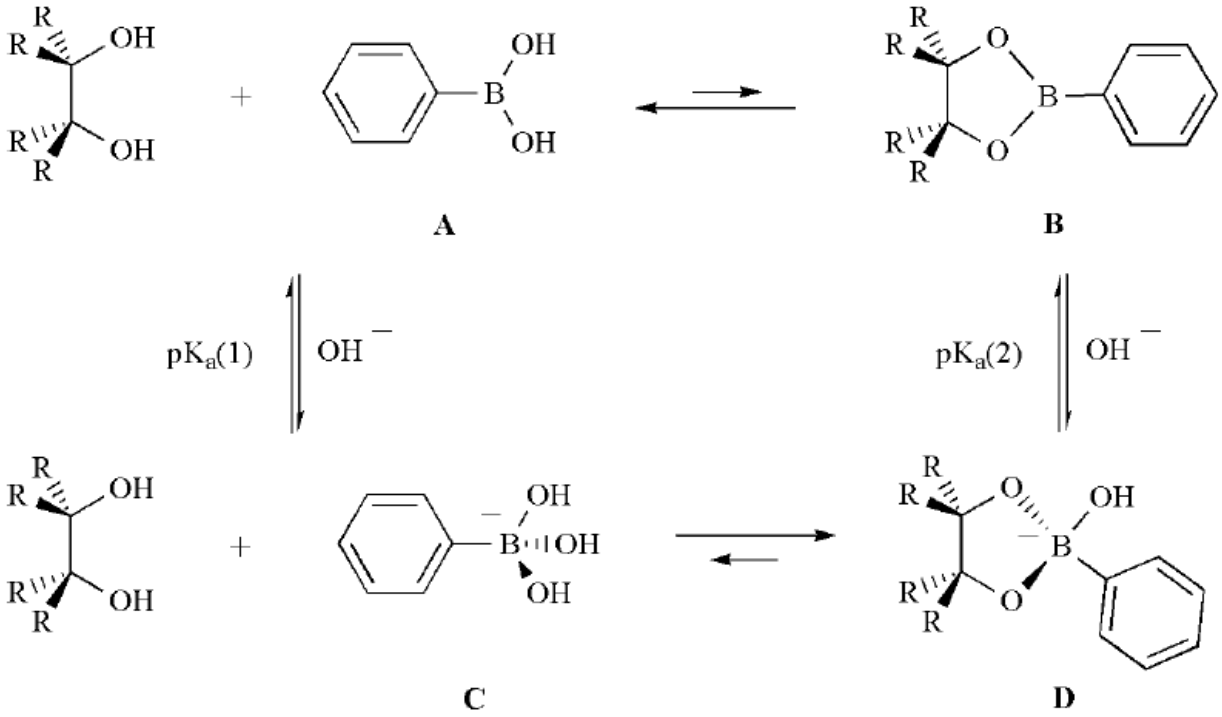






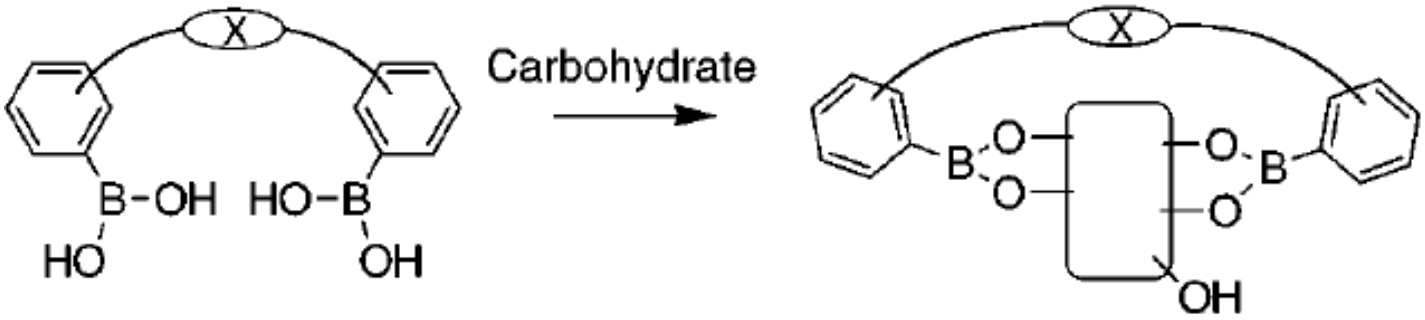
F.-G. Klärner et al., *Acc. Chem. Res.* **2003**, *36*, 919.

Boronic Acid Receptors for Diols



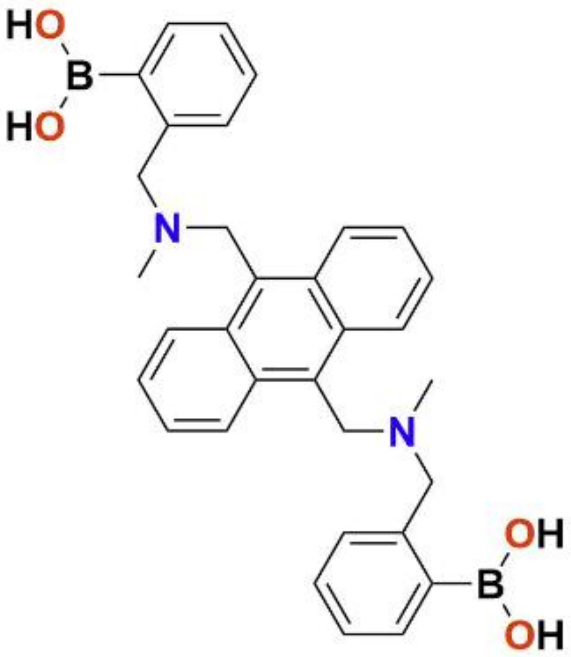
Structure D is only favored under basic conditions or with very acidic boronic acids. Since simple aromatic boronic acids have a pK_a ~ 9, it is **difficult to achieve binding at neutral pH**.

Boronic Acid Receptors for Sugars

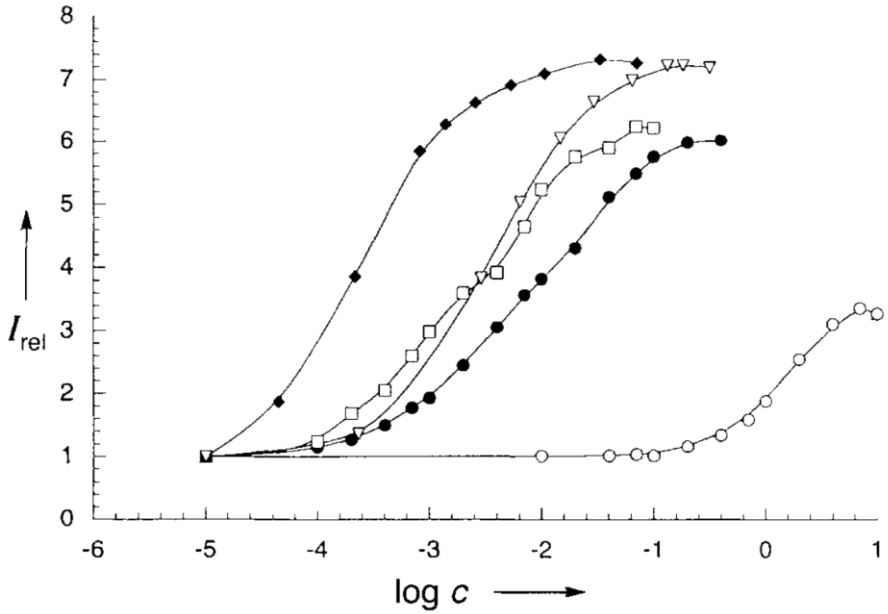


Divalent coordination enhances the binding constant and potentially allows differentiation between sugars.

Fluorescence Sensors for Sugars

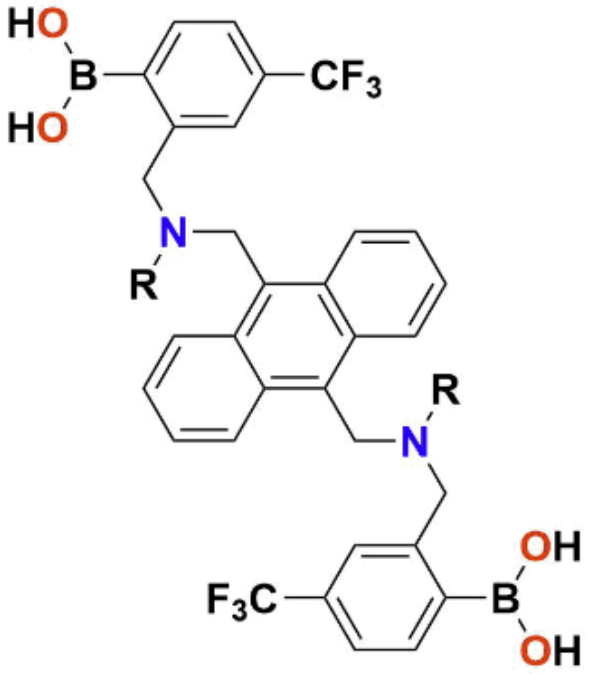


James, Sandanayake and Shinkai (**1994**)

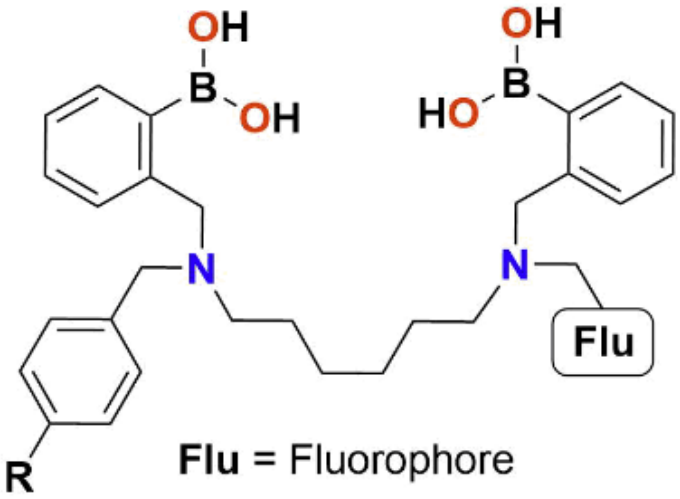


◆ D-glucose, □ D-allose,
▽ D-fructose, ● D-galactose, ○ ethyleneglycol.

Fluorescence Sensors for Sugars



Eversense (**2014**)

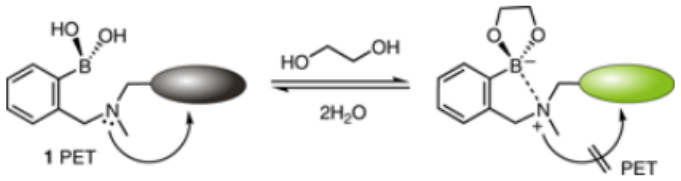
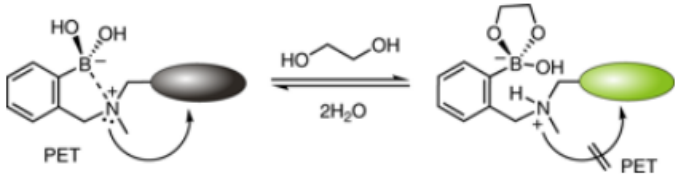
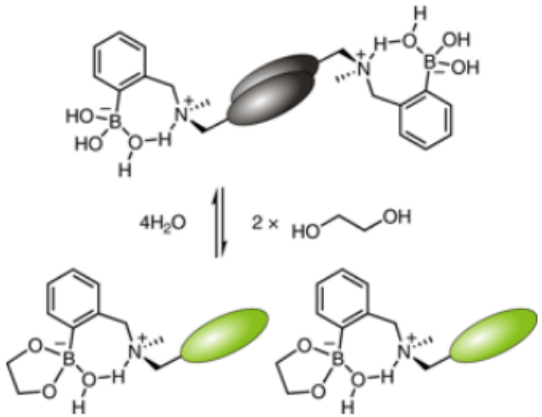
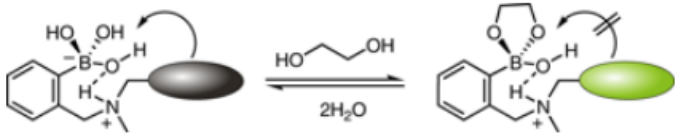


Glysure (**2015**)

The Eversense system received FDA approval in 2019. It is currently available in the United States and in Europe (Via Roche). The Glysure system obtained a CE Mark approval 2015. Both sensors are suitable for continuous glucose monitoring.

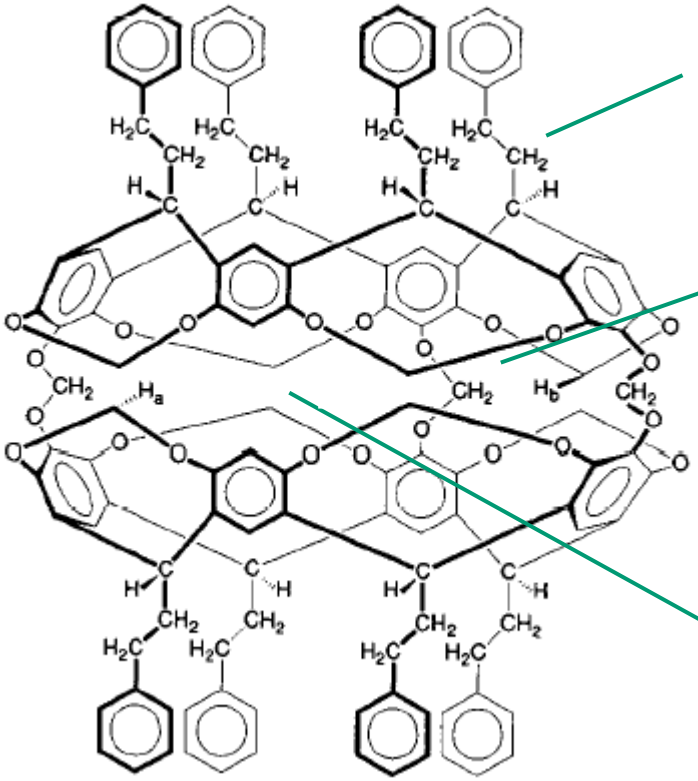
Tony D. James in *Nature Chemistry*

The Debate About the Mechanism

Structure	Theory	Assertor	Year
	N–B bond	Seiji Shinkai, Tony D. James	1994
	pK_a switch	Binghe Wang	2003, 2004
	Aggregation and disaggregation	Eric V. Anslyn, Joseph D. Larkin	2017
	Loose bolt internal conversion	Eric V. Anslyn, Tony D. James	2018

Nature Chemistry **2019**, *11*, 768.

Covalent Container Molecules
"Molecules within Molecules"



Solubilizing groups

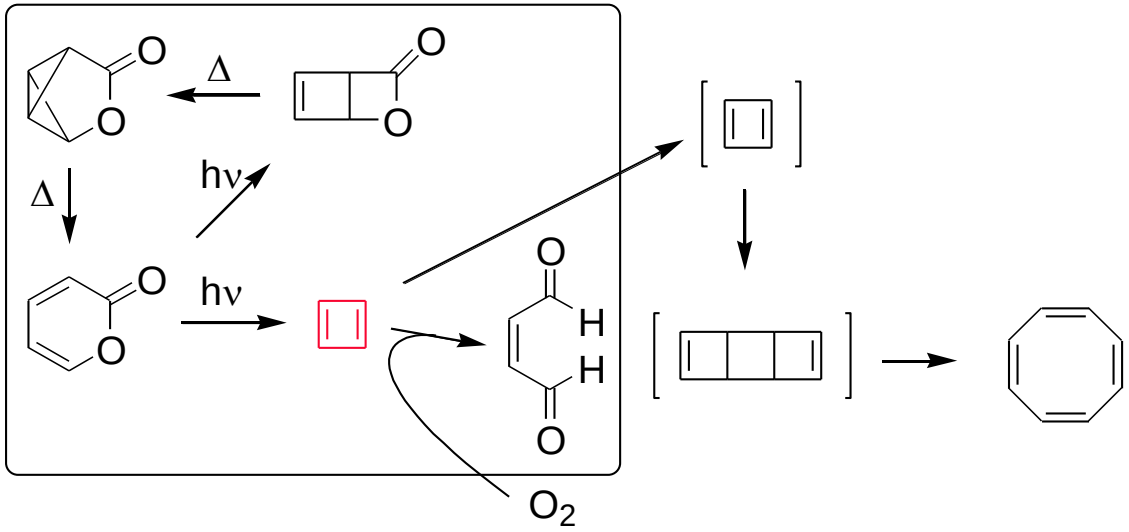
Inner phase large enough to accommodate small guests such as dimethylacetamide, benzene or THF.

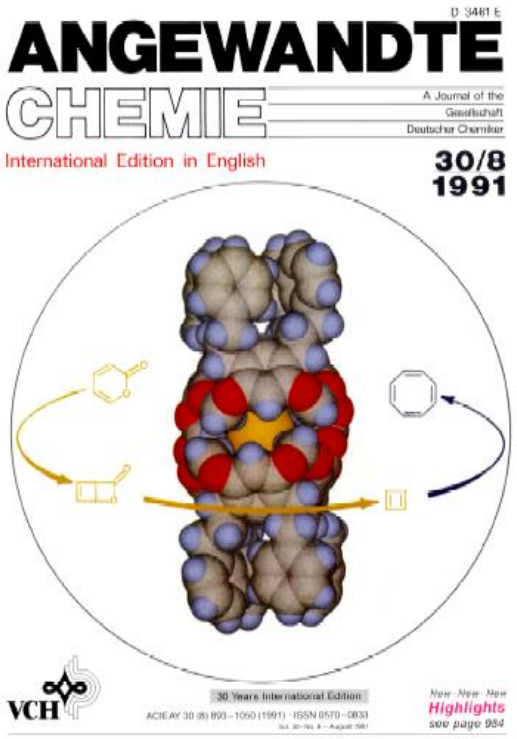
Portal, which allows guest entry and exit at 100 °C (without portal: 'carcerand')

'Hemicarcerand'
with guest: 'Hemicarceplex'

‘The Taming of Cyclobutadiene’

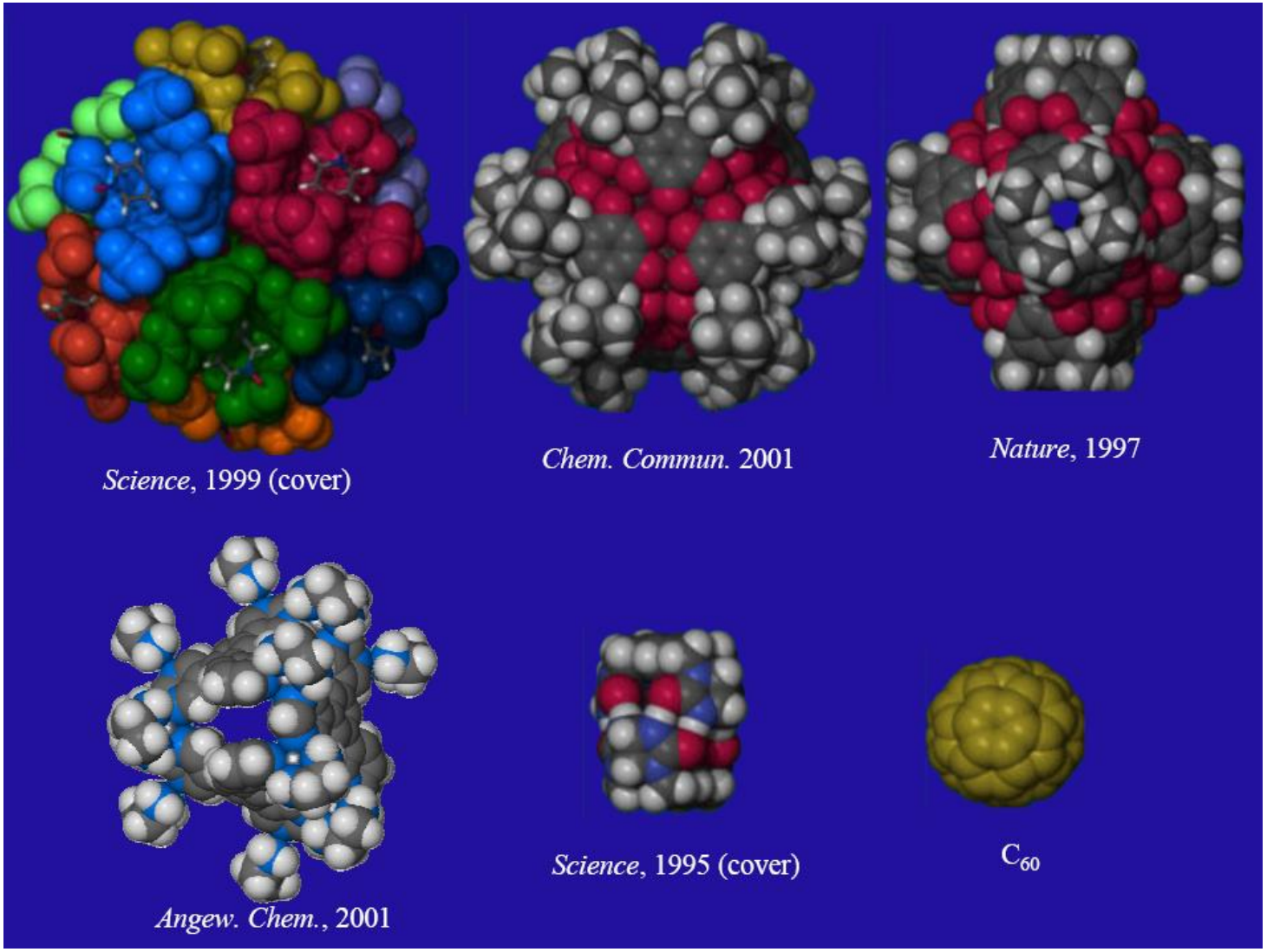
- The cyclobutadiene core is only stable in an argon matrix at 8 K.
- Inside the hemicarcerad, $(CH)_4$ is stable at RT !



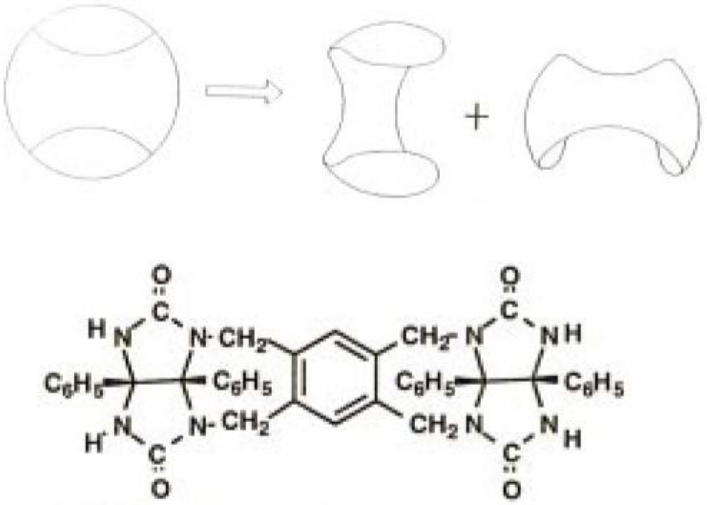


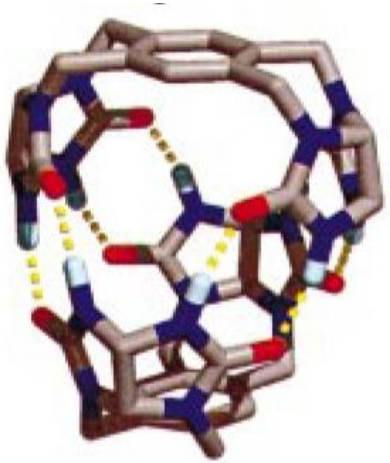
D. J. Cram et al. *Angew. Chem., Int. Ed.* **1991**, *30*, 1024.

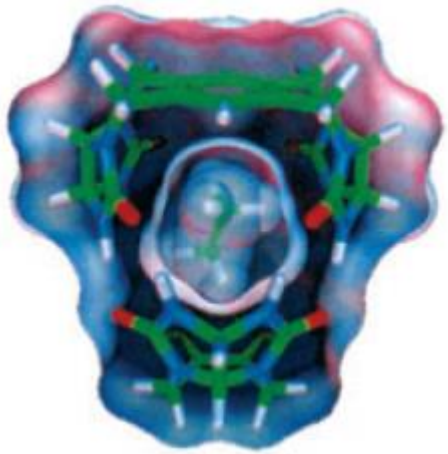
Container Molecules by Self-Assembly



A Molecular Tennis Ball

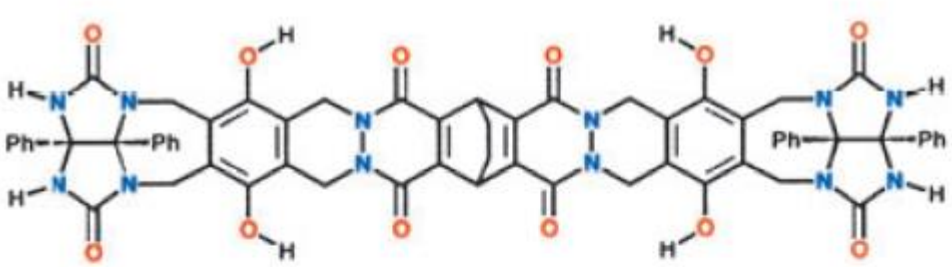




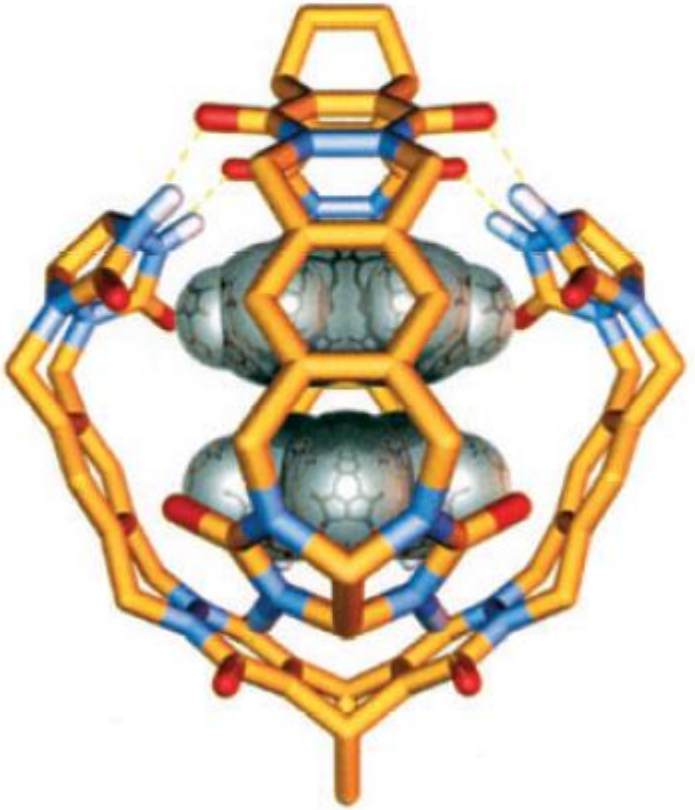


- The monomer consists of **two glycoluril subunits** appended to a central aromatic skeleton.
- The glycoluril units provide curvature and a **self-complementary hydrogen-bonding motif**.
- The tennis ball is held together by **eight hydrogen bonds**, and as a host structure has a tiny cavity capable of housing guests with a volume of about 50 $Å^3$. Accordingly, the tennis ball includes methane, ethane, ethylene, and the noble gases, while larger guests such as propane, allene, and isobutylene are excluded

A Molecular Tennis Ball with Increased Size

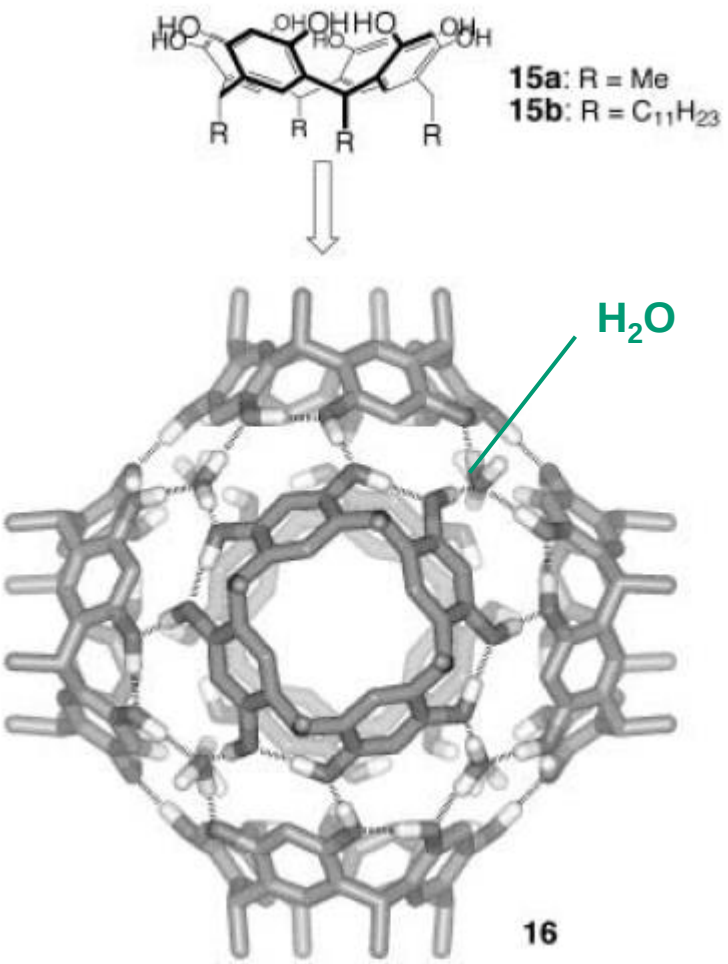


Variation in the spacer leads a larger capsule (“softball”) The same general symmetry remains, but apart from binding larger guests, the softballs (their internal volumes lie between 240 and 320 $Å^3$) are also capable of simultaneously binding *two* copies of moderately sized guests such as benzene.



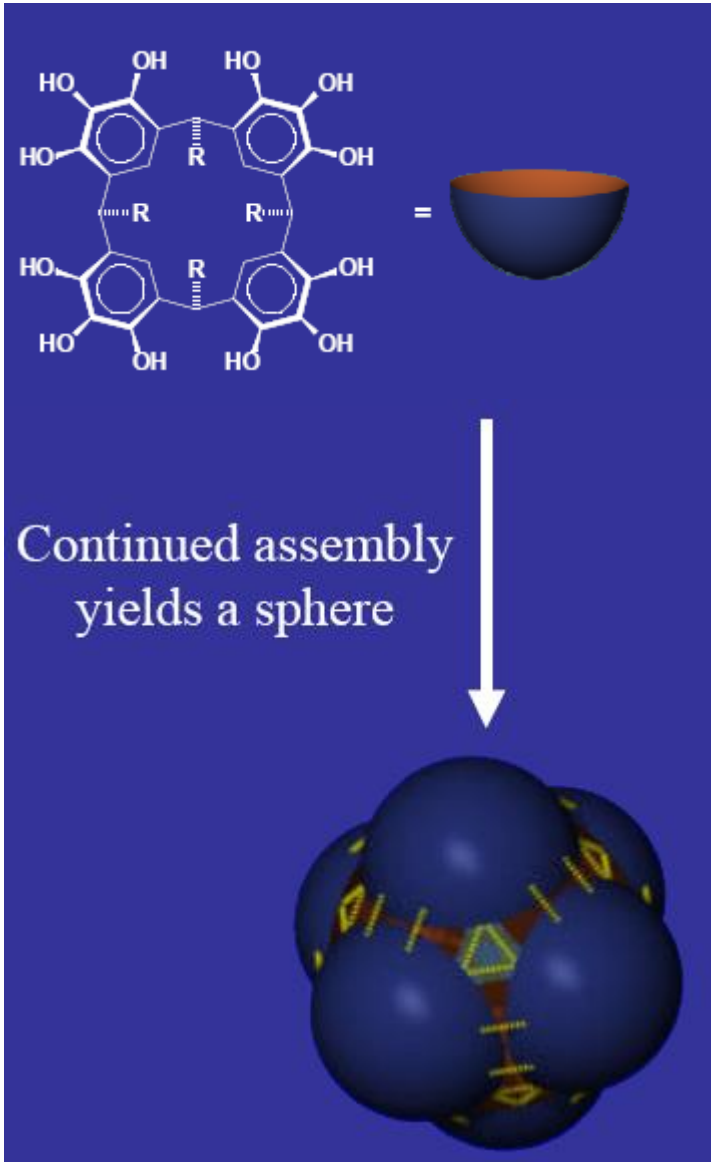
Resorcin[4]arene-Based Capsules

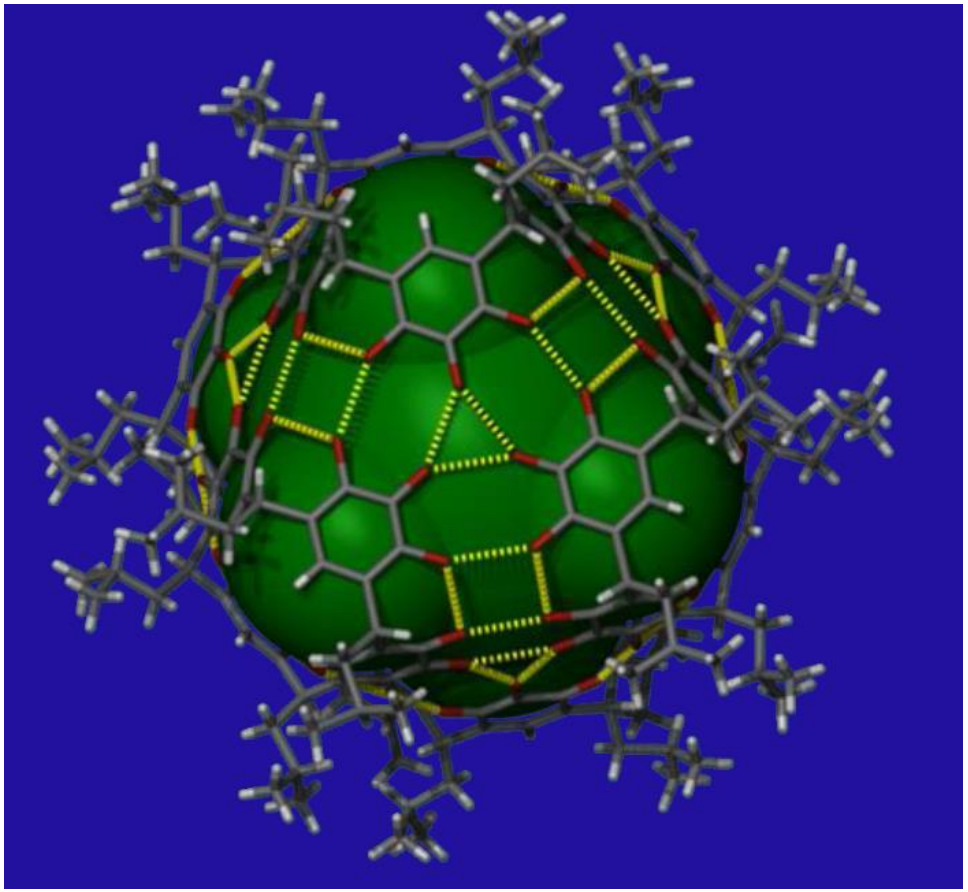
The structure shows the arrangement of **six resorcin[4]arene subunits** enclosing an enormous cavity of about 1375 Å^3. The hexameric capsule features a total of **60 hydrogen bonds**, in which **8 ordered water** molecules are recruited to integrate the architecture.



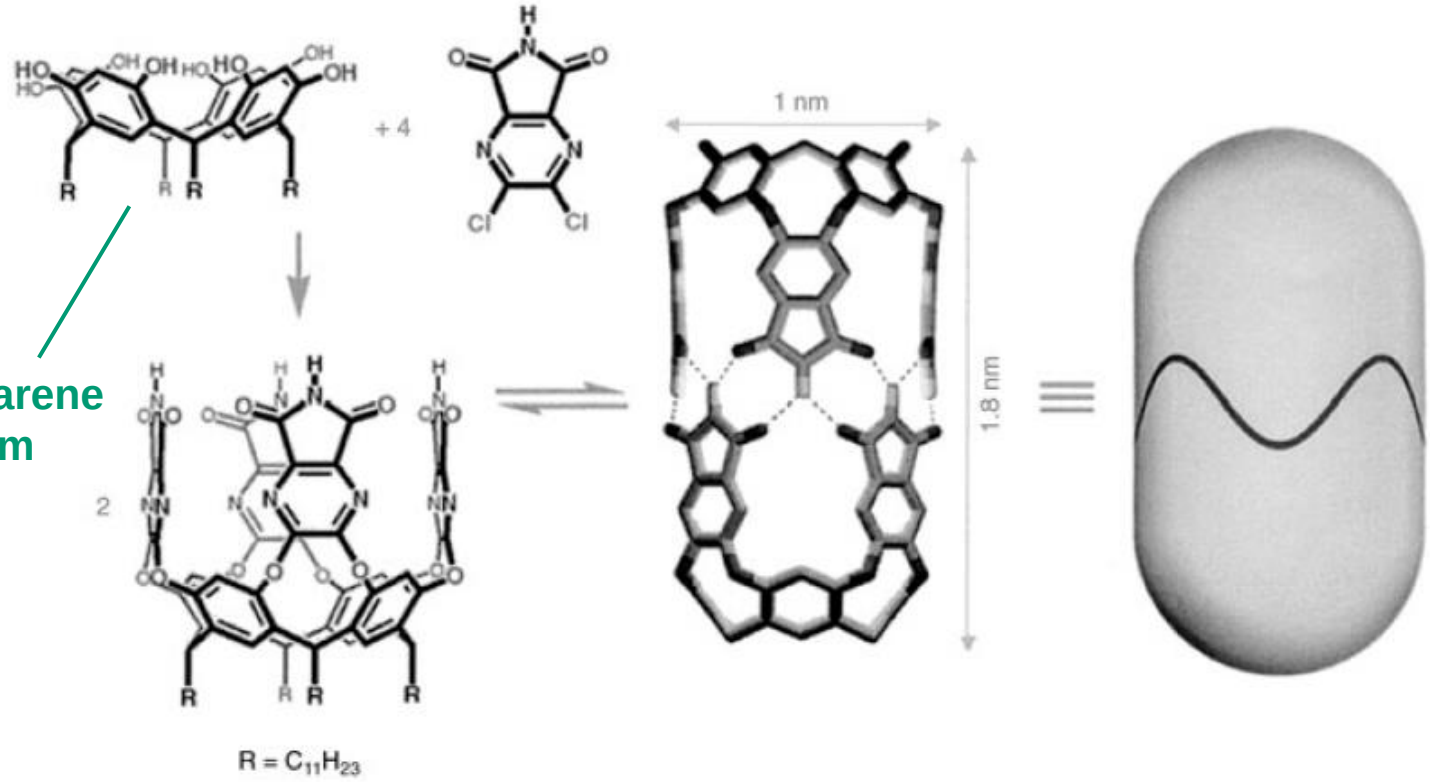
J. L. Atwood et al., *Nature* **1997**, *389*, 469.

Resorcin[4]arene-Based Capsules



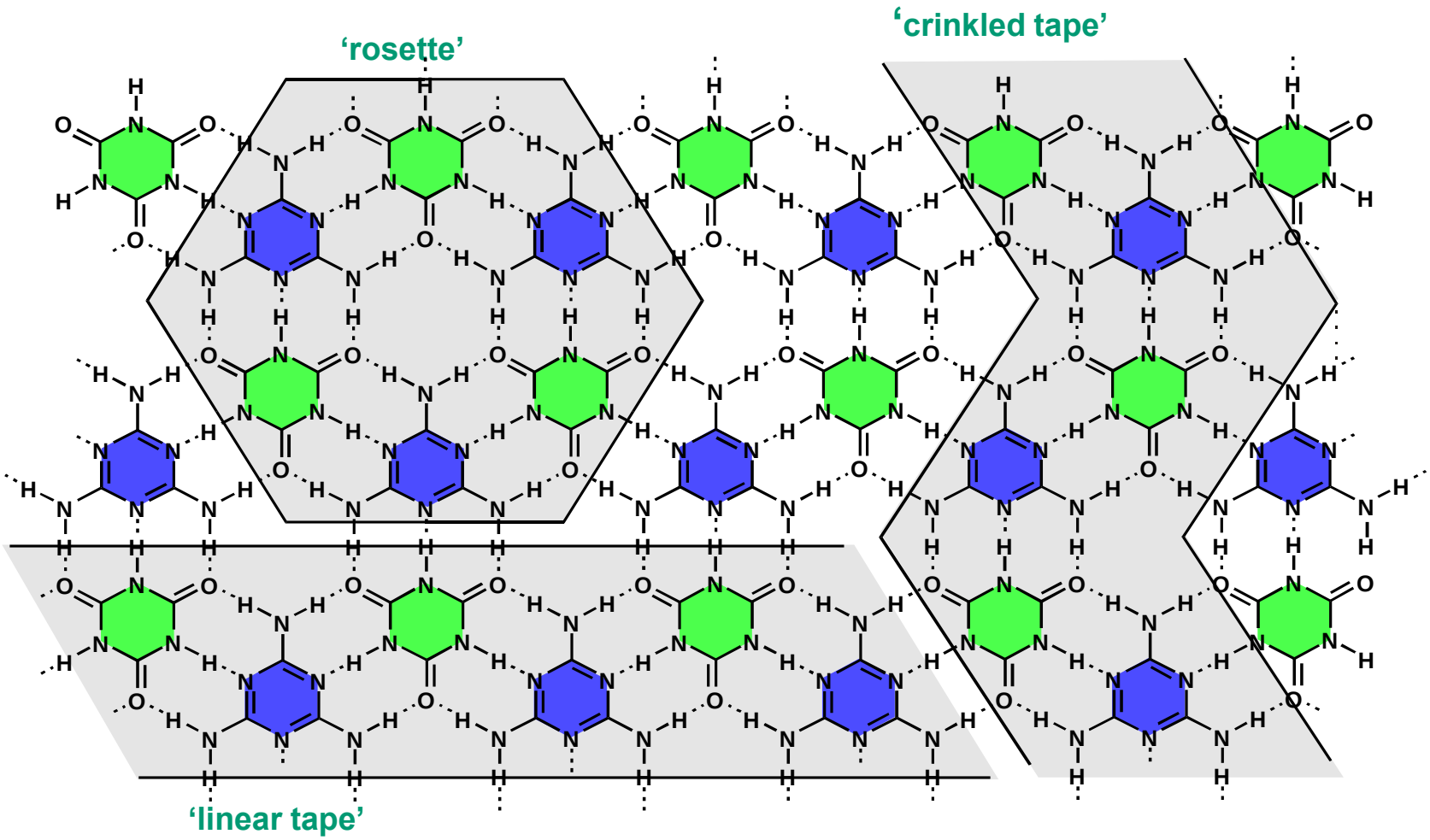


A Cylindrical Capsule



A vase-shaped cavitand structure, which presents four imide functions around its rim. The molecule dimerizes through **bifurcated hydrogen bonds**. The nonspherical shape of the cavity accommodates elongated guests and also promotes the pairwise selection of two simple aromatic compounds in an edge-to-edge manner. Two molecules of benzene or two molecules of toluene are encapsulated simultaneously, while two molecules of *p*-xylene are not.

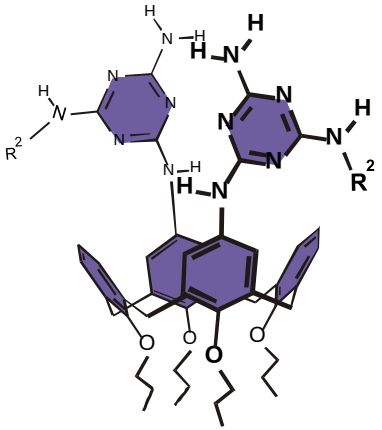
H-Bond Motif: The Cyanuric Acid / Melamine Lattice



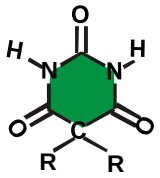
18 H-bonds diss. **$<10^{-2}$ M**

J. Am. Chem. Soc. **2001**, *123*, 7518

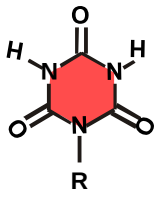
Calix[4]arene-Based Double Rosette Assemblies



+



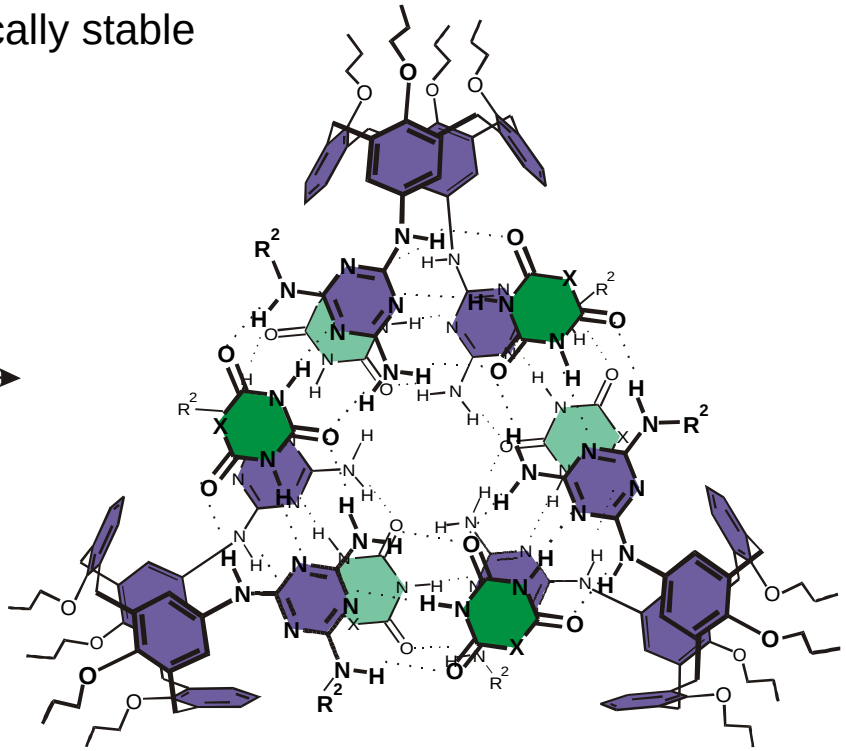
BA



CA

-Spontaneous formation
-Thermodynamically stable

$CDCl_3$
toluene
benzene



36 H-Bonds **diss.< 10^{-4} M**

D. N. Reinhoudt et al., *Chem. Eur. J.* **1997**, *3*, 1823.