

### HOST-GUEST CHEMISTRY: AN OVERVIEW

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#### Summary

Host-guest chemistry deals with the Complexation of organic compounds. It has wide applications in the field of synthetic chemistry, Drug discovery and dosage form designing. It also plays a role in catalysis, scavenging and development of sensors. It has importance in drug delivery systems. Macrocycles has been used in anti cancer, antiviral, antifungal therapy along with active constituents to alter solubility, stability and to minimize the side effects. It also plays a role in mimicking drug action especially drug receptor interaction. The nature and chemistry of receptors can easily be understood with the help of Host-guest chemistry. Thus it has been proved to be effective tool for current research in pharmaceuticals.

**Key words:** Catalysis, crown ethers, Host-guest chemistry, Macrocycles, Scavengers, Supramolecular complexes.

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### Introduction

Host-guest chemistry describes complexes that are composed of two or more molecules or ions held together in unique structural relationships by hydrogen bonding or by ion pairing or by Van der Waals force other than those of full covalent bonds.<sup>1</sup> The host component is defined as an organic molecule or ion whose binding sites converge in the complex and the guest component is defined as any molecule or ion whose binding sites diverge in the complex. Host-Guest Chemistry involves or more molecules, a “host” and a “guest”, involved in non-bonding interactions to form a Supramolecular complex.<sup>2</sup> According to Cram, “The host component is a molecule or ion whose binding sites converge in the complex”. The guest component is any molecule or ion whose binding sites diverge in the complex.

**Table no: 1: Early Development of Host-Guest Chemistry**

1903	Villiers isolates "cellulosine"
1953	Schrödinger prepares Cyclodextrin-iodine Complexes
1954	Freedenberg, Cramer and Plieninger patent nearly all important aspects of Cyclodextrin for drug delivery applications.
1969	First Cyclodextrin-base dintra-complex catalyst.
1970	Cramer publishes <i>Einschlussverbindungen</i> (Inclusion Compounds)
1980	Cyclodextrin-Drug Complexes
1985	Calixarene Research Begins First Calixarene Ion Sensors
1987	D. J. Cram, J-M Lehn, and C. J. Pedersen win the Nobel Prize for work in Supramolecular Chemistry

### Advantages of Complexation

#### 1. Altered solubility

Often increased water solubility

Sequestration and precipitation of products

#### 2. Controlled volatility

–Encapsulation of gases

–Perfume release

#### 3. Altered reactivity

–Selective catalysis

–Stabilized guests

### Macrocycles for Host-Guest Chemistry

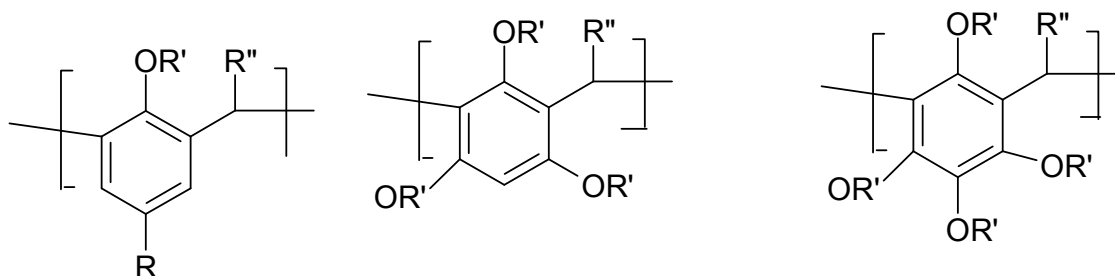
Host compounds recognize and incorporate specific molecules, atoms or ions into the molecule to form complexes. A variety of forces such as electrostatic interaction, hydrophobic interaction, Hydrogen bonding is utilized to create high selectivity. Molecular sensors, synthetic enzymes, separation systems are utilized to create high selectivity are currently developed.<sup>3</sup>

#### 1. Calixarene

A calixarene is a macrocycle or cyclic oligomer based on a hydroxyalkylation product of a phenol and an aldehyde<sup>4</sup>. 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  $R_b$  is added to the name with a prefix C- as in C-methylcalix[6]arene.

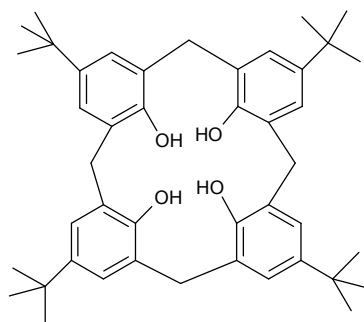
#### Synthesis

The aromatic components are derived from phenol, resorcinol or pyrogallol, The chemical reaction ranks under electrophilic aromatic substitutions followed by an elimination of water and then a second aromatic substitution. In 2005, research produced a pyrogallol[4]arene by simply mixing a solvent-free dispersion of isovaleraldehyde with pyrogallol and a catalytic amount of *p*-toluenesulfonic acid in a mortar and pestle<sup>5</sup>. Calixarenes as parent compounds are sparingly soluble and are high melting crystalline solids<sup>6</sup>.



#### Structure

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. The calixarene based on *p*-tert-butyl phenol is also a cone.



### Host guest interactions

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.<sup>7</sup>

### Applications of Calixarenes

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. A tetrathia [4] arene is found to mimic aquaporin proteins<sup>8</sup>. The construct showed a cluster effect in the production of Tn specific IgG antibodies in mice when compared to an analogous monovalent construct. This reveals perspectives for potential applications in cancer immunotherapy<sup>9</sup>.

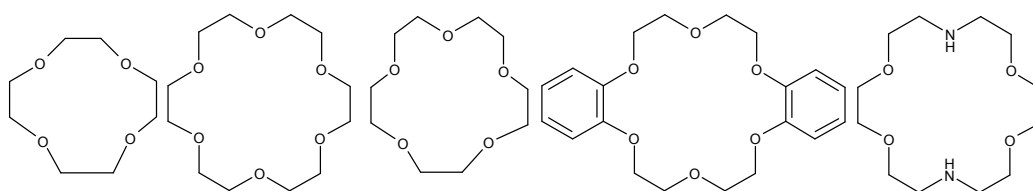
### 2. Cavitand

A cavitand is a container shaped molecule.<sup>10</sup> The cavity of the cavitand allows it to engage in host-guest chemistry with guest molecules of a complementary shape and size. Examples include cyclodextrins, calixarenes, and cucurbiturils.

### 3. Crown ether

Crown ethers are heterocyclic chemical compounds that consist of a ring containing several ether groups. The most common crown ethers are oligomers of ethylene oxide, the repeating unit being ethyleneoxy, i.e.,  $-\text{CH}_2\text{CH}_2\text{O}-$ . Important members of this series are the tetramer ( $n = 4$ ), the pentamer ( $n = 5$ ), and the hexamer ( $n = 6$ ). The term "crown" refers to the resemblance between the structure of a crown ether bound to a cation, and a crown sitting on a head. The first number in a crown ether's name refers to the number of atoms in the cycle, and the second number refers

to the number of those atoms that are oxygen. Crown ethers are much broader than the oligomers of ethylene oxide; an important group are derived from catechol. Crown ethers strongly bind certain cations, forming complexes.<sup>11</sup> The oxygen atoms are well situated to coordinate with a cation located at the interior of the ring, whereas the exterior of the ring is hydrophobic. The resulting cations often form salts that are soluble in nonpolar solvents, and for this reason crown ethers are useful in phase transfer catalysis. The denticity of the polyether influences the affinity of the crown ether for various cations. For example, 18-crown-6 has high affinity for potassium cation, 15-crown-5 for sodium cation, and 12-crown-4 for lithium cation. The high affinity of 18-crown-6 for potassium ions contributes towards its toxicity.<sup>12</sup>



structures of common crown ethers: 12-crown-4, 15-crown-5, 18-crown-6, dibenzo-18-crown-6, and diaza-18-crown-6

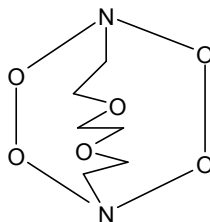
#### Crown ethers in nature

Crown ethers are not the only macrocyclic ligands that have affinity for the potassium cation. Ionophores such as valinomycin also display a marked preference for the potassium cation over other cations.<sup>13</sup>

#### History of synthetic crown ethers

In 1967, Charles Pedersen, who was a chemist working at DuPont, discovered a simple method of synthesizing a crown ether when he was trying to prepare a complexing agent for divalent cations.<sup>14</sup> Pedersen particularly popularized the dibenzo crown ethers.<sup>15</sup> Pedersen shared the 1987 Nobel Prize in Chemistry for the discovery of the synthetic routes to, and binding properties of, crown ethers.<sup>16</sup>

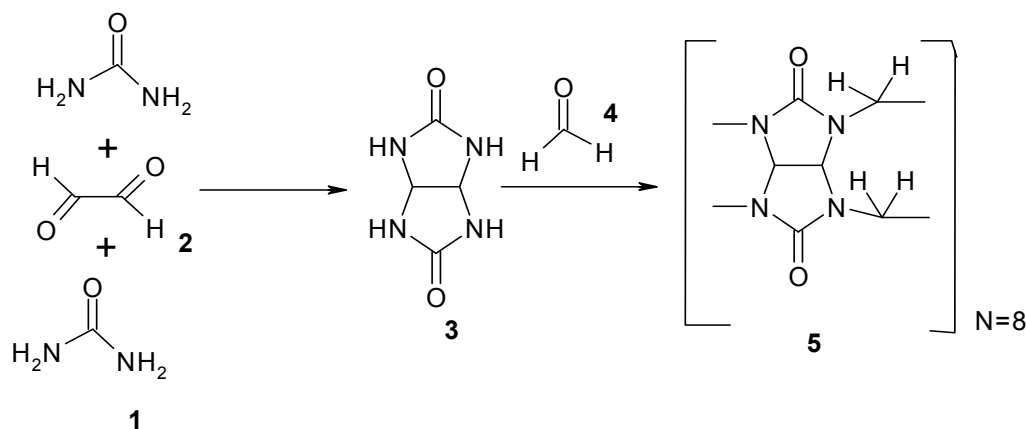
#### 4. Cryptand



Cryptands are a family of synthetic bi- and polycyclic multidentate ligands for a variety of cations.<sup>17</sup> The Nobel Prize for Chemistry in 1987 was given to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen for their efforts in discovering and determining uses of cryptands and crown ethers, thus launching the now flourishing field of supramolecular chemistry.<sup>18</sup> Cryptands enabled the synthesis of the alkalides and electrides. They have also been used in the crystallization of Zintl ions such as  $\text{Sn}_9^{4-}$ .

### 5. Cucurbituril

A cucurbituril is a macrocyclic molecule consisting of several glycoluril [=C<sub>4</sub>H<sub>2</sub>N<sub>4</sub>O<sub>2</sub>=] repeat units, each joined to the next one by two methylene [-CH<sub>2</sub>-] bridges to form a closed band. Cucurbiturils are commonly written as cucurbit[*n*]uril, where *n* is the number of repeat units. A common abbreviation is CB[*n*]. 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.<sup>11</sup> Cucurbiturils were first synthesized in 1905 by Behrend, by condensing glycoluril with formaldehyde,<sup>19</sup> but their structure was not elucidated until 1981.<sup>20</sup> To date cucurbiturils composed of 5, 6, 7, 8, and 10 repeat units have all been isolated,<sup>20</sup> which have internal cavity volumes of 82, 164, 279, 479, and 870 Å<sup>3</sup> respectively. A cucurbituril composed of 9 repeat units has yet to be isolated (as of 2009). Other common molecular capsules that share a similar molecular shape with cucurbiturils include cyclodextrins and calixarenes.



Cucurbiturils are aminated and synthesized from urea **1** and a diketone (e.g., glyoxal **2**) via a nucleophilic addition to give the intermediate glycoluril **3**. This intermediate is condensed with formaldehyde to give hexamer cucurbit[6]uril above 110 °C. Ordinarily, multifunctional monomers such as **3** would undergo a step-growth polymerization that would give a distribution of products, but due to favorable strain and an abundance of hydrogen bonding, the hexamer is the only reaction product isolated after precipitation.<sup>21</sup> The larger sizes are a particularly active

area of research since they can bind larger and more interesting guest molecules, thus expanding their potential applications.

### Applications of Cucurbiturils

- **Supramolecular host molecules**



Crystal structure of a host-guest complex with a p-xylylenediammonium bound within a cucurbit[6]uril reported by Freeman in *Acta Crystallogr B*, 1984, 382-387. Cucurbiturils are efficient host molecules in molecular recognition and have a particularly high affinity for positively charged or cationic compounds. 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. Allosteric control is provided when an adamantane molecule forces a cone conformation with a calixarene - adamantane inclusion complex within a CB[10] molecule.<sup>22,23</sup>

- **Rotaxane macrocycles**

Given their high affinities to form inclusion complexes cucurbiturils have been employed as the macrocycles component of a rotaxane. After formation of the supramolecular assembly or threaded complex with a guest molecule such as hexamethylene diamine the two ends of the guest can be reacted with bulky groups that will then act as stoppers preventing the two separate molecules from dissociating.<sup>24</sup> In another rotaxane system with a CB[7] wheel, the axle is a 4,4'-bipyridinium or viologen subunit with two carboxylic acid terminated aliphatic N-substituents at both ends.<sup>25</sup> In water at concentration higher than 0.5 M complexation is quantitative without need of stoppers. At pH = 2 the carboxylic end-groups are protonated and the wheel shuttles back and forth between them as evidenced by the presence of just two aromatic viologen protons in the proton NMR spectrum. At pH = 9 the wheel is locked around the viologen center.

- **Drug delivery vehicles**

Cucurbituril's host-guest properties have been explored for drug delivery vehicles. The potential of this application has been explored with cucurbit[7]uril that forms an inclusion compound with

the important cancer fighting drug oxaliplatin. The resulting complex was found to have increased stability and greater selectivity that may lead to less side effects.<sup>26</sup>

- **Supramolecular catalysts**

Cucurbiturils have also been explored as supramolecular catalysts. Larger cucurbiturils, such as cucurbit[8]uril can bind multiple guest molecules. CB[8] forms a complex 2:1 (guest:host) with (E)-diaminostilbene dihydrochloride which is accommodated by CB[8]'s larger internal diameter of 8.8 angstrom and height 9.1 angstrom.<sup>27</sup>

## 6. Cyclodextrin

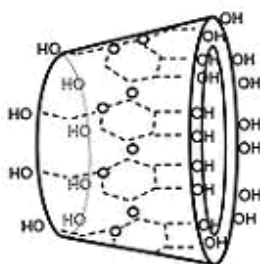
**Cyclodextrins** (sometimes called **cycloamyloses**) make up a family of cyclic oligosaccharides, composed of 5 or more  $\alpha$ -D-glucopyranoside units linked 1- $\rightarrow$ 4, as in amylose (a fragment of starch). Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape. thus denoting:

**$\alpha$ -cyclodextrin**: six membered sugar ring molecule

**$\beta$ -cyclodextrin**: seven sugar ring molecule

**$\gamma$ -cyclodextrin**: eight sugar ring molecule

Cyclodextrins are produced from starch by means of enzymatic conversion. Over the last few years they have found a wide range of applications in food, pharmaceutical<sup>28</sup> and chemical industries as well as agriculture and environmental engineering. It is also the chief active compound found in Procter and Gamble's deodorizing product "Febreze" under the brand name "Clenzaire".



The production of cyclodextrins is relatively simple and involves treatment of ordinary starch with a set of easily available enzymes<sup>29</sup>. Commonly cyclodextrin glycosyltransferase (CGTase) is employed along with  $\alpha$ -amylase. each CGTase has its own characteristic  $\alpha$ : $\beta$ : $\gamma$  synthesis ratio. Purification of the three types of cyclodextrins takes advantage of the different water solubility of the molecules:  $\beta$ -CD which is very poorly water soluble (18.5 g/l or 16.3mM) (at 25C???) can be easily retrieved through crystallization while the more soluble  $\alpha$ - and  $\gamma$ -CDs (145 and 232 g/l



respectively) are usually purified by means of expensive and time consuming chromatography techniques.

### Crystal structure of a rotaxane with an $\alpha$ -cyclodextrin macrocycle.<sup>30</sup>

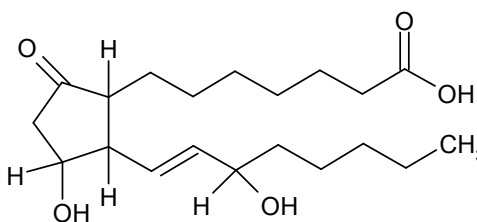
Cyclodextrins are able to form host-guest complexes with hydrophobic molecules given the unique nature imparted by their structure. As a result, these molecules have found a number of applications in a wide range of fields. Other than the above mentioned pharmaceutical applications for drug release, cyclodextrins can be employed in environmental protection: these molecules can effectively immobilise inside their rings toxic compounds, like trichloroethane or heavy metals, or can form complexes with stable substances, like trichlorfon (an organophosphorus insecticide) or sewage sludge, enhancing their decomposition. 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. Weight loss supplements are marketed from alpha-cyclodextrin which claim to bind to fat and be an alternative to other anti-obesity medications.<sup>31,32</sup> Other food applications further include the ability to stabilize volatile or unstable compounds and the reduction of unwanted tastes and odour.

### Applications of Cyclodextrin

The application of cyclodextrin as supramolecular carrier is also possible in organometallic reactions. The mechanism of action probably takes place in the interfacial region.<sup>33</sup> Wipff also demonstrated by computational study that the reaction occurs in the interfacial layer. The application of cyclodextrins as supramolecular carrier is possible in various organometallic catalysis. In 2009, hydroxypropyl beta cyclodextrin (HPBCD) was approved for use by the U.S. Food and Drug Administration (FDA) in a one time clinical trial to treat identical twin girls suffering from Niemann-Pick Type C disease. In addition Johnson and Johnson, a producer of the compound, is currently investigating its use in combination with antiviral drugs for the treatment of HIV.

### Cyclodextrin Complexed Pharmaceuticals

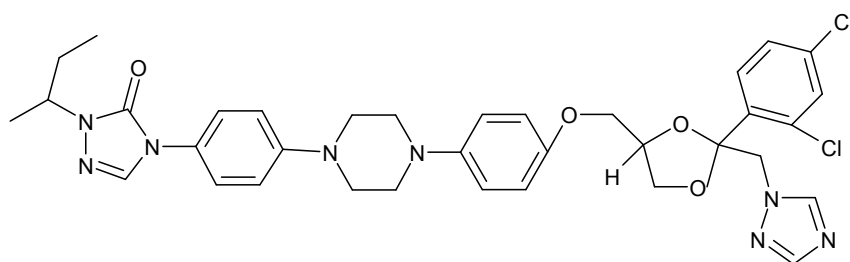
#### 1. Prostavasin



Prostavasin (alprostadil alphadex, PGE1) Prostaglandin-based treatment of peripheral circulatory disorders. Instability requires intra-arterial administration in uncomplexed form.  $\alpha$ -CD complex improved metabolic stability, injectable formulation. Schwartz Pharma product.<sup>35</sup>

## 2. Itraconazole

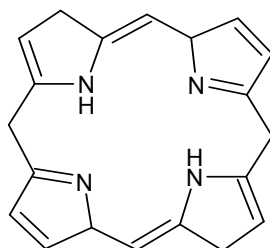
Sporanox (Itraconazole) Antifungal triazole aqueous solubility estimated 1 ng/mL hydroxy propyl  $\beta$ -CD complex improves solubility to 10 mg/mL. First orally available drug effective against *Candida spp.* and *Aspergillus spp.* Janssen product.<sup>35</sup>



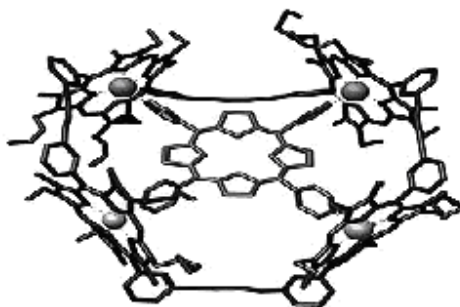
### Cyclodextrin inclusion compounds

Inclusion complexes are formed between cyclodextrins and ferrocene<sup>35</sup>. When a solution of both compounds in a 2:1 ratio in water is boiled for 2 days and then allowed to rest for 10 hours at room temperature orange-yellow crystals form. X-ray diffraction analysis of these crystals reveals a 4:5 inclusion complex with 4 molecules of ferrocene included in the cavity of 4 cyclodextrine molecules and with the fifth ferrocene molecule sandwiched between two stacks of ferrocene - cyclodextrine dimers. Cyclodextrin also forms inclusion compounds with fragrance molecules<sup>36</sup>. As a result the fragrance molecules have a reduced vapor pressure and are more stable towards exposure to light and air.

## 7. Porphyrin



**Porphyrins** are a group of organic compounds of which many occur in nature, most well-known as the pigment in red blood cells. They are heterocyclic macrocycles characterised by the presence of four modified pyrrole subunits interconnected at their  $\alpha$  carbon atoms via methine bridges (=CH-). Porphyrins are aromatic, and they obey Hückel's rule for aromaticity in that they possess  $4n+2$  pi electrons that are delocalized over the macrocycle.



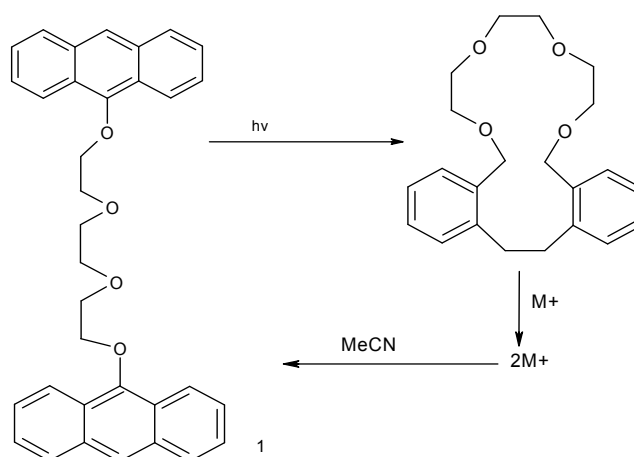
An example of a porphyrins involved in host-guest chemistry. Here, a four porphyrin-zinc complex hosts a porphyrin guest.<sup>37</sup> Porphyrins are often used to construct structures in supramolecular chemistry. These systems take advantage of the Lewis acidity of the metal, typically zinc. An example of a host-guest complex that was constructed from a macrocycle composed of four porphyrins.<sup>37</sup> A guest-free base porphyrin is bound to the center by coordination with its four pyridine substituents.

### Molecular tweezers

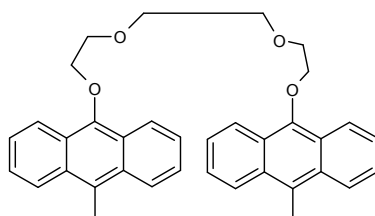
sometimes termed **molecular clips**, are noncyclic macrocyclic molecular complexes with open cavities capable of binding guests<sup>38</sup>. The term "molecular tweezer" was first used by Howard J. Whitlock,<sup>39</sup> but the class of hosts was developed and popularized by Steven C. Zimmerman in the mid-1980s to early 1990s<sup>40</sup>. The open cavity of the molecular tweezer may bind guests using non-covalent bonding which includes hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces,  $\pi$ - $\pi$  interactions, and/or electrostatic effects. These complexes are a subset of macrocyclic molecular receptors and their structure is that the two "arms" that bind the guest molecule between them are only connected at one end. One example of molecular tweezers has been reported by Lehn and coworkers. This molecule is capable of binding aromatic guests. The molecular tweezers are composed of two anthracene arms held at a distance that allows aromatic guests to gain  $\pi$ - $\pi$  interactions from both. Another class of molecular tweezers is composed of two substituted porphyrin macrocycles tethered by a amide linker with a variable length. This example of a molecular tweezer shows the potential mobility of this class of molecules, as the orientation of the porphyrin planes which comprise the tweezer can be altered by the guest which is bound<sup>41</sup>. The binding site between the planes of the tweezer can be designed to bind to an appropriate guest with resulting high association constants and consequent stability, depending on the design of the tweezer. That makes this overall class of macromolecule truly a synthetic molecular receptor.

## Host-guest molecular switches

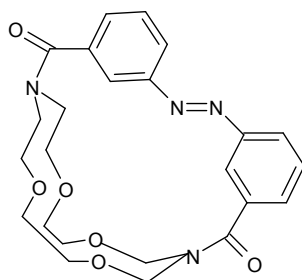
In host-guest chemistry the bistable states of molecular switches differ in their affinity for guests. Many early examples of such systems are based on crown ether chemistry. The first switchable host is described in 1978 by Desvergne & Bouas-Laurent<sup>42,43</sup> who create a crown ether via photochemical anthracene dimerization. Although not strictly speaking switchable the compound is able to take up cations after a photochemical trigger and exposure to acetonitrile gives back the open form.



In 1980 Yamashita *et al.*<sup>44</sup> construct a crown ether already incorporating the anthracene units (an anthracenophane) and also study ion uptake vs photochemistry.



Also in 1980 Shinkai throws out the anthracene unit as photoantenna in favor of an azobenzene moiety<sup>45</sup> and for the first time envisions the existence of molecules with an on-off switch. In this molecule light triggers a trans-cis isomerization of the azo group which results in ring expansion. Thus in the trans form the crown binds preferentially to ammonium, lithium and sodium ions while in the cis form the preference is for potassium and rubidium (both larger ions in same alkali metal group). In the dark the reverse isomerization takes place.



Shinkai employs this devices in actual ion transport mimicking the biochemical action of monensin and nigericin in a biphasic system ions are taken up triggered by light in one phase and deposited in the other phase in absence of light.

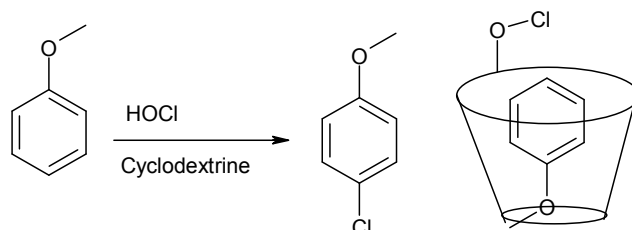
### Host-guest chemistry in gas phase <sup>46</sup>

The kinetic method is a versatile way to measure many types of ligand affinities of macrocycles, and size-selective binding affinities are observed in gas-phase measurements of crown ether complexes. In general, gas-phase ligand affinities do not always follow the same relative trends as solution results, however, the solution and gas phase affinities follow parallel trends when the complexity and steric effects of the gas-phase adducts is increased. The relative order determined for ammonium ion affinities of polyether is different from that determined for proton affinities, and this is rationalized in part because of the different sizes of the cations which promote selective hydrogen-bonding interactions. The bulky ammonium ion may bind via several N-He-O bonds, whereas the proton is most favorably bound by a single near-linear proton bridge. The latter type of binding is more easily achieved by the flexible acyclic ethers rather than the crown ethers, and this is reflected in the generally higher relative proton affinities of the acyclic polyethers. Apparently the "cavity size" concept plays a role in influencing the favorability of multiple binding interactions involved in the ammonium iodocrown ether complexes. The order of relative ammonium ion affinities of crown ethers and acyclic analogs closely parallels the orders of affinities obtained for alkali metal ions of similar size (i.e. K<sup>+</sup>, Rb<sup>+</sup>). The formation of multiple hydrogen-bonds can have striking effects on the dissociation behavior of amine/crown ether ion-complexes because the multiple hydrogen-bonding interactions allow formation of strongly-bound complexes, in contrast to the loosely-bound proton-bridged complexes that are typically formed by ion-molecule association reactions. Both the number of possible interactions and the difference in gas-phase basicity affect the capability of any crown ether and amine for forming a strongly-bound complex. The ability to form multiple bonds can compensate for a relatively large difference in proton binding affinity, but ultimately a very large difference in

gas-phase basicity causes one substrate to be much more strongly coordinated to the proton, resulting in a less stable complex. These studies have provided insight into some of the requirements for multiple binding interactions of simple model host-guest systems in the gas phase.

### Chemical Applications

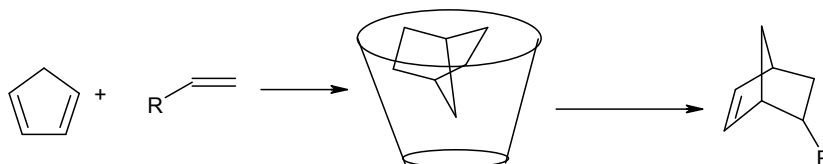
#### 1. Directed Aromatic Chlorination<sup>47</sup>



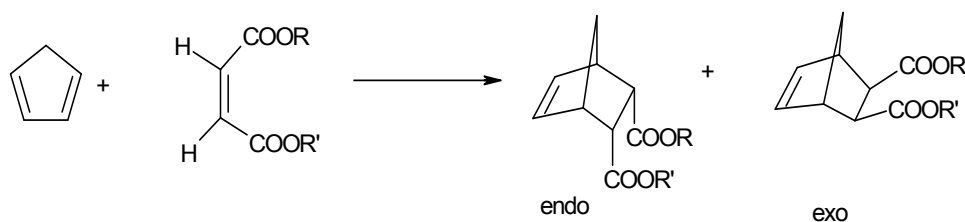
>95% Para chlorination observed with  $\beta$ -CD; 1.48 : 1.0 *p/o* without CD; Internal delivery of Cl from 2°OH; Methylation of all but C-3 2°OH groups affords 4.4x tighter binding and improved selectivity.

#### 2. Cavity Accelerated Diels-Alder<sup>48</sup>

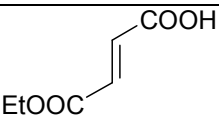
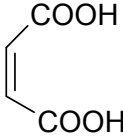
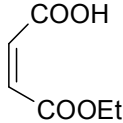
Requires small reaction components; CD shows rate accelerations of up to 1800 x rates in isooctane and 2-10 x those in water for small substrates-CD inhibits reaction even with small substrates.



#### 3. Modest increase in diastereoselectivity observed in Cyclodextrin over reactions in water<sup>48</sup>

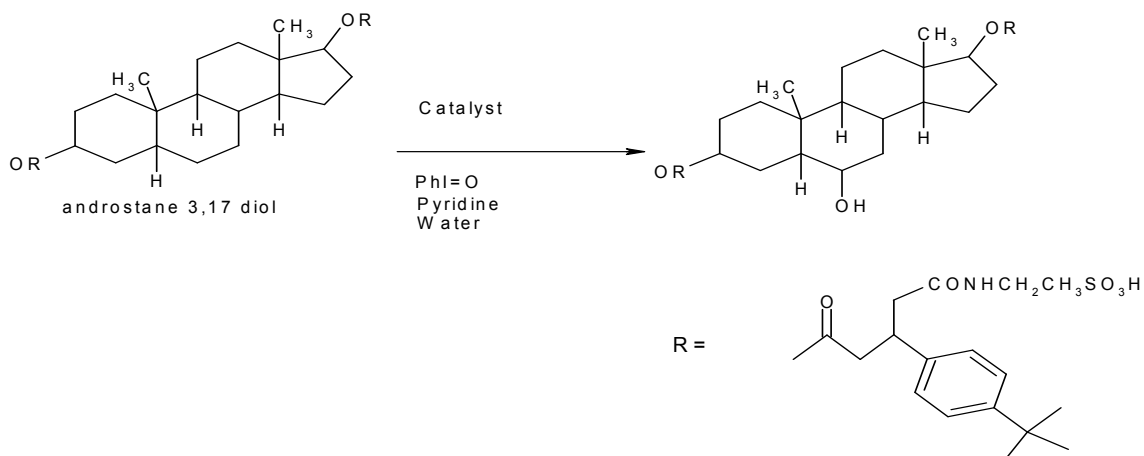


**Table no: 2: increase in diastereoselectivity observed in Cyclodextrin over reactions in water**

Dienophile	Endo/Exo in water	Endo/Exo in 0.015M $\beta$ CD
	1.10±0.05	2.2±0.08
	47±4	69±4
	48.5±4	112±5

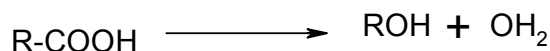
#### 4. Biomimetic Steroid Hydroxylation<sup>49</sup>

Regioselective for C-6•Stereoselective for the  $\alpha$ face.10 equivalents of Ph I=O oxidant and pyridine Reaction in water



#### 5. Antioxidant Enzyme Mimic<sup>50</sup>

Glutathione Peroxidase (GPX) mimics -antioxidant activity; Catalyzes reduction of hydro peroxides by glutathione using natural coenzymes and cofactors; Prevents oxidative damage to biological systems.



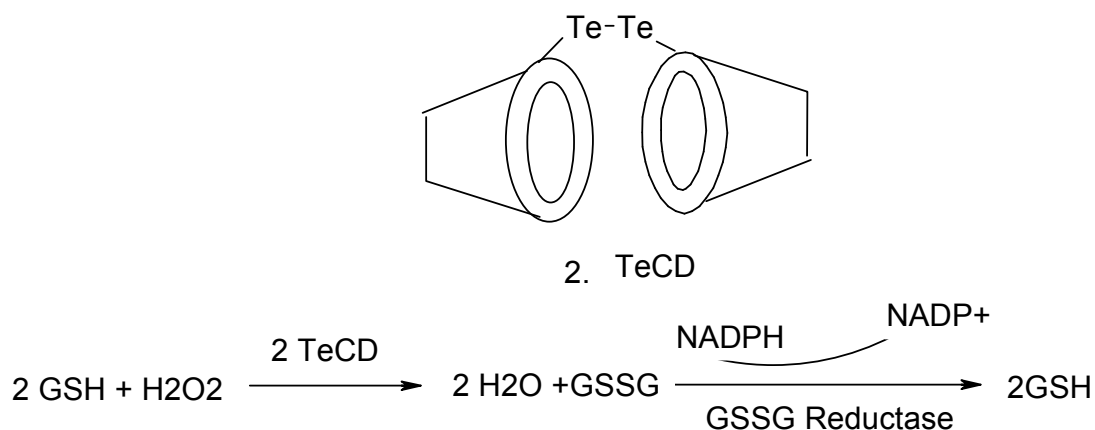


Table no:3: Antioxidant Enzyme Mimic

GPX mimic	Hydroperoxide	Activity ( $\text{U } \mu\text{m}^{-1}$ )
Ebselen	$\text{H}_2\text{O}_2$	0.99
PhSeSePh	$\text{H}_2\text{O}_2$	1.95
2-SeCD	$\text{H}_2\text{O}_2$	7.4
2-TeCD	$\text{H}_2\text{O}_2$	46.7
2-TeCD	t-BuOOH	32.8
2-TeCD	Cumine hydroperoxide	87.3

Superior to Ebselen, a common GPX mimic; Slows damage to mitochondria by hydroperoxides; May be useful in bioelectric devices. GSH = Glutathione, NADPH =  $\beta$ -nicotinamide adenine di nucleotide phosphate

### 6. Anesthetic Scavenger <sup>51</sup>

Rocurionium bromide is a common neuromuscular blocking drug. Conventional reversal medications have many side-effects. Org 25969 is currently in Phase II Human Clinical Trials.

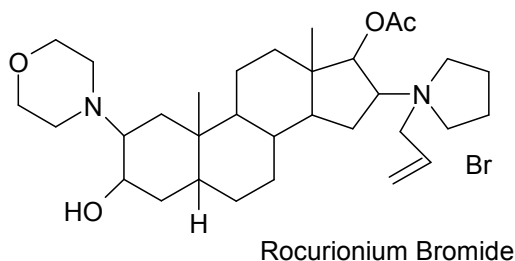




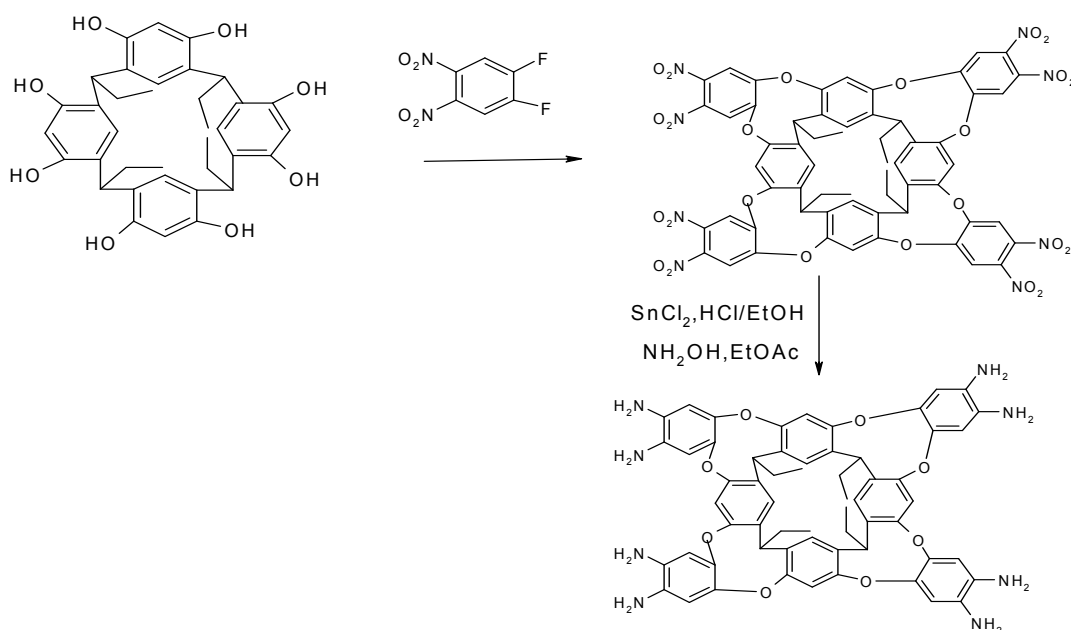
Table no.4: Anesthetic Scavenger

Host	EC <sub>50</sub> [ $\mu$ M]	Max% Reversal
$\alpha$ -CD	> 360	9.7
$\beta$ -CD	>360	29
$\gamma$ -CD	34.6	94.1
Org 25969	1.2	95.1

Extending cavity depth from 7.9 to  $\sim 11$  Å greatly improves complexation. Patients show significant recovery in minutes.

### 7. Receptor Synthesis<sup>52</sup>

Trimethylammonium moiety challenges receptor design. Quaternary ammonium does not allow hydrogen bonding. Roughly spherical shape limits binding site design. Complex stabilized by deep aromatic cavity. Larger NR<sub>4</sub><sup>+</sup> ions excluded from binding. Vase shaped complex “stitched” together by DMSO. Weak H-bond from alcohol to amine (0.6 kcal/mol).

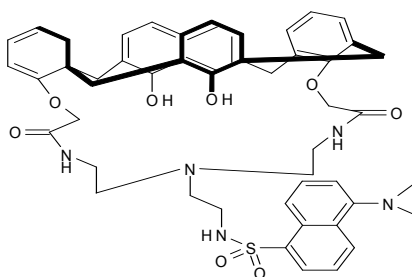


### 8. Sensor Requirements<sup>53</sup>

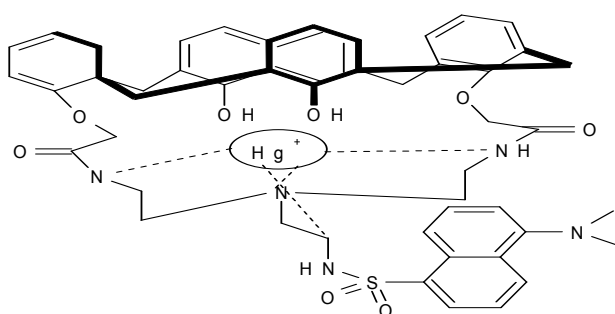
Selective binding; Detection at low levels; Fast response for dynamic sensing; Tolerance for changing conditions; Clear, intense signaling.

#### a. Fluorescent Hg<sup>2+</sup> Sensor

Calix[4]-aza-crown binding site; Maintains activity in aqueous solution; Dansyl fluorescence quenched by binding Hg<sup>2+</sup>.

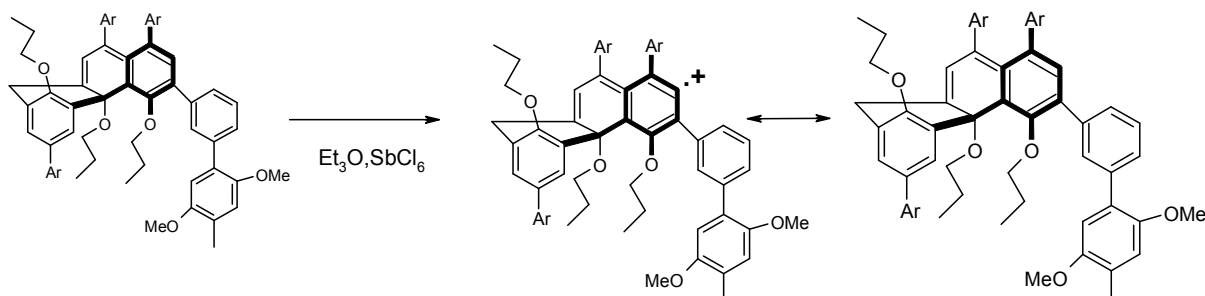


Selective binding over  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Ag}^+$ ,  $\text{Ba}^{2+}$ ; Little selectivity over  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ;  $K_a = 1.31 \times 10^5 \text{ M}^{-1}$ ; Detection Limit  $4.1 \times 10^{-6} \text{ mol/L}$ .



### b. Radical Cation Sensor for Nitric Oxide

Radical cation stabilized by electron-rich substituent; Stable at room temperature



### Conclusion

Host-guest chemistry is applied in Catalysis, Scavenging, Sensors, Pharmaceuticals both drugs and delivery Mimicking and understanding biological systems. New host design opens more fields for research. The field of host-guest chemistry has matured sufficiently to have utility in many important and interesting applications and remains a fruitful area for research.

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