Dr. Babasaheb Ambedkar Marathwada University, Aurangabad

Department of Chemistry

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M.Sc. Chemistry I Semester

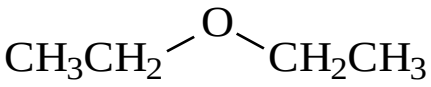
Organic Chemistry Lect: 1

Unit-I: Nature of Bonding in Organic Molecules

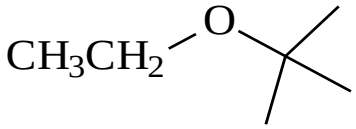
Addition compounds

Ethers (R-O-R)

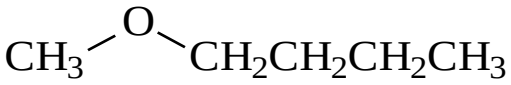
- alkanes with an alkoxy substitutent,
- RO- = alkoxy substitutent,
- Choose the smallest part of the ether as the substituent
- Choose the smallest part of the ether as the substituent



Ethoxyethane
Diethyl ether



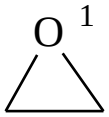
2-Ethoxy-2-methylpropane
t-Butyl ethyl ether



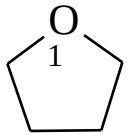
1-Methoxybutane
Butyl methyl ether

Cyclic Ethers

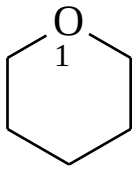
O group is called an "oxa-" substituent: oxacycloalkanes,
Common names are prevalent



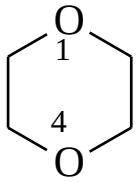
Oxacyclopropane
Epoxide



Oxacyclopentane
Tetrahydrofuran (THF)



Oxacyclohexane
Tetrahydropyran



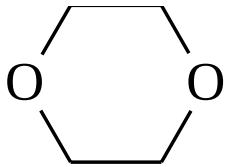
1,4-Dioxacyclohexane
1,4-Dioxane

B.Physical Properties

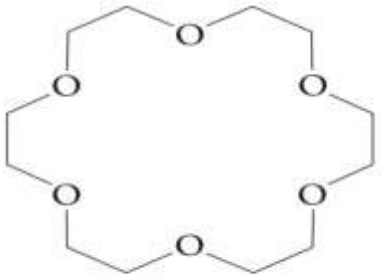
- Same molecular formula as Alcohol: $C_nH_{2n+2}O$
- No Hydrogen Bonding is possible in R—O—R
- Boiling Points are much lower than alcohols, more like haloalkanes
- Water solubility much less than alcohols
- MeOMe and EtOEt have some water solubility
- Larger ethers are insoluble, very much like alkanes
- Fairly unreactive, nonpolar solvents for organic reactions

C.Metal Complexation by Crown Ethers

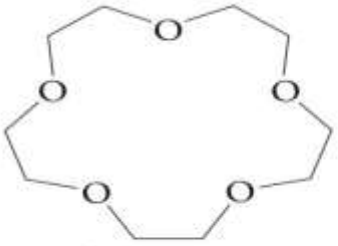
- Crown Ether is a cyclic polyether: --(CH_2CH_2O)—
- Named as: (# of total atoms in ring)-Crown-(# of oxygens)
- Oxygen lone pair can be donated to M^+ to form complexes
- Allows dissolution of metal salts in organic solvents
- Size of cavity dictates which metal fits: 18-crown-6 $K^+ > Rb^+ > Na^+$ etc



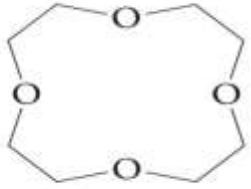
6-crown-2



[18]crown-6
mp 39–40°C



[15]crown-5
(liquid)



[12]crown-4

INTRODUCTION

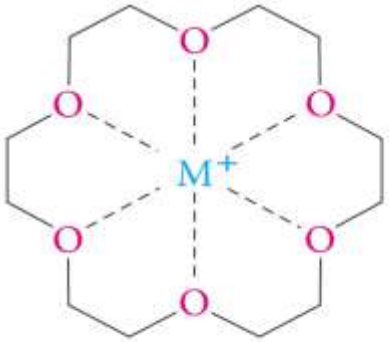
Crown ethers

• **Guest-host binding interactions** of four crown ethers with alkali metal ions were studied by electrospray ionization mass spectrometry (ESI-MS).

• Crown ethers are compounds that are **repeating units of ethylene oxide** (C_2H_4O). The unique binding quality of crown ethers allows for them to bind strongly with ions. The interior of the ring is the portion where Oxygen (in most cases) binds with the metal, whilst the exterior remains hydrophobic. This creates a polar substance that is soluble in a non-polar solvent.

•The origin of the name, crown ether stems from the fact that when an ion enters the middle of the crown it bears a resemblance to a crown placed on a head.

These compounds are called **Crown ethers** because their molecule have a crown-like shape. The bracket number represents the ring size and the terminal numbers gives the number of oxygens. The oxygens are usually separated by two carbons.

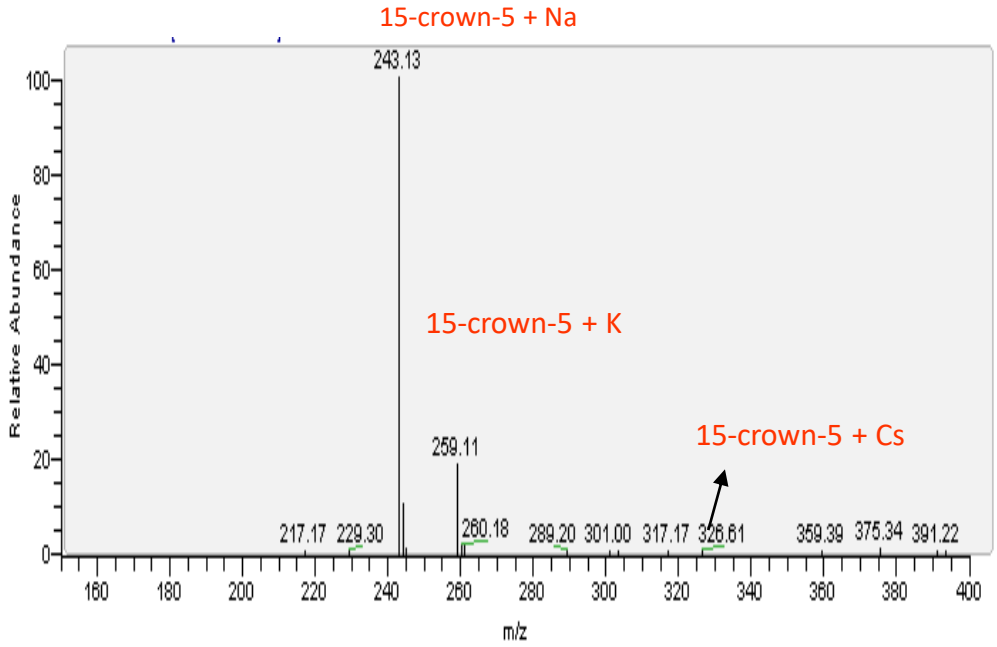


M^+ complexed in [18]crown-6

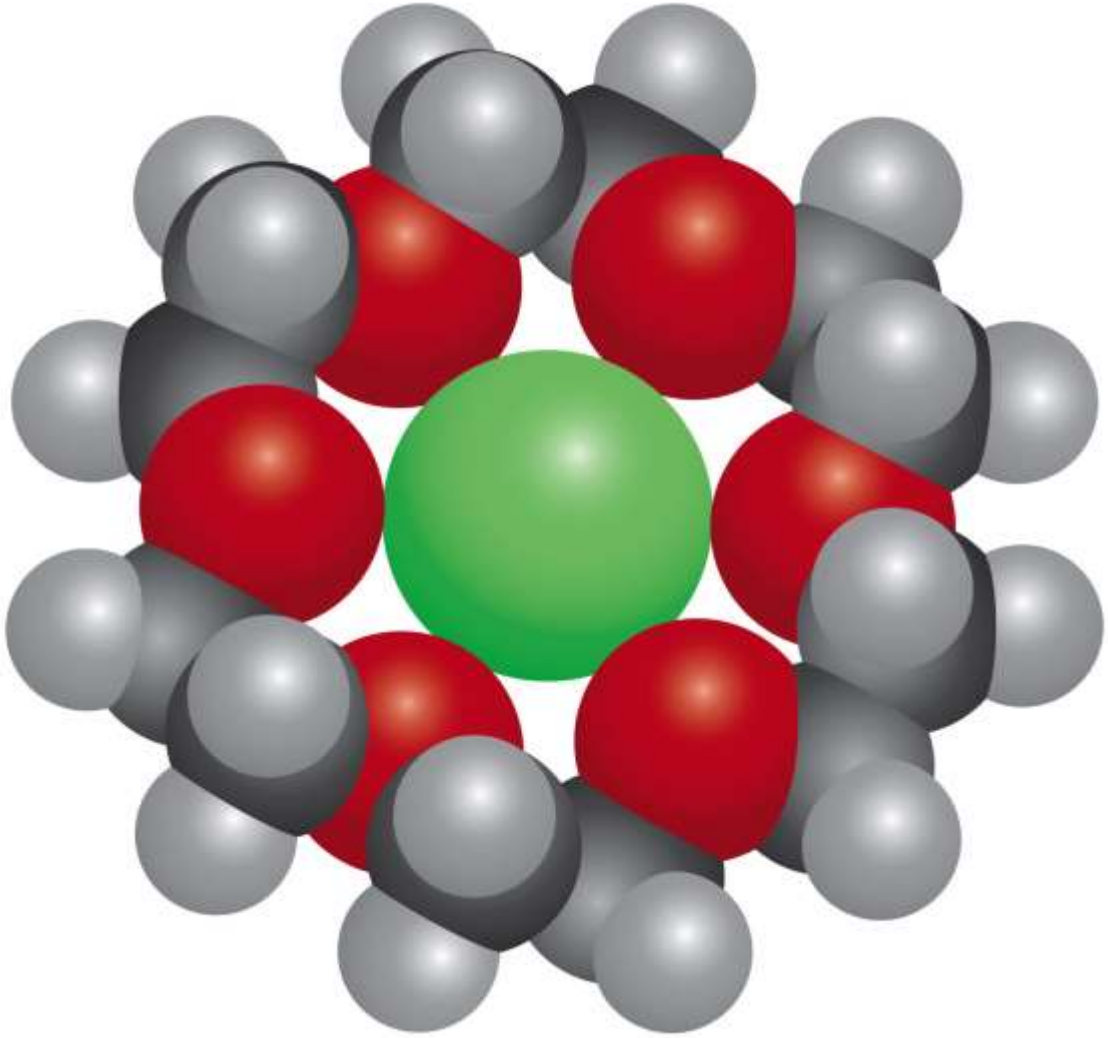
X^-

Cavity diameter		2.6–3.2 Å
Ion diameter	Na^+	1.90 Å
	K^+	2.66 Å
	Cs^+	3.34 Å

Only this ion achieves a snug fit.



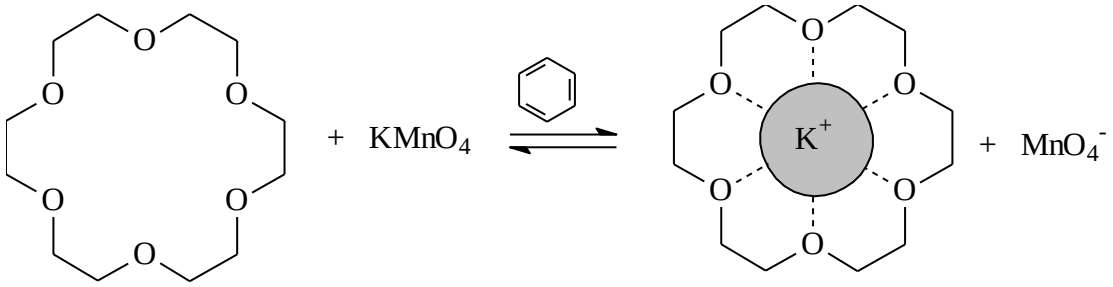
ETHER	CAVITY (A)	BEST FIT (A)
12-crown-4	.6 - .75	Na^+ (1.02)
15-crown-5	.86 - .92	Na^+ (1.02)
18-crown-6	1.34 - 1.43	K^+ (1.38)



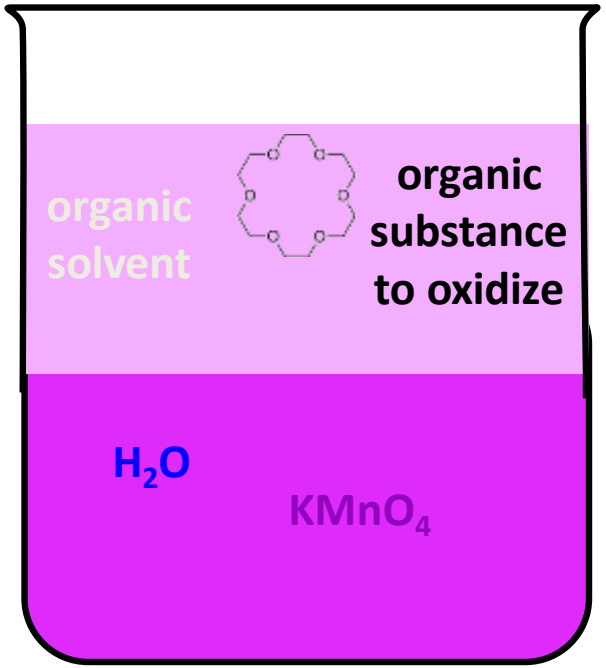
Model of [18]crown-6 complex with K^+

Phase-Transfer Catalysis

By making cation large 18-c-6 "destabilizes" solid or aqueous $KMnO_4$ allowing the salt to dissolve in hydrocarbons. ("purple benzene")



18-crown-6



Similar effect from adding other salts with large organic cations, *e.g.*

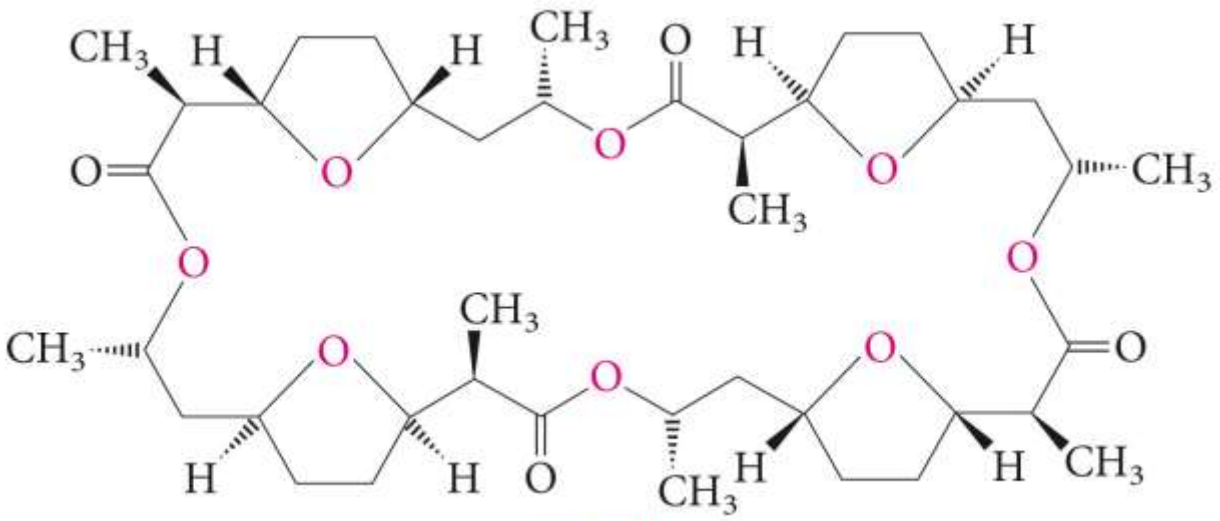
$R_4N^+ Cl^-$

$R_4P^+ Cl^-$

Avoids need for expensive, dangerous solvents like $(CH_3)_2SO$ that dissolve both reagents

Nonactin

a bacterium-generated antibiotic



nonactin

The selective binding of metallic ions by macrocyclic compounds is important in nature. Several antibiotics, such as **nonactin**, have large rings that contain regularly spaced oxygen atoms. Nonactin (which contains four tetrahydrofuran rings joined by four ester links) selectively binds K^+ (in the presence of Na^+) in aqueous media. Thus allowing selective transport of K^+ (but not Na^+) through the cell membranes

D.Cryptands and cryptates

Cryptands are topologically complex polyethers

Greek kryptos = hidden

Even stronger metal binding than crown ethers

Nobel prize for crowns/cryptands 1987 Cram, Pederson, Lehn

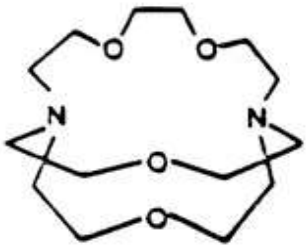
➢**Cryptands** are a family of **synthetic bi- and polycyclic multidentate ligands** for a variety of cations.

➢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.

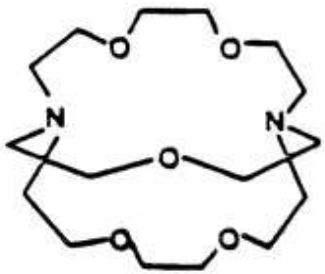
➢The term cryptand implies that this ligand binds substrates in a crypt, interring the guest as in a burial. These molecules are three-dimensional analogues of crown ethers but are more selective and strong as complexes for the guest ions. The resulting complexes are lipophilic.

➢The complex formed is called as cryptates.

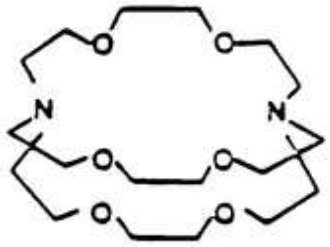
Structure 14

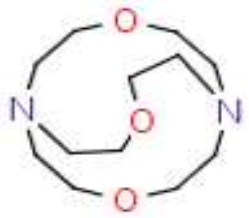


Structure 15



Structure 16

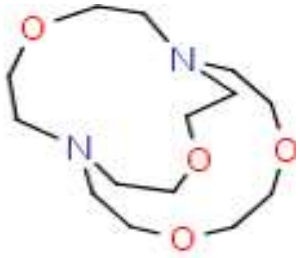




Kryptofix-1,1,1

thia-Kryptofix-1,1,1

Kryptofix-2,1,0



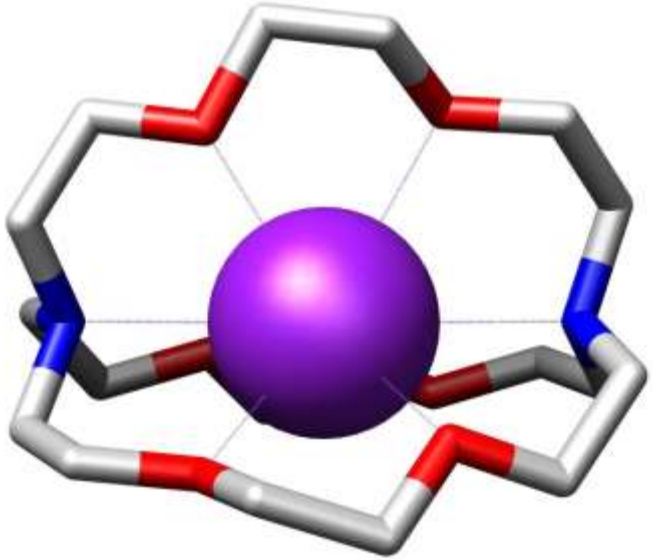
Kryptofix-2,1,1

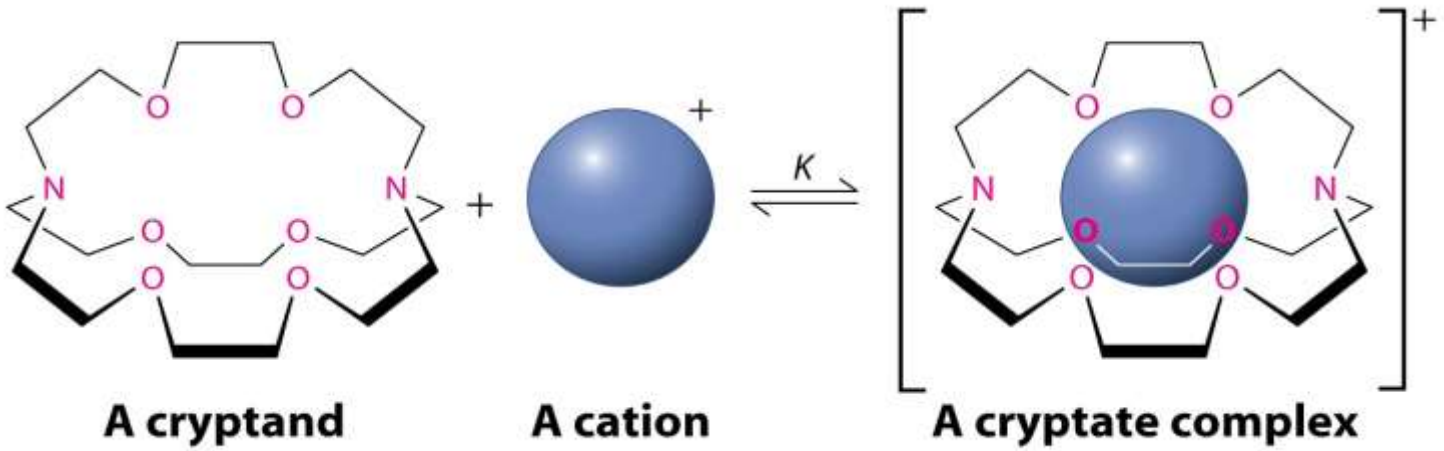
Properties

The 3-dimensional interior cavity of a cryptand provides a binding site – or host – for "guest" ions. The complex between the cationic guest and the cryptand is called a cryptate. Cryptands form complexes with many "hard cations" including NH+4, lanthanoids, alkali metals, and alkaline earth metals. In contrast to crown ethers, cryptands bind the guest ions using both nitrogen and oxygen donors. This three-dimensional encapsulation mode confers some size-selectivity, enabling discrimination among alkali metal cations (e.g. Na^+ vs. K^+).

Uses

Cryptands are more expensive and difficult to prepare, but offer much better selectivity and strength of binding than other complexants for alkali metals, such as crown ethers. They are able to bind otherwise insoluble salts into organic solvents. They can also be used as phase transfer catalysts by transferring ions from one phase to another. Cryptands enabled the synthesis of the alkalides and electrides. They have also been used in the crystallization of Zintl ions such as Sn_9^{4-}

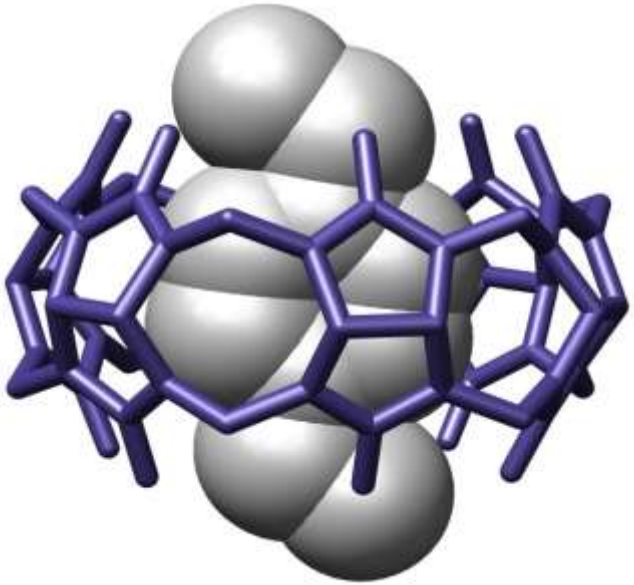




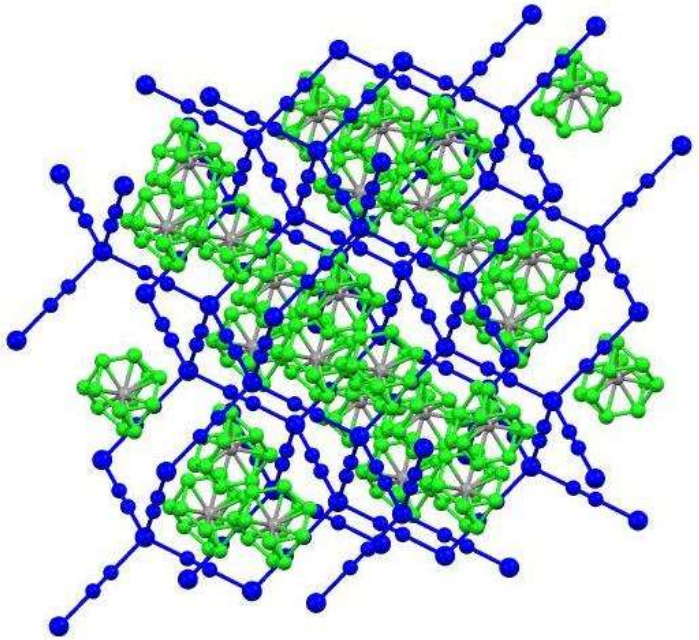
A cryptand **A cation** **A cryptate complex**

Inclusion compound

➢In host-guest chemistry, an **inclusion compound** is a complex in which one chemical compound (the "host") forms a cavity in which molecules of a second "guest" compound are located. The definition of inclusion compounds is very broad, extending to channels formed between molecules in a crystal lattice in which guest molecules can fit. If the spaces in the host lattice are enclosed on all sides so that the guest species is 'trapped' as in a cage, the compound is known as a clathrate.

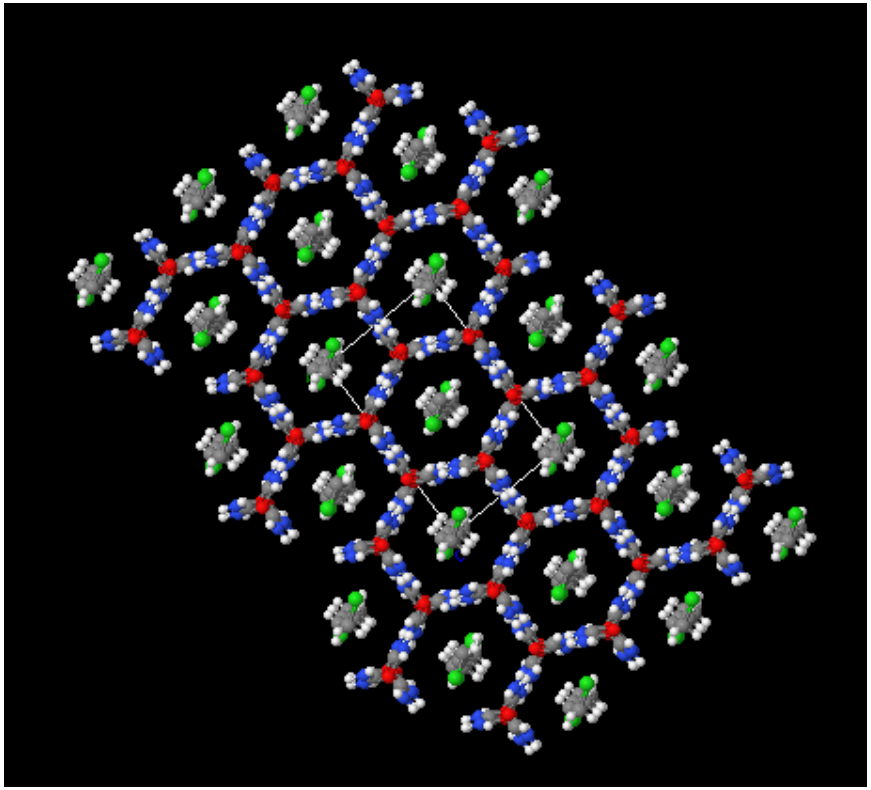


Example of an inclusion complex consisting of a p-xylylenediammonium bound within a cucurbituril



Structure of the clathrate consisting of cadmium cyanide host and carbon tetrachloride guest,Cd(CN)2.CCl4. Blue = Cd(CN)2 framework, gray = C, green = disordered Cl.

➢clathrates are "Inclusion compounds in which the guest molecule is in a cage formed by the host molecule or by a lattice of host molecules."



Structure of the 3:1 inclusion complex of urea and 1,6-dichlorohexane. The framework is composed of molecules of urea that are linked by hydrogen bonds, leaving approximately hexagonal channels into which align the molecules of the chlorocarbon. Color scheme: oxygen is red, nitrogen is blue, chlorine is green.

Cyclodextrin

➢It is a Complexaing agent.

➢Synonym: cavitron, cycloamyloses, cycloglucan, cyclic oligosaccharide

➢It is a important for increasing the solubility of poorly water soluble drugs.

➢Cyclodextrines 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.

➢Cyclodextrines are composed of 5 or more α-D glucopyranoside units linked 1->4, as in amylose linkage.

➢Cyclodextrines contains 32 1,4-anhydroglucopyranoside units, while as a poorly characterized mixture, at least 150-membered cyclic oligosaccharides are also known.

•Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape:

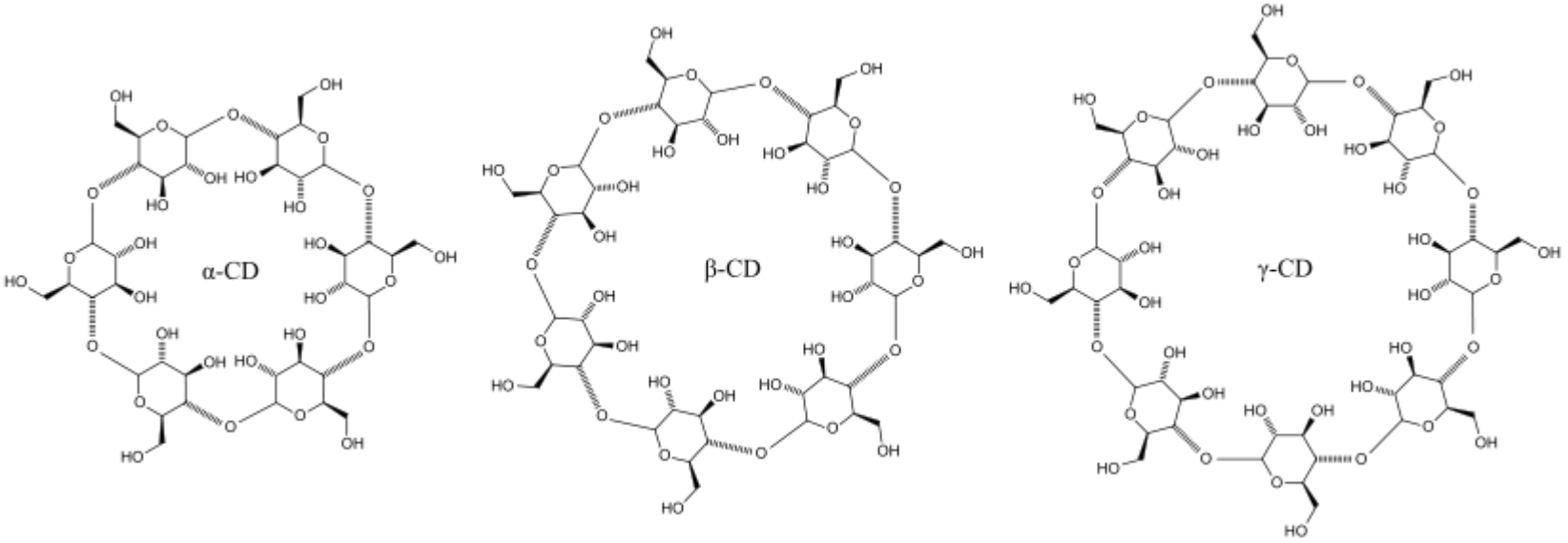
•**α (alpha)-cyclodextrin**: 6-membered sugar ring molecule

•**β (beta)-cyclodextrin**: 7-membered sugar ring molecule

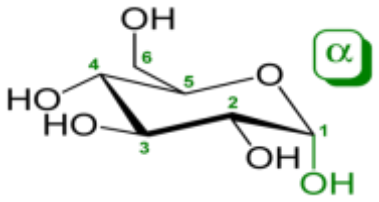
•**γ (gamma)-cyclodextrin**: 8-membered sugar ring molecule

➢ CDs, with lipophilic inner cavities & hydrophilic outer surfaces, are interacting with a guest molecule to form non covalent inclusion complexes.

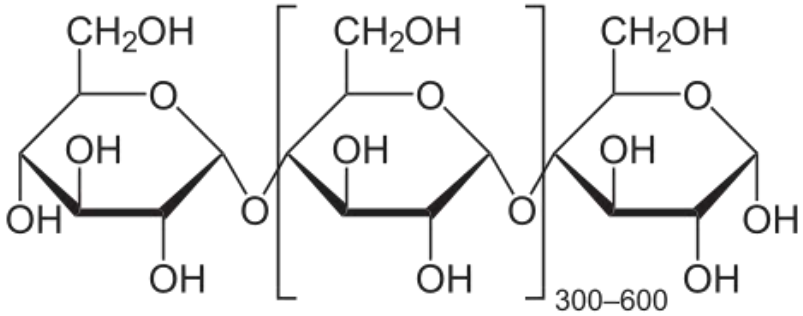
➢Today CDs are only synthesized either by fermentation or enzymatically.



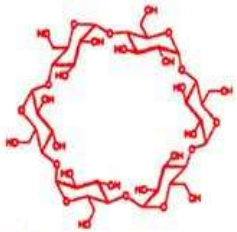
Glucose



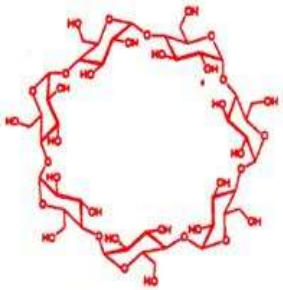
Starch or **amylum** is a polymeric carbohydrate consisting of a large number of glucose units joined by glycosidic bonds.

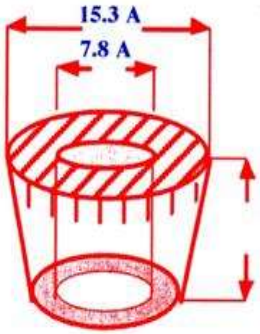


α-Cyclodextrin

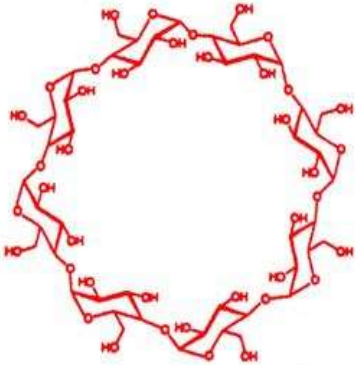


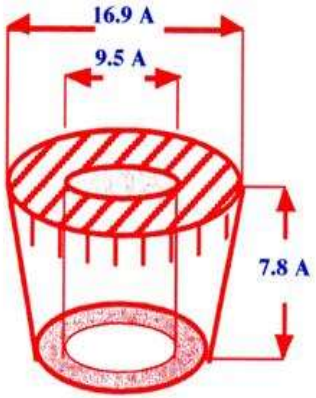
β-Cyclodextrin

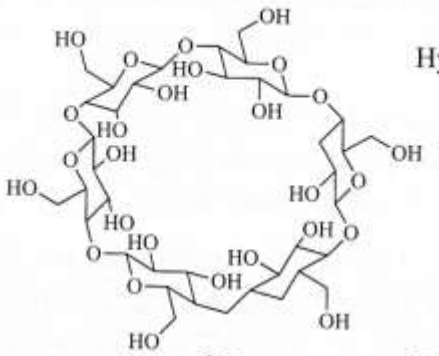


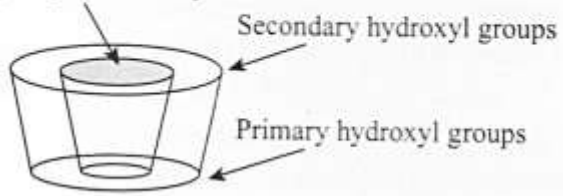


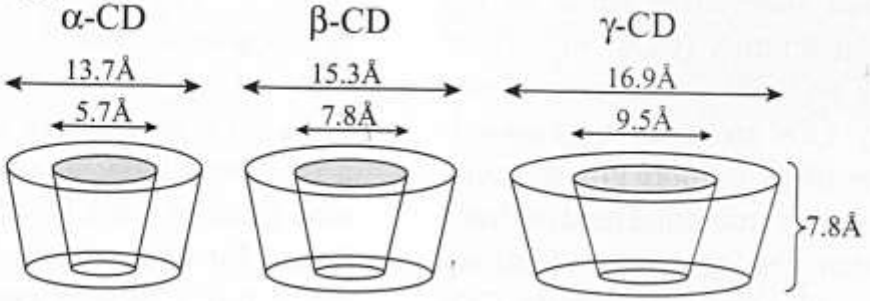
γ-Cyclodextrin







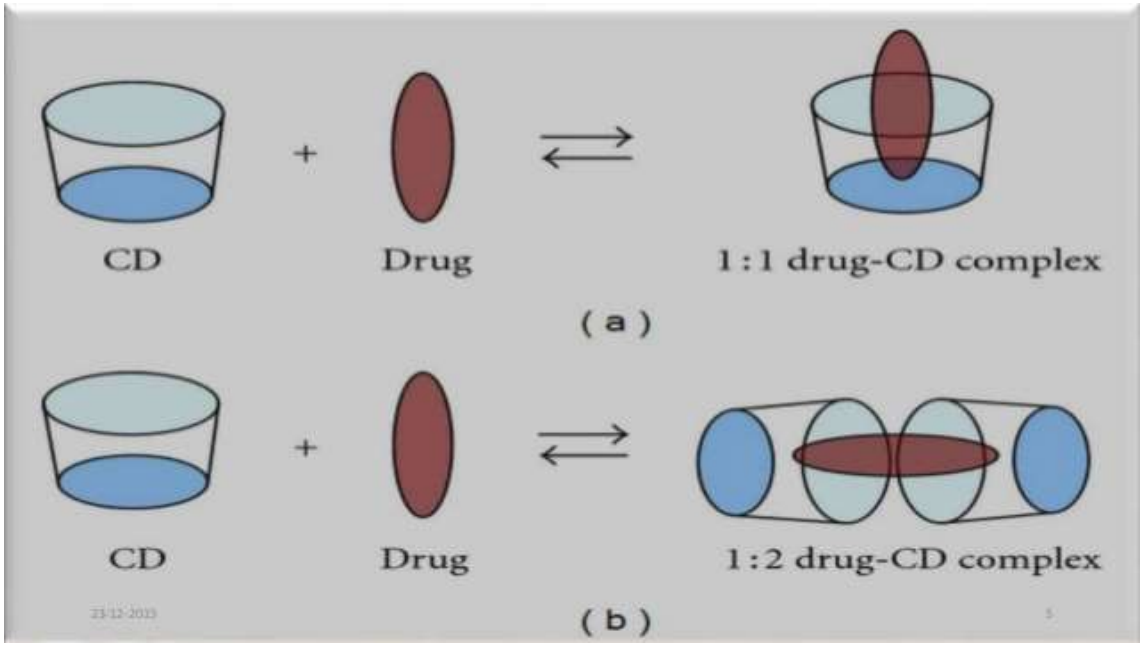




Complexation

➢Complexation is the reversible association between two or more molecules to form a non bonded entity with a well defined stoichiometry . Complexation relies on relatively weak forces such as vander waal forces, hydrogen bonding and hydrophobic interactions.

➢ Inclusion Complexation - These are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. The most commonly used host molecules are cyclodextrines. Cyclodextrines are non- reducing, crystalline , water soluble, cyclic, oligosaccharides. Cyclodextrines consist of glucose monomers arranged in a donut shape ring. CYCLODEXTRIN Hydrphobic Hydrophillic The surface of the cyclodextrines molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non- polar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrines complex.



Manufacture of CDs

Cyclodextrins are manufactured by the enzymatic degradation of starch using specialized bacteria.

Synthesis

The production of cyclodextrins is relatively simple and involves treatment of ordinary starch with a set of easily available 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. Purification of the three types of cyclodextrins takes advantage of the different water solubility of the molecules: β-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 α- and γ-CDs (145 and 232 g/l respectively) are usually purified by means of expensive and time consuming chromatography techniques. As an alternative a “complexing agent” can be added during the enzymatic conversion step: such agents (usually organic solvents like toluene, acetone or ethanol) form a complex with the desired cyclodextrin which subsequently precipitates. The complex formation drives the conversion of starch towards the synthesis of the precipitated cyclodextrin, thus enriching its content in the final mixture of products. Wacker Chemie AG uses dedicated enzymes, that can produce alpha-, beta- or gamma-cyclodextrin specifically. This is very valuable especially for the food industry, as only alpha- and gamma-cyclodextrin can be consumed without a daily intake limit.

Uses

➢ 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. Cyclodextrins can solubilize hydrophobic drugs in pharmaceutical applications, and crosslink to form polymers used for drug delivery. One example is Sugammadex, a modified γ-cyclodextrin which reverses neuromuscular blockade by binding the drug rocuronium. Other than the above-mentioned pharmaceutical applications.

➢ 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 organ phosphorus insecticide) or sewage sludge, enhancing their decomposition. This ability of forming complexes with hydrophobic molecules has led to their usage in supramolecular chemistry. In particular they have been used to synthesize certain mechanically-interlocked molecular architectures, such as rotaxanes and catenanes, by reacting the ends of the threaded guest.

➢The photodimerization of substituted stilbazoles has been demonstrated using g-cyclodextrin as a host. Based on the photodimer obtained, it is established that the halogen-halogen interactions, which play an interesting role in solid state, can be observed in solution. Existence of such interactions in solution has been proved by selective photodimerization of dichloro substituted stiblazoles in Cyclodextrin and Cucurbiturils.

➢The application of cyclodextrin as supramolecular carrier is also possible in organometallic reactions. The mechanism of action probably takes place in the interfacial region. 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 2013, α-cyclodextrin is found to be able to selectively form second-sphere coordination complex with tetrabromoaurate anion ([AuBr4]-) from transition-metal anion mixtures, and thus is used to selectively recover gold from various gold-bearing materials in an environmentally benign Manner.

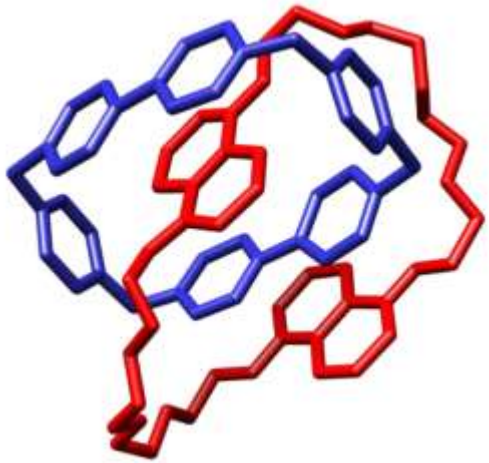
➢.β-cyclodextrins are used to produce HPLC columns allowing chiral enantiomers separation,[and are also the main ingredient in P&G's product Febreze which claims that the β-cyclodextrins "trap" odor causing compounds, There by reducing the odor.

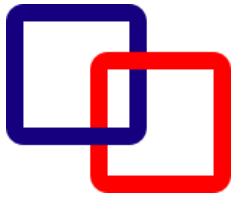
What is a molecular machine?

"An assembly of a discrete number of molecular components designed to perform mechanical-like movements as a consequence of appropriate external stimuli"

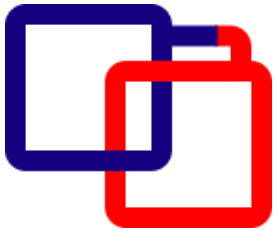
Molecular Switches

catenane is a mechanically-interlocked molecular architecture consisting of two or more interlocked macrocycles. The interlocked rings cannot be separated without breaking the covalent bonds of the macrocycles. Catenane is derived from the Latin *catena* meaning "chain". They are conceptually related to other mechanically interlocked molecular architectures, such as rotaxanes, molecular knots or molecular Borromean rings. Recently the terminology "mechanical bond" has been coined that describes the connection between the macrocycles of a catenane.





Catenanes



Pretzelanes

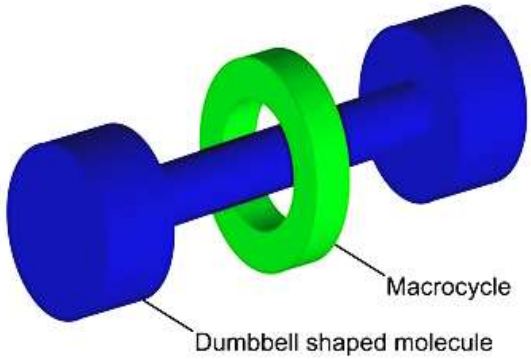
Handcuff-shaped catenanes

Crystal structure of a catenane with a cyclobis(paraquat-*p*-phenylene) macrocycle reported by Stoddart and coworkers.

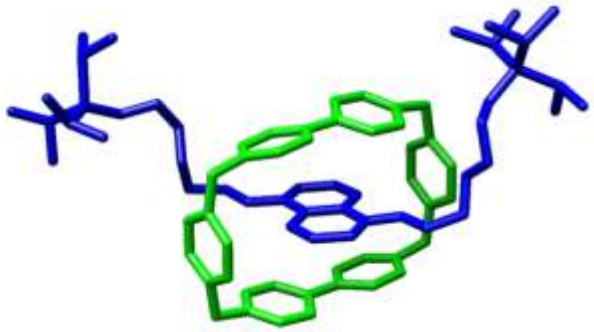
Rotaxane

A **rotaxane** is a mechanically interlocked molecular architecture consisting of a "dumbbell shaped molecule" which is threaded through a "macrocycle" (see graphical representation). The name is derived from the Latin for wheel (rota) and axle (axis). The two components of a rotaxane are kinetically trapped since the ends of the dumbbell (often called stoppers) are larger than the internal diameter of the ring and prevent dissociation (unthreading) of the components since this would require significant distortion of the covalent bonds.

Much of the research concerning rotaxanes and other mechanically interlocked molecular architectures, such as catenanes, has been focused on their efficient synthesis or their utilization as artificial molecular machines. However, examples of rotaxane substructure have been found in naturally occurring peptides, including: cystine knot peptides, cyclotides or lasso-peptides such as



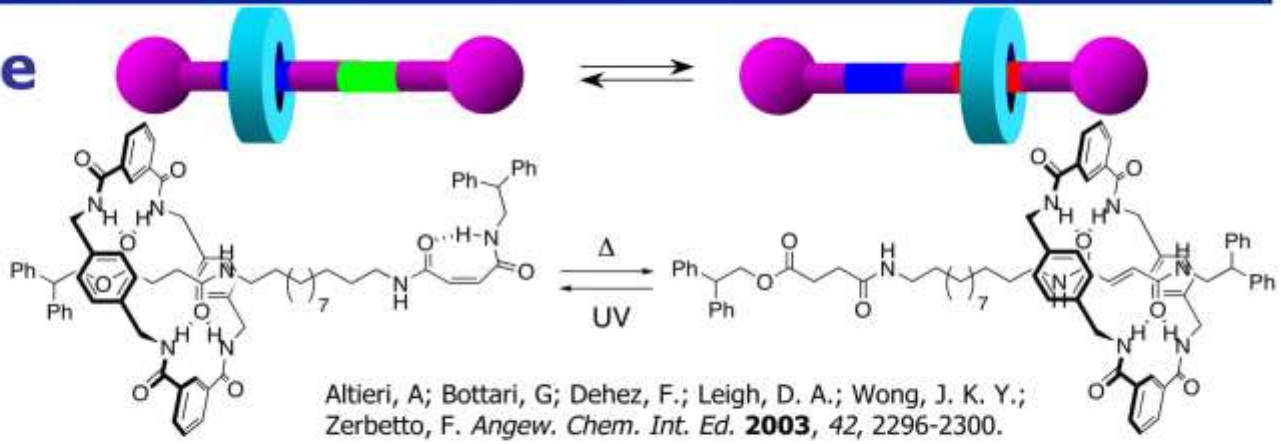
Graphical representation of a rotaxane



Structure of a rotaxane that has a cyclobis(paraquat-*p*-phenylene) macrocycle.[1]

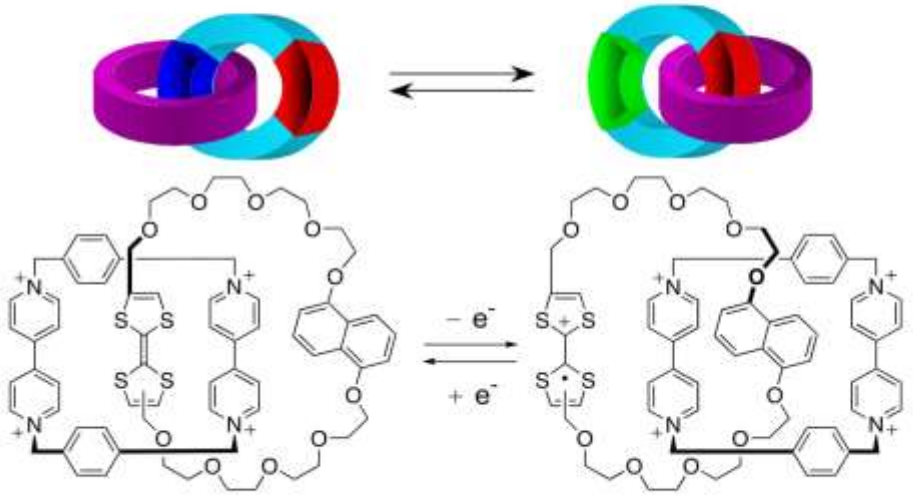
Molecular Switches

Rotaxane



Altieri, A; Bottari, G; Dehez, F.; Leigh, D. A.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 2296-2300.

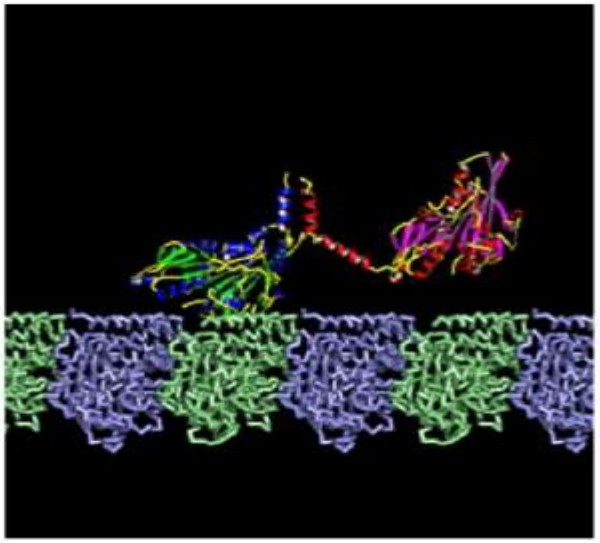
Catenane



Balzani, V.; Credi, A.; Mattersteig, G.; Matthews, O. A.; Raymo, F. M.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 1924-1936.

Natural Molecular Machines - Biomotors

Kinesin - Linear Motor

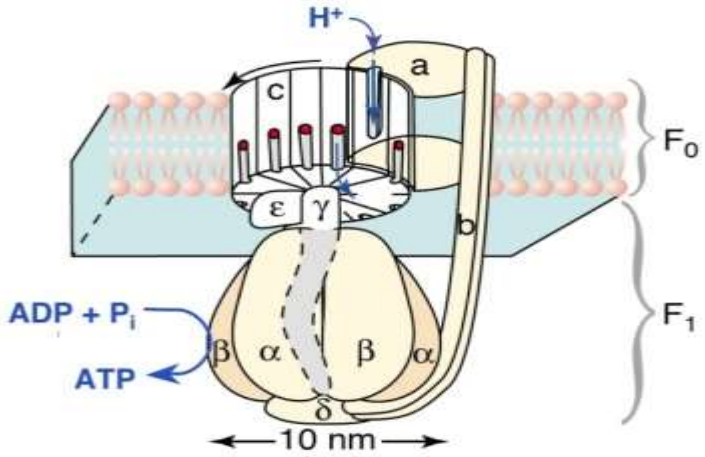


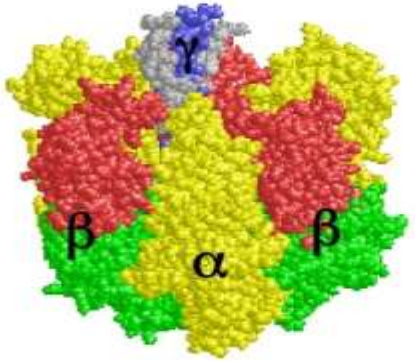
Role: vesicle-transport in the cell along the microtubule in linear fashion

Driving force: ATP hydrolysis

Hoenger, A.; Thormählen, M.; Diaz-Avalos, R.; Doerhoefer, M.; Goldie, K. N.; Müller, J.; Mandelkow, E. *J. Mol Biol* **2000**, *297*, 1087-1103.
http://www.mpasmb-hamburg.mpg.de/ktdock/

ATP synthase - Rotary Motor

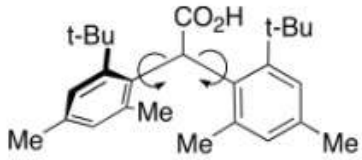




Wang, H.; Oster, G. *Nature* **1998**, *396*, 279-282.
Oster, G.; Wang, H. *Trends Cell Biol.* **2003**, *13*, 114-121.
http://nature.berkeley.edu/~hongwang/Project/ATP_synthase/

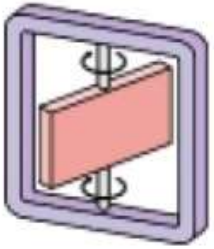
Artificial Molecular Motors

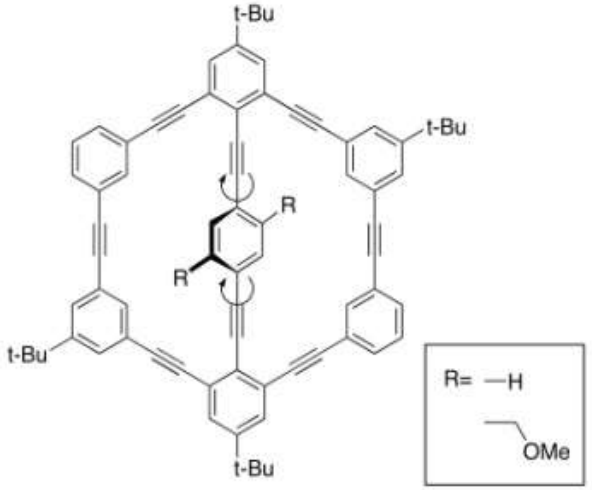
Propeller



Akkerman, O. S.; Coops, J. *Rec. Trav. Chim. Pays-Bas* **1967**, *86*, 755-761; *ibid.* **1970**, *89*, 673-679.

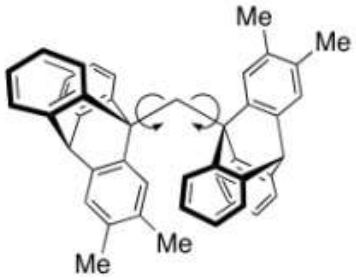
Turnstile





Bedard, T. C.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 10662-10671.

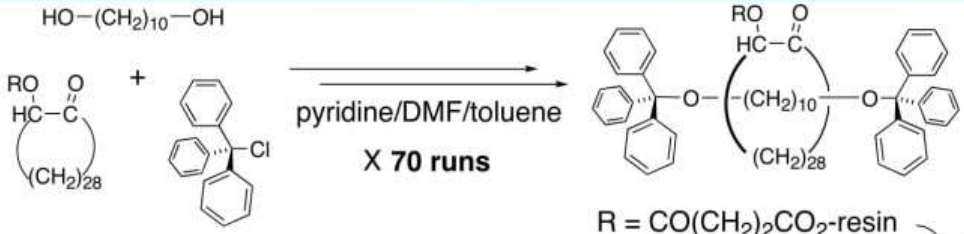
Gear



Cozzi, F.; Guenzi, A.; Johnson, C. A.; Mislow, K.; Hounshell, W. D.; Blount, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 957-958.

First Synthesis of Rotaxanes & Catenanes

$HO-(CH_2)_{10}-OH$

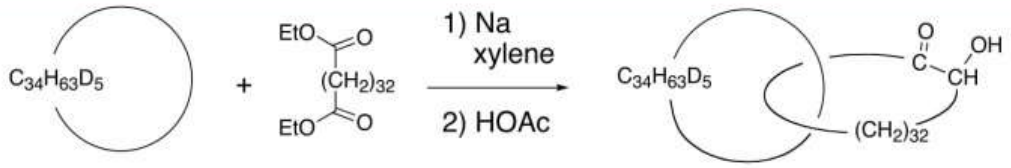


R = $CO(CH_2)_2CO_2$-resin

R = H (**6% yield overall**)

$NaHCO_3$ in MeOH

Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723-5724.



Wasserman. E. *J. Am. Chem. Soc.* **1960**, *82*, 4433-4434.

<1% yield

- **First synthesis** of Rotaxane and Catenane was dependent only on **statistical probability**.

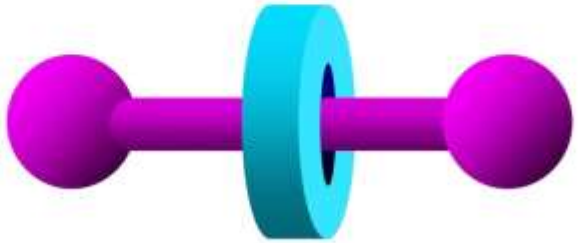
What Are Rotaxanes & Catenanes ?

[n]Rotaxanes

from Latin:

rota **= wheel**

axis **= axle**



[2]rotaxane

[n]Catenanes

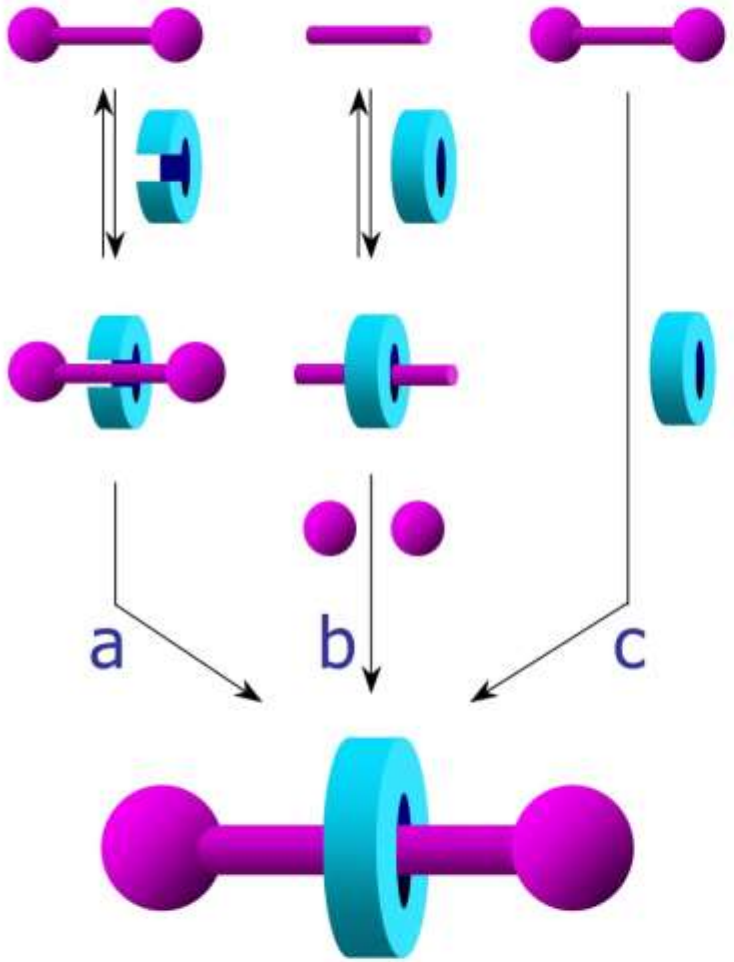
from Latin:

catena **= chain**

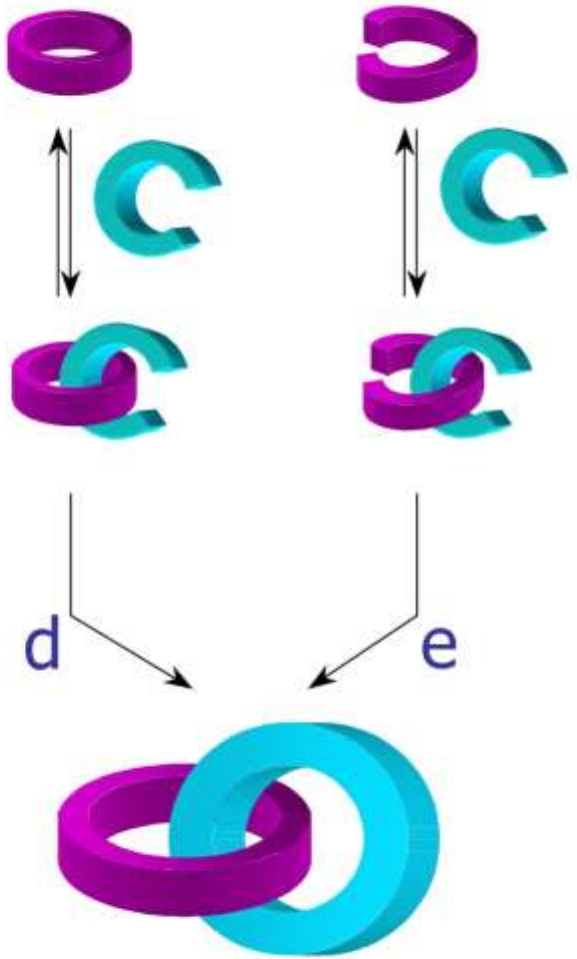
[3]catenane

Note: n = the total # of the interlocked components

How to Construct Rotaxanes & Catenanes ?



a: **Clipping**
b: **Threading & Stoppering**
c: **Slipping**



d: **Threading & Clipping**
e: **Double Clipping**