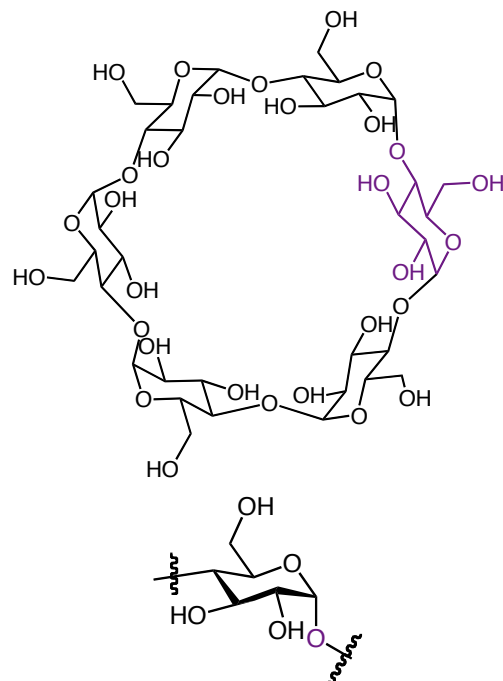


Cyclodextrins

04/29/09

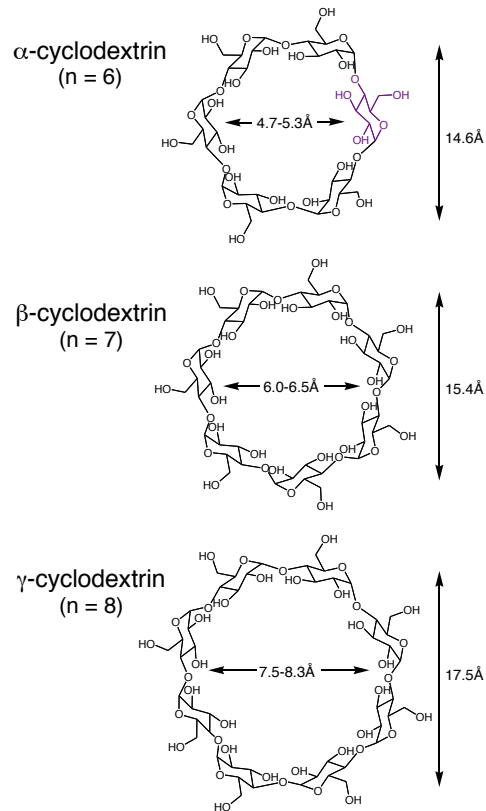
Cyclodextrins

- Cyclodextrins are a family of cyclic oligosaccharides.
- A homooligosaccharide, composed of 6 or more α -(1 \rightarrow 4)-linked D-glucopyranose residues.
- Originally observed as a product of bacterial digestion of starch.
- They are the result of cyclodextrin glucosyl transferase catalyzed degradation of starch.



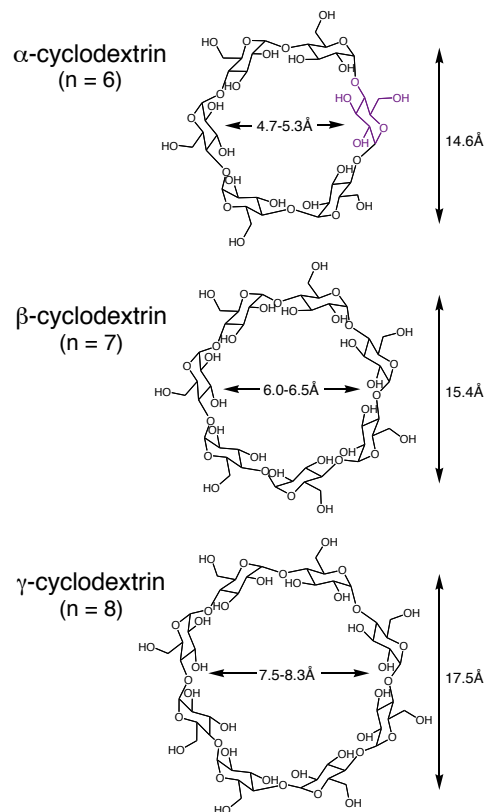
Classes of Cyclodextrins

- Cyclodextrins are assigned a prefix (greek character) indicating the number of glucose residues in the ring.
 - ▶ α -cyclodextrin (6)
 - ▶ β -cyclodextrin (7)
 - ▶ γ -cyclodextrins (8).
- Only cyclodextrins composed of 6, 7 or 8 glucose residues possess rigid well-defined structures and cavities.



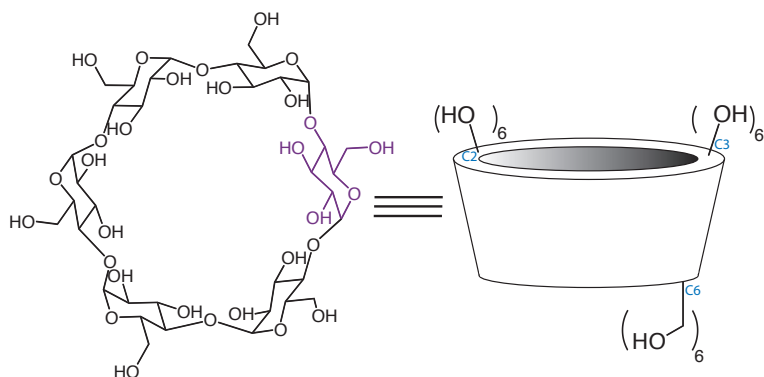
Classes of Cyclodextrins

- The D-glucopyranose residues are all in a standard chair conformation.
- The ring structure of cyclodextrins results in an interior cavity.
- As the number of glucose residues in the cyclodextrin ring increases, so does the diameter of the ring and the cavity within (α being the smallest and γ largest).



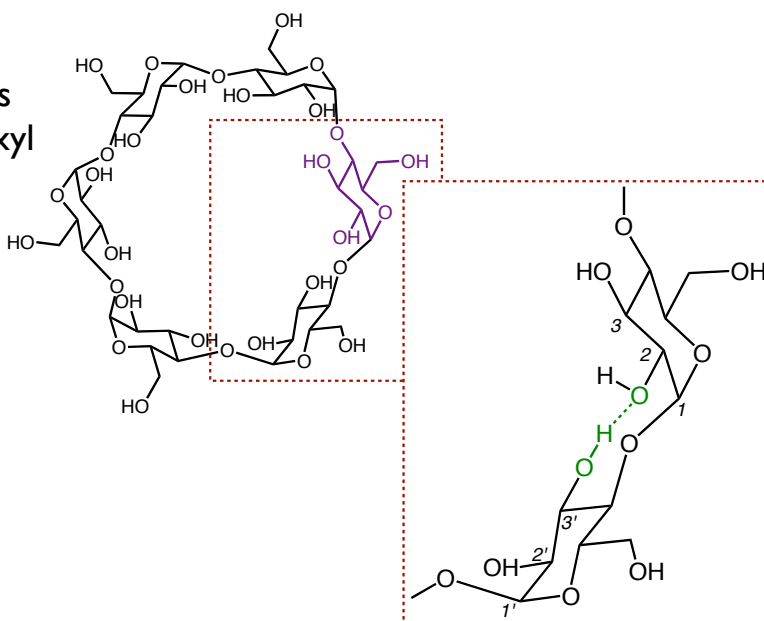
A Truncated Cone

- Overall shape of cyclodextrins can be described as truncated cones (“bucket shaped”).
- Two ends are not identical.
 - ▶ The “wider” end, bears the secondary C2 and C3 hydroxyl groups.
 - ▶ The primary C6 hydroxyl groups are located at the narrower end of the cyclodextrin ring.



Hydrogen Bonding in

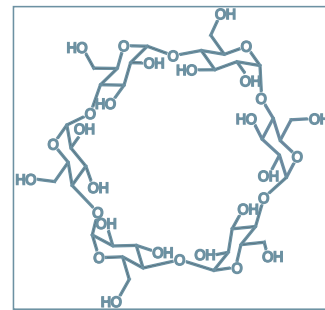
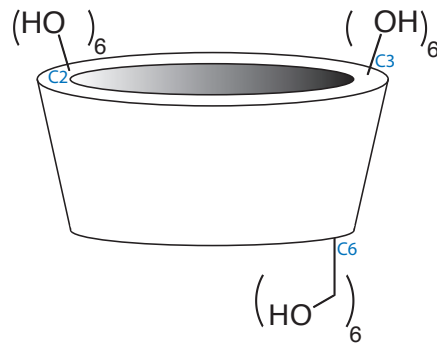
- A strong hydrogen bonding network exists between the 2'-Hydroxyl and the 3-hydroxyl group of adjacent glucose residues.
- 3-hydroxyl group acts primarily as proton donor.
- provides added rigidity and restricts torsion around the glycosidic bonds.



Hydrogen bond strength:
 α -cyclodextrin < β -cyclodextrin < γ -cyclodextrin

Physical Properties

- Cyclodextrin rings are amphipathic molecular architectures.
- The exterior of cyclodextrins is hydrophilic. C1, C2 and C4 hydrogens are displayed on the surface..
- The interior cavity on the other hand is more lipophilic, and is lined with the ring oxygen atoms and the C3 and 5 hydrogens.
- Cyclodextrins can act as hosts, binding an assortment of aliphatic and aromatic (non polar) ligands.

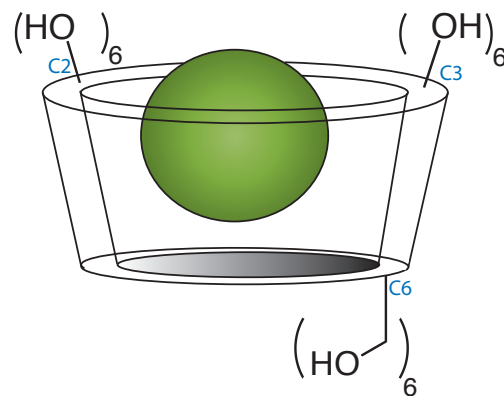


Cyclodextrins and Complex Formation

- Van der Waals interactions:
 - ▶ dipole-dipole
 - ▶ dipole-induced dipole
 - ▶ London dispersion interactions

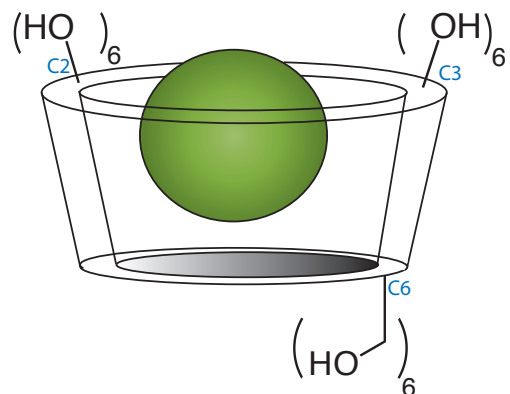
Constitute the primary attractive forces between the interior cavity and the lipophilic ligand.

- While the majority of ligands are hydrophobic, still find some charged and polar ligands such as acids, amines, halides and small ions.



Cyclodextrins and Complex Formation

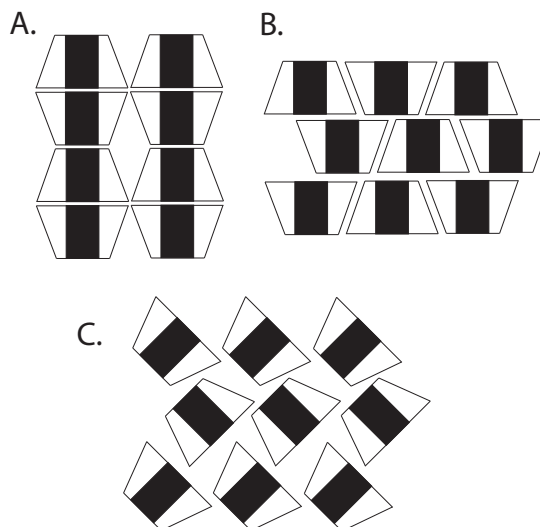
- In binding ligands, it ultimately comes down to complementarity in size and shape.
- The relationship between the host (cyclodextrin) and the guest (the ligand)
- These determine:
 - ▶ Relative affinity.
 - ▶ The shape of the substrate.
 - ▶ The stoichiometry (α and β 's with one substrate molecule per host vs. γ 's which may bind more than one guest molecule).



- X-ray structures from cyclodextrin crystals suggest two general crystal packing schemes.

Crystal Packing

- Channel structures (A.).
- Cage structures (B., C.).
- In channel structures, cyclodextrin stacks are stabilized by intermolecular hydrogen bonds between exposed OH groups displayed on the faces of the ring.
- Cage structures can be further subdivided into two subgroups:
 - Brick wall (B.)
 - Herringbone (C.)
 - Herringbone more common arrangement.
 - Offset layers isolates cavities present in each cyclodextrin molecule from that of

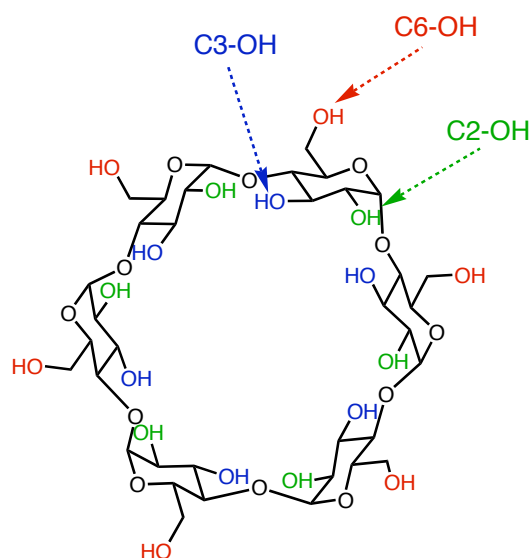


Applications

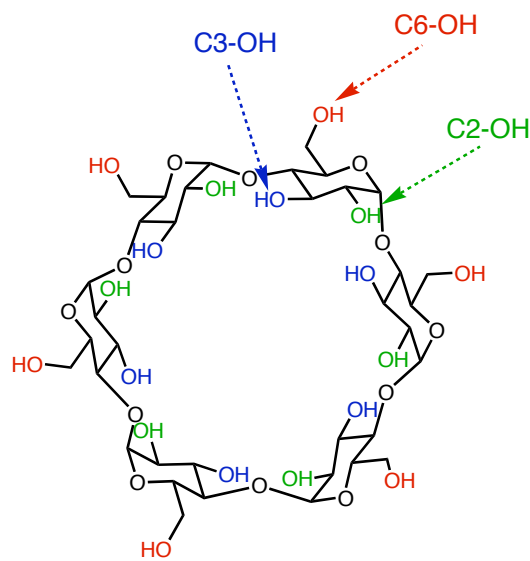
- Cyclodextrins can be used to trap oil, volatile liquid or gas molecules within their cavities affording powders with improved storage, handling and dispersion properties.
- Cyclodextrins show very low toxicity when administered subcutaneously or intravenously, and are harmless when administered orally.
- The formation of cyclodextrin complexes can also be used to minimize/eliminate undesirable properties such as odor or taste in certain food additives.
- Cyclodextrin can also be used to stabilize light- and oxygen-sensitive compounds such as nitroglycerin, used in nitroglycerin tablets.
- The amphipathic nature of cyclodextrin molecules (hydrophilic exterior/lipophilic interior) allows them to be used to increase the water solubility of normally hydrophobic compounds.

Chemical Modification

- Chemical modification of cyclodextrin molecules is used to expand their utility and alter their solubility and binding properties.
- The C2, C3 and C6 hydroxyl groups provide convenient avenues for modification.
- Monosubstitution represents the simplest modification with three possible constitutional isomers.
- The number of possible constitutional isomers increases dramatically with the degree of substitution often resulting in ill defined mixtures of products.

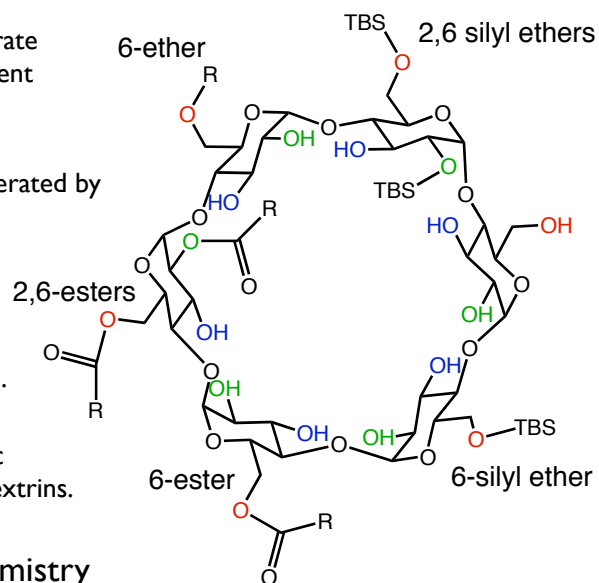


- Cyclodextrins where each glucopyranose residue is identically substituted (C_n symmetry) present the easiest to characterize.
- The most reactive OH group is the C6 primary hydroxyl.
- The slightly less reactive is the 2° hydroxyl at C2.
- The 2° hydroxyl at C3 is much less reactive than either (especially with respect to alkylation).
- It can be difficult to differentiate between the C6 and C2 hydroxyl groups. Sterically demanding substituents generally demonstrate good specificity for the primary OH at C6.



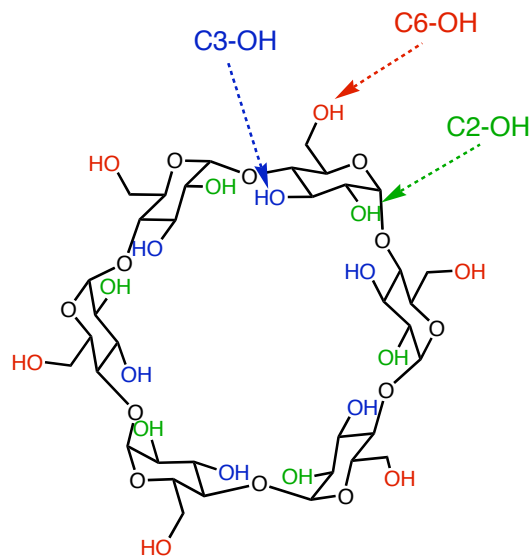
Chemical Modification

- Selective alkylation has been used to alter cyclodextrin solubility in a variety of solvents.
 - Partially methylated cyclodextrins demonstrate higher aqueous solubility relative to the parent cyclodextrins.
 - Insoluble cyclodextrin polymers can be generated by random cross-linking using epichlorohydrin.
- Cyclodextrins are readily acylated.
 - Acylation provides a reversible modification.
 - Acylation used to facilitate chromatographic resolution of mixtures of substituted cyclodextrins.
- Recent development in silylation chemistry has allowed for significant improvement in selective modification.
 - TBS allows selective 6 or 2,6 silylation.



Chemical Modification

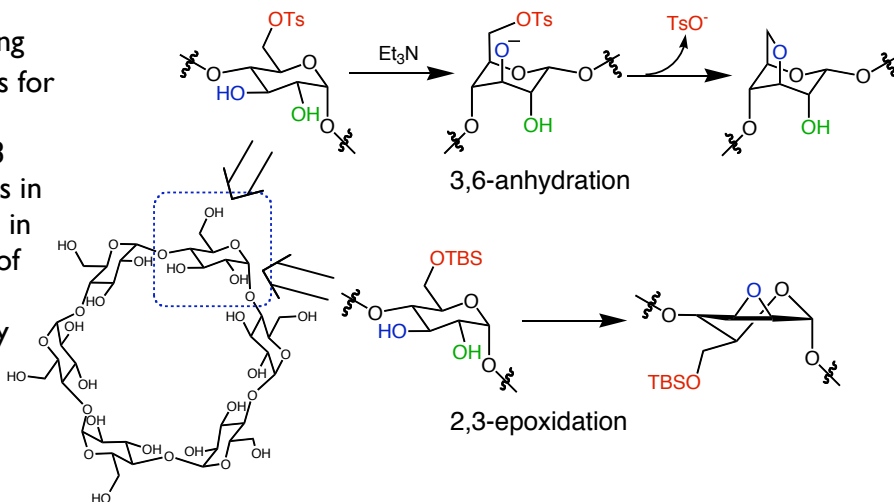
- It is also possible to replace one or more of the cyclodextrin hydroxyl groups with alternate functional groups (i.e. amines or thiols).
- Generally involves initially converting the hydroxyl group to a suitable leaving group.
 - Tosylation / mesylation
 - Halogenation
- Selective functionalization of the primary OH at a 6 position is reasonably straight forward.
- Reactions at the more hindered 2 or 3 positions are a bit more difficult / complicated and may result in inversion of stereochemistry.



Chemical Modification

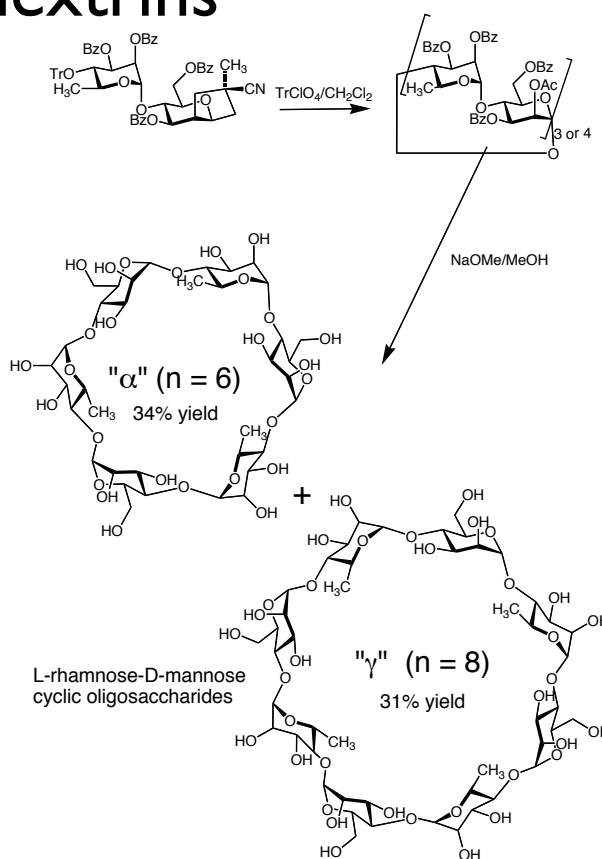
Novel Modifications

- Modifications that result in significant changes in the conformation and flexibility of the D-glucopyranose residues can dramatically affect the physical and chemical properties of the cyclodextrin molecule.
- Normally, glucopyranose residues in cyclodextrin are in a 4C_1 (chair) conformation. **3,6-anhydration** locks glucopyranose residues in a 1C_4 (an alternate chair) conformation. This arrangement places the C2 OH group in an axial position and directs it into the cavity, reducing cavity diameter and increasing polarity.
- Introducing a leaving group at C2 allows for formation of **2,3-epoxides**. Per-2,3 epoxidation results in significant changes in the configuration of the pyranose ring. Such epoxides may provide useful intermediates for further chemical modification.



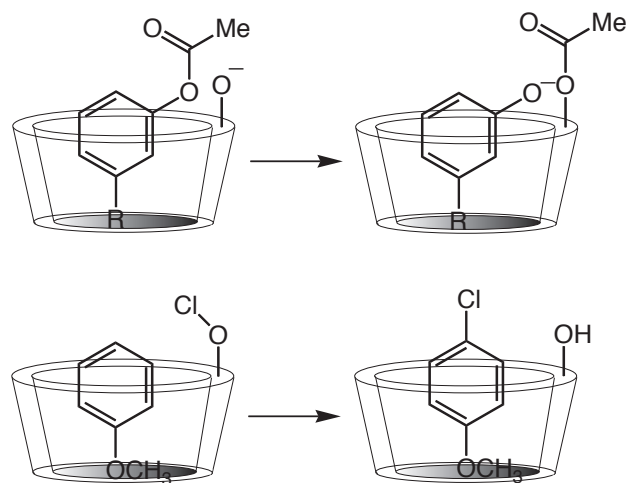
Synthesis of Cyclodextrins

- Most commercially produced cyclodextrins are the result of biological or enzymatic processes.
- Chemical synthesis provides the opportunity to utilize hexoses other than glucopyranose, and the use of functionalized or orthogonally-protected glucopyranoses.
- Semisynthetic approaches which involve opening natural cyclodextrins and recycling after introduction of nonstandard sugars offer similar flexibility.
- Chemical syntheses from linear oligosaccharides usually result in low yields.
- A polycondensation approach assembling cyclodextrins from disaccharide modules has yielded encouraging results.



Cyclodextrins as Catalysts

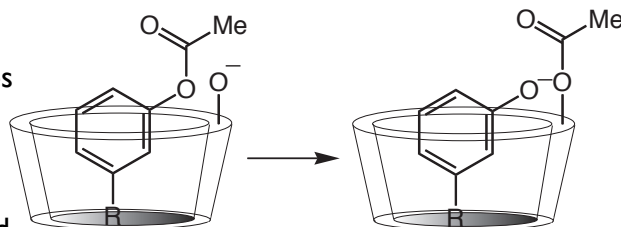
- Cyclodextrins can influence the outcome and kinetics of certain reactions.
- They have been investigated as catalysts for asymmetric reactions and as enzyme mimics.
- Binding a substrate molecule in the cyclodextrin cavity can dramatically affect chemical reactions involving the bound molecule.
- As with enzymes, cyclodextrin binding orients the substrate molecule.



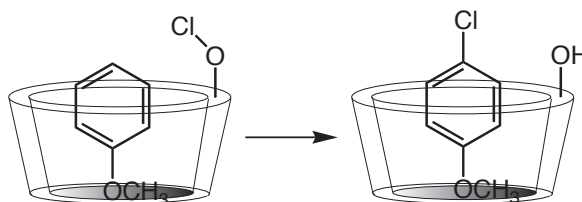
Cyclodextrins as Catalysts

- The three common cyclodextrins (α , β and γ) often demonstrate different catalytic and substrate preferences due to differences in ring size and shape.

- Cyclodextrin hydroxyl groups may play an active role forming covalent intermediates in the course of the catalytic mechanism.



- In the hydrolysis of *meta*-substituted phenyl esters, rate enhancement is realized as a result of transient transfer of the acyl substituent to a cyclodextrin OH.



- In the halogenation of anisole using hypochlorous acid, it is believed that a cyclodextrin hydroxyl group reacts with the hypochlorous acid, this results in the formation of hypochlorite groups on the cyclodextrin. Directs for para chlorination.

Cyclodextrins and Second Sphere Coordination

- Cyclodextrin molecules can also serve as first and second and even third sphere ligands for metal ions.
- Ferrocene binding with α -, β - and γ -cyclodextrins has been investigated. Different binding models have been proposed for each.
- Other organometallic complexes have also been investigated: carboplatin/ α -cyclodextrin and platinum phosphine/ β -cyclodextrin as examples.
- In each case, the the cyclodextrin moiety binds the hydrophobic organic ligand, with additional interactions between cyclodextrin -OH groups and polar ligands on the metal complex.

