Host-Guest Chemistry

*Host-Guest Chemistry* involves the design, synthesis and investigation of simpler organic compounds that imitate working features of naturally occurring compounds.

- molecular recognition
- transport
- regulation
- catalysis

Molecular Recognition

A *molecular recognition* process can be described as a *specific interaction* between two molecules through *multiple non-covalent contacts*

Molecular recognition forms basis for many processes in biology:

- Receptor-Substrate Binding
- Enzyme Catalysis (e.g. Emil Fischer’s lock and key principle)
- Assembly of Multi Protein Complexes
- Active and passive ion-transport across membranes via ion-pumps, ionophores and channels
**Definitions:**

*Host*: Organic molecule containing convergent binding sites. Synthetic counterparts to receptor sites in enzymes, genes, antibodies and ionophores

*Guest*: Molecules or ions containing divergent binding sites. Counterparts to substrates, inhibitors, cofactors, antigens

*Complexes*: Hosts and guests held together in solution in definable structural relationships by *electrostatic forces (enthalpic component)* such as ion-pairing, hydrogen bonding, metal ion-to-ligand attraction, \( \pi - \pi \)-stacking, dipole-dipole interactions, and van der Waals attraction, and the *entropic component* of desolvation.

![Diagram](From Reference 2)

**Examples of Synthetic Host Types**

<table>
<thead>
<tr>
<th>Macroyclic</th>
<th>Clefts</th>
<th>Bowls</th>
<th>Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Macrocyclic](Crown Ether)</td>
<td><img src="Cryptand" alt="Clefts" /></td>
<td>![Bowls](Molecular Tweezer)</td>
<td><img src="Calix%5B4%5Darene" alt="Linear" /></td>
</tr>
</tbody>
</table>

Supramolecular Chemistry Lecture 1
Crown Ether Complexes

18-crown-6 K⁺ complex

1) Binds selectively K⁺ whose size matches that of the cavity
2) Cavity is polar; outside of complex is lipophilic
3) Complex is soluble in very non-polar solvents, e.g. benzene
4) In non-polar solvent, counter anion X⁻ is not solvated. => ‘naked anion’ => very nucleophilic and reactive
   e.g. in water: nucleophilicity I⁻ > Br⁻ > Cl⁻ >> F⁻
   in benzene as ‘naked ion: F⁻ > Cl⁻ > Br⁻’

Passive Ion Transport Across Biological Membranes

Channels          Carrier Mechanism          Gated Ion Channel

Ionophore

e.g. gramicidin A (10⁷ ions/channel/sec)

e.g. Valinomycin (10³-10⁴ ions/molecule/sec)

e.g. voltage gated K⁺ channel
Cyclodextrin

Cyclic oligosaccharides composed of D-glucose units connected via $\alpha$-$1,4'$-glycosidic bonds

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Water solubility</th>
<th>Cavity Diameter</th>
<th>Cavity Height</th>
<th>Cavity Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-cyclodextrin</td>
<td>145 g/L</td>
<td>4.7 - 5.3 A</td>
<td>~ 8 A</td>
<td>174 A$^3$</td>
</tr>
<tr>
<td>$\beta$-cyclodextrin</td>
<td>18.5 g/L</td>
<td>6.0 - 6.5 A</td>
<td>~ 8 A</td>
<td></td>
</tr>
<tr>
<td>$\gamma$-cyclodextrin</td>
<td>232 g/L</td>
<td>7.5 - 8.3 A</td>
<td>~ 8 A</td>
<td>427 A$^3$</td>
</tr>
</tbody>
</table>

Cavity Volume ~ 262 A$^3$

Fischer projection of acyclic D-glucose

$\alpha$-D-glucose 36% (pyranose) + $\beta$-D-glucose 64% (pyranose)

D-glucose $\leftrightarrow$ monosaccharide

Dissaccharides

$\alpha$-$1,4'$-glycosidic linkage more stable

$\beta$-$1,4'$-glycosidic linkage less stable

Anomeric effect:

anti-bonding Sigma C-O

Supramolecular Chemistry Lecture 1
Binding Properties of β-Cyclodextrin

Space-filling models of β-cyclodextrin and of inclusion complex

<table>
<thead>
<tr>
<th>Guest</th>
<th>$K_S$ / M$^{-1}$</th>
<th>Vol / Å$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>740</td>
<td>126</td>
</tr>
<tr>
<td>G</td>
<td>2100</td>
<td>126</td>
</tr>
<tr>
<td>HCG</td>
<td>510</td>
<td>102</td>
</tr>
<tr>
<td>H</td>
<td>110</td>
<td>82</td>
</tr>
<tr>
<td>H</td>
<td>220</td>
<td>120</td>
</tr>
<tr>
<td>OH</td>
<td>175</td>
<td>91</td>
</tr>
<tr>
<td>OH</td>
<td>690</td>
<td>108</td>
</tr>
<tr>
<td>OH</td>
<td>2200</td>
<td>124</td>
</tr>
<tr>
<td>OH</td>
<td>4400</td>
<td>142</td>
</tr>
<tr>
<td>COOH</td>
<td>40000</td>
<td></td>
</tr>
</tbody>
</table>

Space occupancies in inclusion complex: In stable complexes, the guest tends to occupy about 55% of the space available inside the host cavity. The space occupancy is similar to the space occupancy in liquids.