Binding of Neutral molecules

- SOLID-STATE CLATHRATES
- INTRACAVITY COMPLEXES
- RECEPTORS WITH STRONGER INTERACTIONS
Binding of Neutral molecules

Interactions between the guest and the host are in general weaker than those in the case of charged species (no strong permanent electrostatic forces), they are limited to:

- dipole-dipole interactions
- van der Waals forces
- π-π interactions

They are efficiently bonded only via “physical imprisonment“ within solid-state network (clathrates) or within the cavity of a solution species (carceplexes).
Binding of Neutral molecules

Significantly stronger binding is possible via:
- hydrogen bonding
- weak covalent interactions

Applications:
- separation of related compounds
- storage and slow release of compounds
- sensing of compounds
- catalysis
Clathrate Compounds

A. Inorganic solid-state clathrate compounds of:
   • pores and channels forming inorganic solids (ice, zeolites)
   • layered solids (clays, graphite, etc.)

B. Organic solid-state clathrate compounds of:
   • urea and other channel forming organic compounds
   • cage forming organic compounds
Clathrate Hydrates

Pure ice forms regular lattice without any cavities capable to include guest molecules

In the presence of hydrate-forming species, a template reaction occurs: polyhedral cavities are formed according to guest size.
Clathrate Hydrates

Cavity size (pm):

390  430  470

Most common types of cavity found in clathrate hydrates I, II
Clathrate Hydrates

Structure types:
• Most common structure types I and II
• Low-symmetry structures IV-... (even with bigger molecules)

Properties:
• Melting points up to 31.5 °C
• Higher thermal conductivity (up to 5 times)
• Diffusion of guest as well as water molecules (within crystalline lattice)

Applications:
• Storage of natural gas, e.g. CH₄·6H₂O
• Its lattice energy is about 10 % of combustion heat
• For liberation, inhibitors of hydrate formation are added
Zeolites

= crystalline anionic microporous aluminosilicates (SiO$_4$ and AlO$_4^-$ tetrahedrons)
charge balanced by cations within solid cavities and channels

Sodalite  Linde type A  ZSM-5  Faujasite

Normally, 280 – 730 pm pore opening, except:
MCM-41: linear hexagonal channels of 1.5-10 nm diameter
Zeolites

Synthetic zeolites:
(molecular sieves, ZSM-5, MCM-41, etc.)

For their synthesis a templating material is used to determine the pore size, control the Si/Al ratio, pH, sol-gel technique.

<table>
<thead>
<tr>
<th>Cations</th>
<th>Zeolite type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)</td>
<td>Sodalite</td>
</tr>
<tr>
<td>Na(^+) + NMe(_2)^+</td>
<td>Faujasite, sodalite, zeolite-A (LTA)</td>
</tr>
<tr>
<td>Na(^+) + NP(_3)^+</td>
<td>ZSM-5</td>
</tr>
<tr>
<td>Na(^+) + benzyldiphenylammonium</td>
<td>ZSM-11</td>
</tr>
<tr>
<td>Na(^+) + [15]crown-5</td>
<td>High-silica faujasite</td>
</tr>
<tr>
<td>C(<em>n)H(</em>{2n+1})Me(_3)N(^+) (n = 8–16)</td>
<td>MCM-41</td>
</tr>
</tbody>
</table>
Zeolites

Applications

- **ZSM-5**: “superacidic” sites – negative charge is balanced by protons, very active – unsolvated in empty zeolite cavity

- Catalysis of selective \textit{para}-methylation of toluene with methanol, other xylene isomers diffuse within ZSM-5 framework slower, they undergo isomerization

- Separation and isomerization of alkanes mixture to obtain more branched alkanes with higher iso-octane number

- Cracking of long chain linear alkanes

- Diffusion or transition state selectivity
Layered Solids and Intercalates

<table>
<thead>
<tr>
<th>Layered material</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Uncharged layers</td>
<td></td>
</tr>
<tr>
<td>(i) Insulators</td>
<td></td>
</tr>
<tr>
<td>Clays</td>
<td></td>
</tr>
<tr>
<td>Kaolinite, dickite</td>
<td>$\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$</td>
</tr>
<tr>
<td>Serpentine</td>
<td>$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$</td>
</tr>
<tr>
<td>Nickel cyanide</td>
<td>$\text{Ni(CN)}_2$</td>
</tr>
<tr>
<td>(ii) Electrically conducting layers</td>
<td></td>
</tr>
<tr>
<td>Graphite</td>
<td>$\text{C}$</td>
</tr>
<tr>
<td>Transition metal dichalcogenides</td>
<td>$\text{MX}_2$ (M = Ti, Zr, Hf, V, Nb, Ta, Mo, W; X = S, Se, Te)</td>
</tr>
<tr>
<td>Metal(IV) oxyphosphates</td>
<td>$\text{MOPO}_4$ (M = V, Nb, Ta)</td>
</tr>
<tr>
<td>(b) Charged layers</td>
<td></td>
</tr>
<tr>
<td>(i) anionic layers</td>
<td></td>
</tr>
<tr>
<td>Clays</td>
<td></td>
</tr>
<tr>
<td>Montmorillonite</td>
<td>$\text{Na}<em>x(\text{Al}</em>{2-x}\text{Mg}_x)(\text{Si}<em>4\text{O}</em>{10})(\text{OH})_2$</td>
</tr>
<tr>
<td>Saponite</td>
<td>$\text{Ca}_{x/2}\text{Mg}<em>3(\text{Al}<em>x\text{Si}</em>{4-x}\text{O}</em>{10})(\text{OH})_2$</td>
</tr>
<tr>
<td>Vermiculite</td>
<td>$(\text{Na},\text{Ca})<em>x(\text{Mg}</em>{3-x}\text{Li}_x\text{Si}<em>4\text{O}</em>{10})(\text{OH}_2)$</td>
</tr>
<tr>
<td>Muscovite</td>
<td>$\text{KAl}_2(\text{AlSi}<em>3\text{O}</em>{10})(\text{OH})_2$</td>
</tr>
<tr>
<td>$\beta$-alumina</td>
<td>$\text{NaAl}_2\text{O}_17$</td>
</tr>
<tr>
<td>Alkali transition metal oxides</td>
<td>$\text{M}^1\text{XO}_2$ (M$^1$ = alkali metal; X = Ti, V, Cr, Mn, Fe, Co, Ni)</td>
</tr>
<tr>
<td>(ii) Positively charged layers</td>
<td></td>
</tr>
<tr>
<td>Hydrotalcite</td>
<td>$[\text{Mg}_6\text{Al}_2(\text{OH})_6]\text{CO}_3\cdot 4\text{H}_2\text{O}$</td>
</tr>
</tbody>
</table>
Layered Solids and Intercalates

- Intercalation causes the layers to expand or swell,
- Intercalation is reversible
Layered Solids and Intercalates

- Pure graphite: 3.35 Å spacing (optimal \(\pi-\pi\) stacking interactions)
  It readily forms intercalation compounds:

- \(\text{MC}_8\) with metals (K, Rb, Cs, Ca, Sr, Ba, Sm, Eu, Yb) (LiC\(_6\), none with Na) –
  metals provide electrons to the empty low-energy graphite \(\pi^*\)-orbital –
  oxidizing graphite
- Reducible metal fluorides form fluoroanion complexes – reducing graphite
- \(\text{Br}_2\), IBr, ICl (not with other halogens)
Urea Clathrates

Urea itself crystallizes in tetragonal arrangement

In the presence of the suitable guest it forms chiral helices (H-bond)

Removal of the guest (under vacuum) results in collapse of the channel structure

Its accepts linear and not too much branched hydrocarbons

Application in petroleum industry: regiocontrolled dienes polymerization

Larger channels with thiourea
Urea Clathrates

← Host and guest repeat distances in urea inclusion compounds are not necessarily the same.

Commensurate structures:  \( a c_h = b c_g \)
where \( a, b \) – small whole numbers
Otherwise: incommensurate structures
Trimesic Acid Clathrates

TMA.H$_2$O.[2/9 picric acid]  TMA.[0.5 n-tetradecane]
Other Clathrates

Helical tubulands

Hydroquinone
Dianin’s compound
Tri-o-thymotide
Cyclocrideratrylene (CTV)

Or by condensation of veratrol with formaldehyde
Cyclotrimeratrylene (CTV)

Bowl-shaped and saddle conformations

Forms also inclusion complexes with cyclopentadienyl-arene iron (II) cations

1:1 fullerene clathrate  2:1 acetone clathrate
Cyclotrimeratrylene (CTV)

Related compounds
Methods

Thermogravimetric analysis (TGA)  Differential scanning calorimetry (DSC)

Dehydration of $[\text{Zn(H}_2\text{O)}_2(tph)]_x$ thp = terephtalate

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Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

• have relatively small cavity to bind organic hosts
• form well characterizable complexes in solid state

In addition, they are conformationally mobile (only cone suitable conformation) Calix[4]arenes (lower-rim intramolecular ring H-bond) are more conformationally stable than [4]resorcarenes (upper-rim H-bond)

$\Delta G^\# = \sim 19 \text{ kJ mol}^{-1}$

$\Delta G^\# = 63-67 \text{ kJ mol}^{-1}$
Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

Higher complex stabilities are achieved by:
• increasing size of cavity wall, what makes cavity more deep, host more conformationally rigid and more lipophilic in the same time

Whisky tumbler shape barrier for guest (adamantane) exchange $\Delta G^\circ = 71 \text{ kJ mol}^{-1}$ associated with breaking hydrogen-bonded network
Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

Synthesis of resorcarenes
Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

Higher complex stabilities are achieved by:
• change of solvent to water (hydrophobic effect), using solubilising groups attached to the host or anchoring hosts to the solid surface

\[ \log K = 2.5-4.5 \text{ for aromatic guests (durene, naphthalene, chrysene)} \]
Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

In water:

\[ R^1 = H, \quad K = 30 \text{ M}^{-1} \]
\[ R^1 = \text{CH}_3, \quad K = 200 \text{ M}^{-1} \]
Intracavity Complexes
Calix[n]arenes and [n]Resorcarenes

Higher complex stabilities are achieved by:

* increasing size of cavity wall, what makes cavity more deep, host more conformationally rigid and more lipophilic in the same time

Invariably crystallize with small molecules (SO₂, CS₂, MeC≡CH, MeCN, CH₂Cl₂)

R = SiMe₂, X = H  \( K = 25 \text{ M}^{-1} \) for CS₂ in CDCl₃
Intracavity Complexes
Barbiturate receptor

Diaminotriazine derivative of a calixarene

Higher complex stabilities are achieved by:
• attaching groups capable to form stronger H-bonds
Intracavity Complexes
Curcubit[6]uril

Glycoluril

\[ n = 5-9 \]

Curcubit[6]uril

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{HN} & \quad \text{HN} \\
\text{ON} & \quad \text{ON} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{HN} & \quad \text{HN} \\
\text{ON} & \quad \text{ON} \\
\end{align*}
\]

1. Conc. H₂SO₄
2. H₂O. 0-10°C

Solution → Heat → Cucurbituril

Polymeric precipitate

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{HN} & \quad \text{HN} \\
\text{ON} & \quad \text{ON} \\
\end{align*}
\]

+ CH₂O (excess)
**Intracavity Complexes**

Curcubit[6]uril

Curcubit[6]uril: preferably binds amines and diamines as ammonium cations

In aqueous formic acid
Intracavity Complexes

Kohnkene

Kohnkene: too rigid and possesses too small cavity → more suitable dideoxykohnkene

Trinacrene – cage type analogue

24-membered ring
Intracavity Complexes - Kohnkene
Intracavity Complexes - Cyclodextrins

Glucopyranose units, \( n = 5-10 \)

\[ [\text{Glu}]_6 \]

\[ [\text{Glu}]_7 \]

\[ [\text{Glu}]_8 \]

\( \alpha\)-Cyclodextrin

\( \beta\)-Cyclodextrin

1500 tons per year, few €/kg

\( \gamma\)-Cyclodextrin

Known also those derived from mannose, galactose, ...

\( \alpha\)-1,4-Glycosidic link
Intracavity Complexes - Cyclodextrins

<table>
<thead>
<tr>
<th></th>
<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Glu units</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Cavity volume (Å³)</td>
<td>174</td>
<td>262</td>
<td>427</td>
</tr>
<tr>
<td>Cavity volume (cm³ g⁻¹)</td>
<td>0.10</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>[α]₀ (25 °C)</td>
<td>150.5</td>
<td>162.0</td>
<td>177.4</td>
</tr>
<tr>
<td>Hydrolysis by α-amylase</td>
<td>Negligible</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>145 g dm⁻³</td>
<td>18.5</td>
<td>232</td>
</tr>
<tr>
<td>Crystalline hydrate ll</td>
<td>6 H₂O (2 in cavity)</td>
<td>11 H₂O (6.3 in cavity)</td>
<td>14.1 H₂O (7.1 in cavity)</td>
</tr>
</tbody>
</table>
| Common guests               | Benzene, phenol | Naphthalene | Anthracene, crown ethers, 2 glucose | 35
Intracavity Complexes - Cyclodextrins

Preparation
Intracavity Complexes - Cyclodextrins

Host-guest chemistry in solution

Factors:

- steric fit
- hydrophobic effects, van der Waals, dipole-dipole, ion-dipole, hydrogen bonding
- release of high-energy water

\[
\beta_{1b} = \frac{[H_1G_b]}{[G]^b[H]}
\]

\[
bG + H \rightleftharpoons H_1G_b
\]
Intracavity Complexes - Cyclodextrins

Host-guest chemistry in solid state

No hydrophobic effects (weaker interaction).

Packing of cyclodextrin units depends on guest size:
• cage and layer type – guest (small enough) can be enclosed fully within CD cavity
• channel type – guest (larger) requires extended cavity of two CD units (head-to-head) of more CD units (head-to-tail)
Intracavity Complexes - Cyclodextrins

Packing of cyclodextrin units depends on guest size:
• cage and layer type – guest (small enough) can be enclosed fully within CD cavity
  ← Cage type
  α-CD: benzene (height), methanol, propan-1-ol, I₂, krypton, etc.
  β-CD: benzyl alcohol, benzene (width)
  γ-CD: hydrate (only)

← Layer type

β-CD . benzyl alcohol
Intracavity Complexes - Cyclodextrins

Host-guest chemistry in solid state

Packing of cyclodextrin units depends on guest size:
• channel type – guest (larger) requires extended
  ▪ cavity of two CD units (head-to-head)
  ▪ channel of more CD units (head-to-tail)

\[ \gamma\text{-CD . } [\text{Na([12]crown-4)}_2]^+ \]

\[ 2 \alpha\text{-CD . ferrocene} \]
Intracavity Complexes - Cyclodextrins

Applications

Nontoxic, stable, relatively cheap

Slow-release and compound-delivery agents:

- Food: dramatically reduce the amounts of expensive flavour oils and spices, needed in order to achieve the required flavour strength (~ 60 times). Complexed flavourings are in addition much more resistant to oxidation, photochemical degradation, thermal decomposition. It is more easy to store, handle, weigh and transport them
- Cosmetics: slow-release fragrance, etc.
- Pharmaceutics: prevent premature drug metabolism (oral vs. Intravenous delivery), enhance solubility of poorly soluble drugs, relieve local irritation or drug-induced damage, mask unpleasant drug taste
- Analytical chemistry: separation methods – capillary electrophoresis, chromatography (LC, HPLC, GC), including separation of enantiomers (replace for expensive chiral stationary phases)
Intracavity Complexes - Tweezers

\[ \log K = 4.4 \]

\[ \log K = 5.1 \]

Adenine
Intracavity Complexes - Tweezers
Intracavity Complexes - Tweezers

Extracts adenine and adenosine from aqueous solutions
Intracavity Complexes - Tweezers

Inspired by the inhibition of the hydrolysis of aspirin in water by caffeine; ion-dipole and π-stacking interactions
Intracavity Complexes - Cyclophanes

Cyclophanes: organic host molecules containing at least one macrocyclic ring with bridged arylene units

Nomenclature: \([X.X]\text{ortho(meta or para)cyclophane}\)

\(X\) – number of atoms in the bridged between arylene groups

[1.1.1.1]Metacyclophane
Intracavity Complexes - Cyclophanes

Synthesis: Nucleophilic substitution with sulfide and sulfur extrusion

1. Oxidation to \(-\text{SO}_2\)-
2. Pyrolysis

\(\text{Na}_2\text{S}\)
Intracavity Complexes - Cyclophanes

Use of:

- Cesium effect
- Heterogeneous dilution
- Rigid group principle
Intracavity Complexes - Cyclophanes

Synthesis: Homo- and cross-coupling reactions
**Intracavity Complexes - Cyclophanes**

Solution complexes are assisted with permanent electrostatic interactions and H-bonding in addition to $\pi-\pi$ stacking. Also C-H ... $\pi$ interactions

\[ K = 25 \text{ M}^{-1} \text{ in CH}_2\text{Cl}_2 \]

\[ K = 10^5 \text{ M}^{-1} \text{ in CH}_2\text{Cl}_2 \]
Intracavity Complexes - Cyclophanes

Magnetic anisotropy of the hosts aryl rings → large $^1$H NMR chemical shifts are observed on guest complexation

Other examples of water soluble guest (enhanced binding of aromatic guests):

$logK = \sim 7$
**Intracavity Complexes - Cyclophanes**

Predominantly hydrogen bonding hosts form stronger complexes in aprotic solvents than in water

<table>
<thead>
<tr>
<th>Guest</th>
<th>$K$ (water, M$^{-1}$)</th>
<th>$K$ (chloroform, M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagonal_3.png" /></td>
<td>$&lt;5$</td>
<td>230</td>
</tr>
<tr>
<td><img src="image" alt="Diagonal_4.png" /></td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

NMe$_2^+$Cl$^-$

NMe$_2^+$Cl$^-$
Intracavity Complexes - Cyclophanes

Predominantly hydrogen bonding hosts

Binding barbitals (steric fit):
- $R^1 = R^2 = R^3 = H \quad \log K = 4.3$
- $R^1 = R^2 = \text{Et}, R^3 = H \quad \log K = 6.1$
- $R^1 = \text{Et}, R^2 = \text{Ph}, R^3 = \text{Me} \quad \log K = 2.8$

In chloroform
Cryptophanes

Binding halocarbons

$\Delta G^\circ = 54-63 \text{ kJ mol}^{-1}$

In (CDCl$_2$)$_2$: $K = 470 \text{ M}^{-1}$ selective for chloroform
In water: $K = 7700 \text{ M}^{-1}$
Cryptophanes

\[ K = K_{HG} (1 + K_{HS} [S]) \]

- \( K \) – observed equilibrium binding constant
- \( K_{HG} \) – guest binding constant
- \( K_{HS} \) – solvent binding constant
- \([S]\) – solvent concentration (~ 10 M)

\[ K \sim K_{HG} \text{ if } K_{HS} [S] \ll 1 \]

- \( K_{HS} \) should be \(< 10^{-2} \text{ M}^{-1} \)

Cryptophane \( X = -(\text{CH}_2)_2^- \),
- binding of \( \text{CH}_2\text{Cl}_2 \) in \( \text{CDCl}_3 \):
  - \( K = 2.6 \text{ M}^{-1} \)
  - \( K_{HS} (\text{CDCl}_3) = 10 \text{ M}^{-1} \) (found in noncompetitive solvent), \([\text{CDCl}_3] = 12.4 \text{ M}\)
  - \( \Rightarrow K_{HG} (\text{CH}_2\text{Cl}_2) = 325 \text{ M}^{-1} \)
Carcerands - Hemicarcerands

Carcerand – closed molecular cage without portals of sufficient size which guests could either enter or leave – guests are permanently trapped within the cage, they can enter only during the host synthesis (cage closure); carceplex

Hemicarcerand – closed molecular cage from which guest can enter or leave – complex is formed in the presence of guest molecules; hemicarceplex
Carcerands

The first synthesis, Cram 1985
Carcerands

Drawback: low solubility
Solved by replacement of methyl groups by longer chain alkyls

Only small atoms/molecules can enter via “north“ or “south“ pole

5 % free, 60 % Cs⁺,
1 % Cl⁻, 45 % DMF,
15 % THF
Carcerands - Hemicarcerands

Synthesis, template effects

Carcerands can be obtained in high yields only in the presence of the suitable templating guest

<table>
<thead>
<tr>
<th>Guest</th>
<th>Template ratio</th>
<th>$K_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazene</td>
<td>1 000 000</td>
<td>980 000</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>290 000</td>
<td>240 000</td>
</tr>
<tr>
<td>Pyridine</td>
<td>34 000</td>
<td>7100</td>
</tr>
<tr>
<td>Benzene</td>
<td>2400</td>
<td>540</td>
</tr>
<tr>
<td>1,3-dioxane</td>
<td>200</td>
<td>140</td>
</tr>
<tr>
<td>Dimethyl acetamide</td>
<td>20</td>
<td>8.9</td>
</tr>
<tr>
<td>NMP</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

[Chemical structure images]
Hemicarcerands
Hemicarcerands

Inclusion reactions

Carcerands and hemicarcerands – “micro-reaction vessels“ which protect species from the effects of the outside medium.
Intracavity volume: unique fluid-like properties (comparable with very condensed gas state at very high pressures) – distinct from solid, liquid and gas (“new phase of matter“).