Complexation

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Objectives

- Classes of complexes
- Description of chelation
- Uses of inclusion complexes
- Methods of analysis of complexes
- Stoichiometric ratio and stability constant
- Thermodynamic & stability of complexes
Importance of Complexation

- Complexation leads to changing the physical and chemical properties
  1. **Solubility** (e.g. theophylline complexation with ethylenediamine to aminophylline)
  2. **Stability** (e.g. inclusion complexes of labile drugs with cyclodextrins)
  3. **Absorption** (e.g. Tetracycline with Ca ion form non absorbable complex)
  4. **Pharmacokinetics** (e.g. protein binding, renal excretion)
  5. **Pharmacodynamics** (e.g. Change drug receptor binding and so change biological activity).

Complexation Interactions

- Either coordinate bonding or one or more of the following interactions:
  1. Van der Waals forces
  2. Dipolar forces
  3. Electrostatic forces
  4. Hydrogen bonding
  5. Charge transfer
  6. Hydrophobic interactions.
Complexation

- Coordination complex: resulted from Lewis acid-base reaction between donor and acceptor molecules.

- It consists of central atom or ion (coordination center, usually metallic) and surrounded by array of bound neutral molecules or anions (called ligands).

Coordination complex

- **Acceptor**:
  - Central atom
  - Metallic ion
  - Organic gr with free orbital (Lewis acid)

- **Donor**:
  - Ligand gr
  - Non metallic atom
  - Ions or neutral molecules (Lewis base)
**Classification of Complexes, Table 10-1**

<table>
<thead>
<tr>
<th>Metal complexes</th>
<th>Inorganic</th>
<th>Chelates</th>
<th>Organic complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hybridization**

<table>
<thead>
<tr>
<th>Shell</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>s</td>
<td>s</td>
<td>p</td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>p</td>
<td>d</td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>d</td>
<td>f</td>
<td></td>
</tr>
<tr>
<td>Orbital subshell</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>No of electron</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

- C⁶ hybridization is sp³
- N⁷ hybridization is sp³
Bond types, Table 10-2

<table>
<thead>
<tr>
<th>Coordination Number</th>
<th>Orbital Configuration</th>
<th>Bond Geometry</th>
<th>Formula</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>sp</td>
<td>Linear</td>
<td>O₂</td>
<td>O—O</td>
</tr>
<tr>
<td>3</td>
<td>sp²</td>
<td>Trigonal</td>
<td>BCl₃</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>sp³</td>
<td>Tetrahedral</td>
<td>CH₄</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>dsp²</td>
<td>Square planar</td>
<td>Cu(NH₃)₄²⁺</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>dsp³</td>
<td>Bipyramidal</td>
<td>PF₅</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>d³sp³</td>
<td>Octahedral</td>
<td>Co(NH₃)₆³⁺</td>
<td></td>
</tr>
</tbody>
</table>

Molecular Structures

- **Linear**- O₂
- **Trigonal**- BCl₃
- **Tetrahedral** - CH₄
- **Square planar**- Cu(NH₃)₄⁺²
- **Bipyramidal** - PF₅
- **Octahedral**- Co(NH₃)₆⁺³
Metal complexes
• The central part is metal
• Sub classified according to ligand type into:
  a) Inorganic complexes:
    - E.g. Co(NH$_3$)$_6$$^{+3}$: The coordination number is ........ & geometry is ........
  b) Chelates:
    - Should be multi-dentate
    - Should have specific steric orientation
    - E.g. B12, hemoglobin, alcohol dehydrogenase, chlorophyll, and Albumin

EDTA
• Ethylene diamine tetra acetic acid
• It is hexa-dentate (2 from Nitrogen atom and 4 from Oxygen)
• Used to remove Ca, Iron and cupper from solutions.
• The geometrical shape is ........
Organic complexes

- No metal ion.
- Molecules held by weak donor acceptor forces
- E.g.: dimethylaniline with 2,4,6 trinitroanisole

Drug complexes

- Complexation of caffeine (Caf)
- Two types of interaction between Caf + Acidic drugs (e.g. sulfonamide or barbiturate).
  1. Dipole-dipole interaction and H- bonding between polarized carbonyl group of Caf with H of the acids:
  2. Nonpolar interaction between the non polar parts of the molecules
- These interactions lead to change solubility, absorption and bioavailability.
Polymer complexes

- E.g. : PEG, PVP, and Na CMC
- Contain nucleophilic oxygens.
- Can result in:
  1. Incompatibility and stability problems.
  2. Interaction with plastic containers.
  3. Precipitation and solubility problems.

Inclusion/Occlusion compounds

- A class of addition compounds where one of the constituent of the complex is trapped in the other to yield a stable layout.
- Type of Host-Guest compound.
- Depends on the architecture arrangement rather than the chemical affinity.
Inclusion/Occlusion compounds

**Channel Lattice type** –
- The molecular structure within the crystal arrange to form channels that can fit (trap) molecules inside.
- It is useful techniques in compound separation.
- Examples are deoxycholic acid and urea.

**Layer type**
- The crystals arrange in layers that can trap small molecules such as alcohols and glycols.
- Intercalate compounds b/n its layers.
- Example: Bentonite and graphite.
Inclusion/Occlusion compounds

Clathrates –

- Crystallize in a cage-like lattice
- Depends on molecular size of the entrapped component.
- Example: Hydroquinone crystals that traps methanol, CO$_2$ and HCl but not smaller and larger molecules.

Molecular sieves–

- Also called macromolecular inclusion compounds.
- Atoms arranged in 3-D to form cages and channels with different pore size.
- Used to separate molecules with different dimensions.
- Example: zeolites, dextrins and silica gels.
Inclusion/Occlusion compounds

Monomolecular inclusion compounds—

- Involve entrapment of a single guest molecule in the cavity of one host molecule.
- E.g.: Cyclodextrin:
  One of the most important molecular complexations is the interaction between molecules and cyclodextrin to form reversible inclusion complexes.

Inclusion/Occlusion compounds

Cyclodextrin—

- Interaction:

- Types:
  - Alpha 6 molecules
  - Beta 7 molecules
  - Gamma 8 molecules
## Applications of CD

<table>
<thead>
<tr>
<th>Property</th>
<th>Drug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ aqueous solubility</td>
<td>Prostaglandins; NSAIDs</td>
</tr>
<tr>
<td>↑ stability</td>
<td>Aspirin, atropine, digoxin</td>
</tr>
<tr>
<td>↑ absorption &amp; bioavailability</td>
<td>Phenytoin, digoxin</td>
</tr>
<tr>
<td>↑ taste and odor</td>
<td>Prostaglandins, NSAIDs</td>
</tr>
<tr>
<td>Change from liq. To solid</td>
<td>Nitroglycerin, methyl salicylate</td>
</tr>
<tr>
<td>↓ volatility</td>
<td>Menthol, salicylic acid</td>
</tr>
<tr>
<td>↓ stomach irritation</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>↓ incompatibilities</td>
<td>Vitamins</td>
</tr>
</tbody>
</table>

## Method of Analysis

### a) Stoichiometric ratio

- Determination of Donor-Acceptor ratio: \( A_nB_mC_x \)

### b) Stability constant:

- Study the rate of complex degradation is very important in the determination of complex applications
Method of Analysis

1. Continuous Variation

- Determination of physical characteristics such as:
  a) Dielectric constant
  b) Square of refractive index
  c) Spectrophotometric extinction coefficient

- Conditions
  a) Property of additive behavior
  b) Property sufficiently different

- If no interaction occurs when the components mixed, then the value of the property is the weighted mean of the values of the separate species in the mixture.

<table>
<thead>
<tr>
<th>Mole fraction of B</th>
<th>A (5)</th>
<th>B (100)</th>
<th>Property result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(1*5)=5</td>
<td>(0*100)=0</td>
<td>5</td>
</tr>
<tr>
<td>0.2</td>
<td>(0.8*5)=4</td>
<td>(0.2*100)=20</td>
<td>24</td>
</tr>
<tr>
<td>0.4</td>
<td>(0.6*5)=3</td>
<td>(0.4*100)=40</td>
<td>43</td>
</tr>
<tr>
<td>0.6</td>
<td>(0.4*5)=2</td>
<td>(0.6*100)=60</td>
<td>62</td>
</tr>
<tr>
<td>0.8</td>
<td>(0.2*5)=1</td>
<td>(0.8*100)=80</td>
<td>81</td>
</tr>
<tr>
<td>1</td>
<td>(0*5)=0</td>
<td>(1*100)=100</td>
<td>100</td>
</tr>
</tbody>
</table>

Assume a mixture of A and B

The physical property of A = 5
B = 100
Method of Analysis

1. Continuous Variation

2. pH Titration
   - Most reliable method
   - Complexation should be affected by change in pH.
   - E.g.: Glycine with Cupper

![Graph showing indication of a 1:1 complex and curve for no complex.
Graph showing absorbance difference, D, with mole fraction.
Graph showing pH titration of glycine and glycine with copper.
Fig. 10–9. Titration of glycine and of glycine in the presence of copper ions. The difference in pH for a given quantity of base added indicates the occurrence of a complex.]
Method of Analysis

3. Distribution method

- Measure the stability constant by distribution of the complex between 2 immiscible solvents.
- E.g.: Iodine and Potassium Iodide in water and CS$_2$

$$I_2 + I^- \rightleftharpoons I_3^-$$

- Example 10-2, Home work

Method of Analysis

4. Solubility method

- Measure the solubility by shake flask method.
- E.g.: Para amino benzoic acid (PABA) + Caffeine.

- Cases:
  - A
  - B
  - B-C
  - After C
Method of Analysis

5. Spectroscopy

- Absorption spectroscopy in the visible and ultraviolet regions.

- E.g.: I₂ in:
  - CCl₄ = one peak 520nm (Violet)
  - Benzene = 475nm & 300nm (Red)
  - Diethyl ether = 450nm & 300nm (Red)

- I₂ is electron acceptor; in CCl₄ no complex (not a donor). The other 2 solvents act as electron releasing agents and formed charged transfer complex with I₂.

Method of Analysis

Other methods:

- NMR
- IR
- X-ray diffraction
- Electron diffraction
Thermodynamic and Complexation

If $\Delta G^\circ$
- Negative = Stable complex
- Positive = Unstable and depend on the situation.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

TABLE 11—11. Positive and Negative Thermodynamic Functions Resulting from Several Kinds of Interactions

<table>
<thead>
<tr>
<th>Type of Interaction</th>
<th>$\Delta H^\circ$</th>
<th>$\Delta S^\circ$</th>
<th>$-\Delta G^\circ$ is Favored By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Electrostatic</td>
<td>$\sim 0$</td>
<td>$+$</td>
<td>$+\Delta S^\circ$</td>
</tr>
<tr>
<td>2. Hydrophobic</td>
<td>$+$</td>
<td>$+$</td>
<td>large $+\Delta S^\circ$</td>
</tr>
<tr>
<td>3. Chelation (polydentate ligand)</td>
<td>$-$</td>
<td>$+$</td>
<td>$+\Delta S^\circ$ and/or $-\Delta H^\circ$</td>
</tr>
<tr>
<td>4. Donor—acceptor (hydrogen bonding and chelation [monodentate ligand])</td>
<td>$-$</td>
<td>$-$</td>
<td>$-\Delta H^\circ$</td>
</tr>
</tbody>
</table>

Thanks for your attention