

UNIT \Rightarrow 4

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COMPLEXATION AND PROTEIN BINDING

→ Introduction

* Complexation

- It is the association between two or more molecules to form a non-bonded entity with a well defined stoichiometry.

* Ligand

- They consist of lone pairs.
- The ligand is a molecule that interacts with another molecule (metal atom) and form a complex by donating its lone pairs.

e.g. \Rightarrow H_2O and NH_3 .

* Metal atom

- The atom consist of vacant orbital and interact with ligand to form a complex (with covalent bond formation).
- e.g. \Rightarrow Nickel (Ni^{+2}).

Classification of complexation:

1) Coordinate / metal complexes

- Inorganic
- chelates
- olefin
- Aromatic.

2) Organic molecular complexes

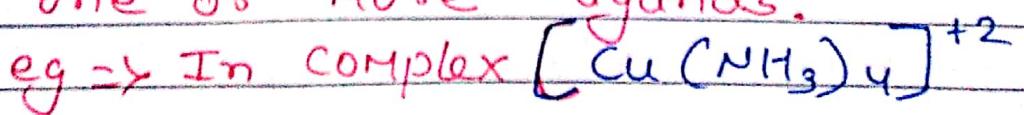
- Quinhydron type
- Caffeine complex
- Picric acid type
- Polymeric complex.

3) Inclusion / occlusion complexes

- clathrate complex
- channel lattice
- layer type
- Monomolecular and macromolecular

1) Coordinate / metal complex:

- A metal complex consist of a central metal atom that is bonded to one or more ligands.

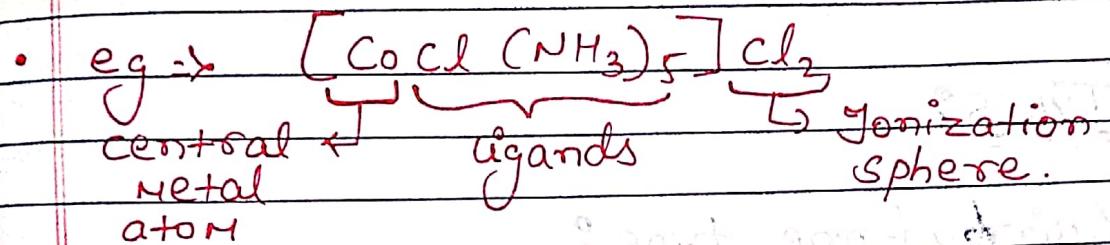


(\therefore 4 Ammonia ligand are attached to the central atom Cu)

→ Types :

i) Inorganic type :

- In inorganic metal complexes, the ligands provides only one site for binding with metal atom. (central).



ii) chelates :

- chelates are a group of metal ion complexes in which a ligand provides 2 or more sites for combine with a central metal atom.
- eg → EDTA.

iii) olefin type :

- Interaction of metal ions with olefin (such as ethylene) to form olefin complexes.

iv) Aromatic complexes :

- Interaction of metal ion with aromatic molecule (such as benzene, toluene) to form aromatic complexes.

2) Organic molecular Complex :

- These types of complexes are formed by interaction b/w organic molecules and ligands held together by Ionic/ covalent/ H-bonding.

→ Types :

i) Quinhydron type :

- They are formed when the alcohol solution of benzoguione and alcoholic solution of the hydroguione is mixed in equimolar concentration.

ii) Caffeine complex :

- when drug like benzocaine, procaine and tetracaine form complexes with caffeine it is known as caffeine-drug complex.

iii) Picric acid complexes :

- Picric acid form complexes with weak base.

iv) Polymer complexes :

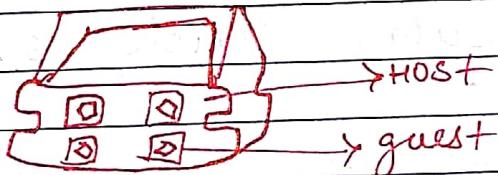
- Polymers such as polyethylene glycols (PEGs), carbowaxes forms complexes with various drugs.

3) Inclusion complexes

- These complexes are also called occlusion complexes in which one of the component is trapped in the open lattice like crystal structure of the other.

i) channel type :

eg -> choleic acid, urea

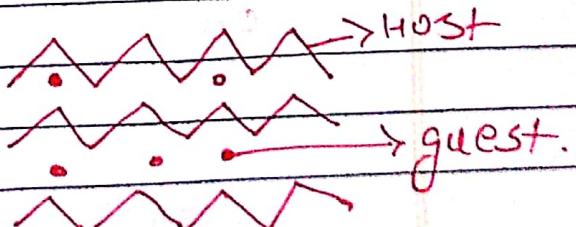


- The channels are formed by crystallization of the host molecules. The guest components is usually limited to long, unbranched chain compounds.

ii) Layer type :

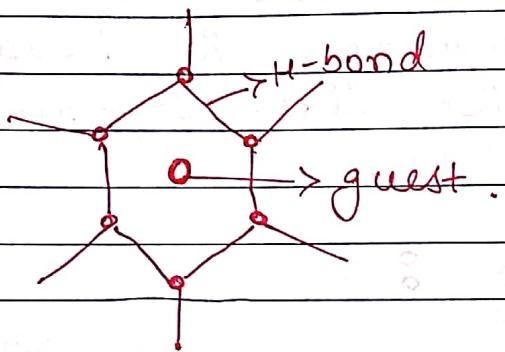
- The guest molecule is entrapped in the layers.

• eg -> Bentonite



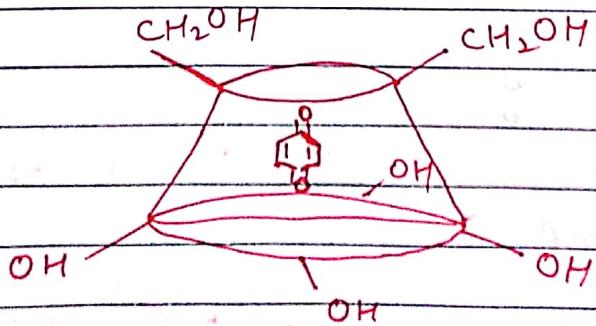
iii) Clathrates :

- It is a cage like complex in which the coordinating compound is entrapped.
- e.g. Cage like structure formed by H-bonding of Hydroquinone molecule.



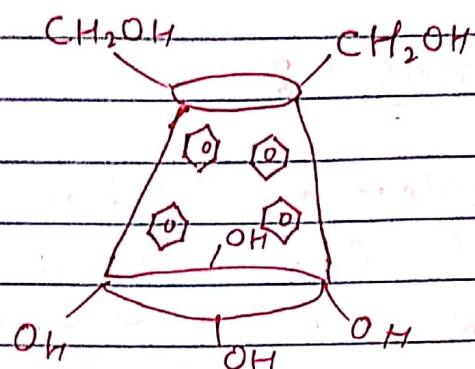
iv) → Monomolecular complexes.

- It involves the entrapment of a single guest molecule in the cavity of one host molecule.
- e.g. Cyclodextrins



→ Macromolecular complexes :

- It involves the entrapment of **more** number of guest molecule in the cavity of host molecule.



Eg ⇒ 3D structure of cyclodextrins.

Application of complexation in Pharmacy

1) In various types of poisonings -

- chelating agents are used as antidote in heavy metal poisoning.
- Eg ⇒ Dimercaprol in case of mercury and arsenic poisoning.

2) In drug absorption and bioavailability from various dosage form :

- Eg ⇒ EDTA and SLS, increase the intestinal absorption of heparin.

3) complexation is used in solubilization

- e.g. complexation of caffeine by sodium benzoate increases solubility of caffeine.

4) In Diagnosis:

- e.g. complex of Technetium (90) used in diagnosis of GFR and kidney function.

5) complex formation can be used to alter the physicochemical and biopharmaceutical properties of drug.

6) Assay of drug:

- e.g. complexometric titration are used to assay of drug.

7) Preservation

- e.g. EDTA & CITRATES are used in preservation of blood.

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Complexation & Protein Binding

Method of Analysis:

→ we generally estimate 2 parameters.

- Stoichiometry ratio: Metal/Donor: Acceptor of Ligand
- Stability constant of complex.

Methods:

- i) Method of continuous variation
- ii) Distribution method
- iii) Solubility method.
- iv) pH titration method

(i) Method of continuous variation:

- This process determines the stoichiometric ratio of complex based on estimation of certain additive properties of the complex like:
 - dissociation constant.
 - dielectric constant
 - solubility pH.
- A/c to this process when two components of a complex are mixed and if no interaction occurs between them, then the value of the property is additive.

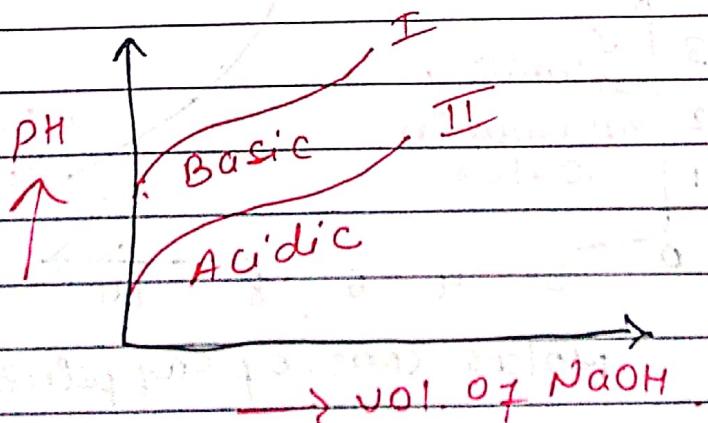
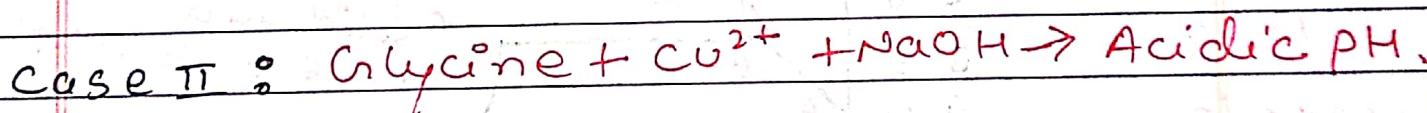
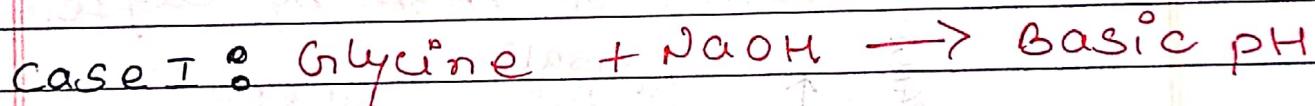
$A + B$

when no complexation \rightarrow Physical properties are additive.

complexation \rightarrow physical properties are different from A & B.

iii) pH titration method :

- This method is used when the complexation is achieved by change in pH. This method is considered as most reliable method for studying complexation.
- e.g. chelation of cupric ion by glycine.



(iii) Distribution method :

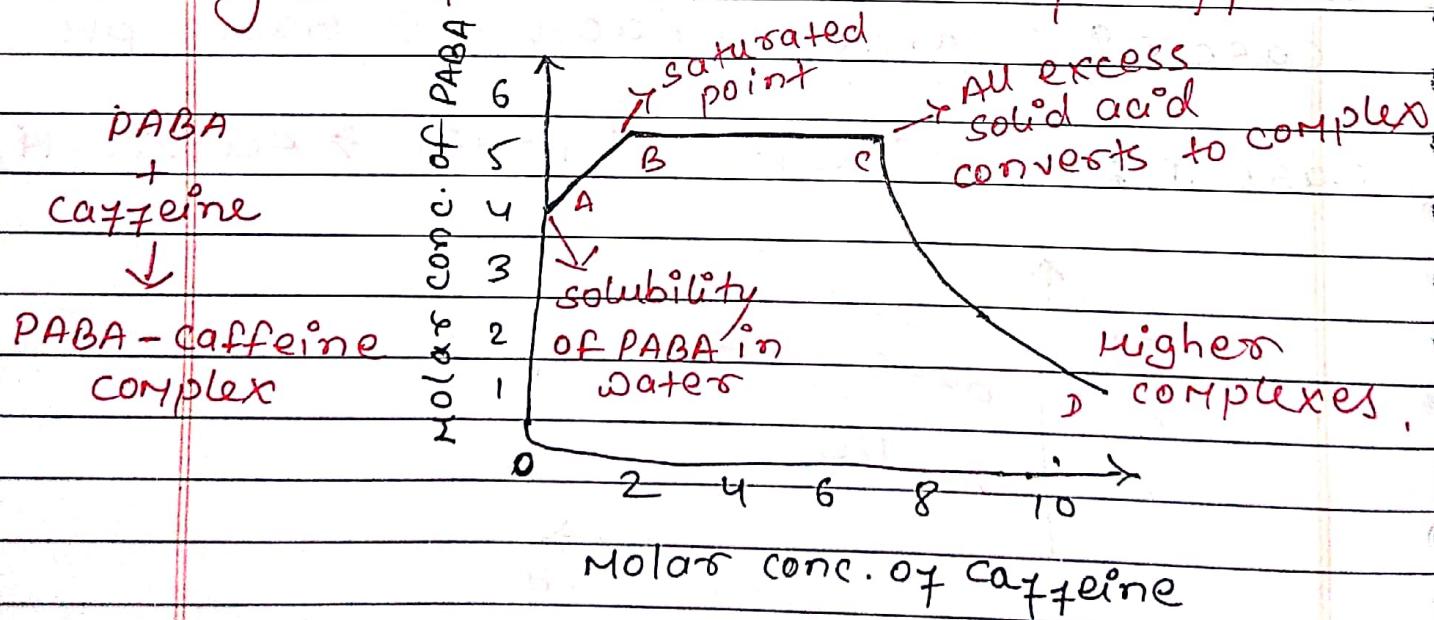
- This method describes the distribution of a solute between two immiscible solvents used to determine the stability constant for certain complexes.

e.g. → complexation of iodine with KI.

(iv) Solubility method :

- In this method, the complex formation is based on the solubility of the components in presence of a complexing agent.

e.g. → complexation of PABA by caffeine.



$$K = \frac{[\text{PABA} - \text{caffeine}]}{[\text{PABA}] [\text{caffeine}]}$$

Protein Binding :

- The phenomenon of complex formation of drugs with proteins is called protein binding.
- Binding of drugs to protein is generally reversible and irreversible.
- Reversible binding generally involves weak chemical bond such as ionic, hydrophilic bonds and vanderwall's force.
- While irreversible drug binding is rare and form covalent bonding.
- The order of binding of drugs to protein
 - ↳ inc. or more affinity to combine.

Albumins > α ,acid glycoprotein > lipoprotein
nose = \checkmark globulin.

Significance of protein binding :

1) Absorption :

- protein binding disturb absorption equilibrium.

2) Distribution :

- Protein binding decrease distribution of drug because protein bound drug does not cross blood-brain barrier, placental barrier etc.

3) Elimination :

- Protein binding prevent the entry of drug to the liver and to glomerulus filtration. only the unbound drug is capable of being eliminated.

factors affecting protein binding

1) Physicochemical properties of drug

- The binding affinity depends on physical and chemical properties of drug.

Increase in lipophilicity of drug inc. the extent of binding!

2) Affinity of drug for binding compound:

e.g. Digoxin has more affinity for proteins of cardiac muscles than those of skeletal muscles proteins.

3) concentration of drug %
= = = = =

- Alteration in the conc. of drug as well as the protein molecules cause alteration in the protein binding.
- At low concentrations, most drugs bind to proteins. At high concentrations more drug free may be present due to limited no. of binding sites on protein.

Complexation & Protein Binding

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complexation and drug action :

- complexes can alter the pharmaceutical activity of drug by inhibiting interaction with receptors.

In some instances, complexation also can lead to poor solubility or decreased absorption of drugs in the body.

e.g. \rightarrow solubility of tetracycline decreases when it complexes with calcium ion.

\rightarrow Intestinal + streptomycin = poorly absorbed complex.

\rightarrow calcium + Tetracycline = poorly absorbed complex

crystalline structures of complexes :

- complex compounds cover the range from quite simple inorganic salts to elaborate metal organic hybrid materials.

- Their present uses and their potential applications are diverse due to their compositions, their molecular and crystalline structures and their physical and chemical properties.
- Besides their use as chemical reactant complex compounds are considered for extraction processes and as active agents in remedies and for drug delivery.

II Thermodynamically Treatment of Stability constant :

- The stability constants of the metal complexes are related to thermodynamic properties such as free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS).
- These values can be computed by usual equation :

Gibbs free energy $\Delta G = -2.303RT \log K$

\Rightarrow ~~K has const.~~ \Rightarrow Temp.

$$\log \frac{K_2}{K_1} = \frac{-\Delta H}{2.303 R} \left(\frac{T_2 - T_1}{T_1 \cdot T_2} \right)$$

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