3/10/19

Unit - 4th

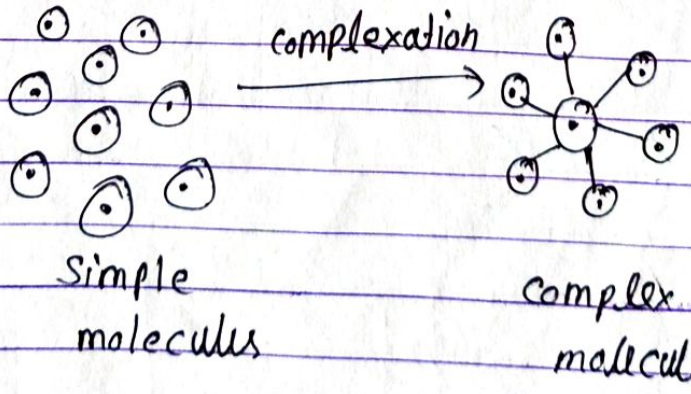
Complexation & Protein Binding

Complex :-

When simple molecules are combined together by any physical or chemical attraction force then they form a complex, and the process of formation of complex is called complexation.

Complex can be form between two molecules in which one each donor ligand atom & other is acceptor metal atom.

Two atom can also form complex by sharing of e^- & some weak force of attraction.



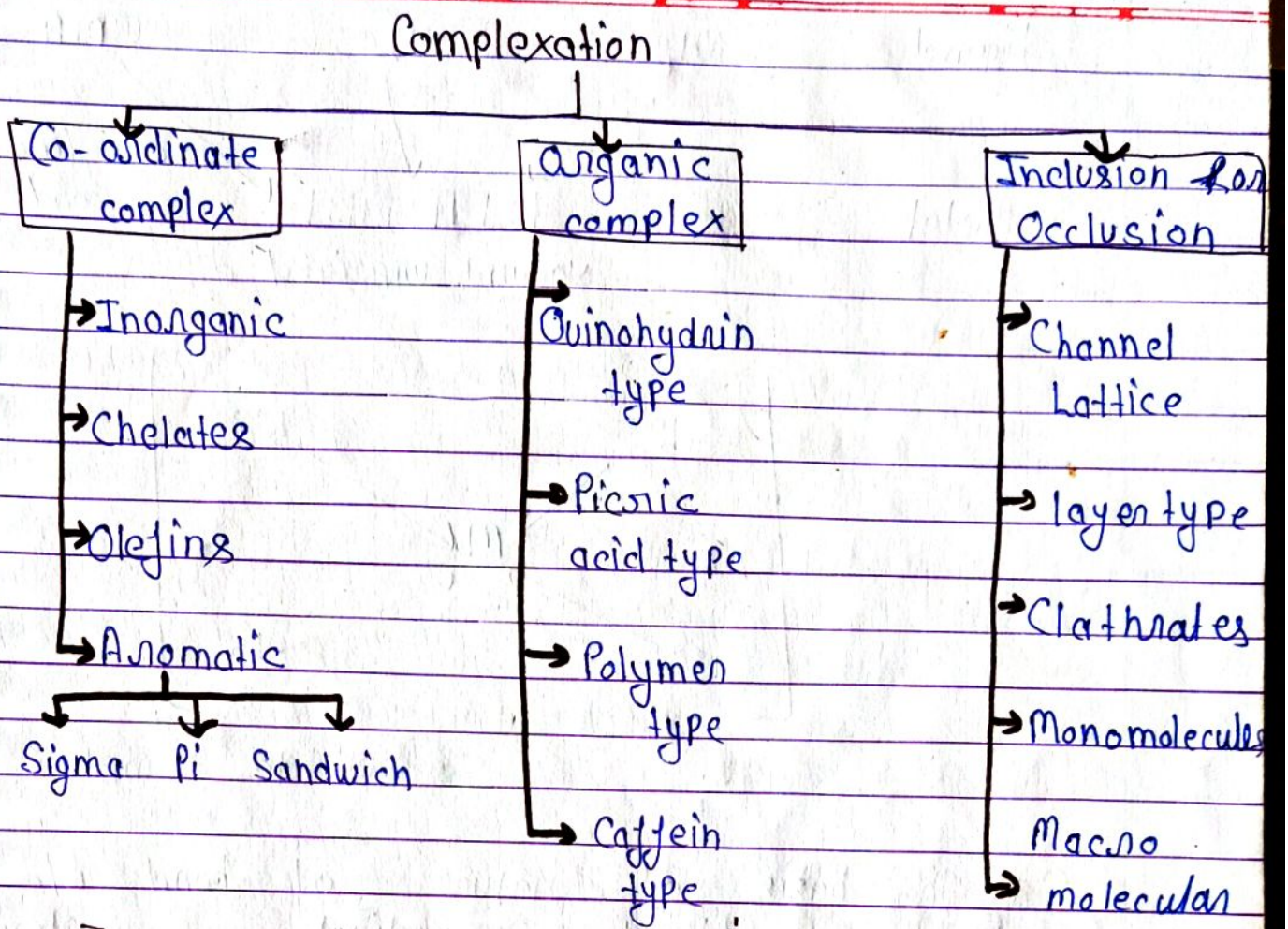
The properties of simple molecules is changes often the complex formation like - solubility, stability, partition coefficient, ~~conductance~~ conductance, absorption & ~~no~~ pharmacological action

when hydrophobic group are attached with simple molecules then solubility is decreas. and if hydrophilic group are attached with simple molecules then their solubility is increase.

By the complex formation of certain drug the rate of absorption can also be Yes and Yes.

Classification of Complexation

On the basis of entraction b/e molecules or the chemical bonding complex are a following type.

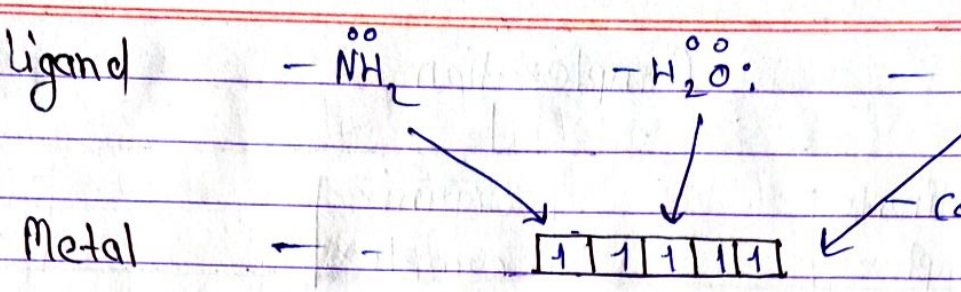


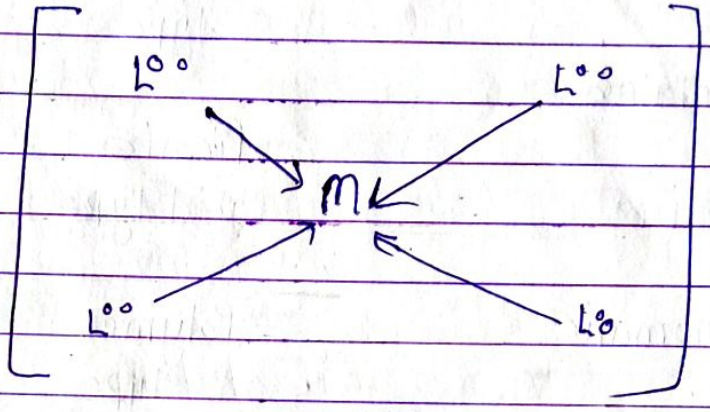
Co-ordinate Complex

Those group and atom which have lone pair of electron they are called ligand.

And ligand donate their lone pair to metal atom and form co-ordinate bonds.

The complex structure of co-ordinate bonded metal & ligand is called co-ordinate complex or metal ion complex.





Co-ondinate complex

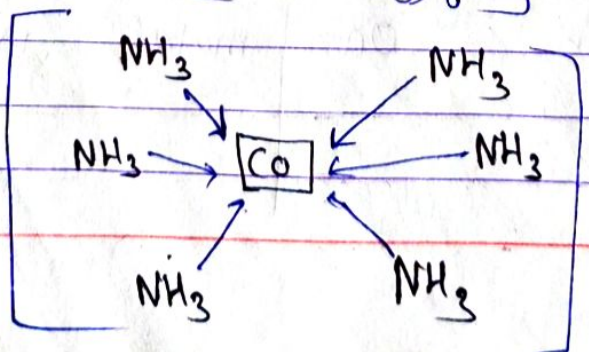
On the basis of nature of bond b/e metal & Ligand Co-ondinate complex is a foun type.

Inorganic complex :-

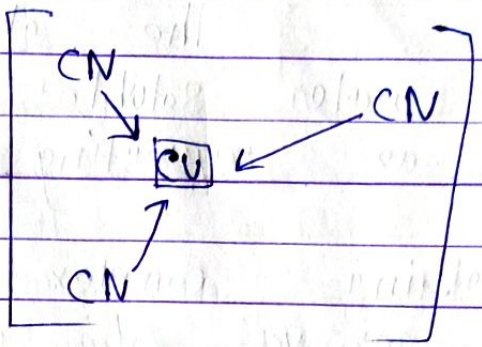
When Ligand are monodentede then they fonm single co-ondinate bond with metal ion this is called inonganic metal complex

hexa amine cobalt

$[Co(NH_3)_6]$



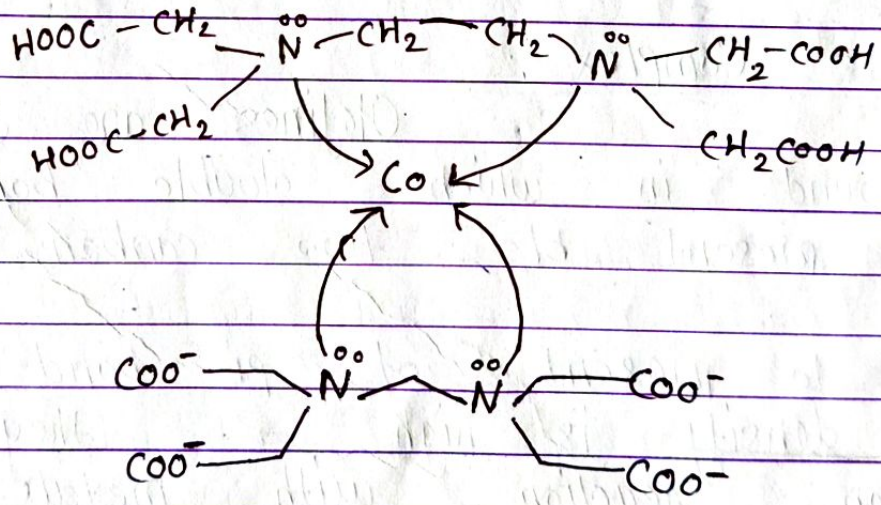
$[Cu(CN)_3]$

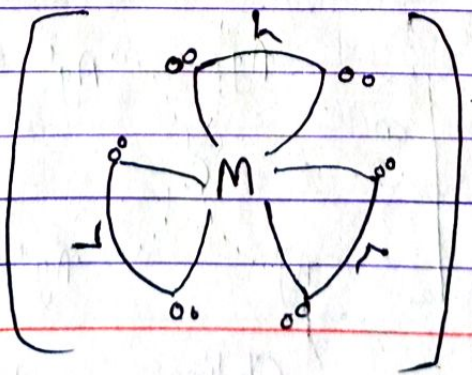


2. **Chelates :-**

When ligand are bidentate or polydentate then they form cyclic structure with metal ion and this type of complex is called chelate complex.

di EDTA Cobolt





alkene (Olefine)
C=C

Properties :-

The chelating complex which are water soluble is also known as sequesting agent.

- Sequestaing complex is used in analysis for removal of unwanted ions in solution.

- Certain chelating agent have been shown anti bacterial activity.

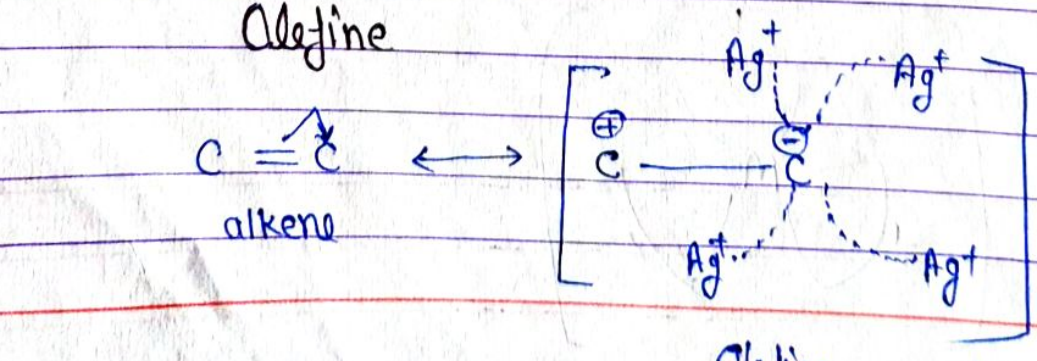
Example —

Metal ion chelate of 8 hydroxy quinoline (Marelia drug)

Olefine Complex :-

Olefines are those compound in which double bond (pi bond) is present ble two carbon

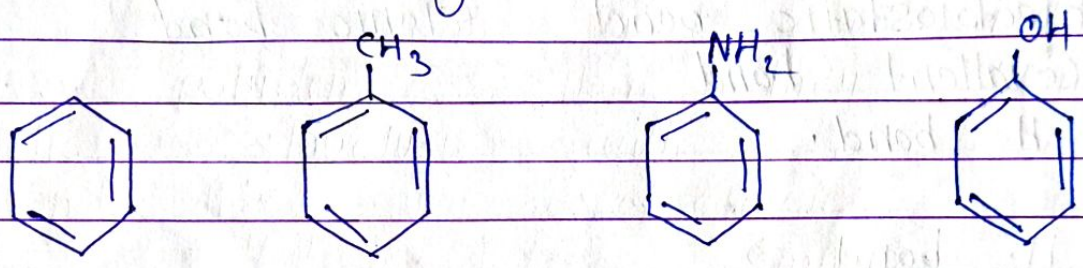
due to present of pi bond there e density is high & they give adition reaction with metals at form olefine complex.



4) **Aromatic Complex :-**

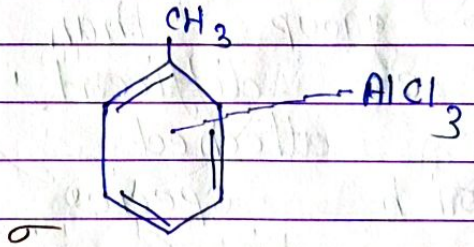
Aromatic compounds like benzen, Toluene aneline and phenol form metalic complex due to present of pi electron dencity.

They can form complex with metal by three type.

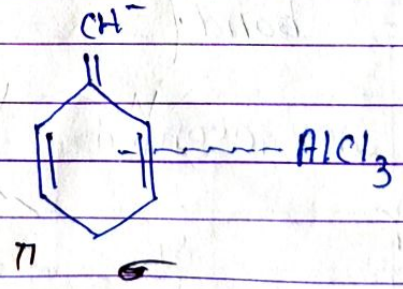


Toluene

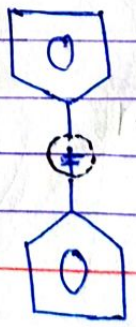
① Singma



2) Pi



3) Sandwich



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Organic Complex

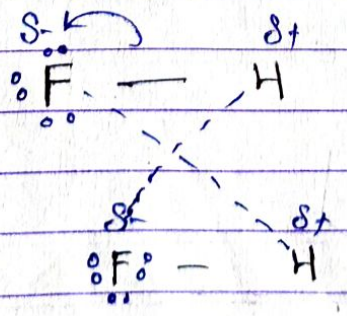
Organic complex are those complex molecules inwhich atom or groups are attached by transfer of e^- and form three type of bond.

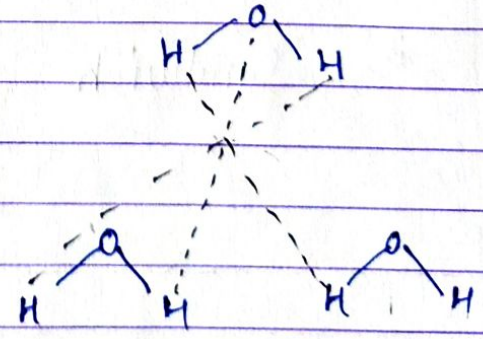
i) Electrostatic bond (ionic bond)
ii) Covallent bond
iii) H- bond.

iii) H. bond ⇒

When H. atom is attached with any strong electronagative atom one group than H ~~at~~ become ~~then~~ e^- diffient, this diffient H is attached with another e^- ~~which~~ ~~such~~ species by a weak bond which is called H- bond.

It is represented by dodded line (---)





Organic complex makes four type of complex structure

i) ~~Quinhydrine~~ Quinohydrine type
ii) Picric acid type
iii) Polymer type
iv) Caffein type

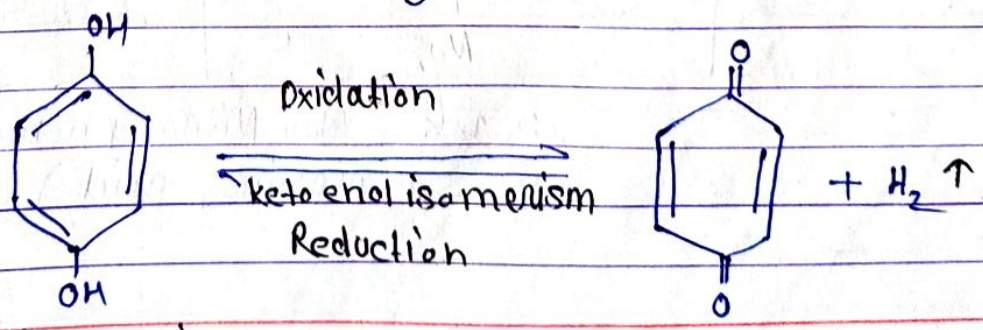
(i) Quinohydrine type :-

The Aromatic hydrocarbons in which co-vallent bond & resonanace is present they form two type of complex structure.

a. ~~Quin~~ Quinohydrine complex
b. Benzoquinone complex

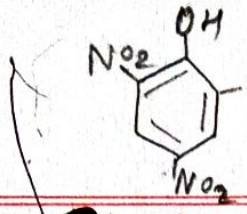
Both complex structure change from one form to another by keto enol isomerism (~~keto~~ tautomerism).

By oxidation quinohydrine is convert into benzoquinone & by reduction benzoquinone is convert into hydroquinone.



quinohydrine complex

benzoquinone complex



(Picric Acid)

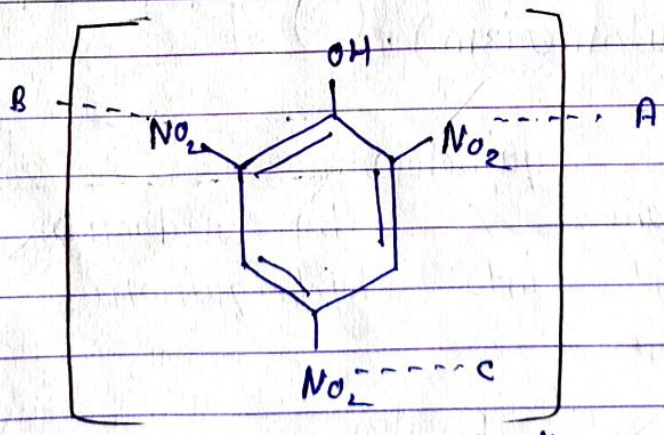
2,4,6 tri Nitro Phenol

Local Anesthetic

2. Picric Acid Complex

Ex - Butesin - PA complex

- Picric acid (2,4,6 tri Nitro phenol) form complex with poly nuclear aromatic hydrocarbon.
- The stability of these complex on the number of e^- attracting group (withdrawing group) & e^- donating group and on the nitro group.
- A will k/w complex of butesin & picric acid is known as butesin picrate
- Butesin picrate is used as t.t. ointment for burn and painfull condition and it has both antiseptic & Anaesthetic



2,4,6 tri Nitro phenol
(picric acid)

Bucalinda (Akaka)

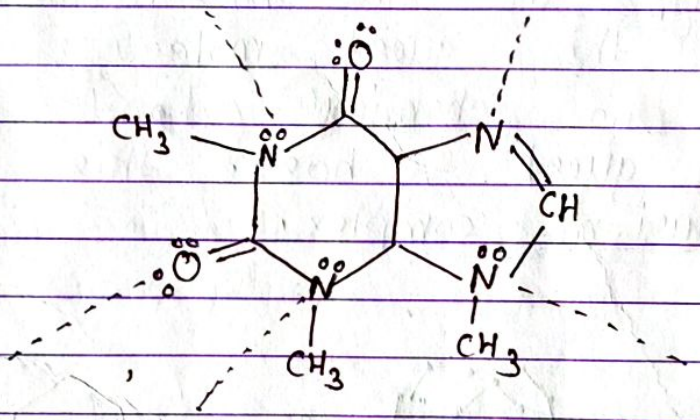
23/10/18

{functional group bonding lone path} ગ્રુપ

3. Caffiene type

In the structure of caffiene N, 4 O atom are present which contain lone pair and they can form complex with different drugs like barbiturate, sulphonamide

Caffiene form complex with many other compounds like salicylate, benzocain, ester, phenol and ketone etc.



Caffiene

4. Polymer type :

When same type of monomer molecules are combinde and form a long chain structure this is called polymer complex.

Example -

Polythene

$$n\,CH_2=CH_2 \xrightarrow{\text{Peroxide}} -(CH_2-CH_2-)$$

Ethene → Polythene

- PVC (Poly Vinyl chloride)

$$n\,CH_2=\underset{\text{vinyl chloride}}{\underset{|}{\overset{Cl}{CH}}} \xrightarrow{\text{Peroxide}} \underset{\text{poly vinyl chloride}}{(-CH_2-\underset{|}{\overset{Cl}{CH}}-)}$$

Bakelight, Nylone-66, Peresilene, cellulose, DNA Nuc.

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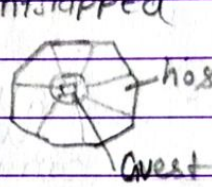
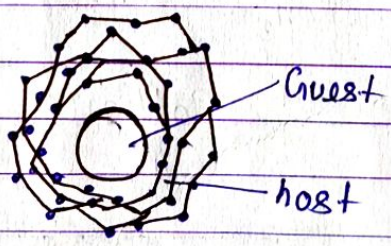
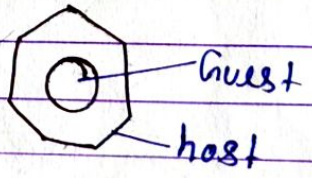
Inclusion or Occlusion type



In this type of the host molecules entrapped the guest molecules within it and no chemical bond is present between guest & host, this is called inclusion complex.





Type of Inclusion

① Channel type :-

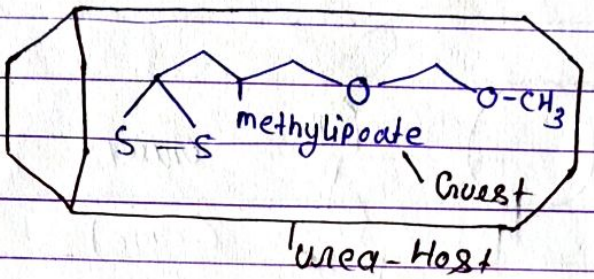
Channel are form by crystallization of host molecules

The guest component is usually limited

to long, unbranch and straight chain compound.

Example :-

Urea crystlise like a channel & enthapped methyl lipoate drug.

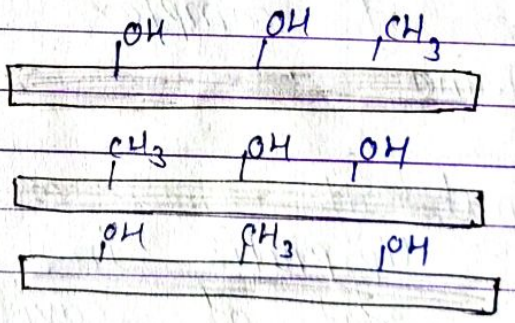


2) Layer Type :-

Some clay like substance bentonite, koline are the adsonbent they adsonve some hydrocanbon & hydroxide group on theine surface and form a monolayer this is called layer type complex.

Bentonite

$Al_2O_3 \cdot 4SiO_2 \cdot H_2O$

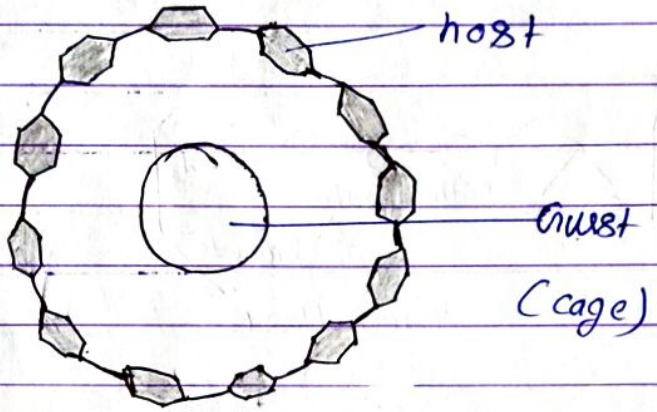


3.) Clathanates :-

The clathanates crystline in the form of cage like structure & the guest molecule is enthapped with in the cage.

Example :-

Isopropyl alcohol & sodium warfarin in the form of a white crystline powder.



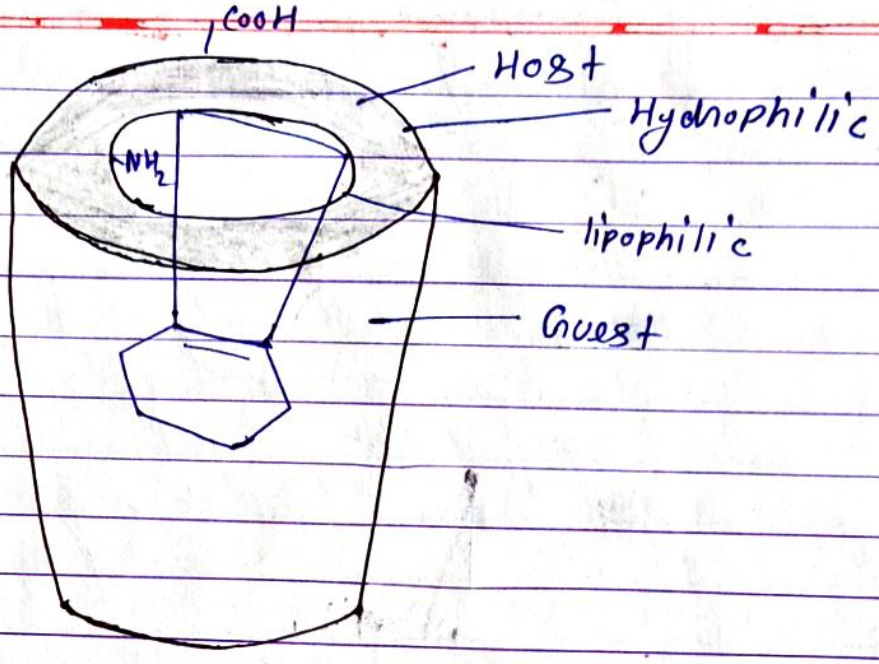
4) Mono Molecular Inclusion Compound :-

Mono molecular Inclusion compounds involve the entrapment the single guest molecules in the cavity of host molecules.

This type of complex is seen in cyclodextrins.

The enternal of the cavity is relativaly lipophilic in nature & the extennal part of cavity is hydrophilic in nature.

The guest molecules is connected with host molecules by hydrophilic or lypophilic likage.


COOH
Host
Hydrophilic
NH_2
lipophilic
Guest

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Application of Complexation

Often complexation the solubility, nature, machenism, absorption and bioavailability of the drug is changes

The complexation of drug has following application.

1. Solubility Inhancement (बढ़ाना)

The solubility of some poor soluble drug can be ↑es by complexation.

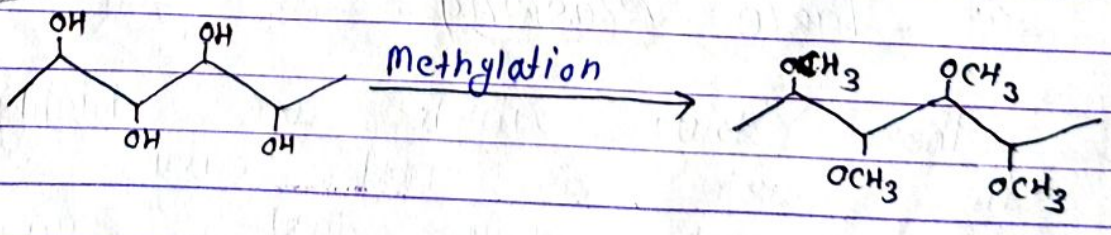
Retinoic acid - 0.5 mg/Ltr

↓ BCD (cyclodextrin)

β-CD - Retinoic complex - 160 mg/Ltr

By methylation β of some hydroxy group solubility can be ↓es.

Chloroform



SR - Sostained
C.R - contro

2. Bioavailability Enhancement :-

The actual amount of the drug which rich into systemic circulation (blood) is called bioavailability of the drug.

By the complexation with cyclodextrin the bioavailability of drug can be ↑es.

Example -

Tolbutamide (oral) is an oral hypoglycimic drug, their bioavaibbility can be ↑es by complexation with β cyclodextrin

3. Modifying Drug Release :-

The rate of drug release is controlled by its complexation.

By complexation with cyclodextrin the sustained and release drug are prepared which ↑es the duration of action of drug.

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4. Taste Masking :-

Those drug which are highly bitten in taste & not easy ingolf for such drug taste can be mask by complexation which some

other material.

- These complex break into stomach & drug become free.

Drug (Bitter)
↓ CD
CD - Drug complex (inert)
↓ Stomach
CD + Drug
↓
Action

5. Administration of Theraputic Agent

Some impontent theraputic agents are unstable in free form and they can not taken in free form as a drug.

But they are stable in a form of complex & given orally.

Example -

- Iron is given in the form of ferrous ascarbate, ferrous gluconate
- Calcium is given in the form of calcium gluconate & calcium conbonate
- Insulin is given in the complex with

Zinc & Vitamine B_{12}.

6. In treatment of Poising

By the machenism of complexation poisning affect can be minimize.

By the complexation poisning effect can be reduced by two way.

- By inhibit the absonption on toxin into blood.
- By inactivation of toxin substance.

- In the cause of metal posining. the solubility of metal is res often complexation and eliminated from body through kidney.

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Method of Analysis of Complexation

* When metal & ligand or acepter & donar are a combind in a solution then they form complex.

* To determine the complex formation & the Staichiometric conc. of metal & ligand is determine by analysis of complexation.

Metal + Ligand ⟶ M-L complex

* The analysis of complexation can be determine by following method.

i) Method of Continuous variation
ii) Spectroscopy method.
iii) Distribution method
iv) PH titration method
v) Solubility method
vi) Crenedal method.

i) Method of Continuous Variation

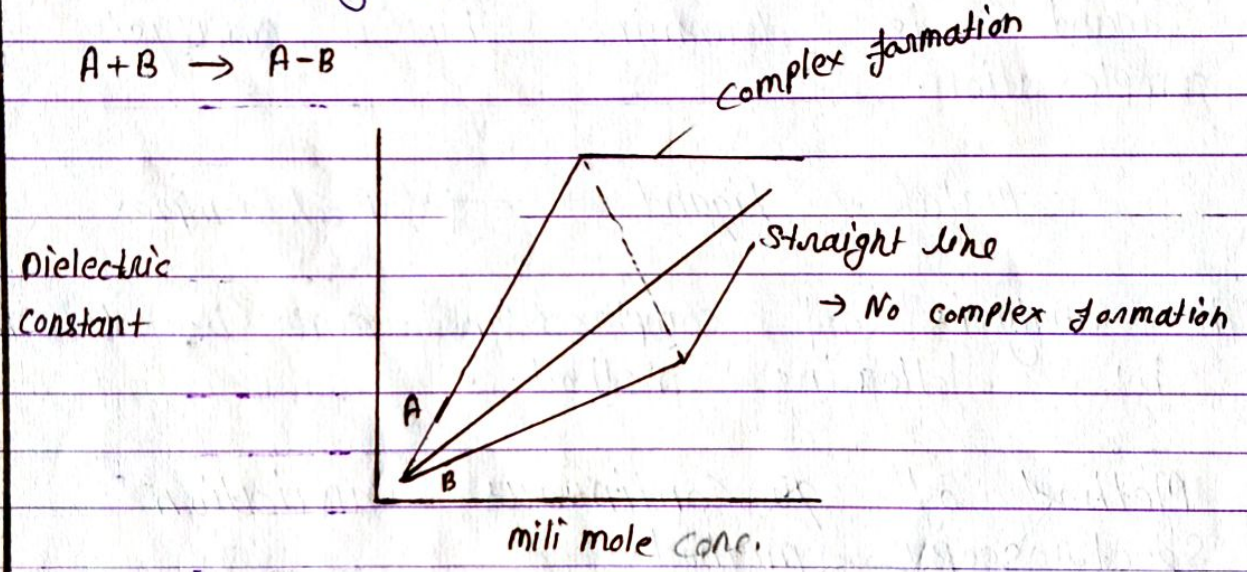
This method is depend upon the additive properties like dielectric constant.

If the properties of two species is different & well when they are mixed so no intraction occur.

then a straight line graph is obtain.

- In this method a graph is ploted b/w milimole conc. & dielectric constant. If complex is farm then the dielectric constant for complex is changes & elevation (~~शुरुवात~~) is obtain in graph.

$A + B \rightarrow A-B$



ii) Spectroscopic

This method measure the absorbence of the solution of various mole fraction in which the complex is formed.

Take the absorbence different in this solution & plot a graph b/e mole fraction & absorption

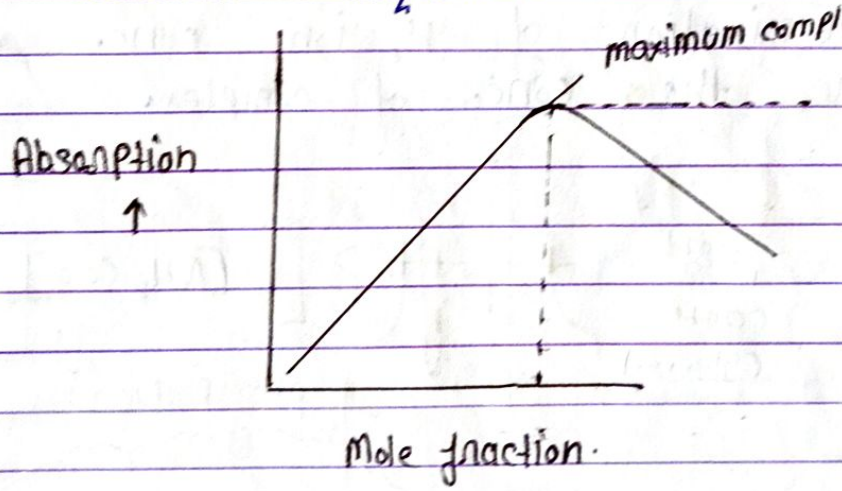
This method is based on the principle that absorption is directly

perpotional to the complex formation.

Absorption of complex formation

In a graph as well as the conc. of complex is ↑es graph ↑es is straight line ↑ but when the complex formation is stop than the slow becomes down ↓ an move in straight line without ~~elimination~~ elivation.

With the help of this graph ~~be~~ we can determine the conc. of complex ↑ number of moles of ligand ↑ metal solution required.



pH titration Method

This method is used for those complexation in which pH is reduce after complexation.

for example —

When cupric ion solution react with glycine ↑ NH_3 solution then it release H_2 ion

& pH is reduced.

If pH is reduced it means complexation is achived & if there is no change in pH it means no complexation occurs.

This complex solution is again titrated with Sodium Hydroxide solution by using acid-base indicator, & we can calculate the conc. of Acid (H^+) is present in solution.

After determination of H_2 ion conc. we can determine the conc. of complex.

$$Cu^{++} + NH_3 + \begin{matrix} COOH \\ | \\ COOH \end{matrix} \longrightarrow \left[Cu[NH_2COO^-]_2\right]^{+2} + 2H^+\uparrow$$

Cupric ion (Glycein)

pH Reduce

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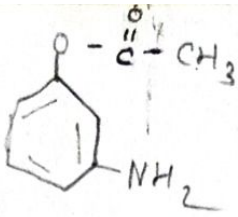
iv) **Distribution Method**

The method of distribution a solute into two immiscible solvent can be used to determine the stability constant for certain compound.

e.g.s.

The complexation of iodide by potassium iodide may be used.

Paracetamol structure

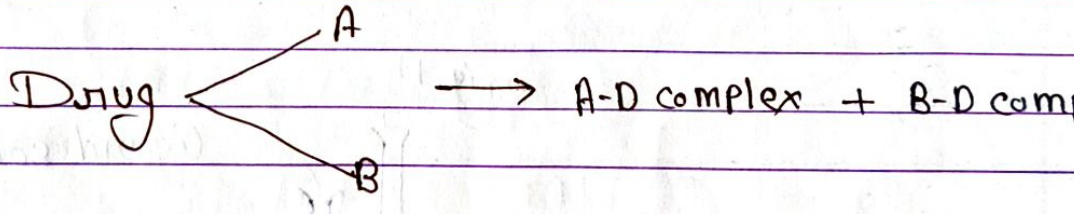


ligand eg - EDTA

The complexy action of kaffine, glycol and number of acidic drug using this method for determination of complexation.

- The drug is dissolve in two different solvent & it form complex with both solvent.

- The distribution ratio of drug is calculated by the ratio of drug complex in both solvent.



$$\text{distribution Ratio} = \frac{\text{A-D complex}}{\text{B-D complex}}$$

v) **Solubility Method**

This method was develop by scientist Higuchi & Lach so it is also known as Higuch Lach method.

In this method a cantainer is taken with closed system, add drug into the cantainer along with the solution of complexing Agent.

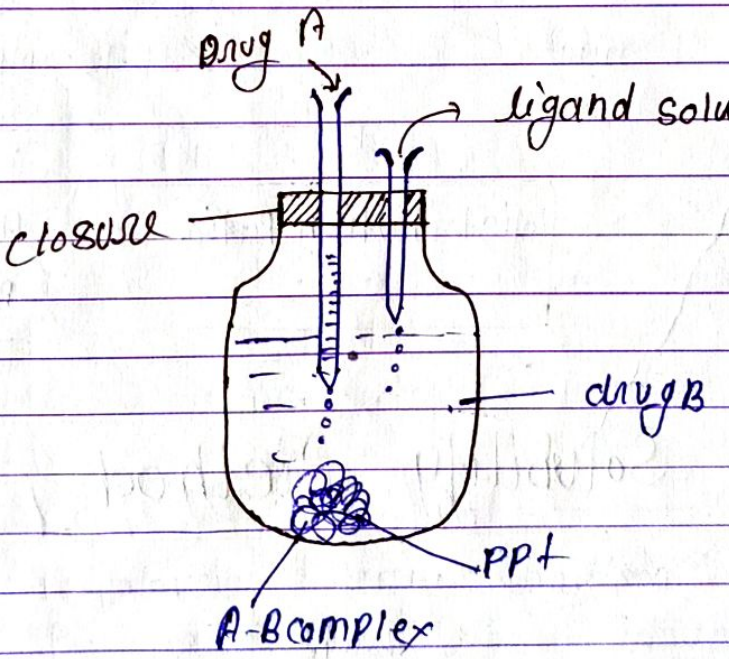
Make Series of solution of different conc. of complexi agent and bottol are agitated in a constant temp bath.

After the formation of ppt remaining in liquid is remove & ppt is filter.

By weighing the ppt conc. of complex is calculated

Example

The drug PABA (P- amino benzoic acid) is form complex with caffine.



Other Method

H - NMR Method
Circular Dichroism method
IR Method (Infra - rate)

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Protein Binding

The action of drug molecules in our body is depends upon the drug protein binding complex.

In our blood basicaly four type of protein are present which is Albumin, Globulin Glycoprotein, Lipoprotein

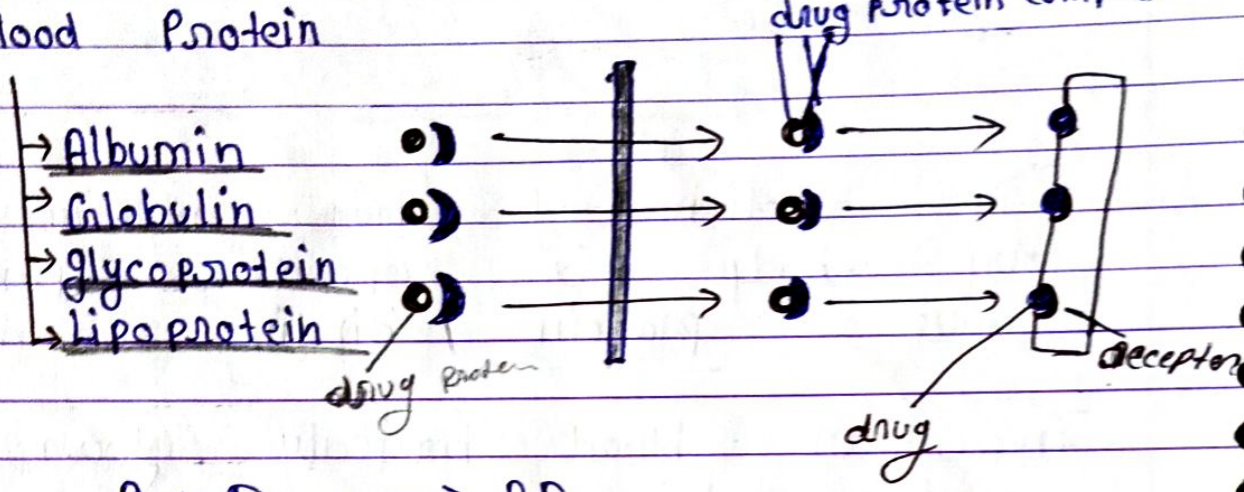
The hydrophilic drug bind with plasma protein and cross the membrane & after binding with recepter it give particular respons.

When drug is less strongly bonded with protein then drug become free easly and give action, action is quick but for short duration.

When drug is bind with protein strongly then action delay and form long duration.

If the drug is binded with very strongly then drug will not be free than drug will not be give action.

Blood Protein



$P + D \longrightarrow PD$

apply law of mass action

$$K = \frac{[PD]}{[P][D]}$$

$$K \times [P][D] = [PD]$$

$$\boxed{[PD] = K[P][D]} \quad - eq\text{-}1$$

where - PD - Conc. of Protein Drug Complex
K - Constent
[P] - Conc. of protein
[D] - Conc. of drug

$$P_t = P + PD$$

$$\boxed{P = P_t - PD} \quad - eq\text{-}2$$

$$[PD] = K[D][P]$$

$$[PD] = K[D] \times [[P_t] - [PD]]$$

$$[PD] = K[D][P_t] - K[D][PD]$$

$$[PD] + K[D][PD] = K[D][P_t]$$

$$[PD][1+K[D]] = K[D][Pf]$$

$$\frac{[PD]}{[Pf]} = \frac{K[D]}{[1+[KD]]}$$

$$\gamma = \frac{K[D]}{[1+[KD]]}$$

where -

γ = Rate of protein drug binding

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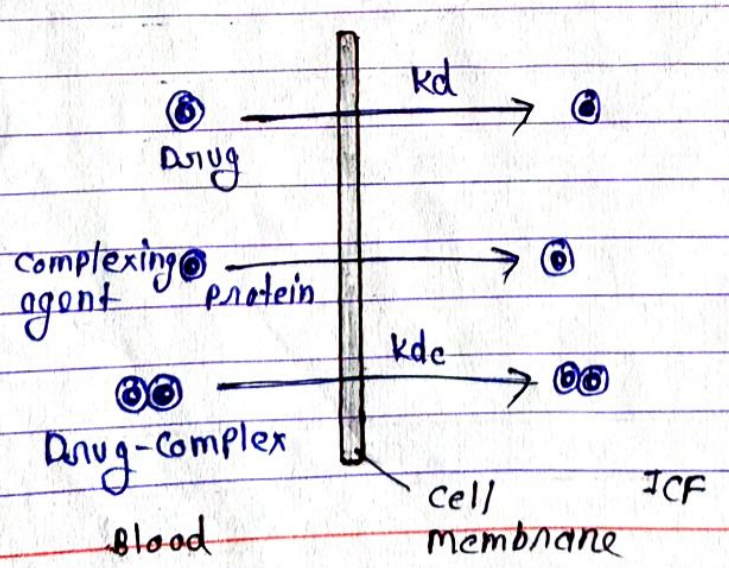
Complexation / Protein-Complex & Drug Action :-

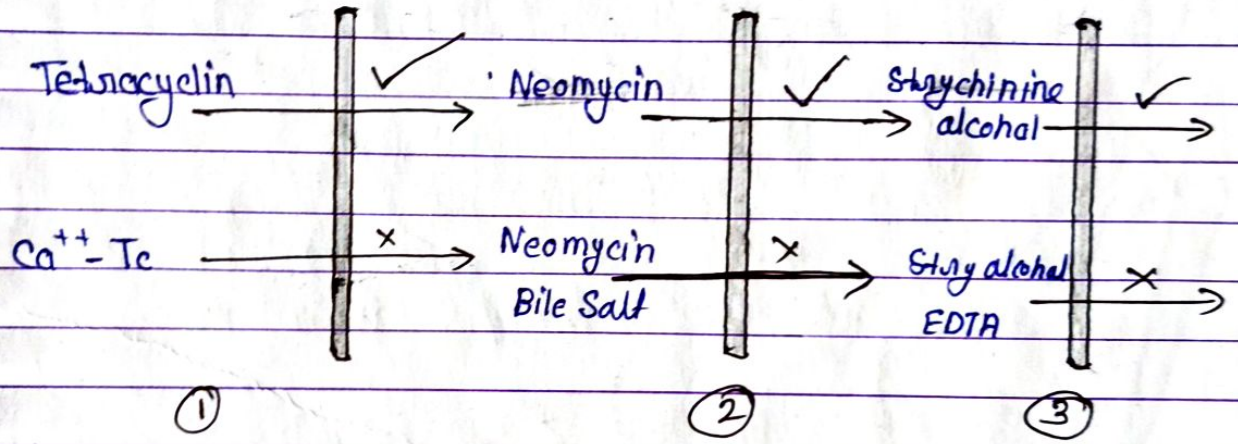
- The action of drug is change after complexation with protein or other substance.
- After complex formation if the rate of absonption is ↓es (kd > kdc) then the drug action will be ↓es.
- And when after complexation if the rate of drug absonption is ↑es (kd < kdc) then the drug action will be ↑es.
- The absonption of drug molecules it also depends upon some other factor like Partition coefficient, solubility and size of drug.



If $k_d > k_{dc}$ → Absonption slow → Drug action ↓es

If $k_d < k_{dc}$ → Absonption high → Drug action ↑s

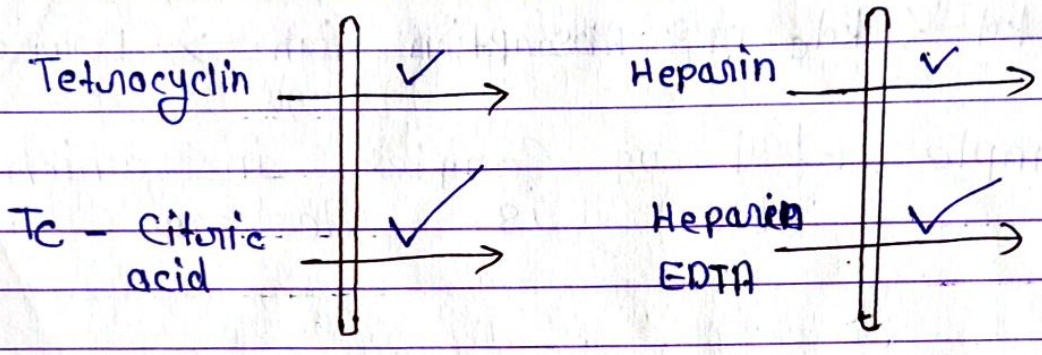
Example of Drug Complex in which drug is decrease :-



tetracyclin :-

When tetracyclin is combind with Ca^{++} then the drug action is ↓es.

Example of Drug Complex in which drug is increase :-



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Crystalline Structure of Complex

When Metal & ligand or acceptor & donor form complex with each other then they form three types of complex -

1. Simple Inorganic salt
2. Metal Hybrid structure
3. Bioactive metalloprotein

The physical & chemical properties of all these complexes are different.

These complexes are used as bioactive agents, drug, remedis & in extraction.

Thermodynamic Treatment of Stability Constant

In the formation of Metal - ligand complex the amount of energy involve is called thermodynamic of complex complex

The valve of energy for any complexation can be calculated by using this equation.

$$\Delta G = -2.303 RT \log K$$

Where -

ΔG = Gibbs gives free energy
R = Rydberg constant
T = Absolute temp.

K = Stability Constant

When any complex structure is change one into another form or from one system into another then the stability constant can be calculated by following equation.

$$\log \frac{K_2}{K_1} = 2.303 R \frac{T_2 - T_1}{T_2 \times T_1}$$

The rate of complexation & stability constant can also be explained by Gibb's ~~give~~ free energy equation.

At high temperature the valve of ΔG becomes negative (-ve) & the valve of stability constant is ↑es.

At low temp the valve of ΔG becomes positive (+ve) & the valve of stability constant is ↓es.

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

ΔG = -ve ⟶ Rate ↑es
ΔG = +ve ⟶ Rate ↓es
if temp. ↑es ⟶ ΔG = -ve
temp. ↓es ⟶ ΔG = +ve