UNIT-4

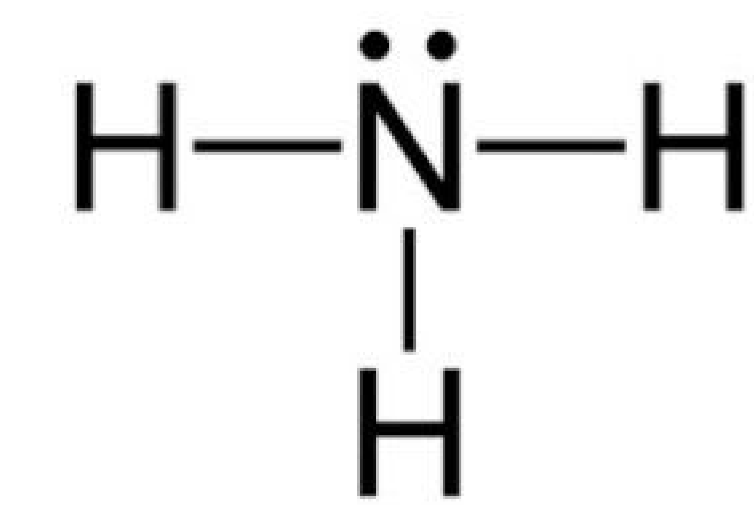
COMPLEXATION

AND

PROTEIN BINDING

[DEPTH OF BIOLOGY]

- COMPLEXATION- formation of complexes occurs by the association of 2 or more chemical species.
- Donor-acceptor mechanism creates complexes.
- Eg- NH_3 [donor- ligand which has lone pair]



[DEPTH OF BIOLOGY]

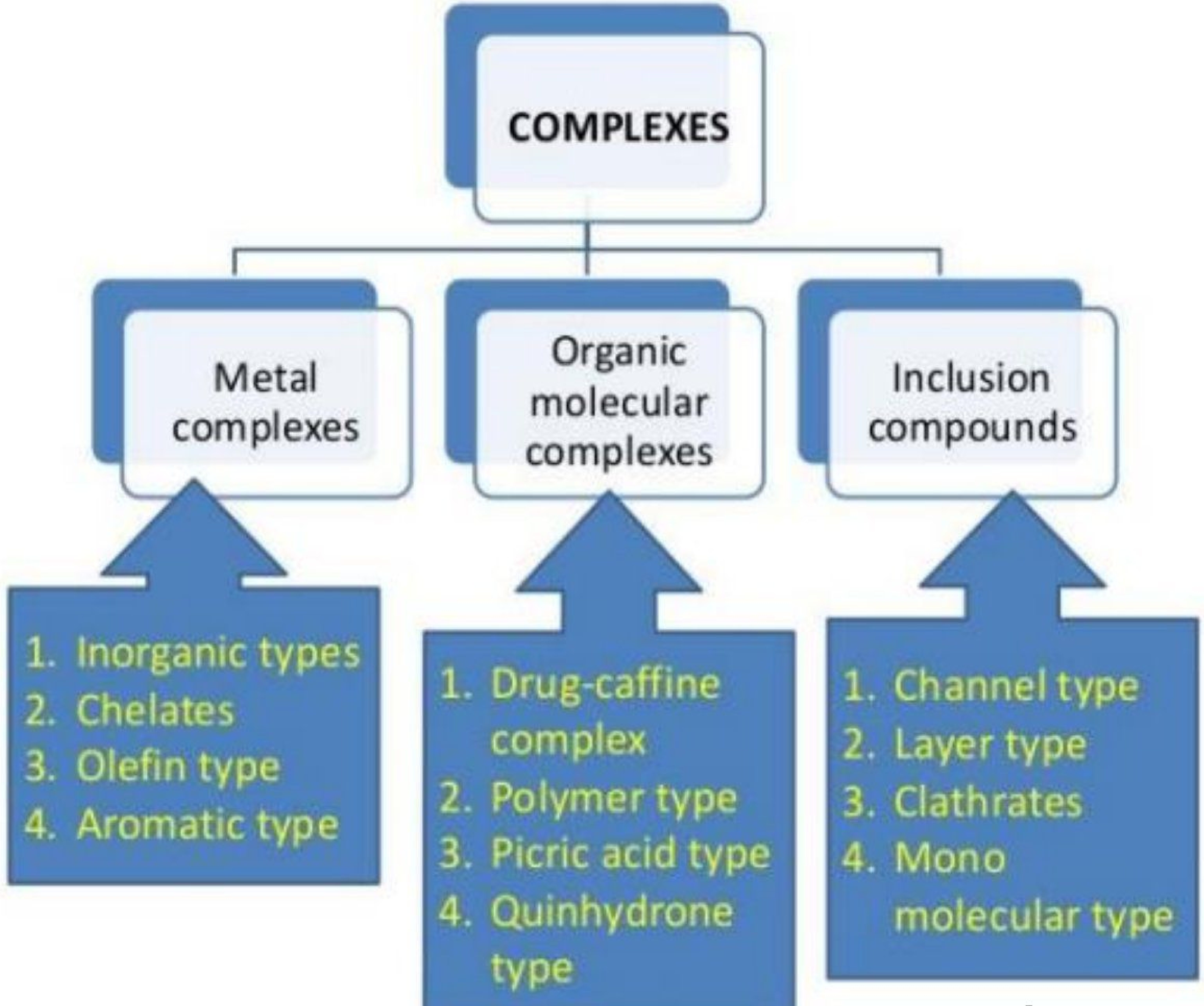
- The donor compound is non – metallic atom/ion which donate electron pair
- The acceptor compound is metallic/neutral atom/ion which accept electron pair

[DEPTH OF BIOLOGY]

- So, acceptor molecule is referred as central atom & donor [which is attached to C.A.] is referred as ligand

[DEPTH OF BIOLOGY]

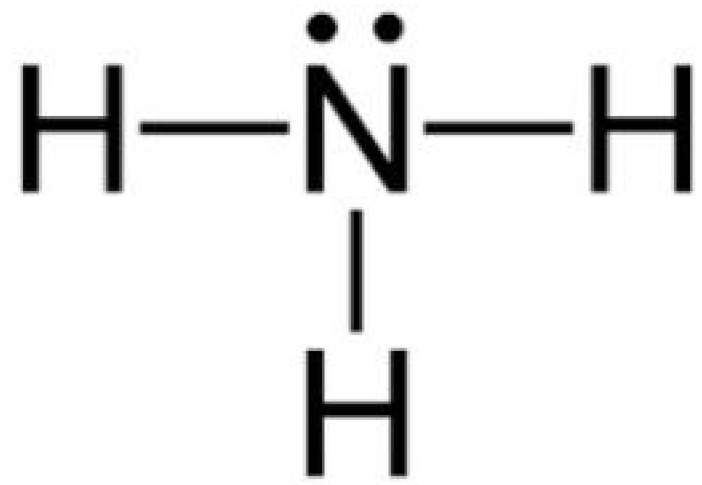
CLASSIFICATION OF COMPLEXATION:

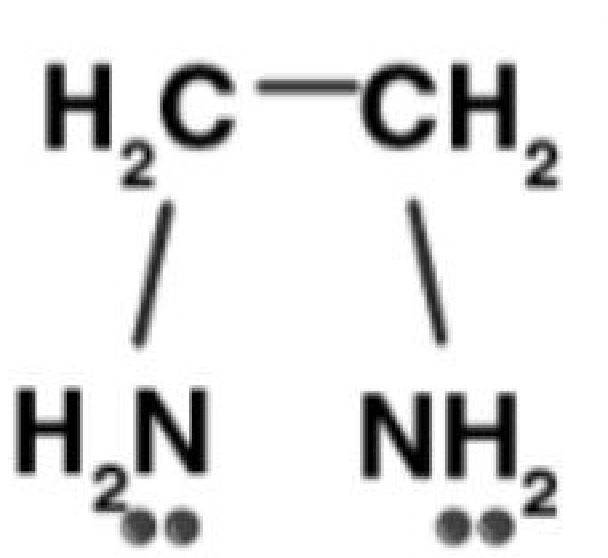


TYPES OF LIGANDS

- ***MONO DENTATE LIGANDS*** [DEPTH OF BIOLOGY]

Monodentate ligands are also called "one-toothed" because they bite the metal atom only in one place.



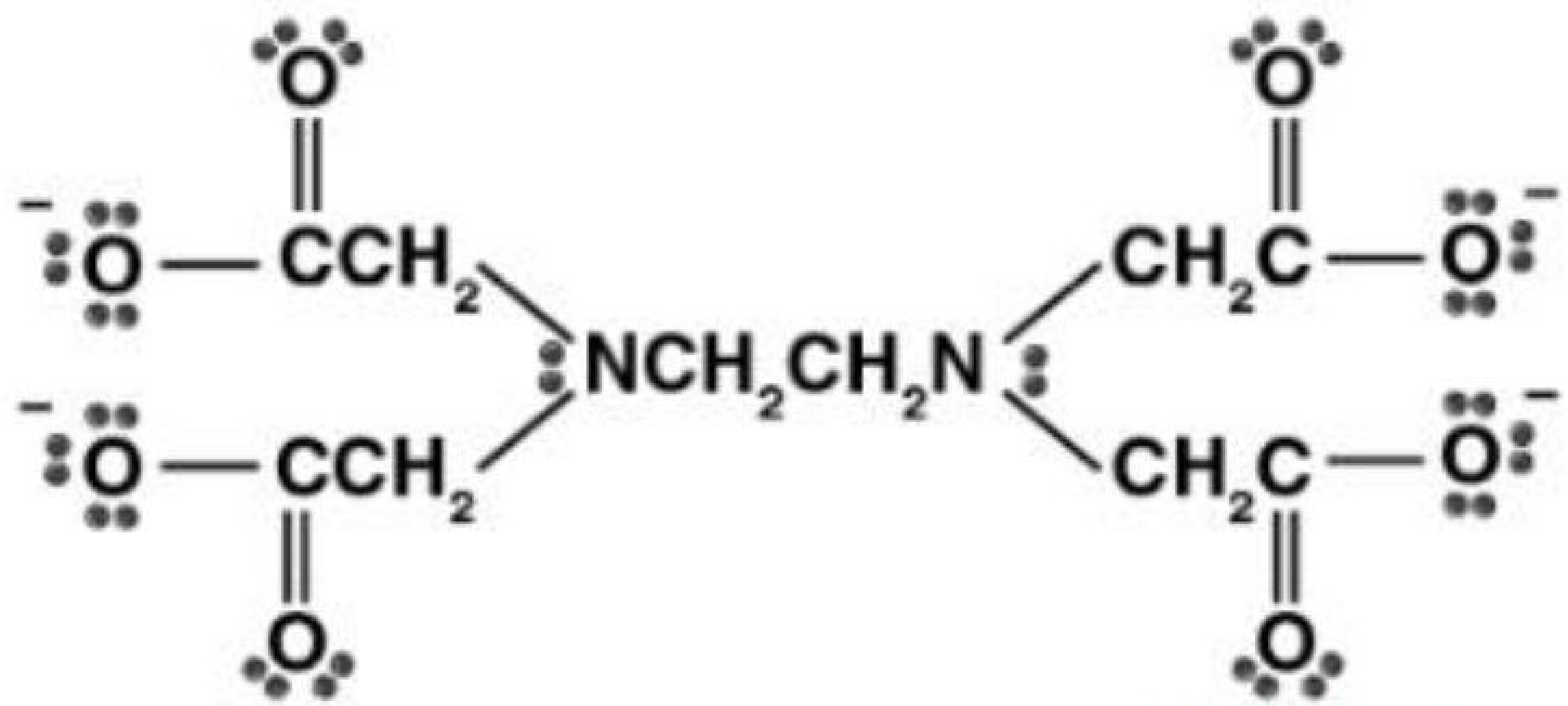


- ***BIDENTATE LIGANDS***

Lewis base which donates two lone pairs of electrons to the central metal atom is known as bidentate ligands.

[DEPTH OF BIOLOGY]

- ***POLYDENTATE LIGANDS***
- Tridentate ligands have three lone pairs of electrons to the central metal atom or ion. Molecules with four donor atoms are called tetradentate. [DEPTH OF BIOLOGY]
- five donor atoms are called pentadentate and six donor atoms are called hexadentate.
- They are generally mentioned as polydentate ligands. [DEPTH OF BIOLOGY]



Ethylenediaminetetraacetate (EDTA)

[DEPTH OF BIOLOGY]

Applications of Complexation:

- ***Physical state:***
  - Complexation process improves processing characteristics by converting liquid to soild complex. β-cyclodextrine complexes with nitroglyerine.

- ***Solid state stability:***
  - Complexation process enhances solid state stability of drugs.
  - β-cyclodextrine complexes with Vitamin A and D.

- ***Antidote for metal poisoning:***
  - BAL (British Anti Lewisite) reduces toxicity of heavy metals by complexing with As, Hg and Sb.

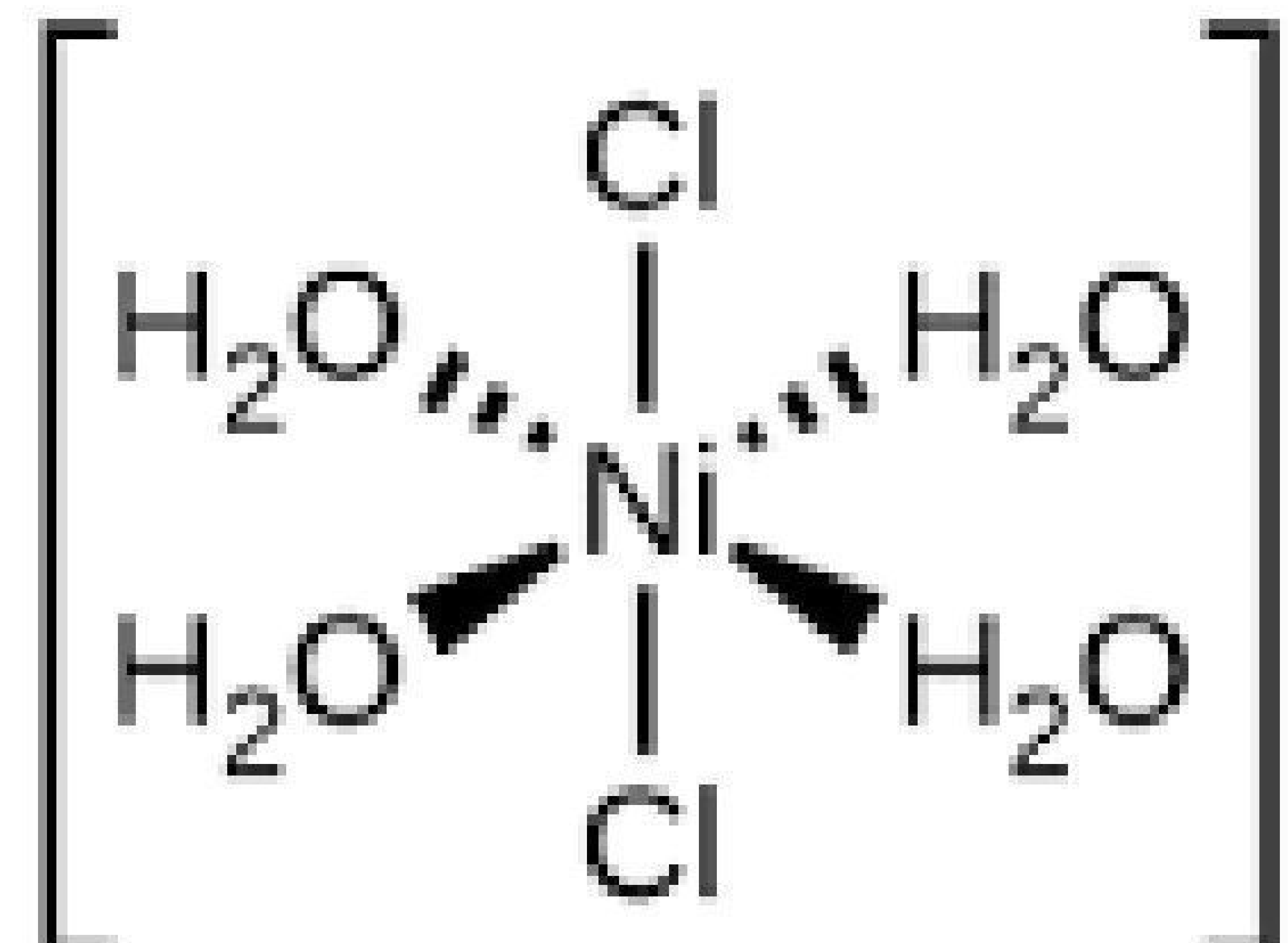
- ***Solubility:***
  - Complexation process enhances solubility of drug.
  - Caffeine enhances solubility of PABA (Para Amino Benzoic Acid) by complex formation.
- ***Dissolution:***
  - Complexation process enhances dissolution of drug.
  - β-cyclodextrine increases the dissolution of Phenobarbitone by inclusion complex.
- ***Absorption and Bioavailability:***
  - Complexation process reduces the absorption of Tetracycline by complexing with cations like Ca^{+2}, Mg^{+2} and Al^{+3}.
  - Complexation process enhances the aborption of Indomethacine and Barbiturates by complexing with β-cyclodextrine.

➢ METAL ION COMPLEXES/ COORDINATE COMPLEX-

in this type, metal ion constitute as central atom and interacts with ligands.

1. INORGANIC COMPLEXES- inorganic ligand attached with metal atom [DEPTH OF BIOLOGY]

EG: NH_3 , H_2O, CN .



trans

➢ Ligand attached to metal atom

With coordinate bond & Cl

Attached with simple ionic bond

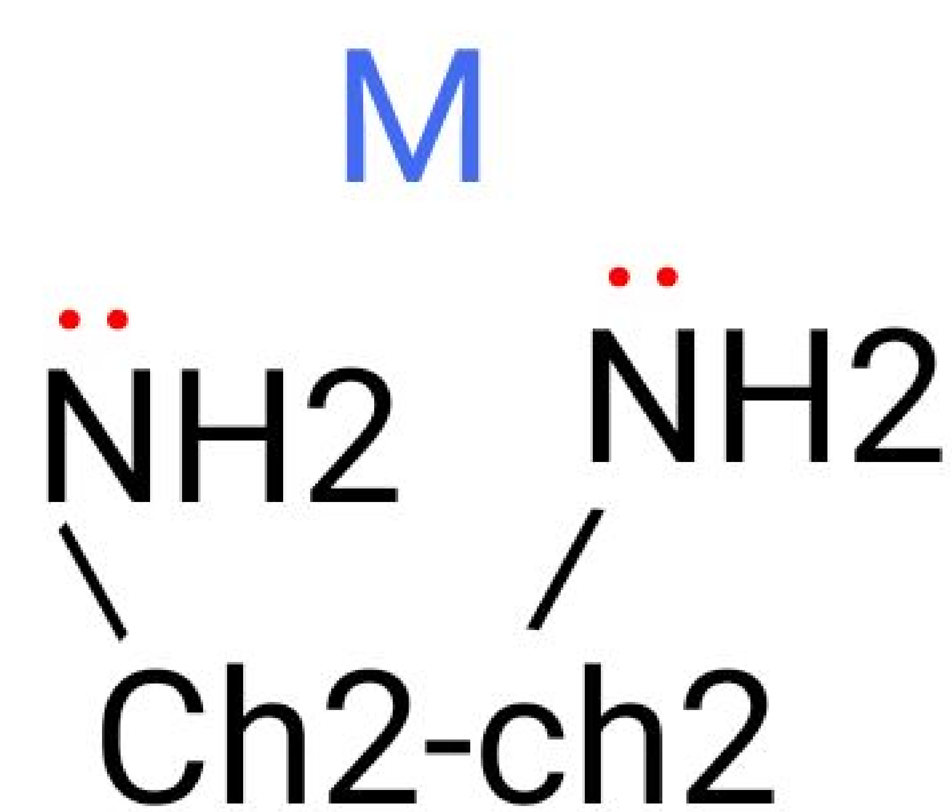
[DEPTH OF BIOLOGY]

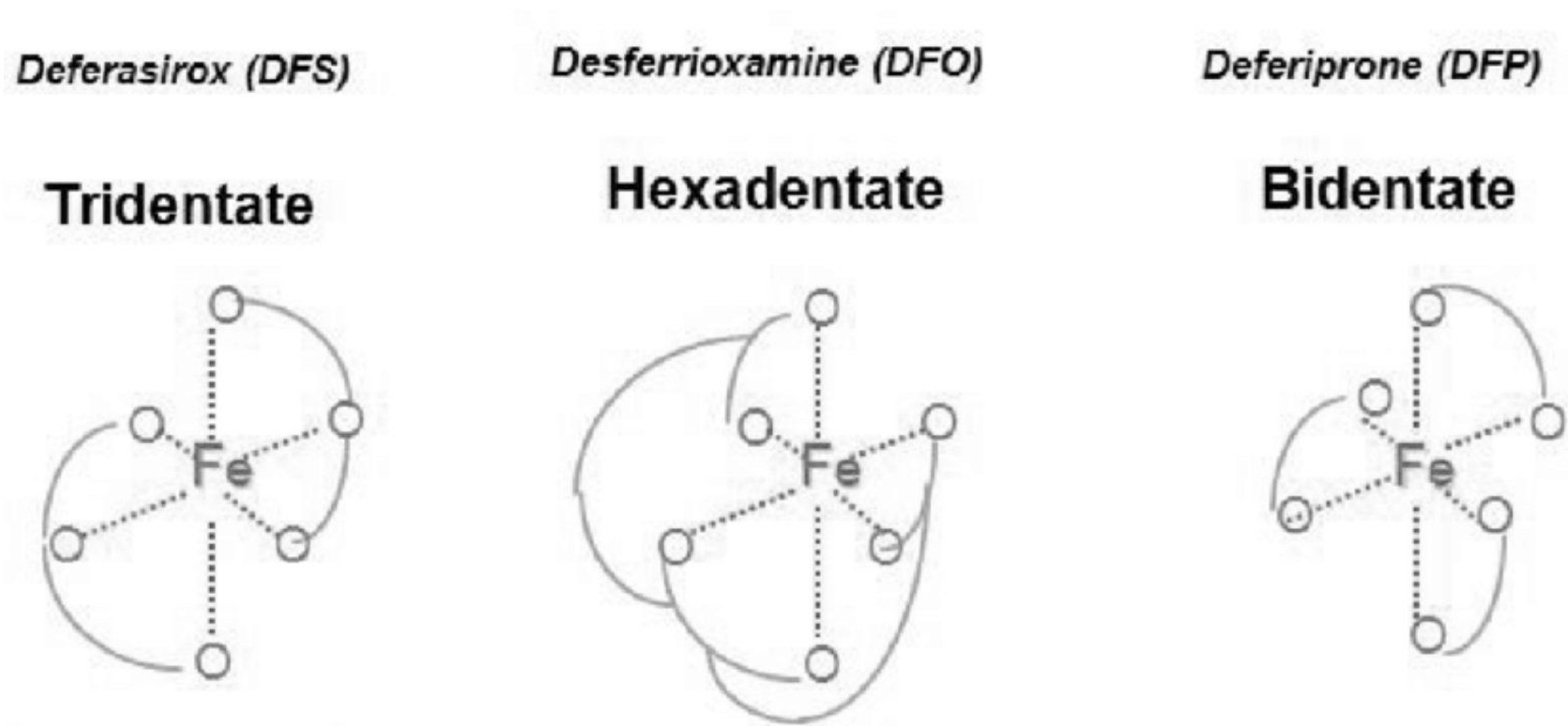
VALANCIES

- Primary valancy- ionic bond $_2$
- Secondary valancy- coordinate bond or total no. Of ligands attached to central atom $_4$

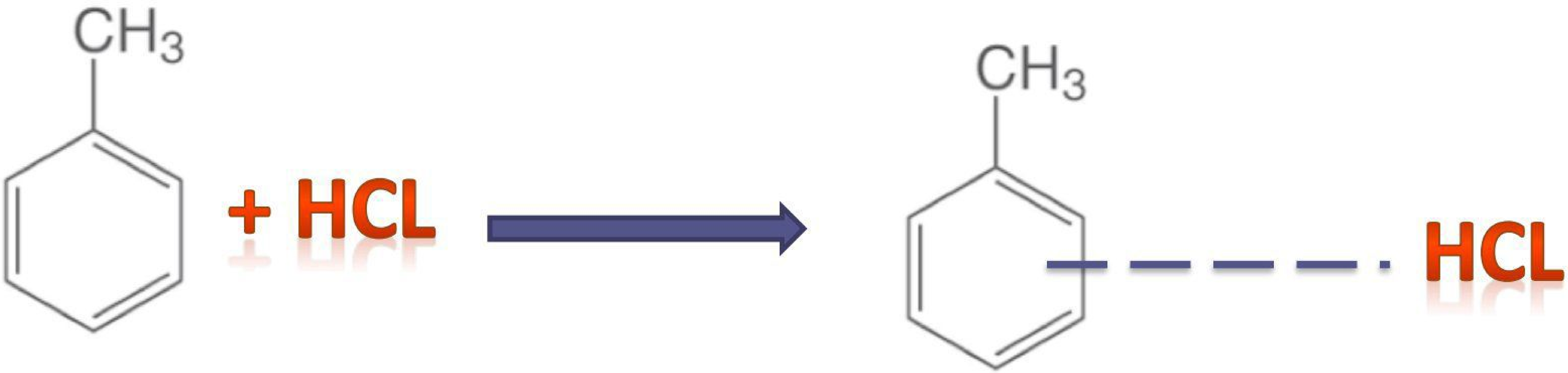
- COORDINATION NUMBER- max no. Of atom binding to the central atom $_6$

- CHELATES- provides two or more donor groups to combine with a metal ion
- Some of the bonds in a chelate may be ionic or of the primary covalent type, whereas others are coordinate covalent links [DEPTH OF BIOLOGY]
- It may be bi/tri/polydentate
- When metal atom attached with these ligand it form cyclic structure




Deferasirox (DFS)
Tridentate
Fe
Desferrioxamine (DFO)
Hexadentate
Fe
Deferiprone (DFP)
Bidentate
Fe

- ***OLEFIN TYPE -*** The aqueous solution of certain metal ions like Pt, Fe, Pd, Hg and Ag can absorb olefins such as ethylene to yield water soluble complexes. [DEPTH OF BIOLOGY]
- These are uses as catalyst in the manufacture of bulk drugs and analysis of drugs.
- ***AROMATIC COMPLEXES-*** formed by interaction of metal ion as acceptor with aromatic molecules such as benzene, toluene xylene [DEPTH OF BIOLOGY]

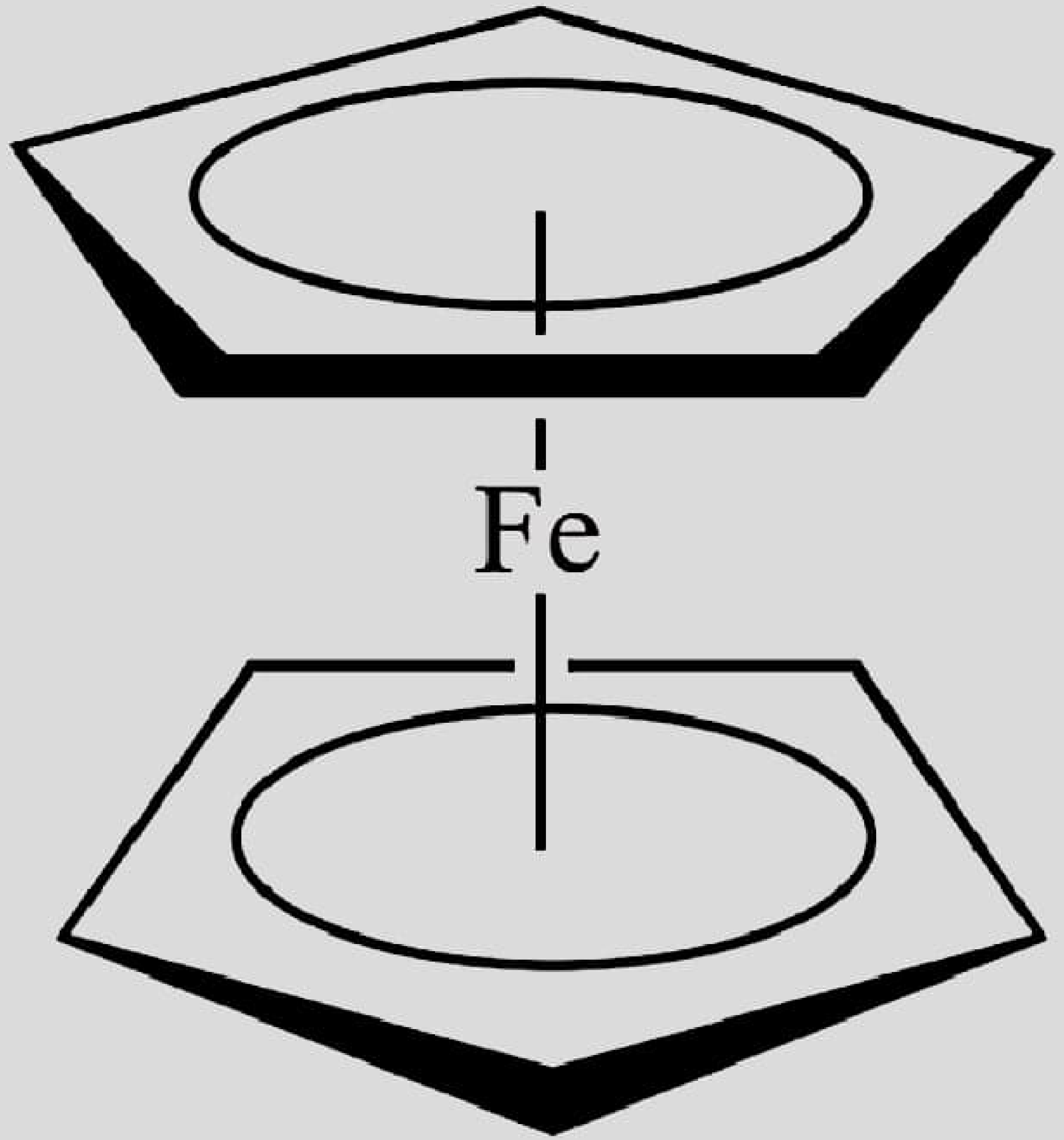


[DEPTH OF BIOLOGY]

1. sigma bond
2. π - bond
3. sandwich bond

- ***SANDWICH COMPOUNDS –*** These are relatively stable complexes involving in the delocalized covalent bond between the d-orbital of transition metal and a molecular orbit of the aromatic ring.

[DEPTH OF BIOLOGY]

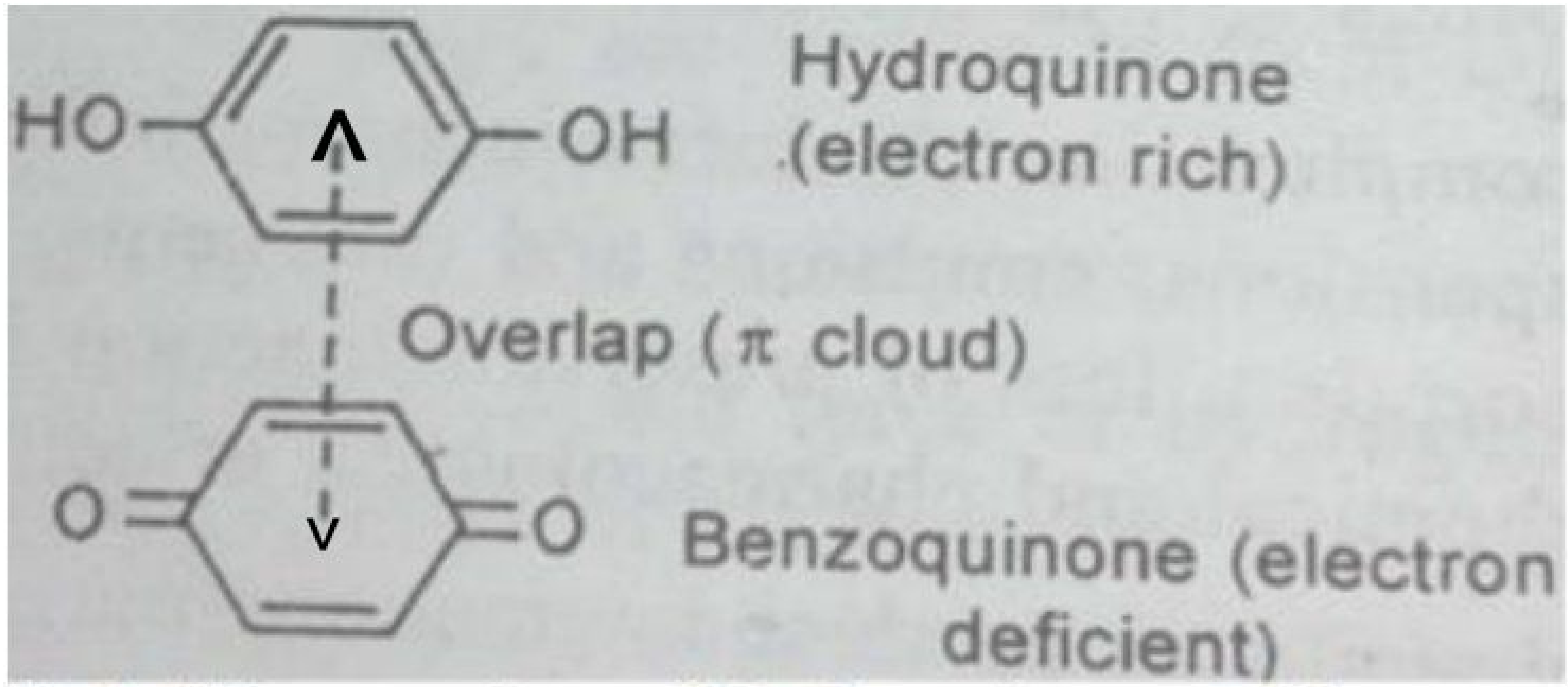


2. ***ORGANIC MOLECULAR COMPLEXES***:

- Also known as addition complexes [DEPTH OF BIOLOGY]
- Formed by union of 2 organic molecules & held together by electrostatic, ionic, covalent force and also by hydrogen bonded complexes
- ***The charge transfer Complexes*** - In this one molecule polarizes the other, resulting in a type of ionic interaction or charge transfer, and these molecular complexes are often referred to as charge transfer complexes. The resonance makes the complex more stable. The intermolecular bonding is quite higher compared to donor-acceptor type complexes. For example, the polar nitro groups of trinitrobenzene induce a dipole in the readily. [DEPTH OF BIOLOGY]

QUINHYDRONE TYPE –

- The molecular complex of this type is obtained by mixing alcoholic solutions of equimolar quantities of hydroquinone and benzoquinone. [DEPTH OF BIOLOGY]



[DEPTH OF BIOLOGY]

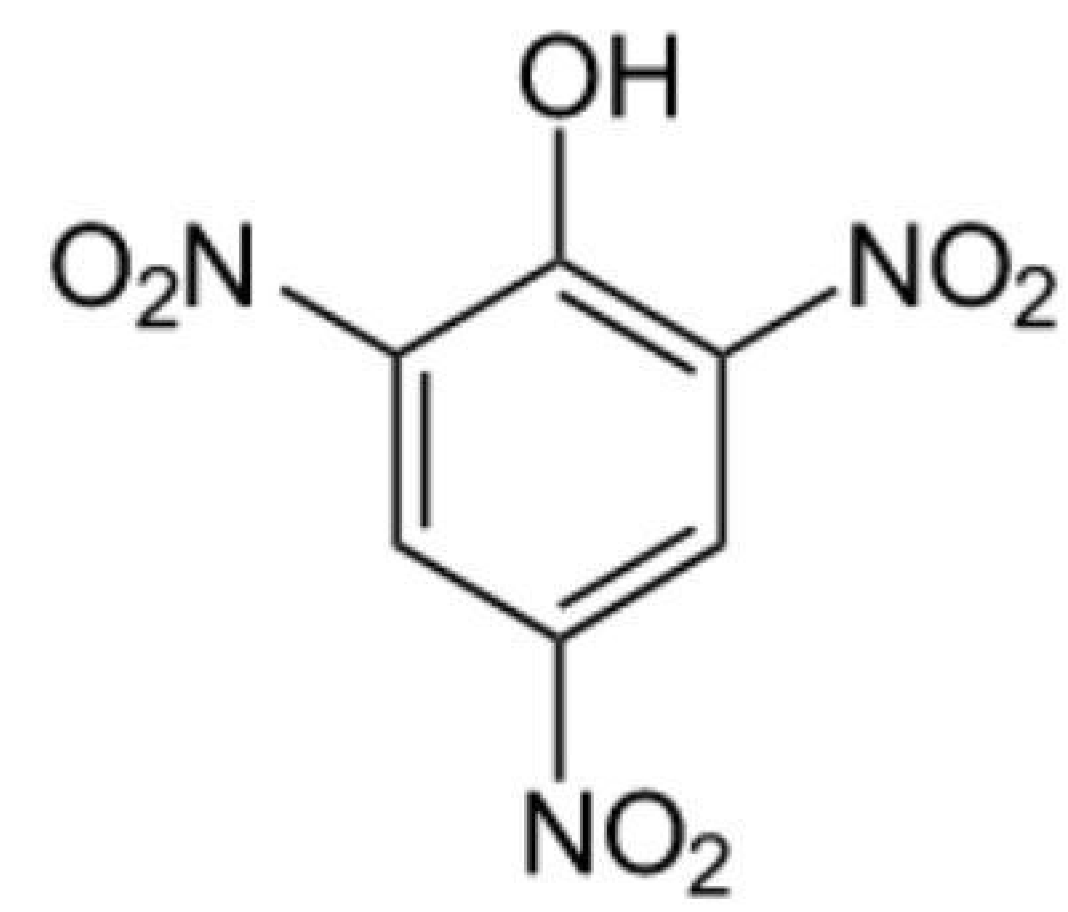
The complexes of hydroquinone and benzoquinone.

PICRIC ACID TYPES –

- Picric acid, being a strong acid, forms organic molecular complexes with weak bases, whereas it combines with strong bases (anesthetic activity of butesin) to yield salts.

(local)

[DEPTH OF BIOLOGY]



Caffeine and other drug complexes

- Drugs such as benzocaine, procaine and tetracaine form complexes with caffeine.
- A number of acidic drugs are known to form complexes with caffeine.

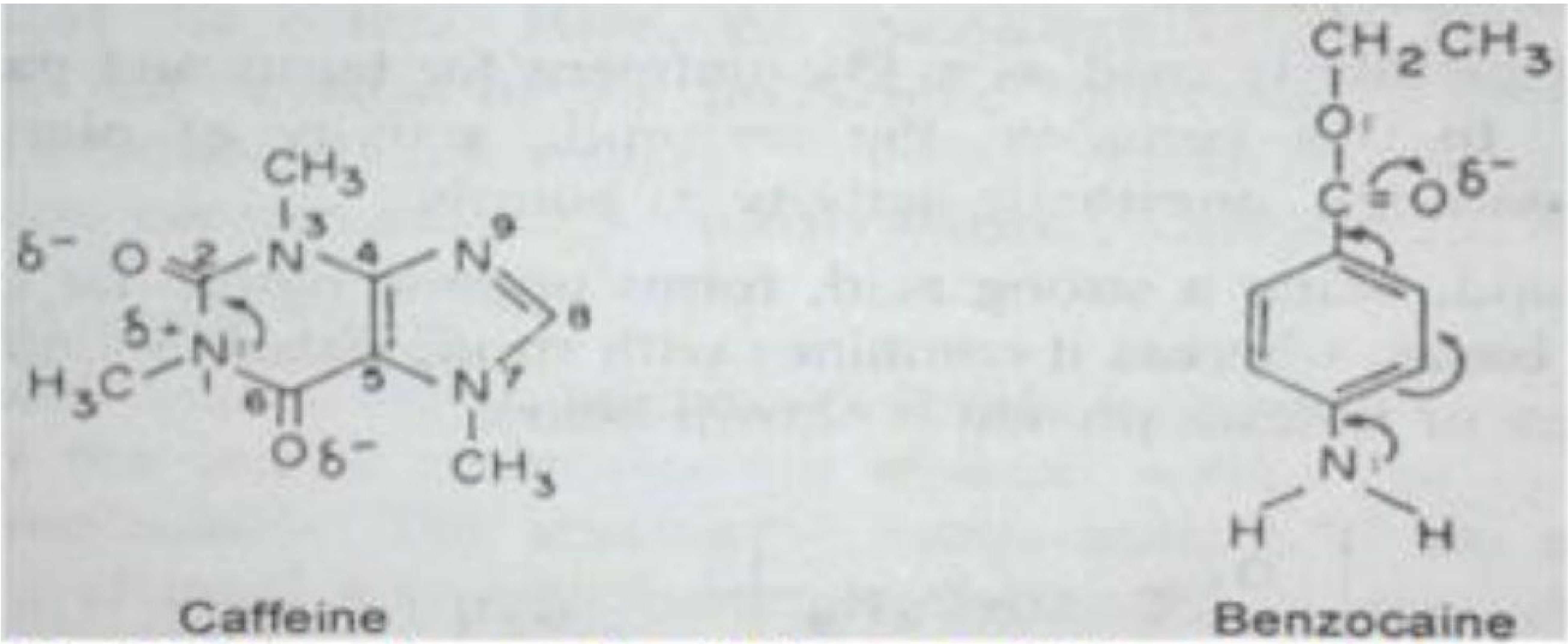


Fig 2. Structure of caffeine and Benzocaine.

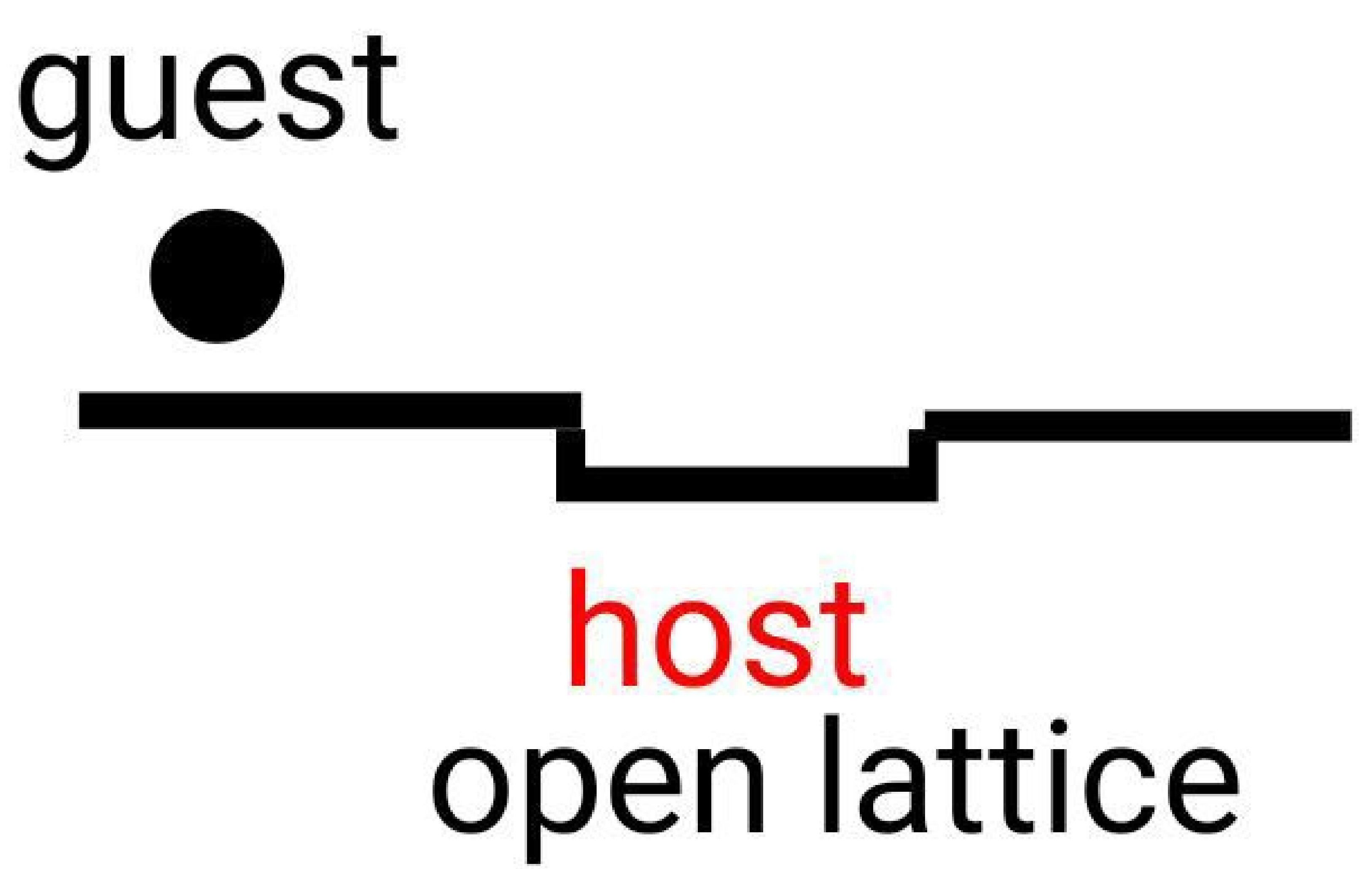
[DEPTH OF BIOLOGY]

POLYMERS TYPE –

- Many pharmaceutical additives such as polyethylene glycols (PEGs), carboxymethyl cellulose (CMC) contain nucleophilic oxygen. These can form complexes with various drugs. [DEPTH OF BIOLOGY]
- E.g. Polymers: carbowaxes, pluronics etc. Drugs: tannic acid, salicylic acid, phenols etc.
- Carboxy methyl cellulose + Amphetamine – Poorly absorbed drugs. [DEPTH OF BIOLOGY]

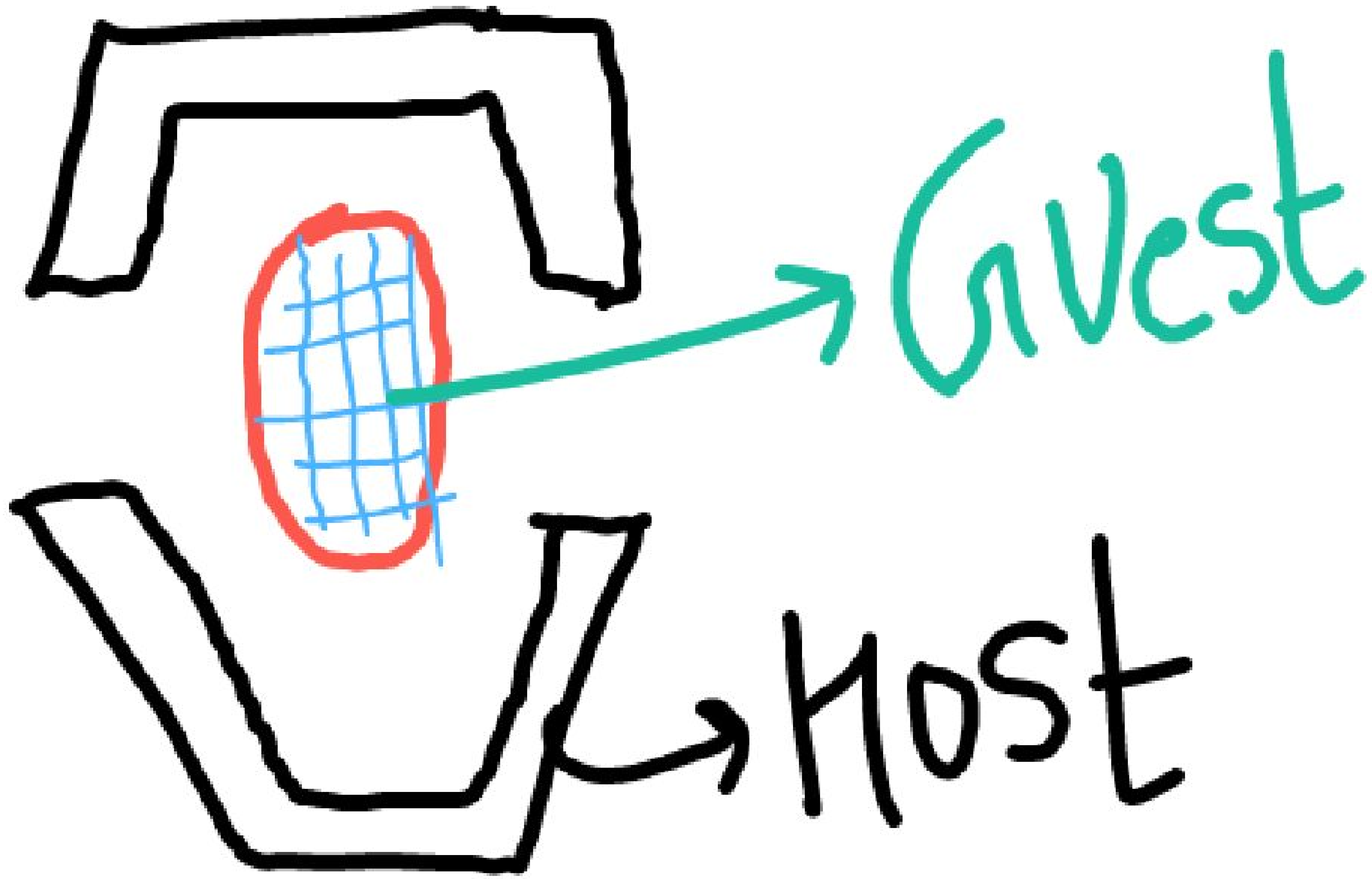
3. INCLUSION COMPLEXES:

- These complexes are also called occlusion compounds in which one of the components is trapped in the open lattice or cage like crystal structure of the other.
- No involvement of any type of bond so called no-bond complexes. [DEPTH OF BIOLOGY]



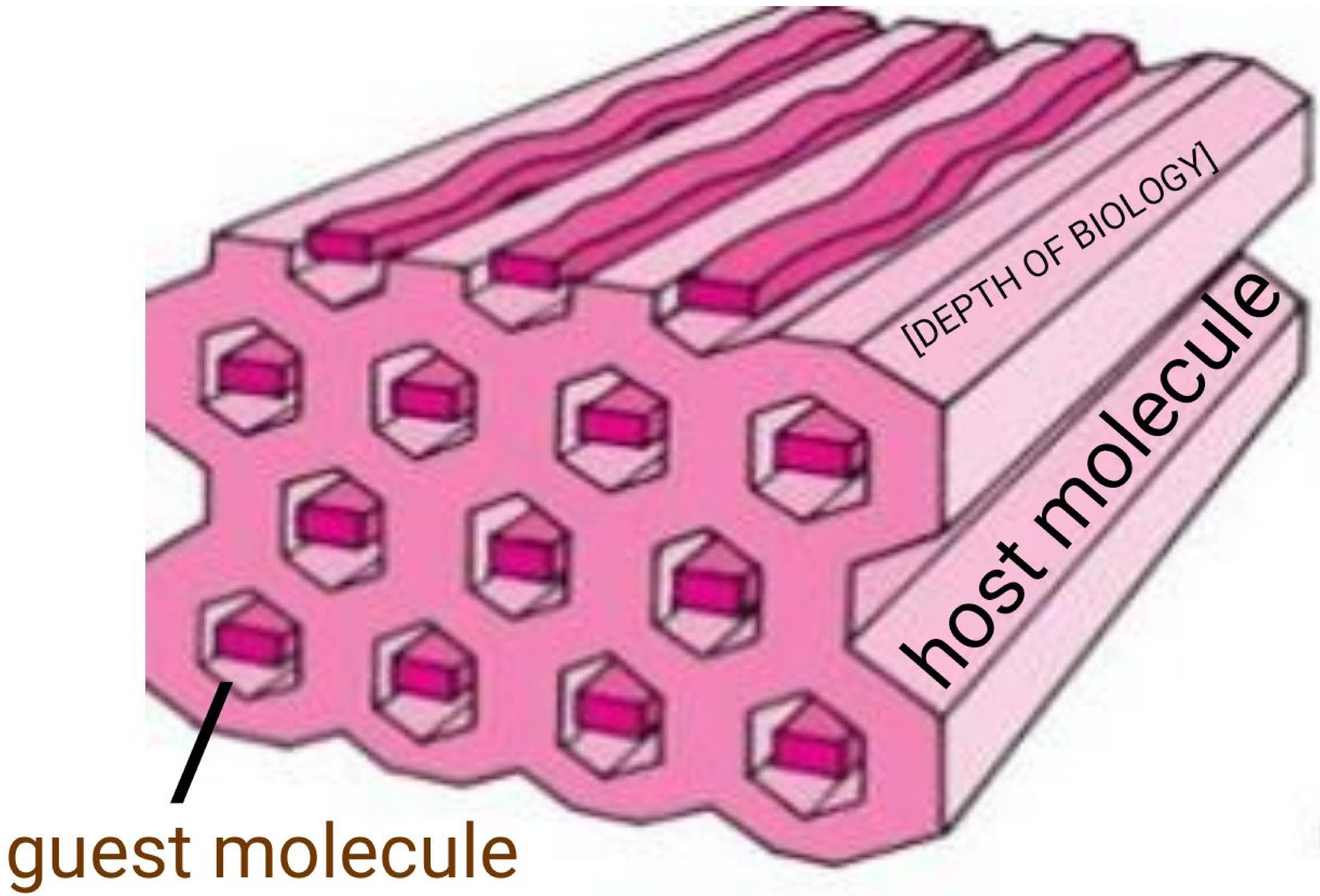
a. *CLATHRATES -* [DEPTH OF BIOLOGY]

- It is available as white crystalline powder, during crystallization, certain substances form a cage-like lattice in which the coordinating compound is entrapped.



b. ***CHANNEL LATTICE TYPES –***

- Channels are formed by crystallization of the host molecules, the guest component is usually limited to long, unbranched straight chain compounds
- Host (tubular channel)- Deoxycholic acid, urea, thiourea, amylose [DEPTH OF BIOLOGY]
- Guest (long unbranched straight chain compounds)- paraffin, esters, acids, ethanol.
- Example: Starch-iodine solution (starch-host) Urea-methyl α-lipolate (ureahost) [DEPTH OF BIOLOGY]



[DEPTH OF BIOLOGY]
host molecule
guest molecule

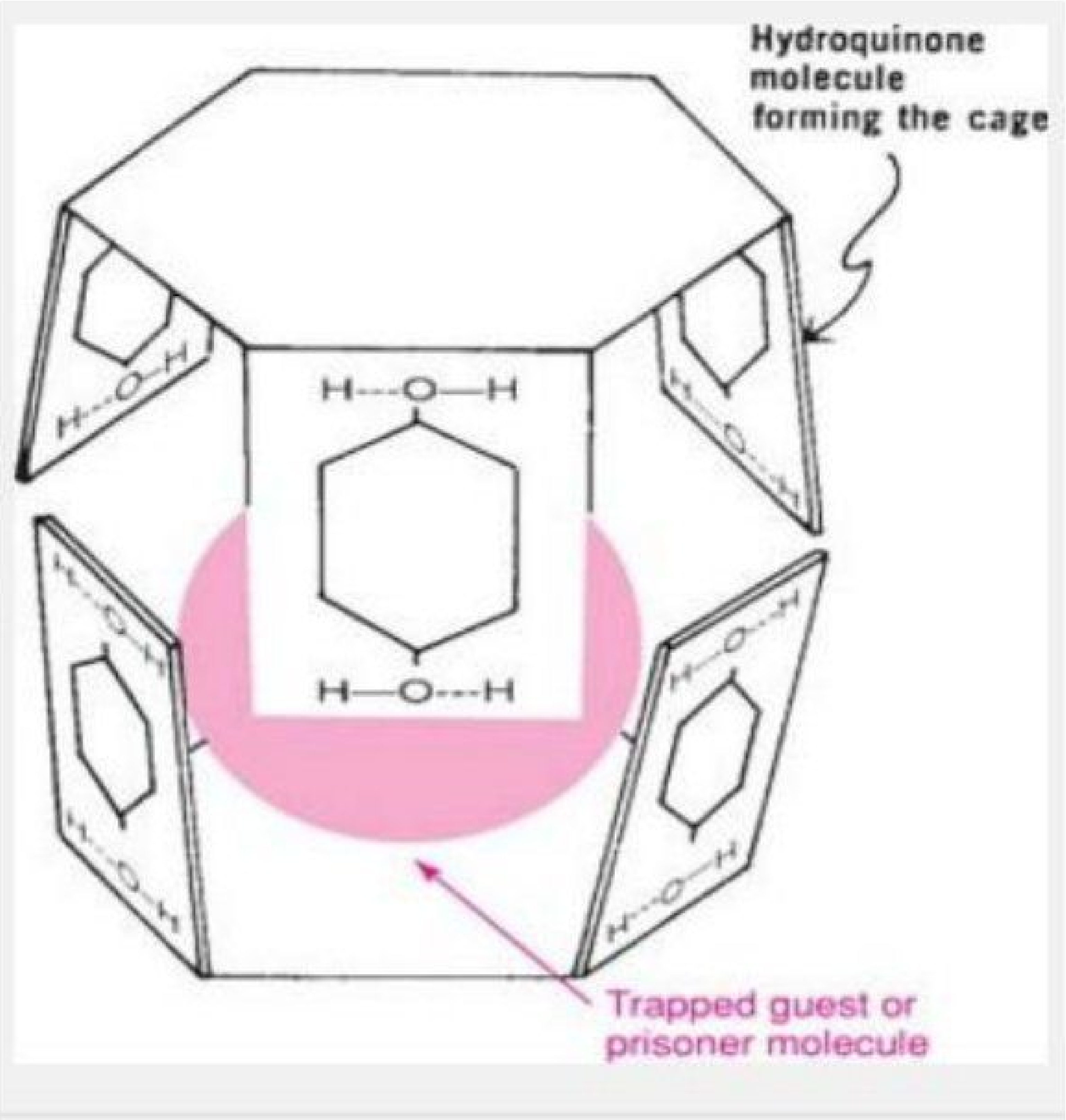
LAYER TYPES –

- In this type guest molecule is diffused between the layers of carbon atom , hexagonally oriented to form alternate layers of guest and host molecules
- Eg- clays, montmorillionete
- Hand made diag*

[DEPTH OF BIOLOGY]

MONOMOLECULAR TYPES –

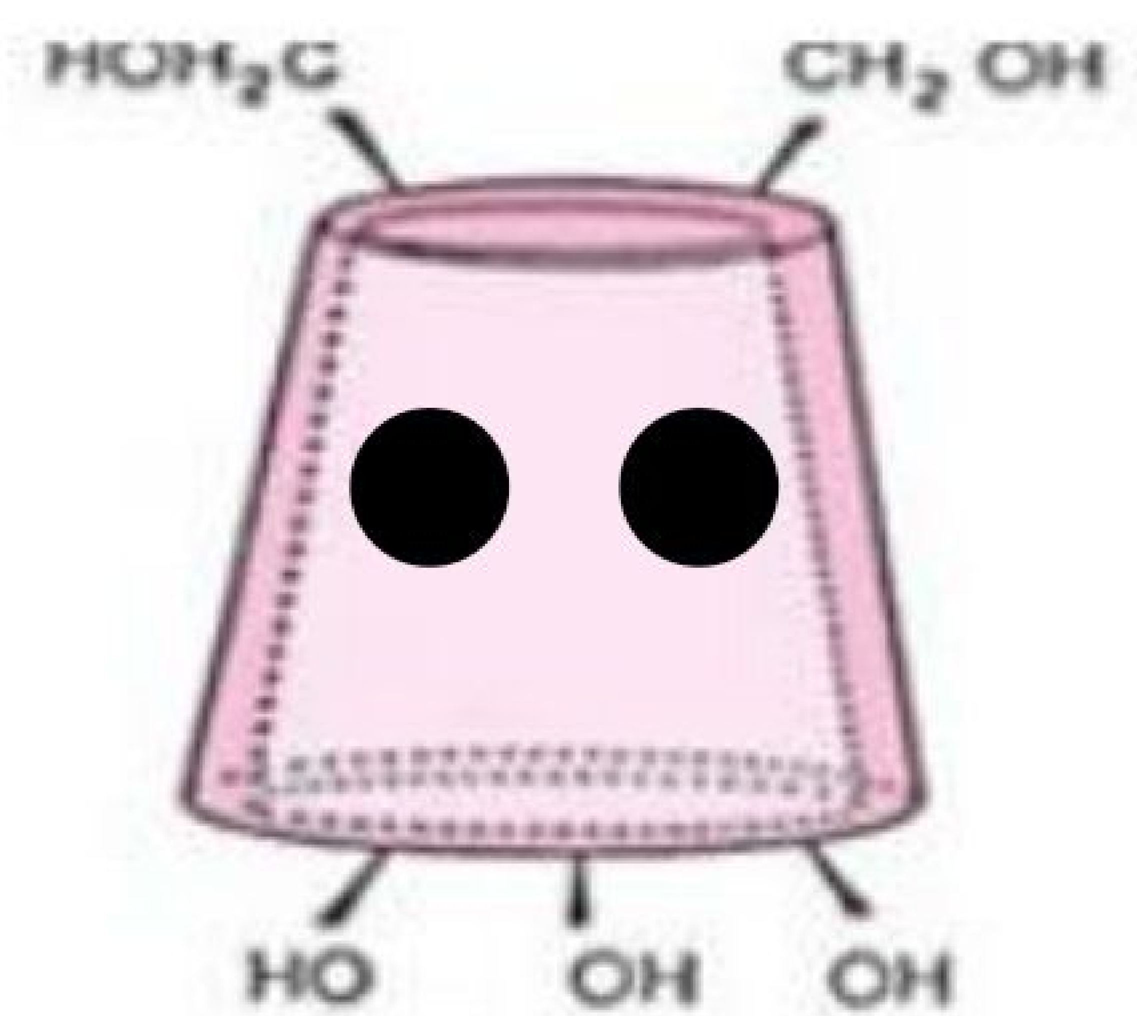
- involve the entrapment of a single guest molecule in the cavity of one host molecule. [DEPTH OF BIOLOGY]
- Most of the host molecules are cyclodextrins.



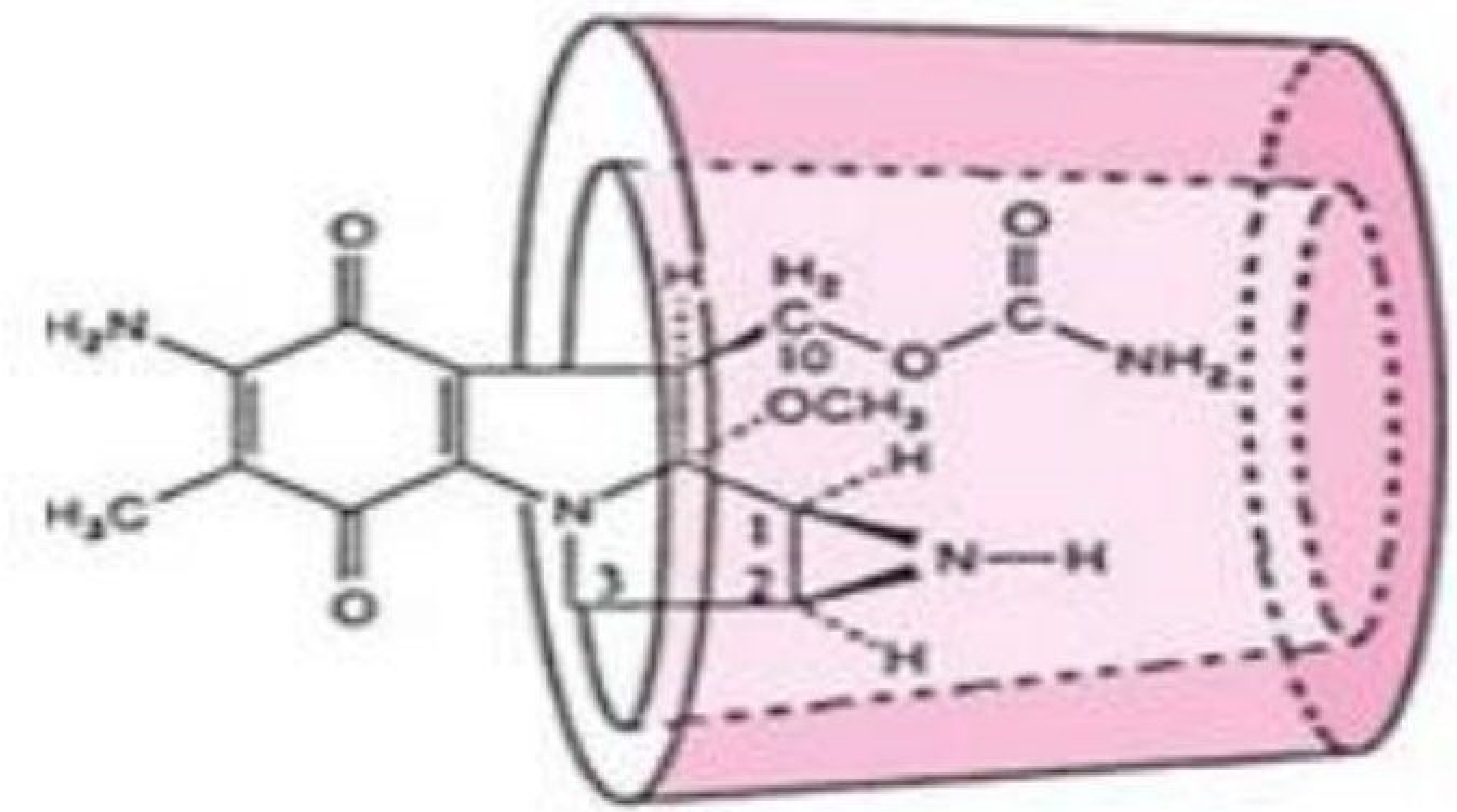
MACROMOLECULAR COMPLEXES

- In this complex more than one guest molecules is entrapped in the cavity of the host molecule
- Eg. Cyclodextrin as host molecules

[DEPTH OF BIOLOGY]



(a)



(b)

METHODS OF ANALYSIS COMPLEXATION

- Method of continuos variation

- Distribution method
- Solubility method
- pH titration method

METHOD OF CONTINUOUS VARIATION:

- When there is no complexation between the species, the value of property is additive. On complexation these properties changes but additive rule do not hold good. The change in the characteristics proves that the complexation has been taken place. [DEPTH OF BIOLOGY]
- Let's take two species A and B whose individual dielectric constant in solid form and Absorbance in solution form were measured. Then two species in both forms were mixed. The dielectric constant and absorbance were determined. [DEPTH OF BIOLOGY]

- The individual values are subtracted with mixed additive values and result was found out. [DEPTH OF BIOLOGY]
- If result is zero then no complexation and if result is not zero then there is complextaion.

$$X + Y \longrightarrow XY$$

<u>DISTRIBUTION METHOD:</u>

- To find partition coefficient [DEPTH OF BIOLOGY]
- K= x in oil/ x in water
- Now, if complex formed then it`s solubiltiy increase in oil/water or due to it, its partition coefficient change
- Let- [DEPTH OF BIOLOGY]

1. ***WHEN COMPLEX IS NOT FORMED: iodine in 30 ml CCl4 & 30 ml WATER***,

For this let partition coeffiicent [K]= a

2. WHEN COMPLEX IS FORMED/ NOT FORMED (check) : iodine in 30 ml CCl4 & 30 ml KI,

For this let partition coeffiicent [K]= b

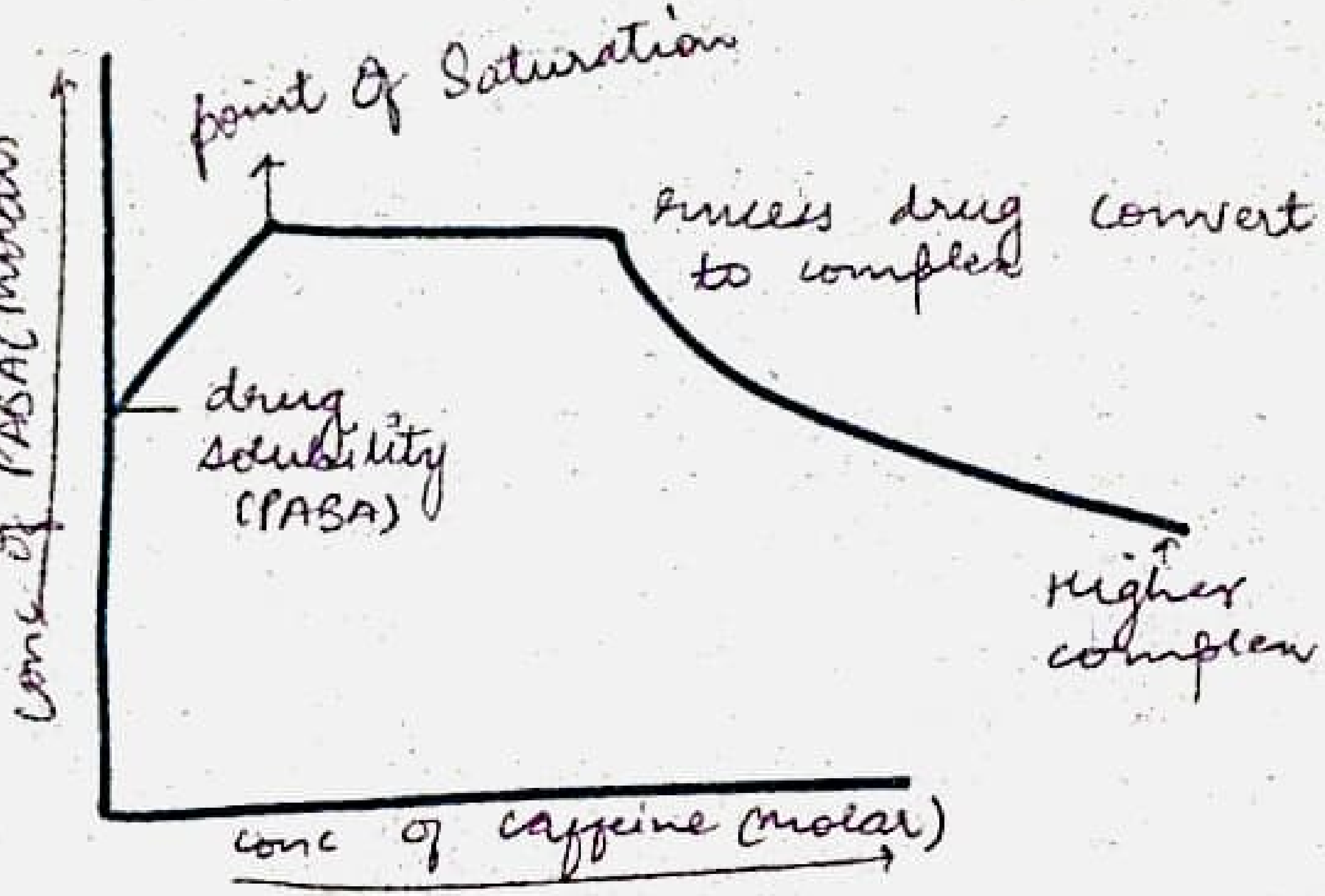
3. IF COMPLEX FORMED IN 2ND CONDITION: then a is not equal to b

4. IF COMPLEX IS NOT FORMED IN 2ND CONDITION: then a =b

[DEPTH OF BIOLOGY]

SOLUBILITY METHOD:

- Principle - When the component in a mixture produce a complex, the solubility of one of the components may be increased or decreased. The change in solubility is a sign of complexation. [DEPTH OF BIOLOGY]
- Example – PABA and Caffeine
  drug complexing agent
- If K value increase: complexation increase
- If K value decrease : complexation decrease



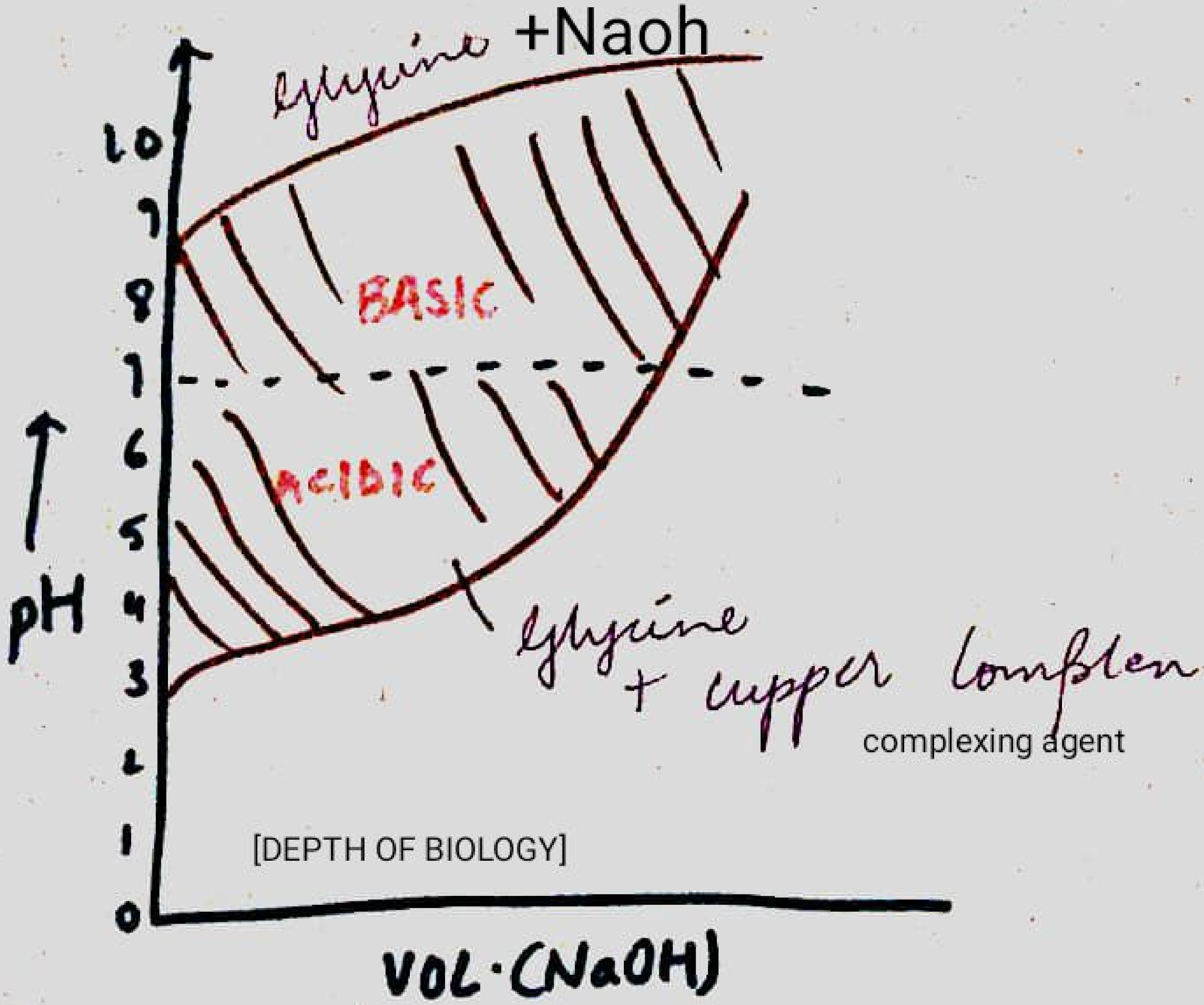
PABA + Caffeine $\longleftrightarrow$ PABA-caffeine complex

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

pH TITRATION METHOD

- pH changes when complexation occur [DEPTH OF BIOLOGY]
- Firstly, check pH before & after complexation
- If there is difference in pH value it means complex is formed & no change means no complexation
- Eg- Let us take 75 ml of glycine solution and it is titrated with strong alkali NaOH solution. The pH was recorded. A graph was drawn between pH and volume of NaOH added.
- In another test, complex solution of glycine and copper salt is titrated. The change in pH with increments of NaOH solution also recorded. A graph was drawn between pH and volume of NaOH added. [DEPTH OF BIOLOGY]

- The two plots are compared and it is seen that the plot of glycine with copper is well below that of the pure glycine, which indicated that complexation is obtained throughout the titration range [DEPTH OF BIOLOGY]


+Naoh
glycine
10
9
8
7
6
5
4
3
2
1
0
BASIC
ACIDIC
pH
glycine
+ copper complex
complexing agent
[DEPTH OF BIOLOGY]
VOL·(NaOH)

PROTEIN BINDING

- ❖ The phenomenon of complex formation of drug with protein is called as protein binding of drug.
- ❖ The interacting molecules are generally the macromolecules such as protein, DNA or adipose. The proteins are particularly responsible for such an interaction.
- ❖ The proteins which involves in this complexation are-

1. Albumin
2. Alpha acid glycoprotein
3. Lipoprotein
4. globulin [DEPTH OF BIOLOGY]

- There are also some drug which bind with protein of blood cell & protein of extra vascular tissue
- But in maximum cases, drug bind with blood protein [DEPTH OF BIOLOGY]

Mechanisms of protein drug binding:

- ***Reversible*** generally involves weak chemical bond such as: 1. Hydrogen bonds 2. Hydrophobic bonds 3. Ionic bonds 4. Van der Waal's forces
- All these forces easily release drug so it becomes free and binds with the receptor [DEPTH OF BIOLOGY]
- Responsible for pharmacological action

- ***Irreversible*** drug binding, though rare, arises as a result of covalent binding and is often a reason for the carcinogenicity or tissue toxicity of the drug.
- Drug cannot be released after binding hence it does not becomes free resulting in no pharmacological action. [DEPTH OF BIOLOGY]

COMPLEXATION AND DRUG ACTION:

- Complexation can alter the pharmacological action of drug by interfering interaction with receptor.
- Protein binding inactivates the drugs because sufficient concentration of drug cannot be build up in the receptor site for action.
- e.g. Naphthoquinone.
- Only free drug participate in drug action.

- The action of drug to remove the toxic effect of metal ion from the human bodies is through the complexation reaction. [DEPTH OF BIOLOGY]
- It has been seen that in some instance complexation can also lead to poor solubility or decreased absorption of drug in the body, which decreases the bioavailability of drug in the blood. Thus the drug action gets altered [DEPTH OF BIOLOGY]

- Examples :

➢ Tetracycline and Calcium – Poor absorbed complex.

➢ Polar drug and complexing agent – Well absorbed lipid soluble complex.

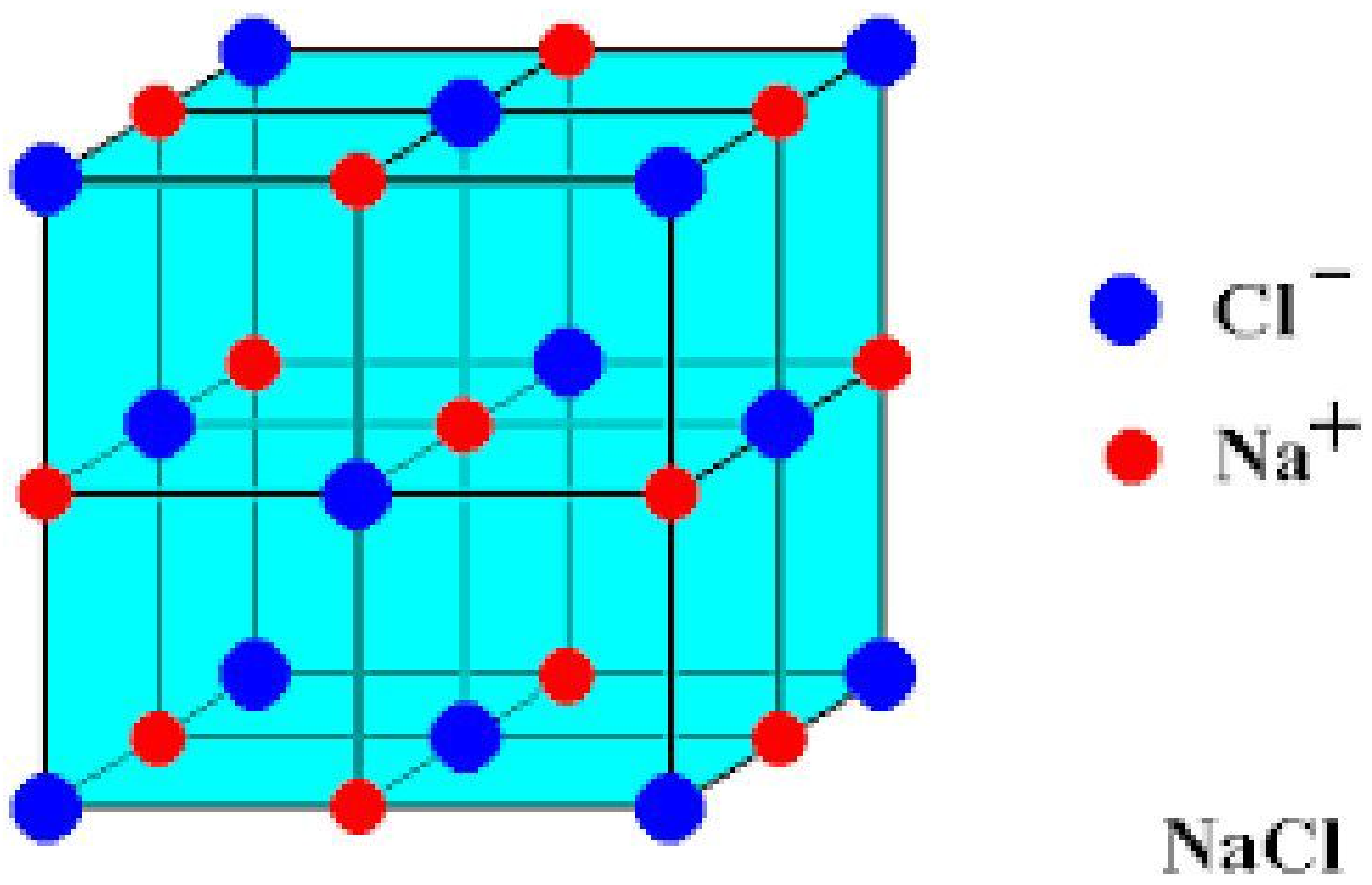
➢ Carboxy methyl cellulose and amphetamine – Poor absorbed complex.

➢ PVP and I2 – Better absorption

CRYSTALLINE STRUCTURE OF COMPLEX

- Any structure of ions, atoms or molecules held together in ordered 3D arrangement.

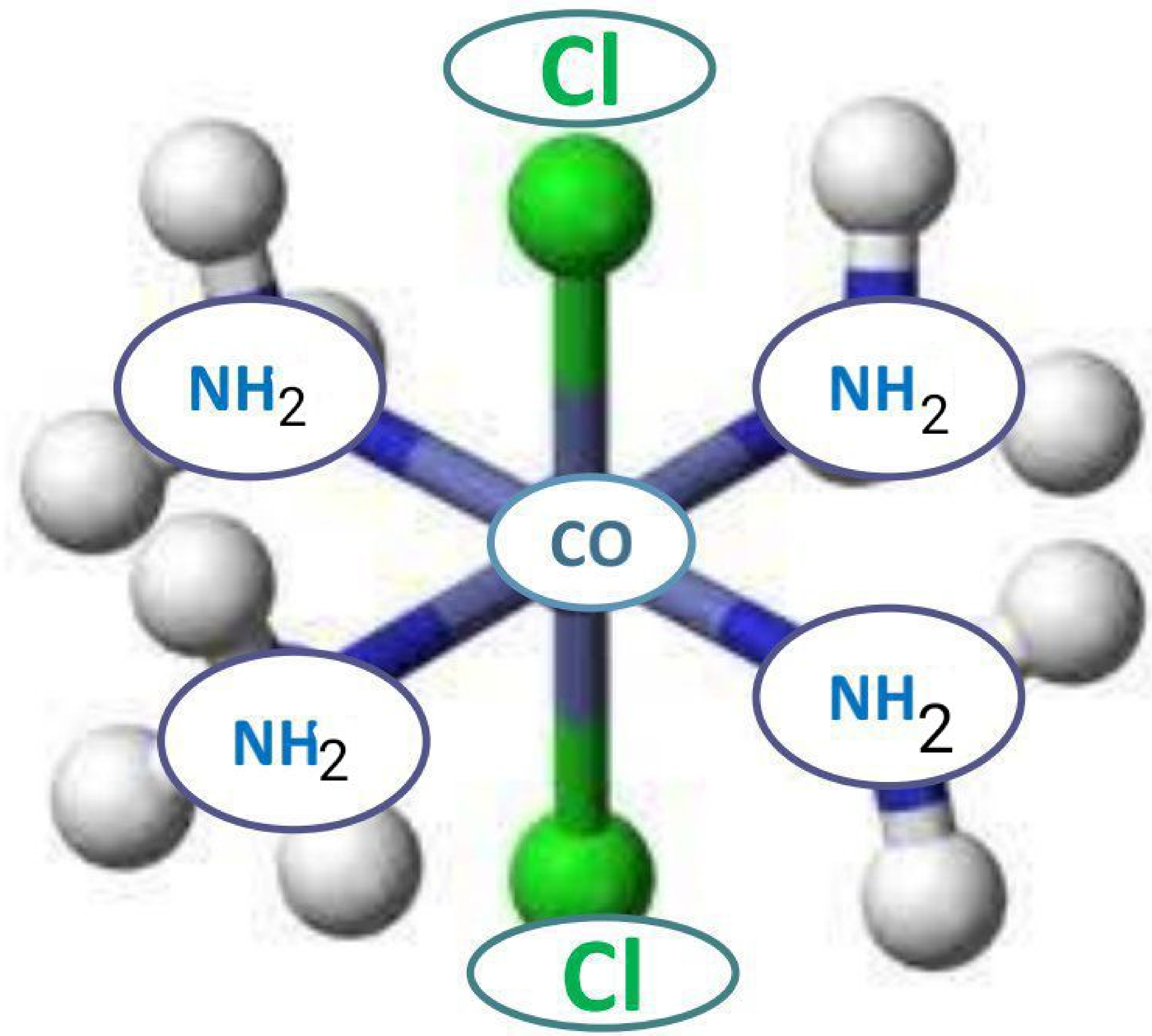
[DEPTH OF BIOLOGY]



[DEPTH OF BIOLOGY]

- Complex compounds cover the rangefrom quite simple inorganic salts to elaborate metal organic hybrid materials

[DEPTH OF BIOLOGY]



THERMODYNAMIC TREATMENT OF STABILITY CONSTANTS COMPLEXES

- The stability constants of the metal complexes are related to thermodynamic properties such as free energy, enthalpy and entropy change

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

where: [DEPTH OF BIOLOGY]

Gibbs free energy= ΔG

Enthalpy= ΔH

Entropy = ΔS

Temperature =T

- ΔG= -ve = rate of complexation increase therefore stability constant Increases
- ΔG = +ve = rate of complexation decrease therefore stability constant decrease [DEPTH OF BIOLOGY]

- Temperature increase= ΔG becomes –ve
- Temperature decrease= ΔG becomes +ve

[DEPTH OF BIOLOGY]

STABILITY CONSTANT- a stability constant is an equilibrium constant for the formation of a complex in solution. [DEPTH OF BIOLOGY]

It is a measure of the strength of the interaction between the reagents that come together to form the complex.

[DEPTH OF BIOLOGY]