Complexation and Protein binding

BP302T

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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 from 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).

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Complexation Interactions

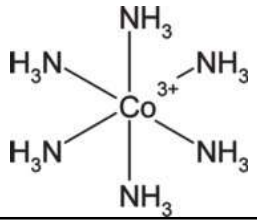
➢➢Either coordinate bonding or one or more of the following interactions:

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***).



5

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)

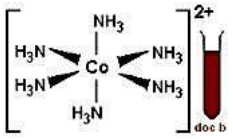
6

Classification of Complexes , Table 10-1

Metal complexes

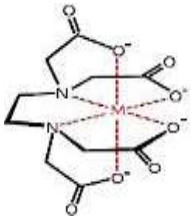
- Inorganic

Octahedral of hexamine cobalt

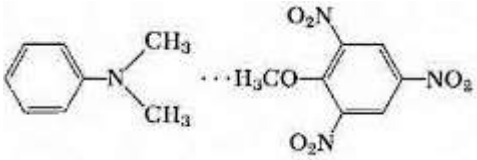


- Chelates

Ca or Mg EDTA

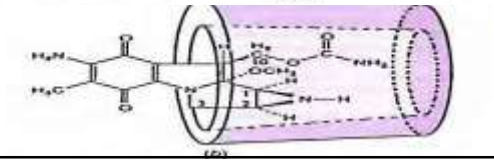


Organic complexes



Dimethyl aniline + Trinitro anisole

Inclusion complex



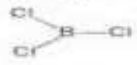
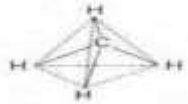
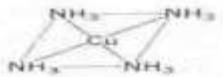
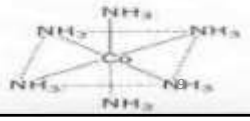
Hybridization

Shell	1	2		3			4			
Orbital subshell	s	s	p	s	p	d	s	p	d	f
No of electron	2	2	6	2	6	10	2	6	10	14

- C^6 hybridization is sp^3
- N^7 hybridization is sp^3

8

Bond types, Table 10-2

Coordination Number	Orbital Configuration	Bond Geometry	Formula	Structure
2	sp	Linear	O_2	O—O
3	sp^2	Trigonal	BCl_3	
4	sp^3	Tetrahedral	CH_4	
4	dsp^2	Square planar	$Cu(NH_3)_4^{2+}$	
5	dsp^3	Bipyramidal	PF_5	
6	d^2sp^3	Octahedral	$Co(NH_3)_6^{3+}$	

Molecular Structures

Linear- O_2

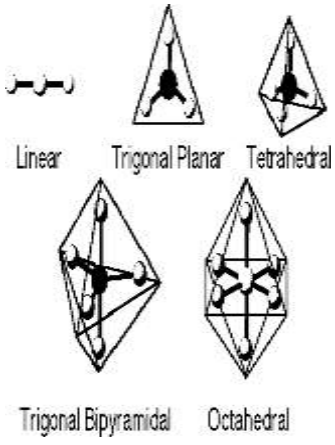
Trigonal- BCl_3

Tetrahedral -CH_4

Square planar -$Cu(NH_3)_4^{+2}$

Bipyramidal -PF_5

Octahedral -$Co(NH_3)_6^{+3}$



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:

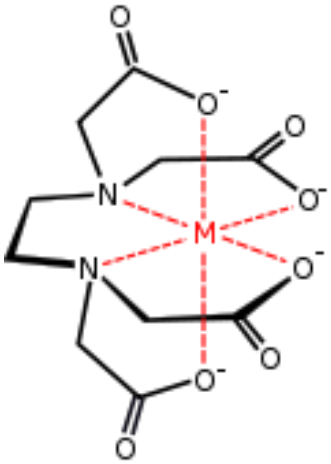
➢➢Should be multi-dentate

➢➢Should have specific steric orientation

➢➢Eg. B12, hemoglobin, alcohol dehydrogenase, chlorophyll, and Albumin

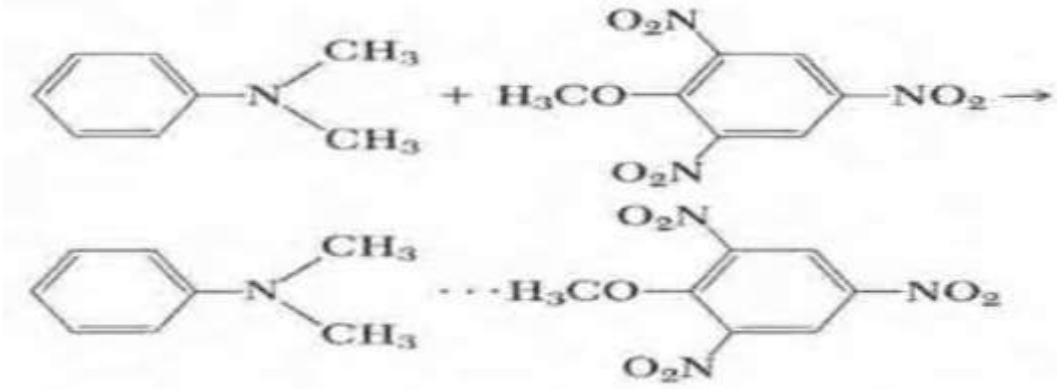
EDTA

- 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



13

Drug complexes

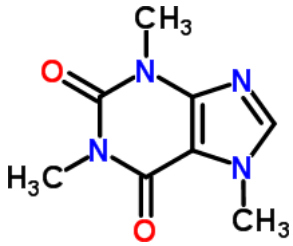
➢➢Complexation of caffeine (Caf)

-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

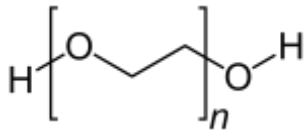
-These interactions lead to change solubility, absorption and bioavailability.

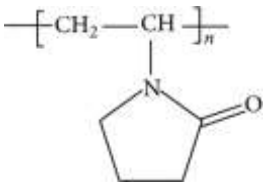


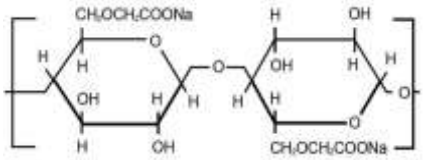
CAFFEINE

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.
  4. Changing dissolution rate, absorption, and bioavailability.

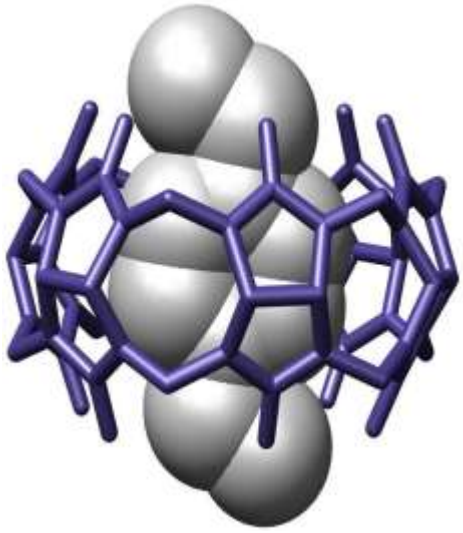






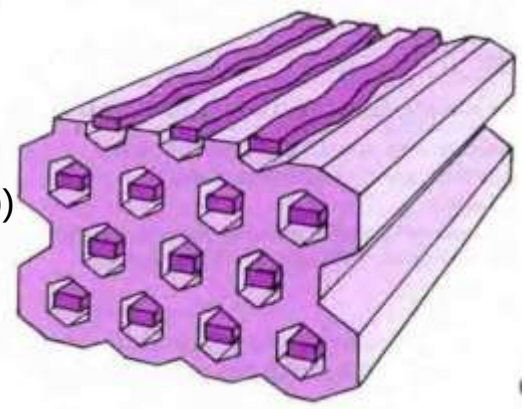
Inclusion/Occlusion compounds

- A class of addition compounds where one of the constituent of the complex is trapped in the 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.

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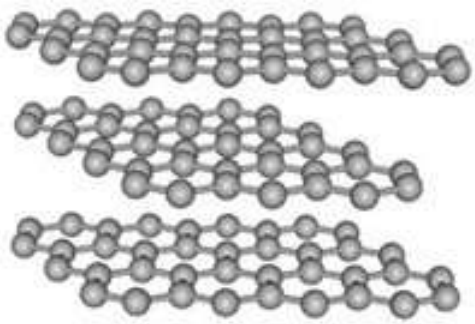
Inclusion/Occlusion compounds

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



Graphite

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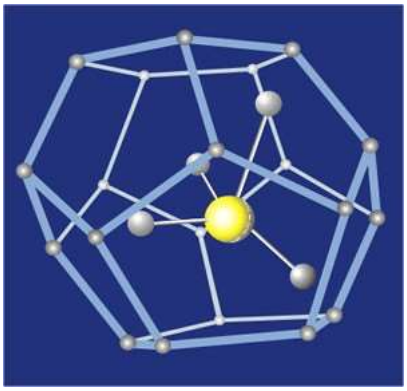
Inclusion/Occlusion compounds

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.



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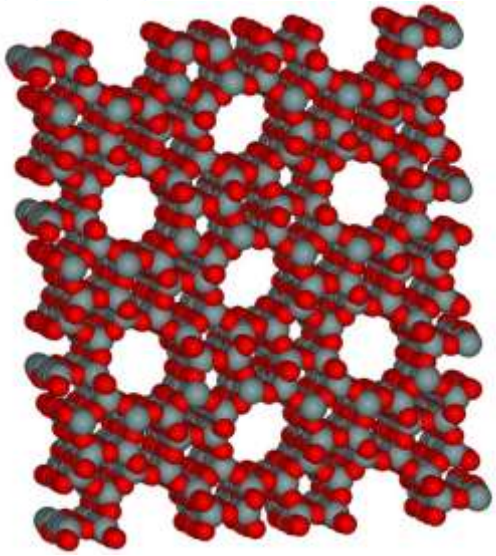
Inclusion/Occlusion compounds

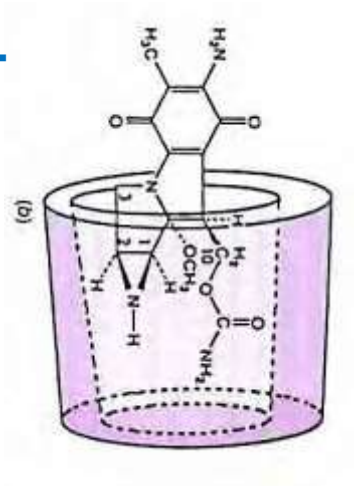
Molecular sieves–

- 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.

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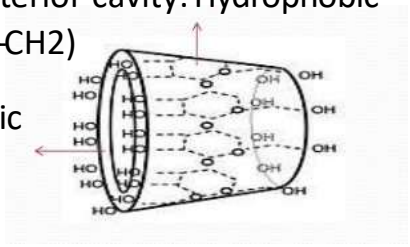
Inclusion/Occlusion compounds

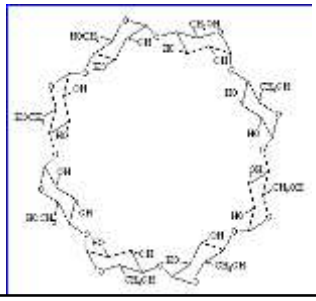
Cyclodextrin–

Interior cavity: Hydrophobic (-CH2)



➢➢Interaction:

Entrance : Hydrophilic (-OH)



➢➢Types:

- Alpha 6 molecules
- Beta 7 molecules
- Gamma 8 molecules

Applications of CD

Property	Drug Examples
↑ aqueous solubility	Prostaglandins;; NSAIDs
↑ stability	Aspirin, atropine, digoxin
↑ absorption & bioavailability	Phenytoin, digoxin
↑ taste and odor	Prostaglandins, NSAIDs
Change from liq. To solid	Nitroglycerin, methyl salicylat
↓ volatility	Menthol, salicylic acid
↓ stomach irritation	NSAIDs
↓ incompatibilities	Vitamins

23

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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

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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.

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Method of Analysis

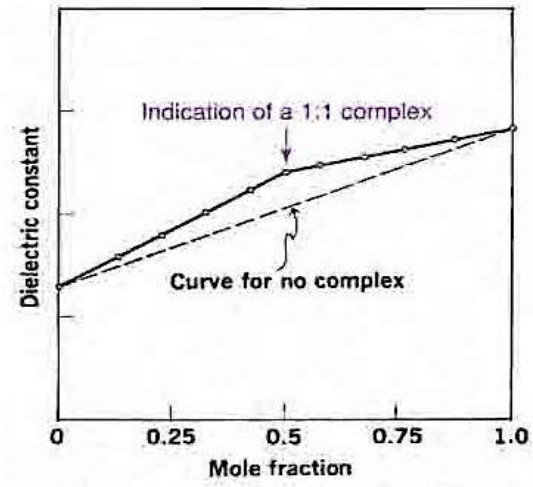
1. Continuous Variation

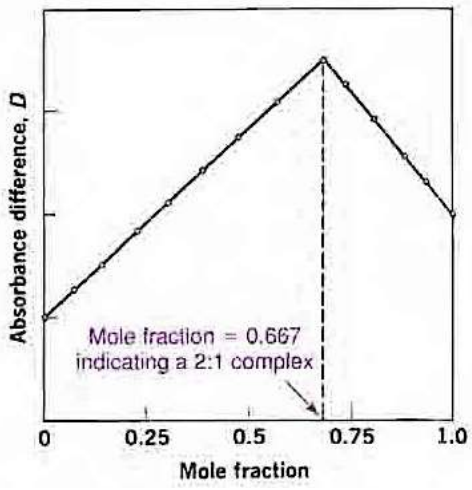
- Assume a mixture of A and B
- The physical property of A =5
  B =100

Mole fraction of B	A (5)	B (100)	Property result
0	(1*5)=5	(0*100)=0	5
0.2	(0.8*5)=4	(0.2*100)=20	24
0.4	(0.6*5)=3	(0.4*100)=40	43
0.6	(0.4*5)=2	(0.6*100)=60	62
0.8	(0.2*5)=1	(0.8*100)=80	81
1	(0*5)=0	(1*100)=100	100

Method of Analysis

1. Continuous Variation





Method of Analysis

2. pH Titration

- Mostreliable method
- Complexation should be affected by change in pH.
- E.g.: Glycine with Cupper

$$Cu^{2+} 2NH_3^+ CH_2COO^- = Cu(NH_2CH_2COO)_2 + 2H^+$$

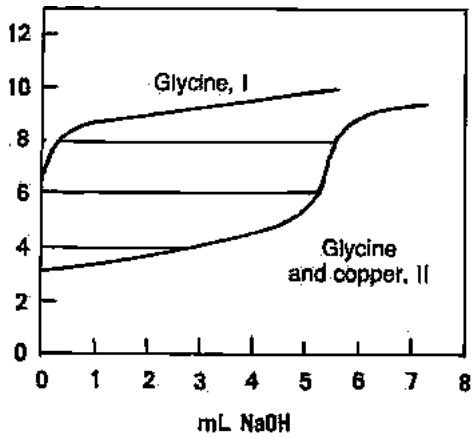


Fig. 10–9. Titration of glycine and of glycine in the presence of cupric ions. The difference in pH for a given quantity of base added indicates the occurrence of a complex.

Method of Analysis

3. Distribution method

- Measure the stability constant by distribution of the complex bet 2 immiscible solvent.
- E.g.: Iodine and Potassium Iodide in water and CS_2

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

- Example 10-2 , Home work

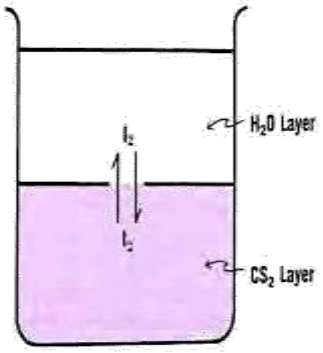


Fig. 10–11. The distribution of iodine between water and carbon disulfide.

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Method of Analysis

4. Solubility method

- Measure the solubility by shake flask method.
- E.g.: Para amino benzoic acid (PABA) + Caffeine.
- Cases:
  - A
  - B
  - BC
  - After C

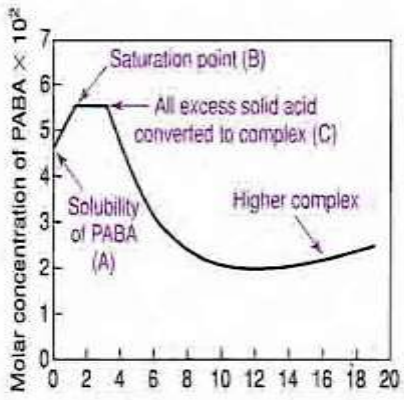
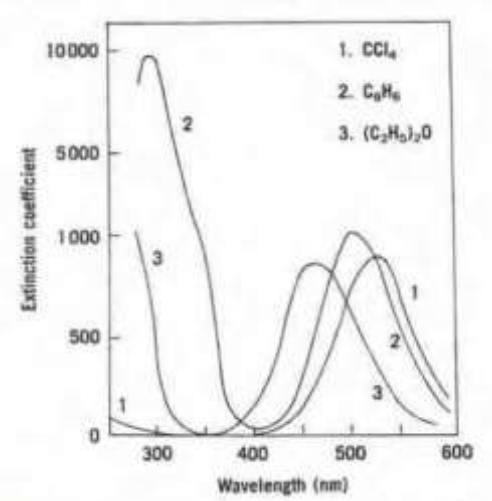


Fig. 10–12. The solubility of *para*-aminobenzoic acid (PABA) in the presence of caffeine. (From T. Higuchi and J. L. Lack, J. Am. Pharm. Assoc. Sci. Ed. **43**, 525, 1954.)

Method of Analysis

5. Spectroscopy

- Absorption spectroscopy in the visible and ultraviolet regions.
- E.g.: I_2 in:
  - CCl_4 = one peak 520nm (**Violet**)
  - Benzene = 475nm & 300nm (**Red**)
  - Diethyl ether =450nm & 300nm (**Red**)
- I_2 is electron acceptor;; in CCl_4 no complex (not a donor). The other 2 solvents act as electron releasing agents and formed charged transfer complex with I_2.



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Method of Analysis

Other methods :

- NMR
- IR
- X-ray diffraction
- Electron diffraction

Thermodynamic and Complexation

- If ΔG°

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

  - Negative = Stable complex
  - Positive = Unstable and depend on the situation.

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

Type of Interaction	Sign on ΔH°	Sign on ΔS°	$-\Delta G^\circ$ is Favored By
1. Electrostatic	~0	+	$+\Delta S^\circ$
2. Hydrophobic	+	+	large $+\Delta S^\circ$
3. Chelation (polydentate ligand)	−	+	$+\Delta S^\circ$ and/or $-\Delta H^\circ$
4. Donor—acceptor (hydrogen bonding and chelation [monodentate ligand])	−	−	$-\Delta H^\circ$

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Thanks for your attention