



# 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

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## Importance of Complexation

- Complexation leads to changing the physical and chemical properties
1. **Solubility** (e.g. theophylline complexation with ethylenediamine to form 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).



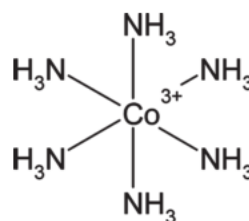
## Complexation Interactions

- 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**).



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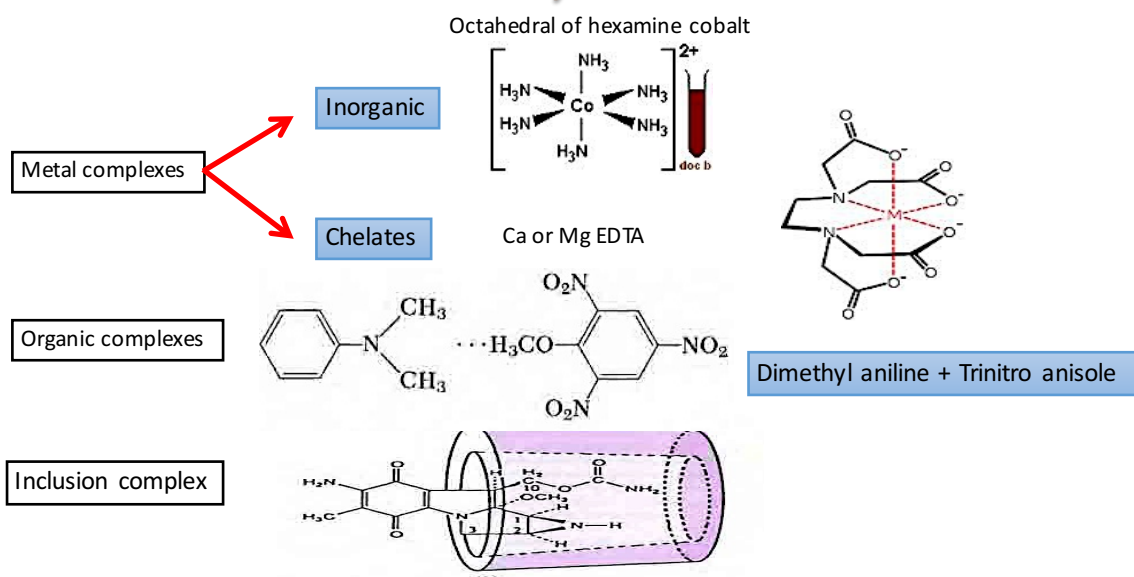
## Coordination complex

- **Acceptor:**
  - Central atom
  - Metallic ion
  - Organic gr with free orbital (Lewis acid)
- **Donor:**
  - Ligand gr
  - Non metallic atom
  - Ions or neutral molecules (Lewis base)

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## Classification of Complexes , Table 10-1



## 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<sup>6</sup> hybridization is sp<sup>3</sup>
- N<sup>7</sup> hybridization is sp<sup>3</sup>



## Bond types, Table 10-2

Coordination Number	Orbital Configuration	Bond Geometry	Formula	Structure
2	sp	Linear	O <sub>2</sub>	O—O
3	sp <sup>2</sup>	Trigonal	BCl <sub>3</sub>	
4	sp <sup>3</sup>	Tetrahedral	CH <sub>4</sub>	
4	dsp <sup>2</sup>	Square planar	Cu(NH <sub>3</sub> ) <sub>4</sub> <sup>2+</sup>	
5	dsp <sup>3</sup>	Bipyramidal	PF <sub>5</sub>	
6	d <sup>2</sup> sp <sup>3</sup>	Octahedral	Co(NH <sub>3</sub> ) <sub>6</sub> <sup>3+</sup>	



## Molecular Structures

Linear- O<sub>2</sub>

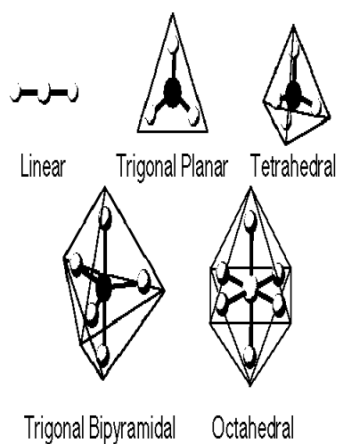
Trigonal- BCl<sub>3</sub>

Tetrahedral - CH<sub>4</sub>

Square planar -Cu(NH<sub>3</sub>)<sub>4</sub><sup>+2</sup>

Bipyramidal - PF<sub>5</sub>

Octahedral -Co(NH<sub>3</sub>)<sub>6</sub><sup>+3</sup>





## Metal complexes

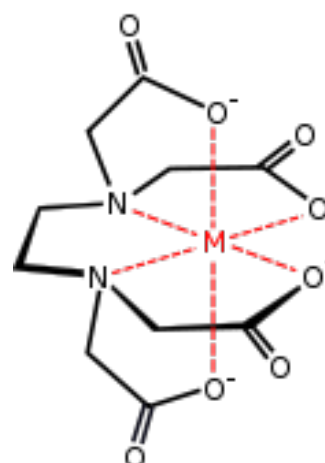
- The central part is metal
- Sub classified according to **ligand type** into:
  - a) Inorganic complexes :
    - E.g.  $\text{Co}(\text{NH}_3)_6^{+3}$  : The coordination number is ----- & geometry is -----
  - b) Chelates:
    - Should be multi-dentate
    - Should have specific steric orientation
    - E.g. B12, hemoglobin, alcohol dehydrogenase, chlorophyll, and Albumin

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## EDTA

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

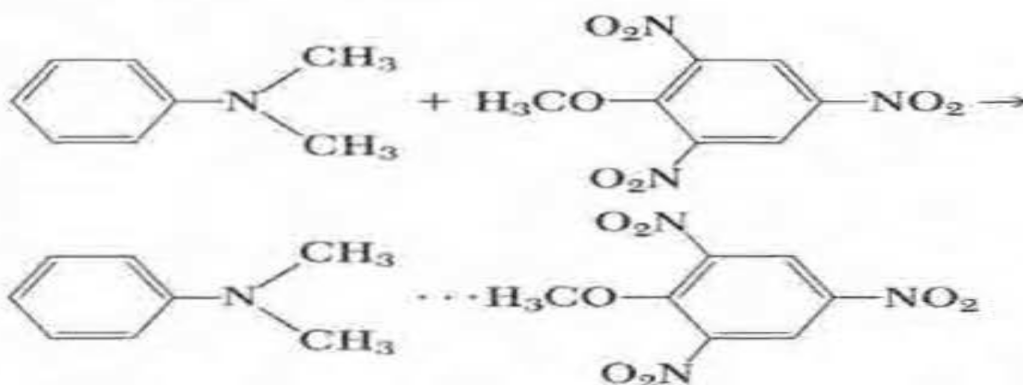


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## Organic complexes

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



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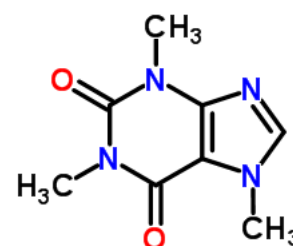
## Drug complexes

### ➤ 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.

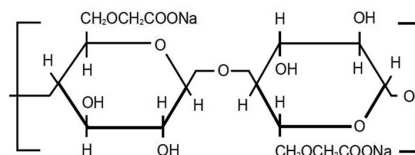
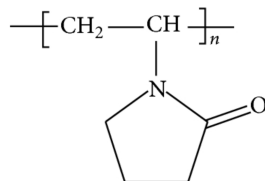
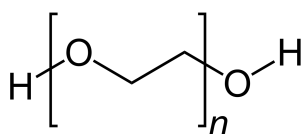


**CAFFEINE**



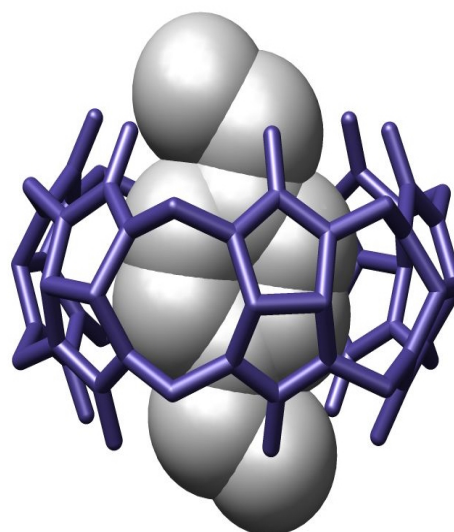
## Polymer complexes

- 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.



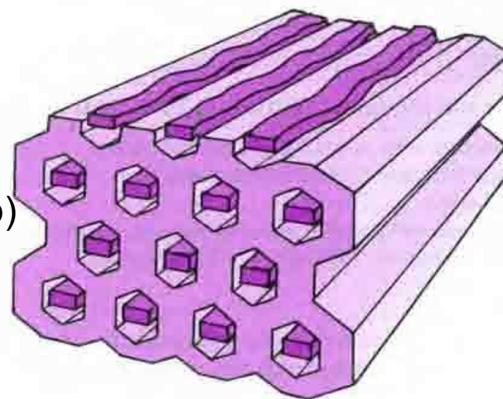




## Inclusion/Occlusion compounds

### Channel Lattice type –

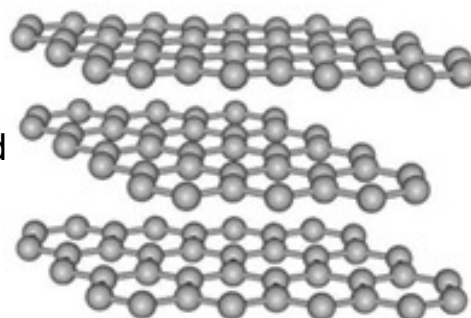
- The molecular structure within the crystal arrange to form channels that can fit (trap) molecules inside.
- It is useful techniques in compound separation.
- examples are deoxycholic acid and urea.



## 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



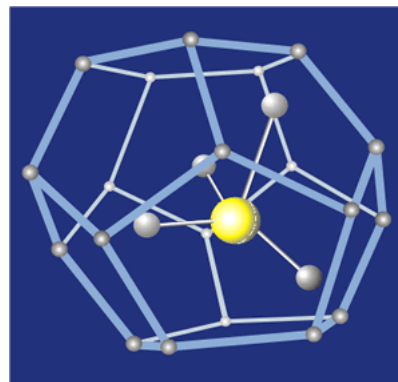
Graphite



## Inclusion/Occlusion compounds

### Clathrates –

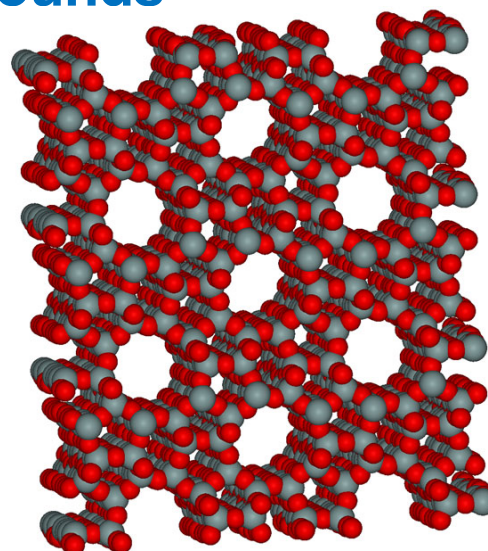
- Crystallize in a cage-like lattice
- Depends on molecular size of the entrapped component.
- Example: Hydroquinone crystals that traps methanol, CO<sub>2</sub> and HCl but not smaller and larger molecules.



## 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, dextrans and silica gels.

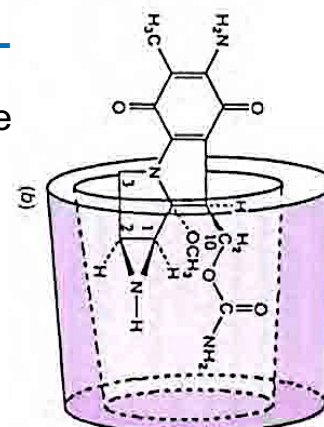




## Inclusion/Occlusion compounds

### 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.



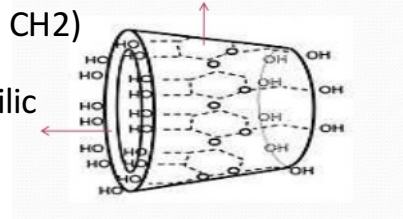
## Inclusion/Occlusion compounds

### Cyclodextrin–

- Interaction:

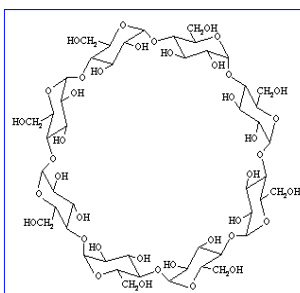
Entrance : Hydrophilic  
(- OH)

Interior cavity: Hydrophobic  
(- CH<sub>2</sub>)



- Types:

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





## Applications of CD

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

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## Method of Analysis

### a) Stoichiometric ratio

➤ Determination of Donor-Acceptor ratio:  $A_n B_m C_x$

### 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.



## Method of Analysis

### 1. Continuous Variation

- Assume a mixture of A and B

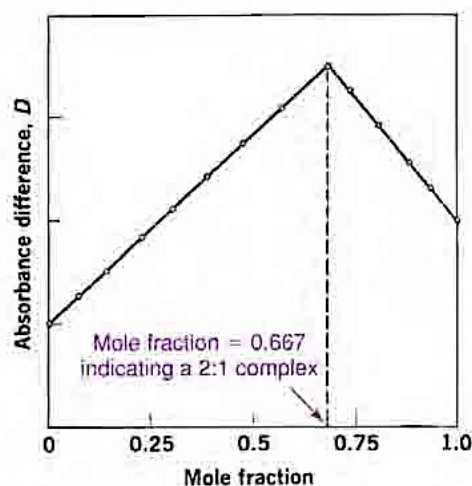
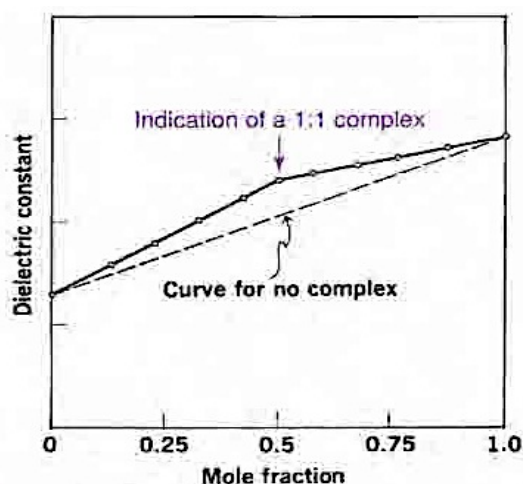
- The physical property of A =5  
B =100

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



## Method of Analysis

### 1. Continuous Variation



## Method of Analysis

### 2. pH Titration

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

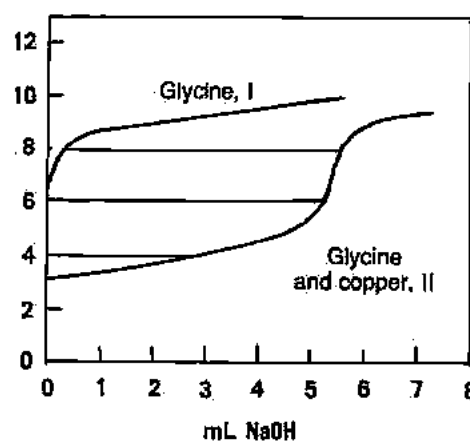
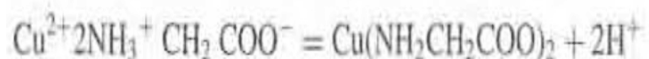


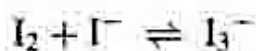
Fig. 10-9. Titration of glycine and of glycine in the presence of cupric ions. The difference in pH for a given quantity of base added indicates the occurrence of a complex.



## 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<sub>2</sub>



- Example 10-2 , Home work

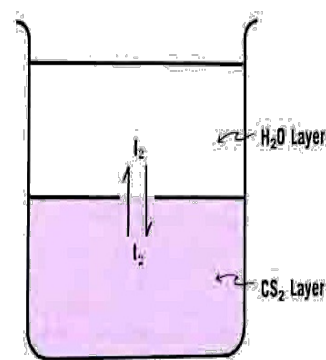


Fig. 10-11. The distribution of iodine between water and carbon disulfide.



## 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

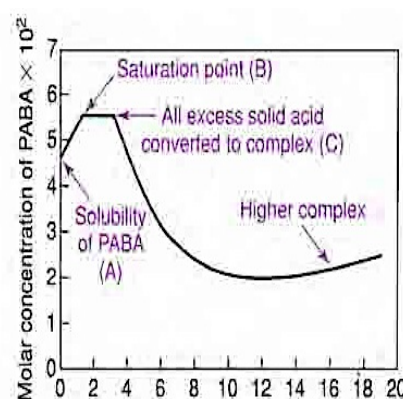


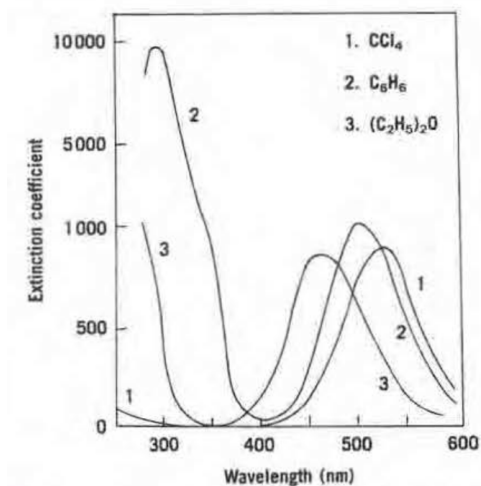
Fig. 10-12. The solubility of *para*-aminobenzoic acid (PABA) in the presence of caffeine. (From T. Higuchi and J. L. Lack, J. Am. Pharm. Assoc. Sci. Ed. 43, 525, 1954.)



## 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  $I_2$ .



## 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**

Type of Interaction	Sign on		$-\Delta G^\circ$ is Favored By
	$\Delta H^\circ$	$\Delta S^\circ$	
1. Electrostatic	$\sim 0$	+	$+\Delta S^\circ$
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])	–	–	$-\Delta H^\circ$



Thanks for your attention

