Chelation and Possible Application in Medicine

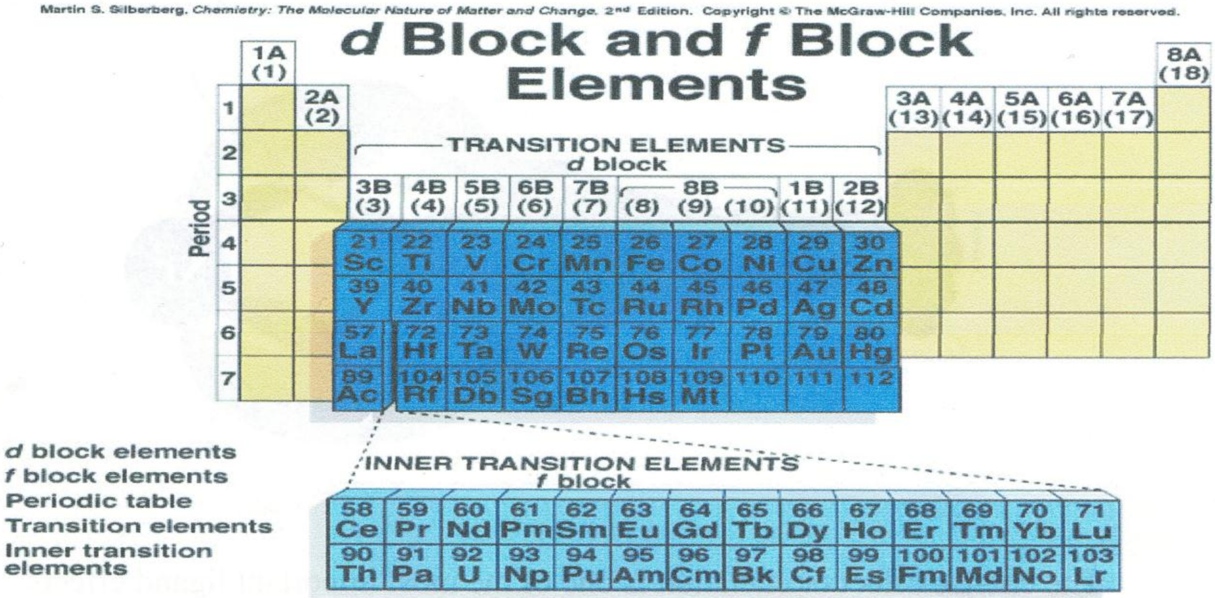
Lec.19

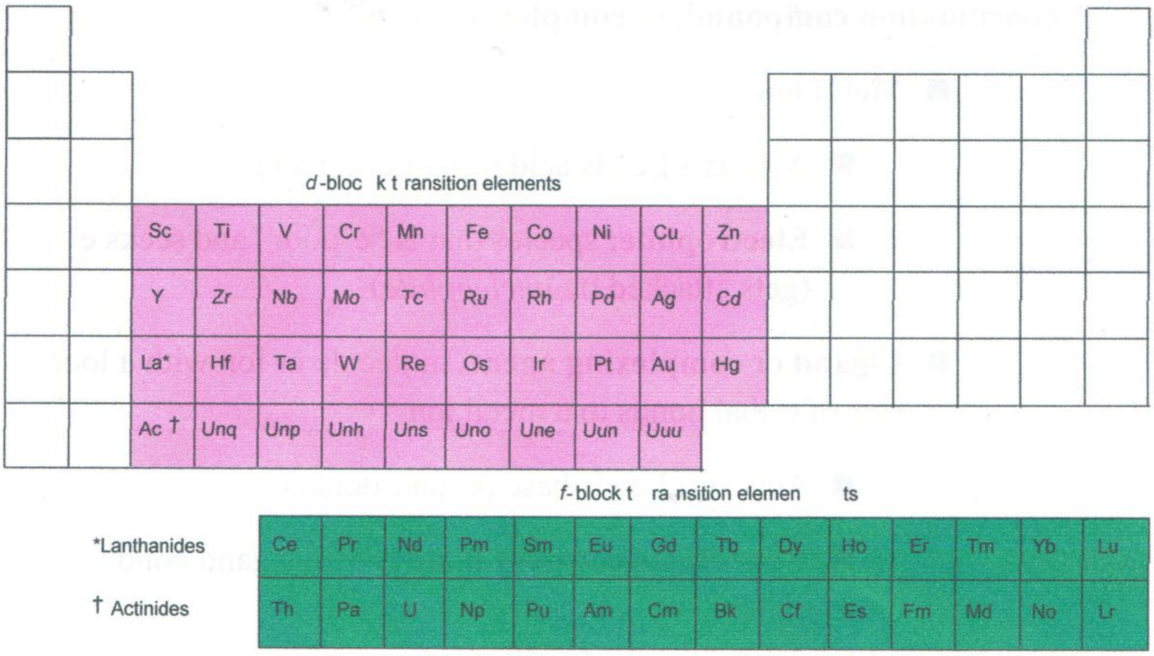
By: Dr. Tamathir Abbas 23/1/2018

Transition Metals

Similarities within a given period and within a given group.

Last electrons added are inner electrons (*d*'s, *f*'s).





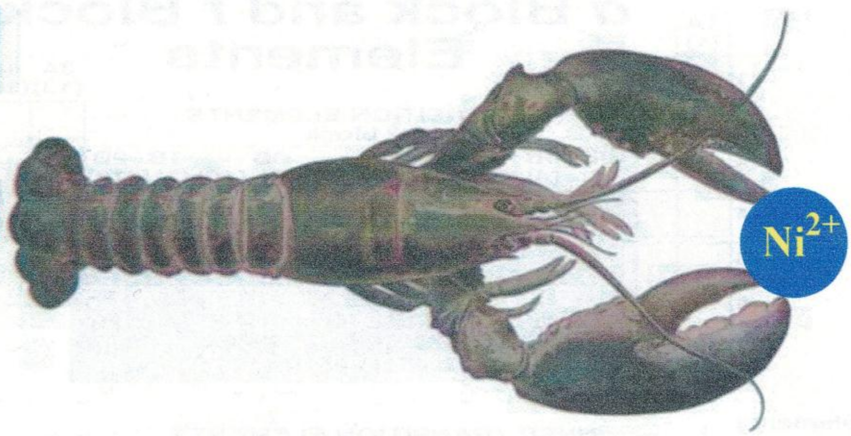
Structure of Complexes

Complex: species in which a central metal ion (usually a transition metal) is bonded to a group of surrounding molecules or ions

Coordination compound: compound that contains a complex ion or ions.

Coordination Equilibria & Chelate effect

"The adjective chelate, derived from the great claw or chela **(chely - Greek)** of the **lobster**, is suggested for the groups which function as two units and fasten to the central atom so as to produce heterocyclic rings."



The chelate effect or chelation is one of the most important ligand effects in transition metal coordination chemistry.

A **coordination compound**, or **complex**, consists of:

- **Metal ion**
  - Acts as a Lewis acid (e^- pair acceptor)
  - **Electrophile:** species that is "e^- poor" and seeks e^- (gets attacked by *nucleophile*)
- **Ligand** or **complexing agent:** molecule or ion with a lone pair of e^- that bonds to a metal ion
  - Acts as a Lewis base (e- pair donor)
  - **Coordinate covalent bond:** metal-ligand bond

- **Nucleophile:** species that is "e$^-$ rich" and seeks an e$^-$ poor area of a molecule (seeks an *electrophile*)

Lewis Structures of common ligands

NH_3 CN^-

$S_2O_3^{2-}$ SCN^-

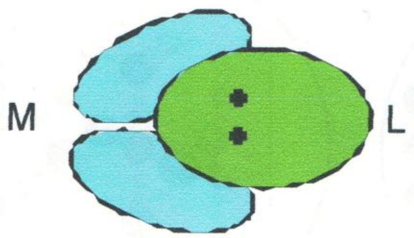
H_2O (not always included in formula, however)

Complexation reactions

- Ligand usually added "in excess" on AP
- Usually result in color changes (colors generally originate from e$^-$ transitions in a partially filled d shell)
- Change properties of metal ion
  - Thermodynamic (DH, DS, DG)
  - Electrochemical (E°)

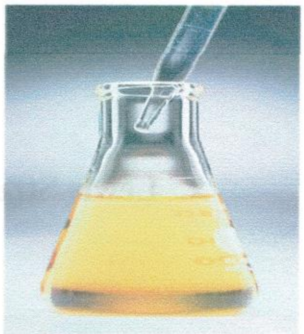
What is Coordination?

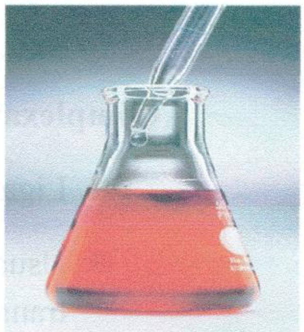
- When an orbital from a ligand with lone pairs in it overlaps with an empty orbital from a metal



Sometimes called a coordinate covalent bond

So ligands *must* have lone pairs of electrons.

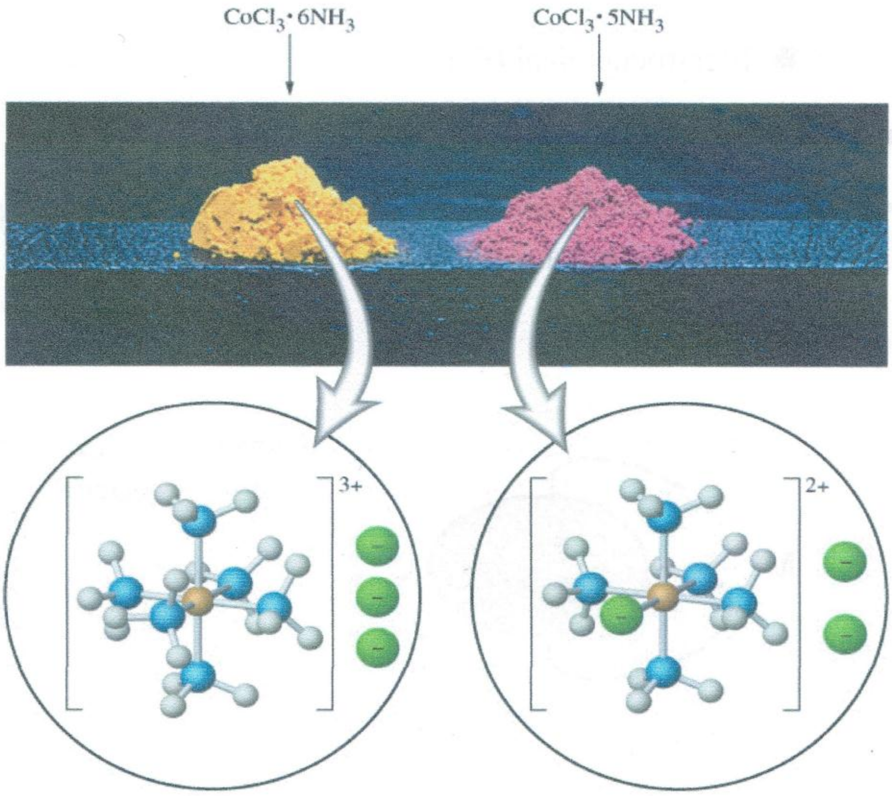




Metal-Ligand Bond

The metal's coordination ligands and geometry can greatly alter its properties, such as color, or ease of oxidation.

- The golden-orange compound is $CoCl_3.6NH_3$
- while the purple compound only has 5 ammonia molecules in the coordinated compound. As shown in the ball-and-stick model, the chlorides serve as counter ions to the cobalt/ammonia coordination complex in the orange compound, while one of the ammonia molecules is replaced by Cl in the purple compound. In both cases, the coordination geometry is octahedral around Co.



Oxidation States of Manganese

Table 1 Some Oxidation States of Manganese

Oxidation state*	Mn(II)	Mn(III)	Mn(IV)	Mn(VI)	Mn(VII)
Example	Mn^{2+}	Mn_2O_3	MnO_2	MnO_4^{2-}	Mno_4^{-}
Ion configuration	d^5	d^4	d^3	d^1	d^0
Oxide acidity	BASIC				ACIDIC

*Most common states in boldface.

© McGraw-Hill Higher Education/Stephen Frisch, photographer

Theories explaining coordination chemistry of transition metals

1- Werner Coordination Theory

2- 18 electron rule

3- Valence Bond Theory

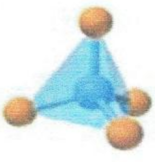
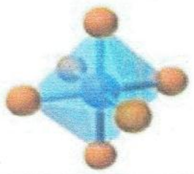
4- Crystal field theory

5- Molecular orbital approach

Common Geometries of Complexes

Complex Ions: Coordination Numbers, Shapes

Table 2 Coordination Numbers and Shapes of Some Complex Ions

Coordination Number	Shape		Examples
2	Linear		$[CuCl_2]^-$, $[Ag(NH_3)_2]^+$, $[AuCl_2]^-$
4	Square planar		$[Ni(CN)_4]^{2-}$, $[PdCl_4]^{2-}$, $[Pt(NH_3)_4]^{2+}$, $[Cu(NH_3)_4]^{2+}$
4	Tetrahedral		$[Cu(CN)_4]^{3-}$, $[Zn(NH_3)_4]^{2+}$, $[CdCl_4]^{2-}$, $[MnCl_4]^{2-}$
6	Octahedral		$[Ti(H_2O)_6]^{3+}$, $[V(CN)_6]^{4-}$, $[Cr(NH_3)_4CL_2]^+$, $[Mn(H_2O)_6]^{2+}$, $[FeCl_6]^{3-}$, $[Co(en)_3]^{3+}$

Complex charge = sum of charges on the metal and the ligands

$[Fe(CN)_6]^{3-}$

+3

6(-1)

Neutral charge of coordination compound = sum of charges on metal, ligands, and counterbalancing ions

$[Co(NH_3)_6]Cl_2$

+2

6(0)

2(-1)

◆ Ligands

- classified according to the number of donor atoms
- Examples
  - monodentate = 1
  - bidentate = 2
  - tetradentate = 4
  - hexadentate = 6
  - polydentate = 2 or more donor atoms

chelating agents

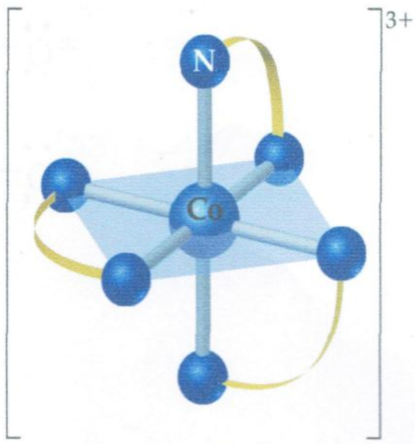
◆ Monodentate

- Examples:
  - H_2O, CN^-, NH_3, NO_2^-, SCN^-, OH^-, X^- (halides), CO, O^{2-}
- Example Complexes
  - $[Co(NH_3)_6]^{3+}$
  - $[Fe(SCN)_6]^{3-}$

- Bidentate
    - Examples
        - oxalate ion = $C_2O_4^{2-}$
        - ethylenediamine (en) = $NH_2CH_2CH_2NH_2$
        - ortho-phenanthroline (o-phen)
    - Example Complexes
        - $[Co(en)_3]^{3+}$
        - $[Cr(C_2O_4)_3]^{3-}$
        - $[Fe(NH_3)_4(o\text{-}phen)]^{3+}$
- Hexadentate
    - ethylenediaminetetraacetate (EDTA) = $(O_2CCH_2)_2N(CH_2)_2N(CH_2CO_2)_2^{4-}$
    - Example Complexes
        - $[Fe(EDTA)]^{-1}$
        - $[Co(EDTA)]^{-1}$

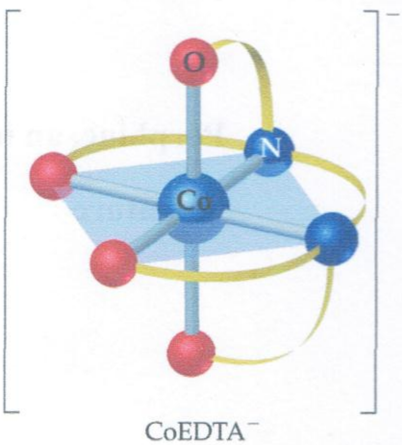
Polydentate Ligands

- Some ligands have two or more donor atoms.
- These are called polydentate ligands or chelating agents.
- In ethylenediamine, $NH_2CH_2CH_2NH_2$, represented here as en, each N is a donor atom.
- Therefore, en is bidentate.



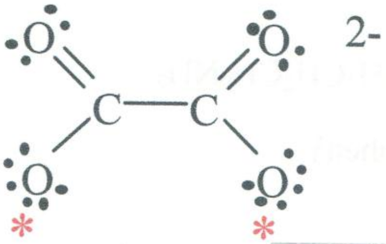
$[Co(en)_3]^{3+}$

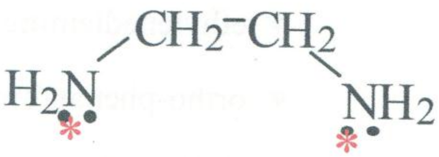
Ethylenediaminetetraacetate, mercifully abbreviated EDTA, has six donor atoms.



$CoEDTA^-$

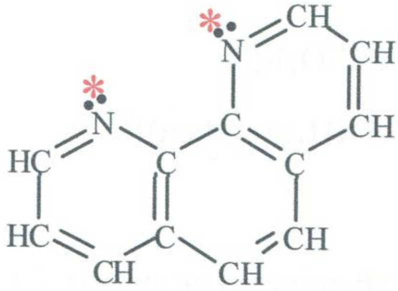
Ligands



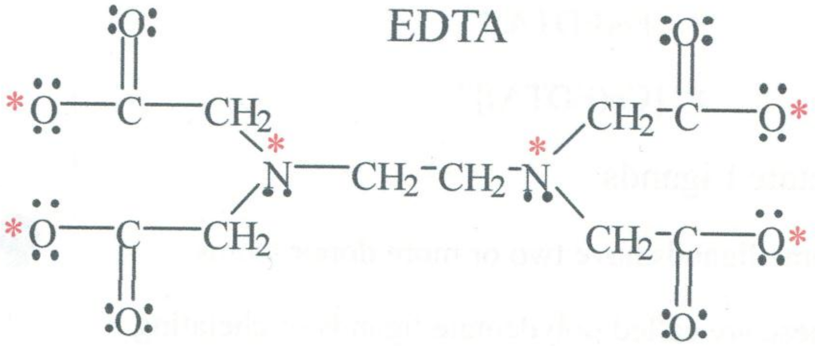


ortho-phenanthroline

Donor Atoms

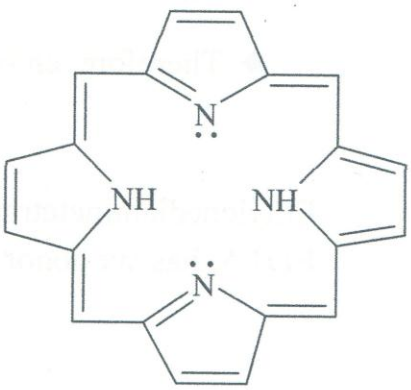


EDTA

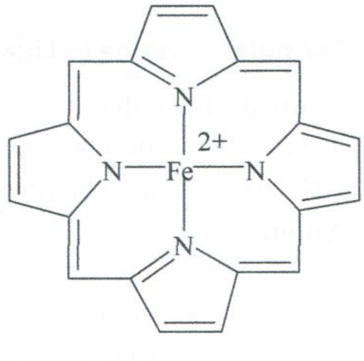


Donor Atoms

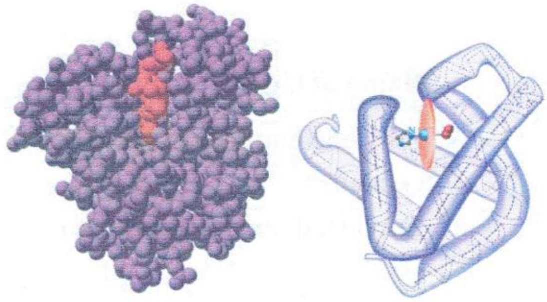
Porphine, an important chelating agent found in nature



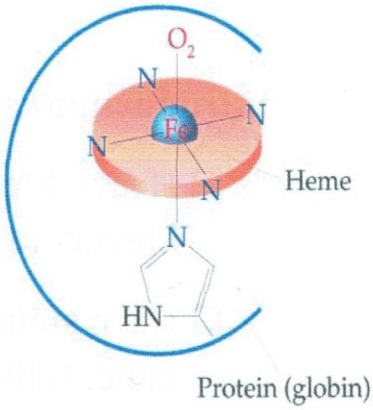
Metalloporphyrin

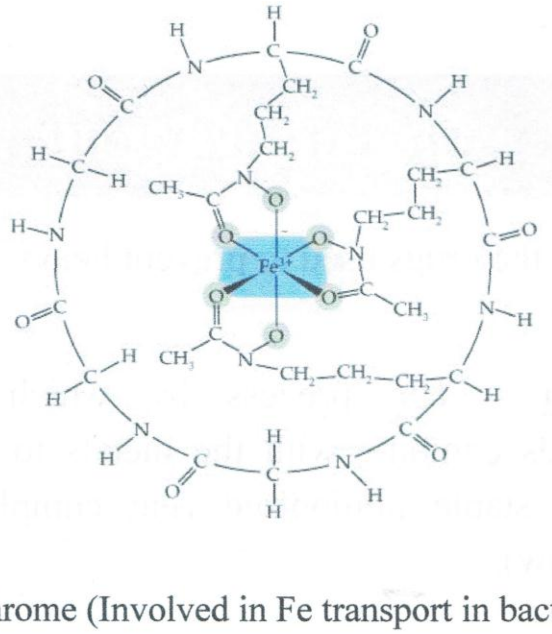


Myoglobin, a protein that stores O_2 in cells



Coordination Environment of Fe^{2+} in Oxymyoglobin and Oxyhemoglobin





Ferrichrome (Involved in Fe transport in bacteria)

MONODENTATE					
Formula[a]	Name as Ligand[b]	Formula[a]	Name as Ligand[b]	Formula[a]	Name as Ligand[b]
Neutral Molecules					
NH_3	Ammine	NO	Nitrosyl	H_2O	Aqua
CH_3NH_2	Methylamine	CO	Carbonyl	C_5H_5N	Pyridine
Anions					
F^-	Fluoro	OH^-	Hydroxo	NCS^-	Thiocyanato-*N*
Cl^-	Chloro	NO_2^-	Nitrito-*N*	SCN^-	Thiocyanato-*S*
Br^-	Bromo	ONO^-	Nitrito-*O*	OSO_3^{2-}	Sulfato
I^-	Iodo	CN^-	Cyano	SSO_3^{2-}	Thiosulfato

POLYDENTATE		
Name of Ligand[b]	Abbreviation	Formula[a]
Ethylenediamine	en	$H_2NCH_2CH_2NH_2$
Oxalato	ox	$[OOCCOO]^{2-}$
Ethylenediaminetetraacetato	EDTA	$[(OOCCH_2)_2NCH_2CH_2N(CH_2COO)_2]^{4-}$

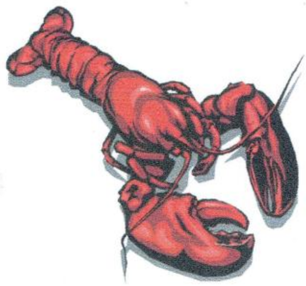
Chelating agents

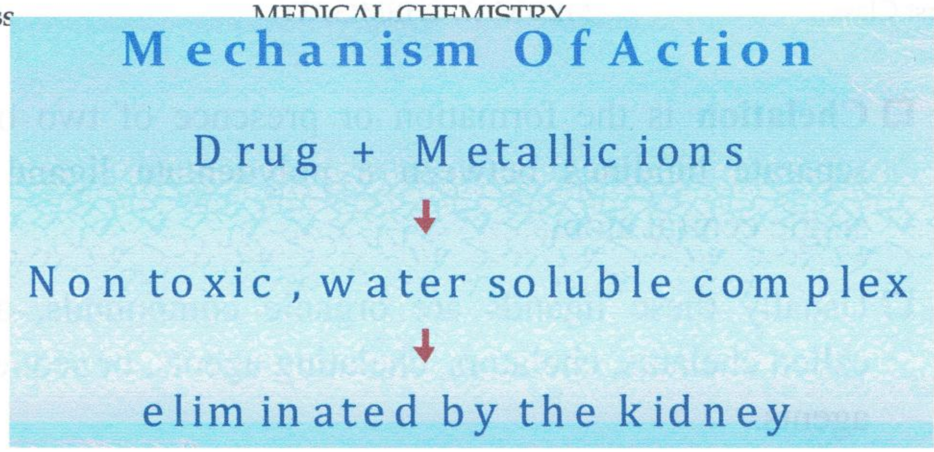
Introduction

- Heavy Metal acts as general protoplasmic poison and impairs the cell function.
- Have ability to form complexes with important biological radicals like sulfhydryl hydroxyl, carboxyl, amino acid, imidazole.

Chelating Agent

- These are the drugs used to prevent heavy metal poisoning.
- **<u>Chelation</u>** : The process by which these organic compounds combine with the metals to form relatively stable nonionised ring complexes (chele-clow).





- Heavy metals exert their toxic effects by combining with and inactivating functional groups (ligands) of **enzymes** and important **biomolecules** - sulfhydril, hydroxyl, carboxyl etc. leading to inactivation
- Chelating agents compete with body ligands for the heavy metal – also differ in affinity for different metals
- Chelating agents have high affinity for such metals and combine with them to form non toxic and water soluble complexes for elimination
- Possesses: –ve charged groups to attract +ve charged toxic metals

Ideal chelating agent

1. Ideal chelating agents have higher affinity for toxic metals than for body Ca++ (readily available in plasma and ECF(**extracellular fluid)**).
2. Should also have higher affinity for toxic metals than body ligands.
3. Ideally should be water soluble and distribution should correspond to that of the metal intended to Interval of administration between exposure to metals and chelating agents should be less.

- **Chelation** is the formation or presence of two or more separate bindings between a polydentate ligand and a single central atom.
- Usually these ligands are organic compounds, and are called chelants, chelators, chelating agents, or sequestering agents.
- Have two or more electronegative groups that form stable coordinate covalent bonds with the cationic metal atom
- **Chelator –metal complex** is stable, biologically inert and excreted in urine
- Thus appropriate chelating agent can be effectively used in cases of **heavy metal poisoning.**

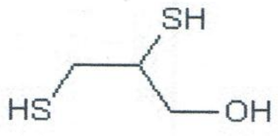
Useful chelating agents

- **Chelating agents useful as drugs are:**
  - Dimercaprol (BAL)
  - Dimercaptosuccinic acid (DMSA)
  - Dimercaptopropane sulfonic acid (DMPS)
  - Disodium edetate
  - Calcium disodium edetate
  - Pencillamine
  - Desferrioxamine
  - Deferiprone

Classification

Drug		Used against
EDTA	---------------	Lead
Dimercaprol	--------------	Arsenic.copper.mer.
Succimer	--------------	Lead.arsenic.mercury
Penicillamine	------------	Copper.mercury.lead
Trientine	------------	Copper
Deferrioxamine	----------	Iron
Deferiprone	-----------	Iron

Dimercaprol (BAL)



- It was synthesized during the world war II by Britishers as an antidote to arsenic war gas lewisite
- Oily, pungent smelling, viscous fluid
- It is administered i.m in oil (arachis oil)
- -SH ligands of dimercaprol compete with –SH groups of enzymes for heavy metal
- Dimercaprol –metal complex is stable and excreted in urine

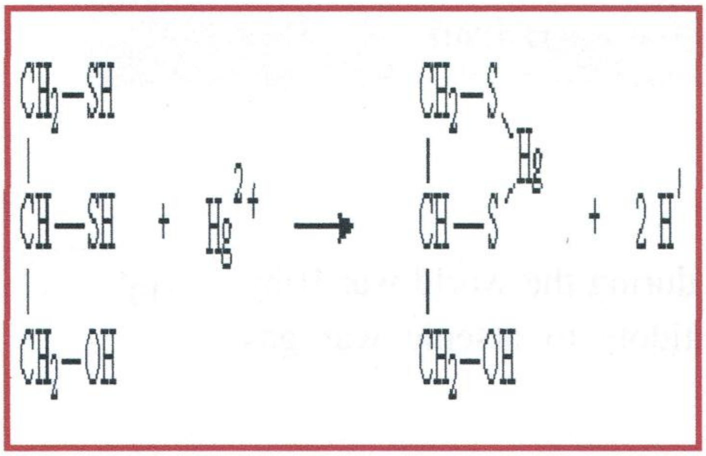
Uses:

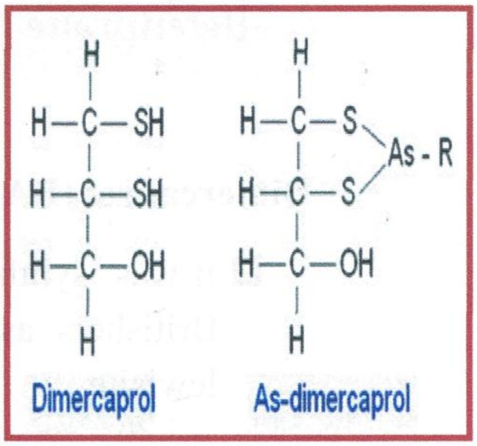
- For the treatment of **arsenic and mercury poisoning**
- As adjuvant to Cal. disod. Edetate in lead poisoning
- As an adjuvant to pencillamine in copper poisoning and in Wilson's disease

Contraindicated in iron and cadmium poisoning

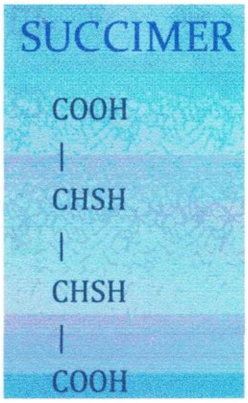
Adverse effects:

- Frequent, dose related, but generally not damaging
- Rise in BP, tachycardia, tingling and burning sensations, inflammation of mucous membranes, sweating, cramps, headache and anxiety
- Dose 5mg/kg followed by 2-3mg/kg 4hr/2days





DMSA (Succimer):



- Dimercaprol analogue
- Water soluble, less toxic and orally effective
- Marketed in USA and some other countries, not in India for the treatment of lead intoxication
- Side effects are nausea, anorexia and loose motions
- Dose-10mg/kg 8hrly/5days

DMPS (unithiol):

- Dimercaprol analogue
- Water soluble, less toxic
- Can be administered orally as well as IV

- Used for severe acute poisoning by mercury and arsenic
- Also effective in the treatment of lead poisoning
- Dose-3-5mg/kg 4hrly by i.v in 20min

Adverse effects are low, except for mild self-limited urticaria

Disodium edetate (Na_2 EDTA)

- It is a disodium salt of EDTA
- Potent chelator of calcium
- Causes tetany on i.v. injection (but not on slow infusion)
- Can be used for emergency control of hypercalcaemia (rare) 50mg/kg i.v. over 2-4hours

Note: Tetany or tetany seizure is a medical sign consisting of the involuntary contraction of muscles, which may be caused by disease or other conditions that increase the action potential frequency. Muscle cramps that are caused by the disease tetanus are not classified as tetany; rather, they are due to a blocking of the inhibition to the neurons that supply muscles.

Calcium disodium edetate (Ca Na_2 EDTA)

- Calcium chelator of Na2 EDTA
- Has a high affinity for lead
- Most important use is *lead poisoning*
- Poorly absorbed from GI –given i.m or i.v.
- i.m is very painful –i.v. preferred
- Not metabolized
- Excreted by glomerular filtration and tubular secretion

Adverse reactions:

- Does not produce tetany –relatively safe
- Kidney damage with proximal tubular necrosis –but dose related
- An acute febrile reaction with chills, body ache, malaise, tiredness occurs in some individuals
- Dose- 50-75mg/kg /day i.v

Penicillamine

- Dimethylcysteine
- Water soluble degradation product of penicillin
- D –isomer is used-relatively non toxic compared to L –isomer (optic neuritis)
- Easily absorbed from GIT
- Little metabolized, excreted in urine and faeces
- It has strong ***copper*** chelating property and was used in 1956 for Wilson's disease
- It selectively chelates Cu, Hg, Pb and Zn

Uses:

- **Wilson's disease (hepatolenticular degeneration)**
- **Copper**/ mercury (alternate to BAL & DMSA) poisoning
- Adjuvant to cal. disod. Edetate in lead poisoning but DMSA is preferred
- Cystinuria and cystine stones
- Scleroderma –benefits by increasing the soluble collagen

- It was used as a disease modifying drug in rheumatoid arthritis, but now replaced by safer drugs

Adverse effects:

- Short term administration –does not cause much problem (cutaneous reactions)
- Long term use –produces pronounced toxicity
    - Dermatological, renal, hematological and collagen tissue toxicities

Dose-0.5-1g daily in divided doses

Trientine (triethylene tetramine)

- Chelates copper and is used in Wilson's disease
- May be less toxic than pencillamine
- However, in animal studies it has been found to be teratogenic

Desferrioxamine

- Ferrioxamine Obtained from actinomycete, long chain iron containing complex
- Chemical removal of iron from it yields desferrioxamine
- 1gm is capable of chelating 85mg of elemental iron
- Low affinity for calcium
- Little of orally administered desferrioxamine is absorbed
- Parenterally –partly metabolized, rapidly excreted in urine

Uses:

- Acute iron poisoning: mostly in children, important and life saving
- Transfusion siderosis

Adverse effects:

- Hypotensive shock due to histamine release
- Abdominal pain, muscle cramps, fever and dysuria
- Dose- i.v ,10-15mg/kg/hr infusion
- Orally active
- Used in transfusion siderosis
- Somewhat less effective, alternate to injected desferrioxamine
- Side effects and cost of treatment are reduced
- Also indicated in iron poisoning (less effective than desferrioxamine) and iron load in liver cirrhosis

Side effects are:

- Anorexia, vomiting, altered taste, joint pain, reversible neutropenia, rarely agranulocytosis
- Long term safety is not yet known
- Dose-50-100mg/kg

Conclusions

Primary goals of chelation therapy:

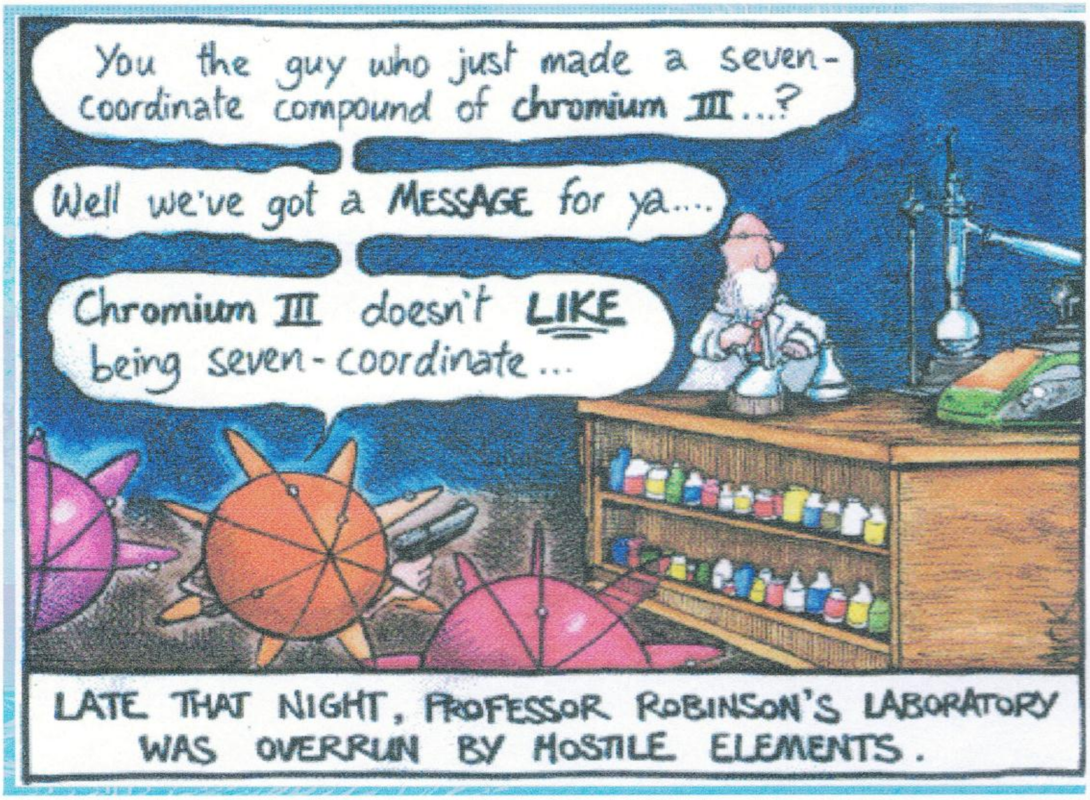
- To reduce metal retention
- To decrease morbidity and mortality
- To prevent complications

Many efficient chelators exist today

Administer less toxic chelator when possible

Unsolved issues:

- ☐ Chelation of cadmium, chromium, platinum…
- ☐ Chelation therapy in infants, children and during pregnancy
- ☐ Combined chelation therapy (chelators, vitamins, minerals…)



Good Luck