INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Fundamentals of Medicinal and Pharmaceutical Chemistry

FUNCHEM.11 Biocoordination Chemistry I

Professor Dan Wu

DATE: 23rd October 2024

Learning outcomes

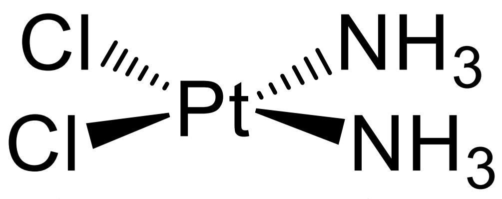
At the end of this lecture, the learner will be able to

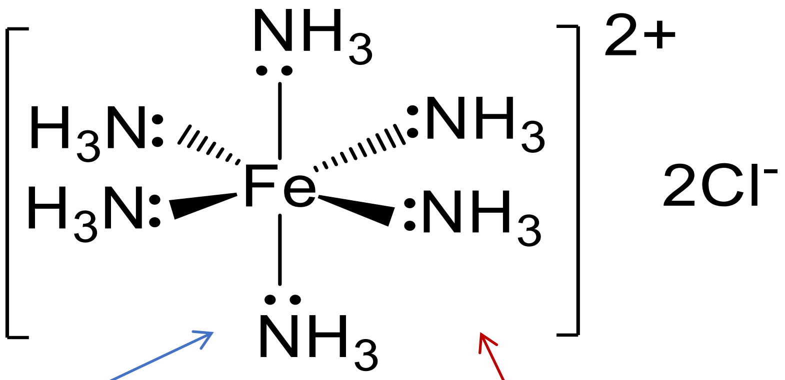
- Define ‘chelating agent’ and ‘chelate’.
- Recall and explain relationship between ring size and chelate stability.
- Recall and identify examples of bidentate, tridentate, tetradentate and hexadentate ligands.
- Draw the structure of a metal – EDTA complex given the structure of EDTA.
- Explain the high stability of a metal-EDTA complex.
- Define ‘chelation therapy’.
- Recall examples of chelating agents in clinic use and describe how they are used.

Recommended reading

- General Chemistry - The Essential Concepts by Chang and Goldsby 7e
  - Chapter 20
  - Chapter 10, Section 10.1 on molecular geometry

Recall from previous lecture



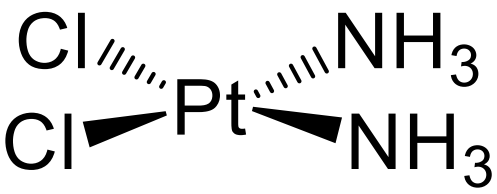


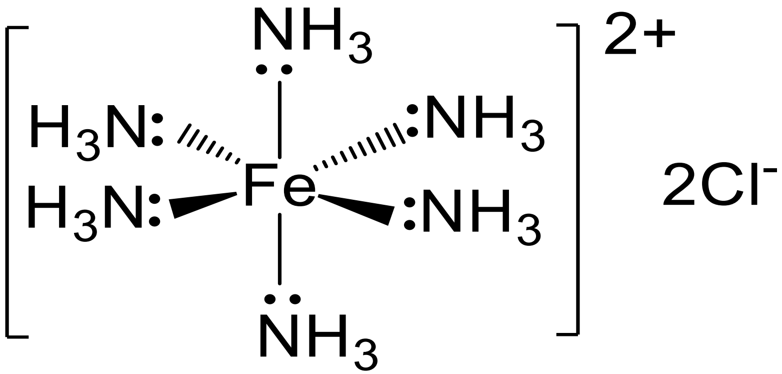
Each ligand is classified according to the number of donor atoms – in this case, each N in NH_3 and each Cl^- donates one pair of electrons, hence they are monodentate ligands

CN = 4 and CN = 6

Coordination number is the number of donor atoms bonded to the central metal ion in the complex

Oxidation State of the Metal Ion





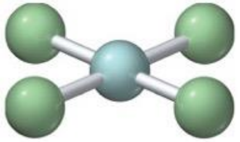
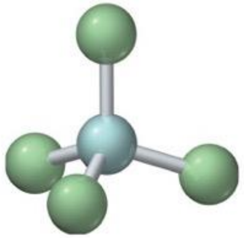
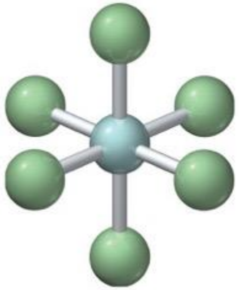
Each Cl is -1 i.e. Cl^-
Each NH_3 is neutral
Complex is neutral

$Pt + 2\ Cl^- + 2\ NH_3 = 0$
$Pt + 2(-1) + 2(0) = 0$
$Pt = +2$

Each NH_3 is neutral
Complex ion has a charge of 2+

$Fe + 6\ NH_3 = +2$
$Fe + 6(0) = +2$
$Fe = +2$

Geometries in Complex Ions

Coordination Number	Shape	Model	Example
2	Linear		$[Ag(NH_3)_2]^+$
4	Square planar		$[PdCl_4]^{2-}$
4	Tetrahedral		$[Zn(NH_3)_4]^{2+}$
6	Octahedral		$[Fe(H_2O)_6]^{3+}$

Ligand Denticity - refers to the number of donor groups in a single ligand that bind to a central metal ion in a coordination complex

- monodentate = 1
- bidentate = 2
- tridendate = 3
- tetradentate = 4
- hexadentate = 6
- polydentate = 2 or more donor atoms

The word *denticity* is derived from *dentis*, the Latin word for tooth. The ligand is thought of as biting the metal at one or more points

Recall examples of monodentate ligands

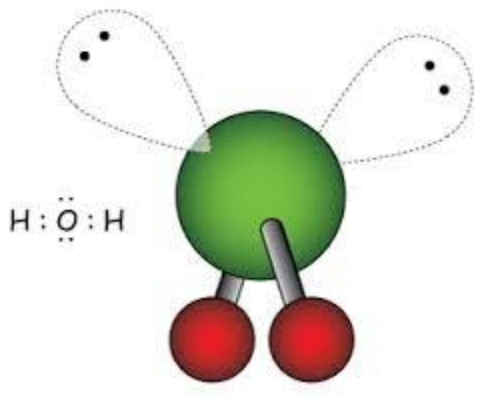
$H_2\ddot{O}:$ $H_2\ddot{S}:$ $H\ddot{S}:^-$ $CH_3\ddot{O}H$ $CH_3\ddot{S}H$ $:\ddot{F}^-$ $:\ddot{O}H^-$

All of the above are examples of monodentate ligands, since they donate one lone pair of electrons to a given metal ion

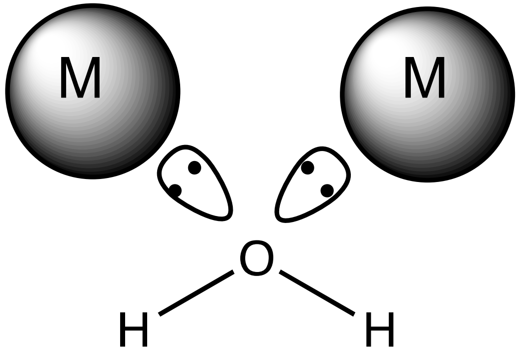
H_2O, although it contains two lone pairs, cannot be bidentate.

Why?

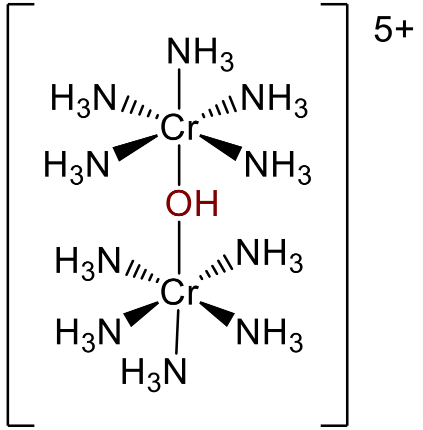
The two lone pairs are at an angle > 109^o relative to each other, and so cannot be donated to the same metal ion

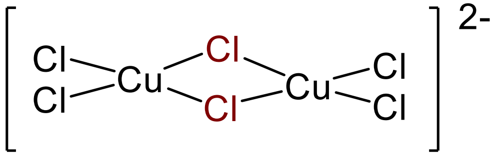


However a Lewis base such as H_2O with > 1 lone pair of electrons can act a bridging ligand - the ligand acts as a bridge between the metal ions



Examples of metal complexes having bridging ligands

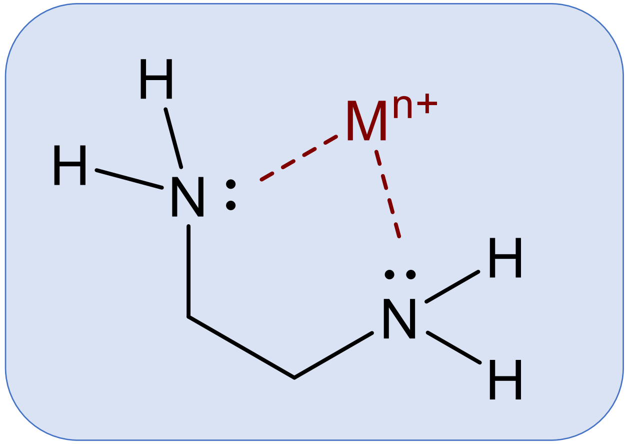


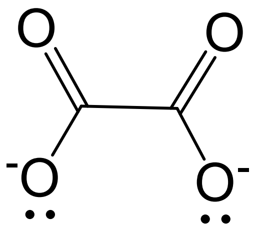


$[Cu_2Cl_6]^{2-}$

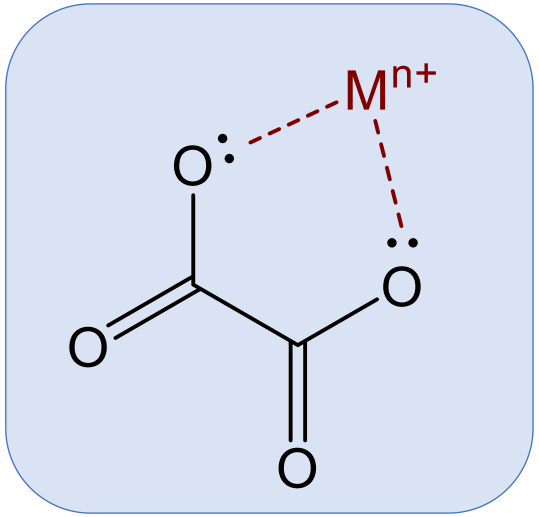
Recall examples of bidentate ligands

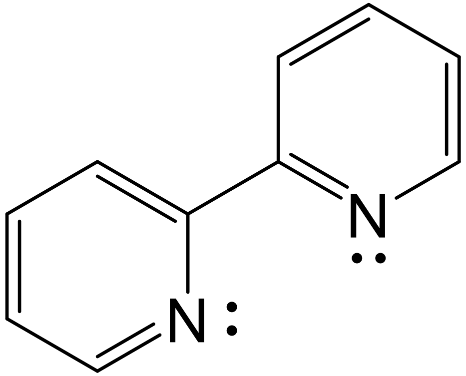
The bidentate ligand
1,2-diaminoethane or
ethylenediamine (en)



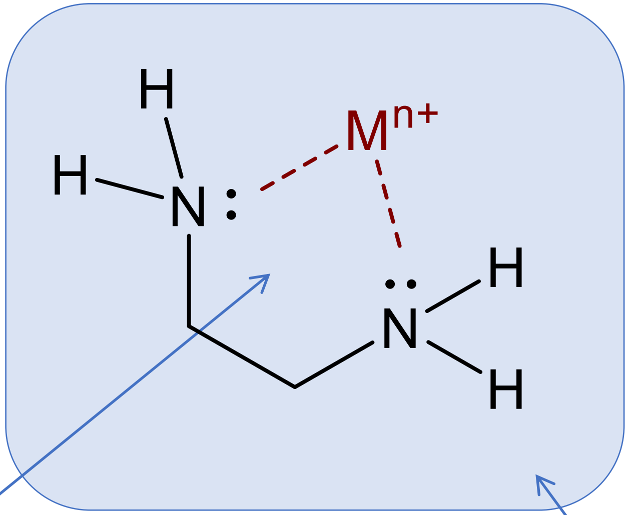


oxalate (ox)





2,2'-bipyridine

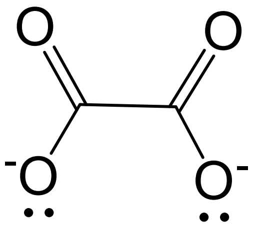


The bidentate ligand 1,2-diaminoethane or ethylenediamine (en)

The complex is called a chelate

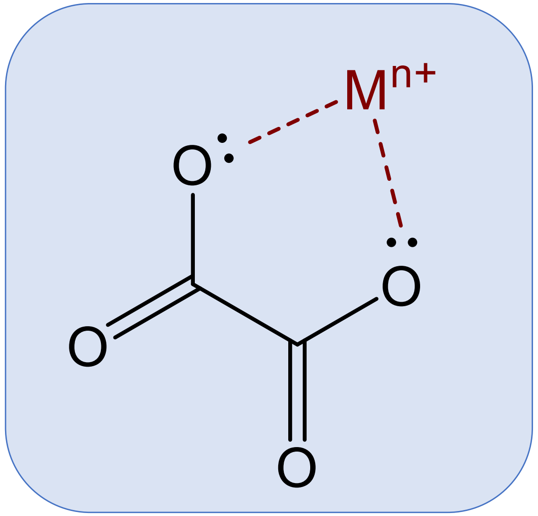
En forms a ring around the metal ion
The en ligand is called a chelating agent
- it forms two dative bonds with the same metal ion

Chelate is from the Greek word for claw, chele,– the chelating ligand ‘claws’ the metal (M)

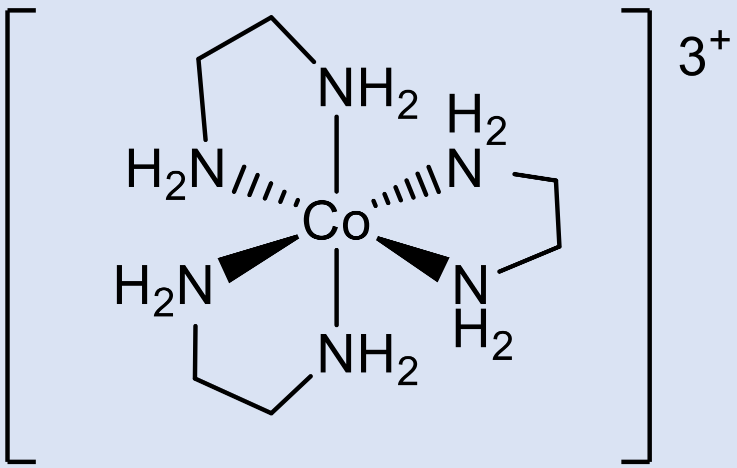


oxalate (ox)

Chelating agent
forms two dative bonds with the same metal ion



Chelate

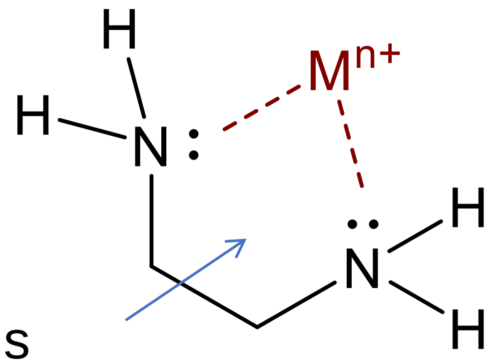


$[Co(en)_3]^{3+}$

In this metal complex:
coordination no. = 6 *(not 3)*
oxidation no of metal ion = +3
geometry around metal = octahedral

Chelate Stability

Chelates are more stable than non-chelates;
stability depends on the size of the ring.



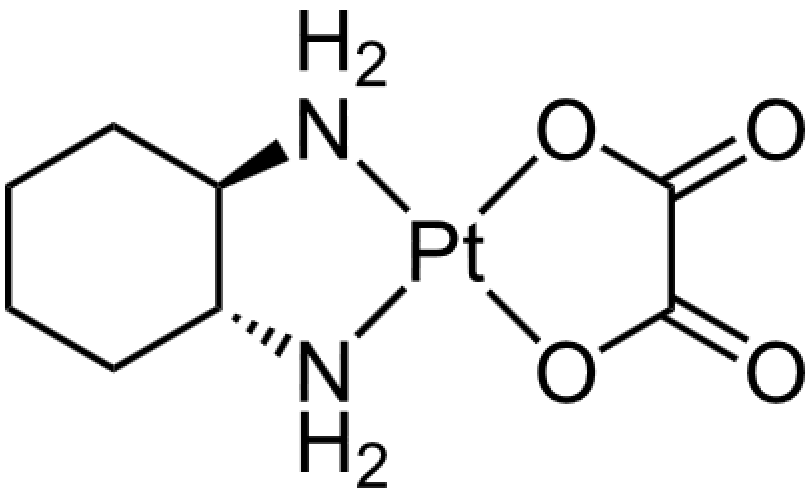
en forms 5-membered (5 sides) ring chelates and this is the most stable ring size in metal complexes.

Order of chelate stability according to ring size:

3 < < < 4 < < 5 > 6 >> 7 >> 8

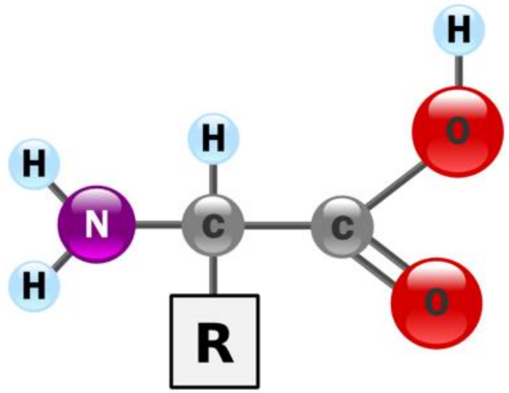
A 3-membered ring is very strained (bond angles 60°),
a 4-membered ring is quite strained (bond angles 90°).
Big rings (7-, 8- etc) are floppy!

Structure of Oxaliplatin



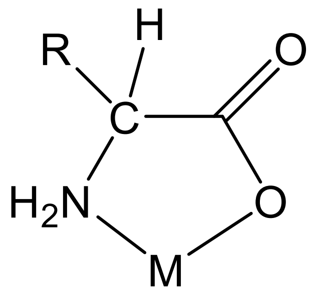
Amino acids – the building blocks of proteins

They are composed of amine (-NH_2) and carboxylic acid (-COOH) functional groups, along with a side-chain (R) specific to each amino acid.

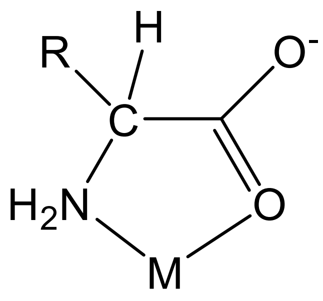


The generic structure of an α-amino acid in its un-ionized form

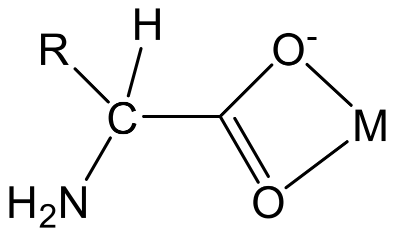
A metal complex with an α - amino acid ligand can, in principle, have any of the three structures below. Which is the most stable and why?



I

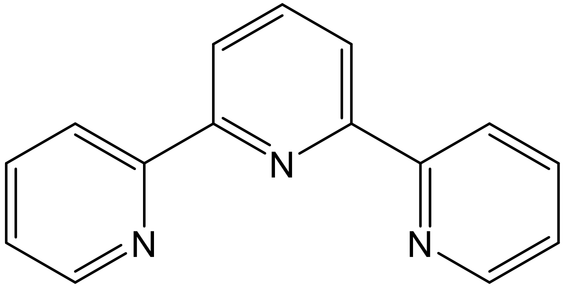


II

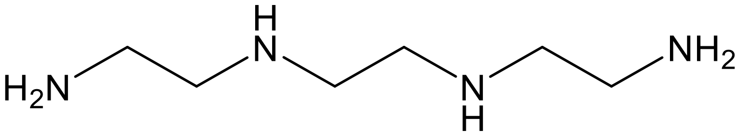


III

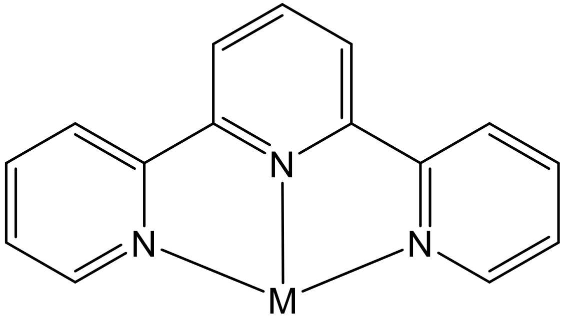
Recall examples of tridentate and tetradentate ligands

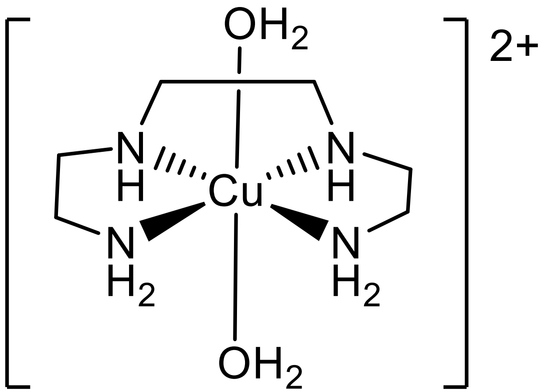


terpyridine

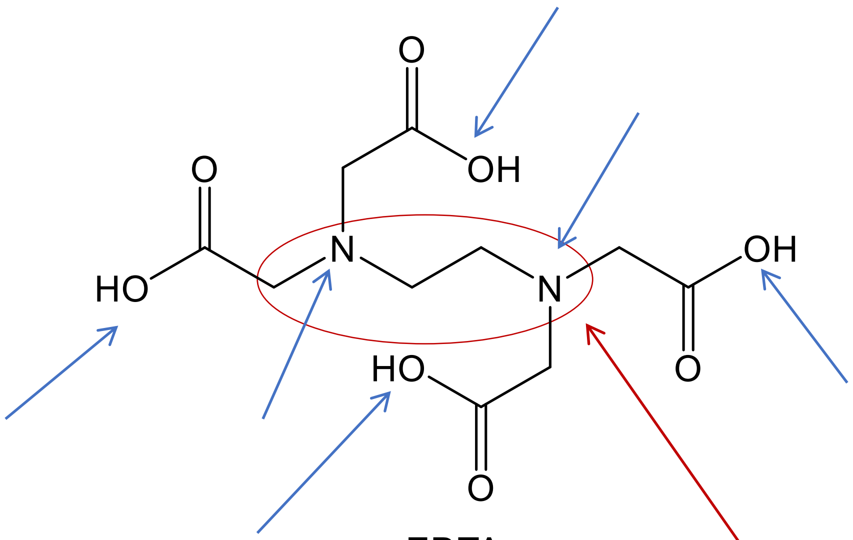


triethylenetetramine,
abbreviated trien





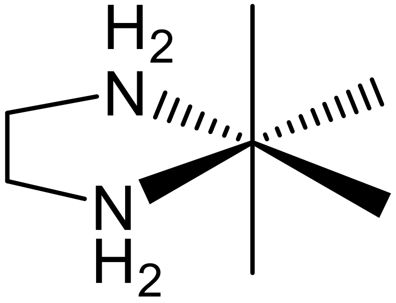
Recall examples of hexadentate ligands

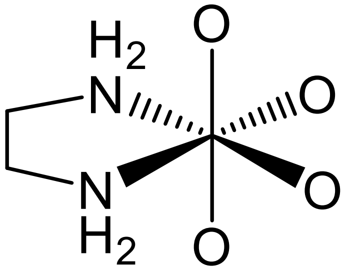


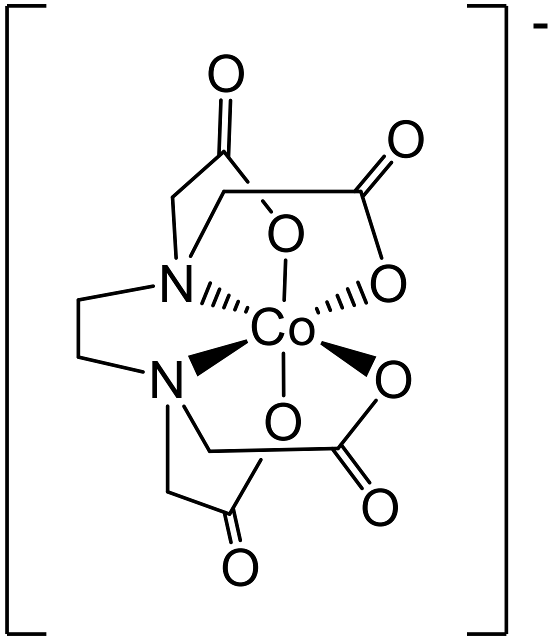
EDTA

Derived from en

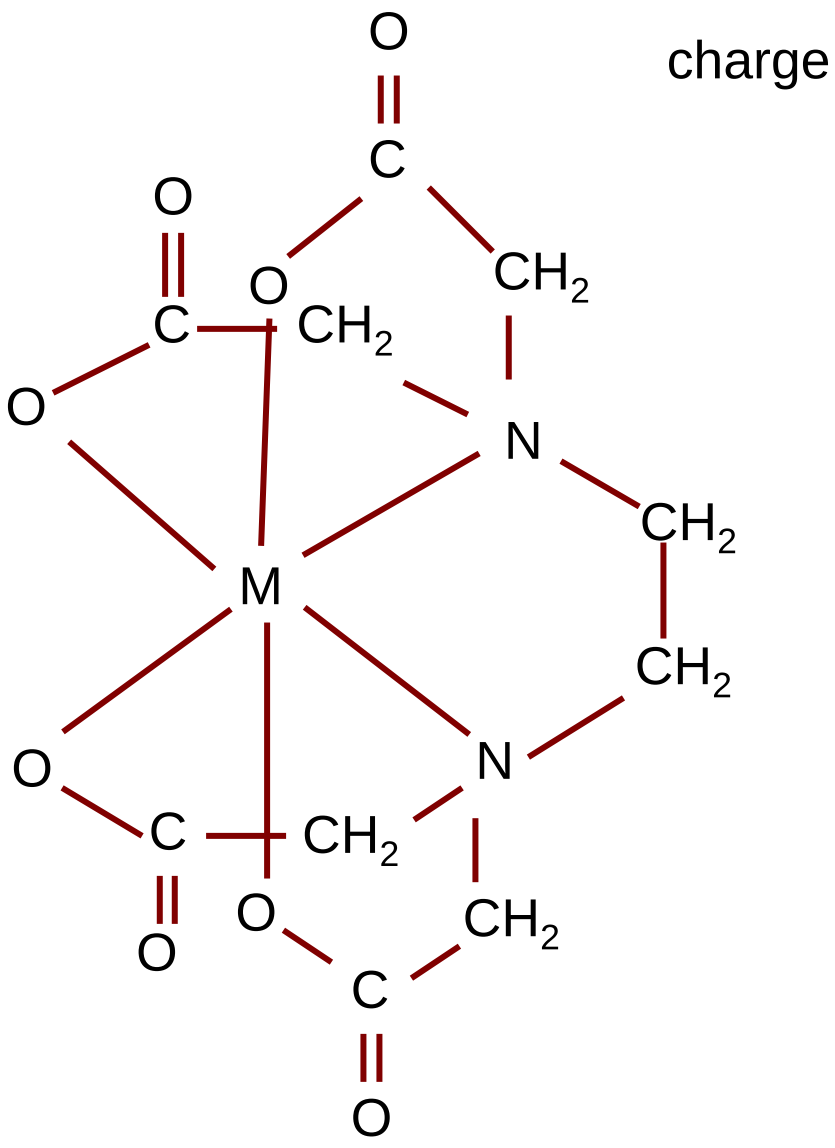
Hexadentate ligand





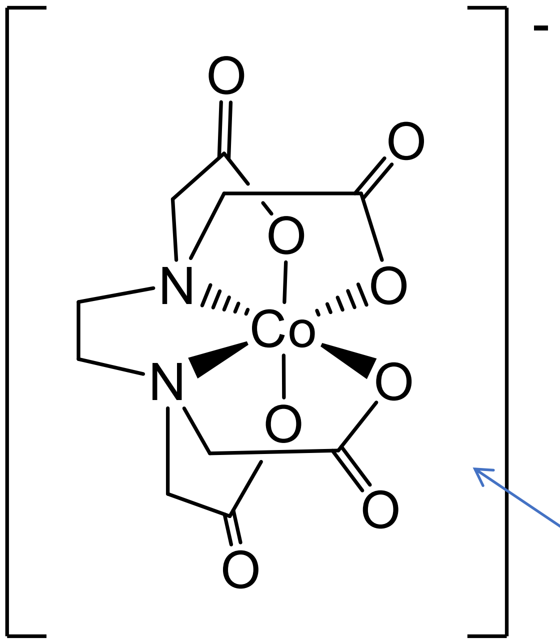


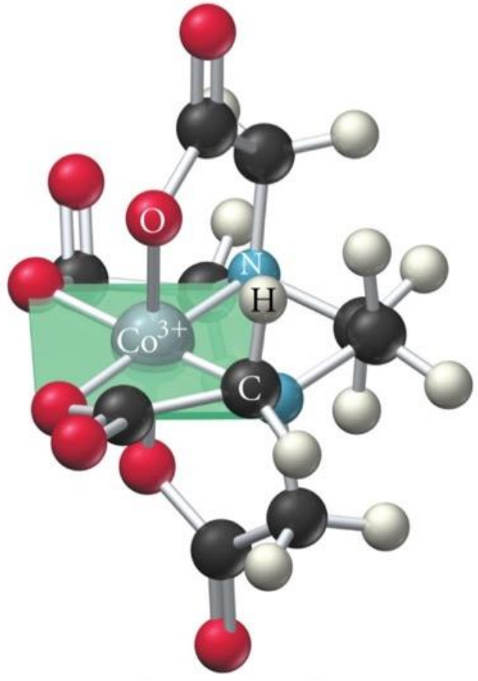
How to draw the structure of a metal-EDTA complex



1. Write metal symbol.
2. Insert octahedral bonds.
3. Insert donor atoms.
4. Connect N,N donor atoms by $-CH_2-CH_2-$
5. Connect N,O donor atoms by $–CH_2C(=O)-$
6. Insert charge

Recall examples of hexadentate ligands





Charge on complex ion = -1

This complex has five 5–membered rings and is very stable.

Coordination no. of metal ion = 6

Oxidation state of metal ion = +3

Chelation Therapy

Chelation therapy is the administration of chelating agents (by intravenous infusions, intramuscular injections or oral administration) to mobilise and remove unwanted or excess metal ions from the body.

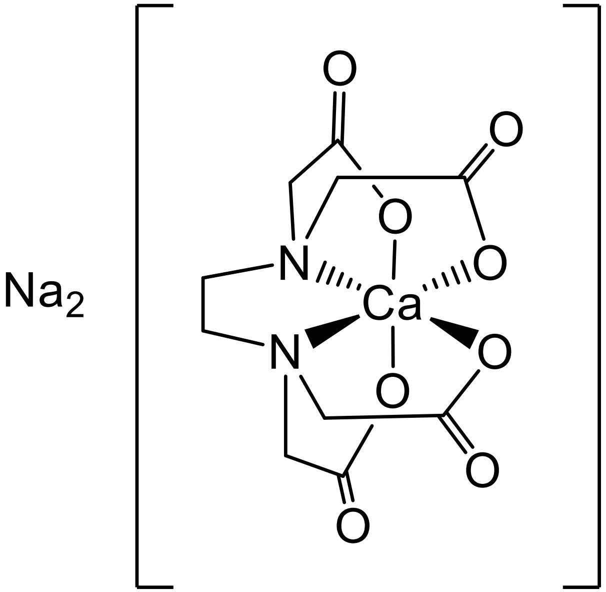
Three areas of clinical use of chelating drugs:

i. Removal of metal ions that accumulate in tissues due to genetic disorders.

ii. Treatment of heavy metal (e.g. Pb, Hg, Cd) toxicity due to environmental pollution.

iii. Treatment of degenerative diseases of blood vessels (removal of Ca-containing plaques).

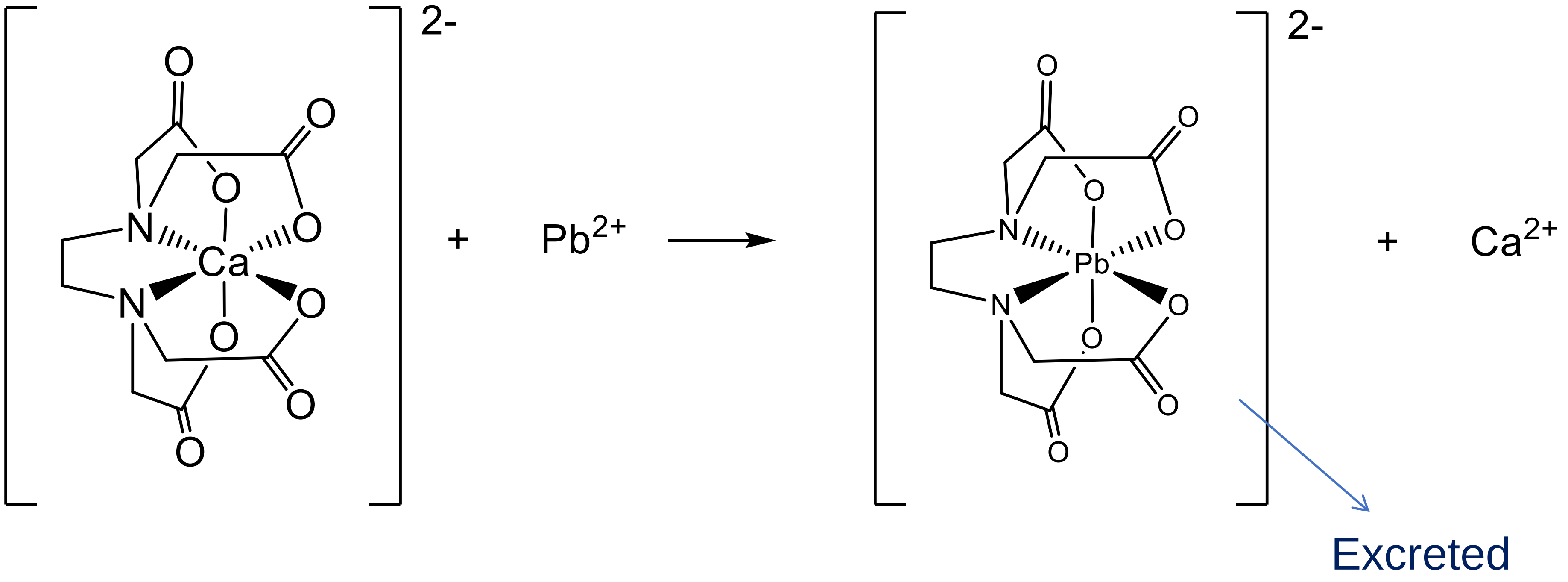
Chelation Therapy using EDTA



The sodium salt of this complex, Na_2 [Ca(EDTA)], is used as a drug (Calcium disodium versenate®) to treat lead poisoning

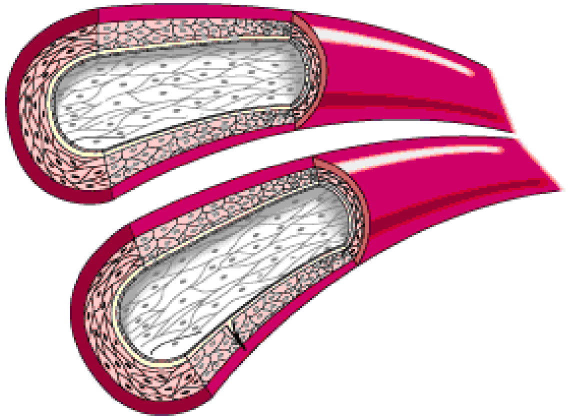
Lead poisoning is derived from absorption of lead-contaminated food and drink, airborne particles, lead in petrol
Lead accumulates in liver, kidneys, bones
It binds to S atoms in proteins and enzymes and prevents their normal functions

$[Ca(EDTA)]^{2-}$ - used to treat lead poisoning



$EDTA^{4-}$ has a higher affinity for Pb^{2+} than Ca^{2+}.
Pb^{2+} is larger than Ca^{2+} and $EDTA^{4-}$ fits better around it.

Chelation Therapy using EDTA

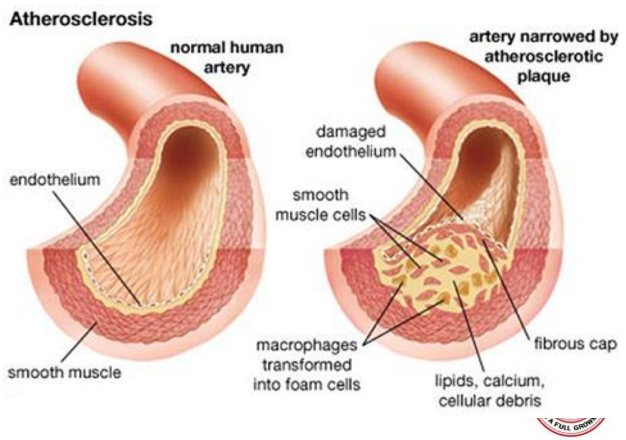


EDTA is also used to treat some forms of coronary artery disease

CORONARY ARTERY DISEASE

Coronary artery disease generally refers to the build up of plaques in the inside layers of the arteries. As shown above, this will slowly narrow blood flow through the vessel, and the muscle it supplies will not get enough blood. The plaque weakens the wall. As shown in the lower artery, a crack may develop in the plaque and a blood clot may form - this is the mechanism of most heart attacks.

Atherosclerosis is a disease process in which lipids and/or calcium compounds and abnormal cells accumulate in the walls of the coronary arteries, forming plaques, and leading to blockage of the arteries

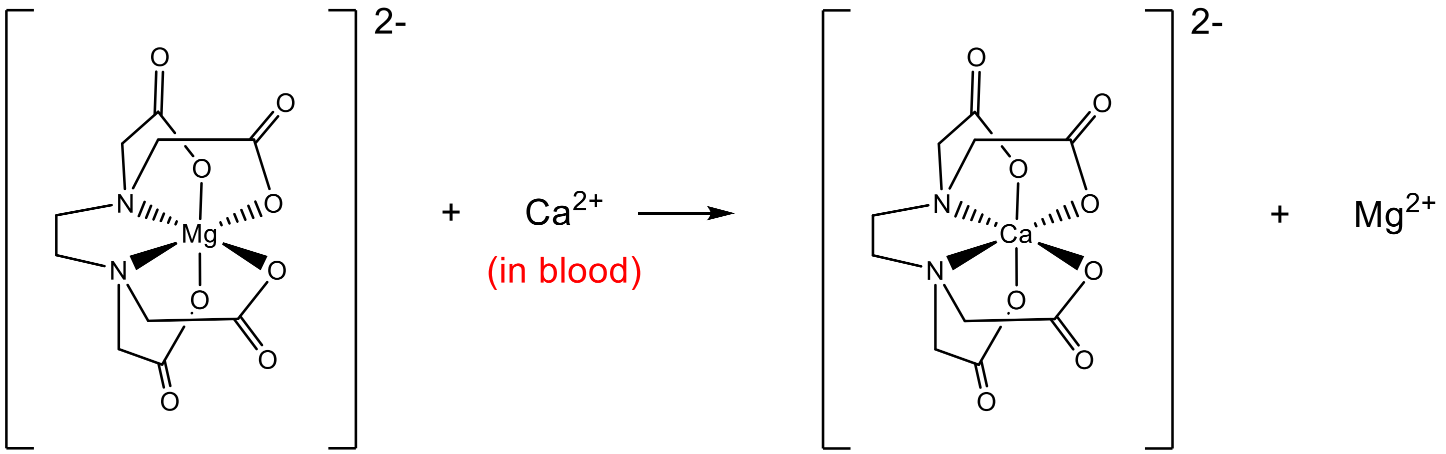


Chelation Therapy using EDTA

Atherosclerosis

Treated by bypass surgery (expensive) or chelation therapy which can remove calcium containing deposits

The compound used to remove calcium-containing plaques is $Na_2[Mg(EDTA)]$

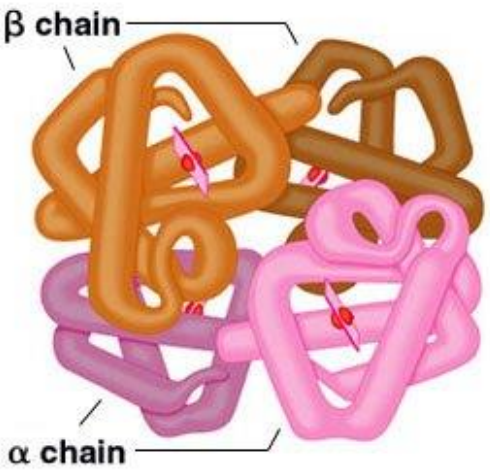


$[Mg(EDTA)]^{2-}$

$[Ca(EDTA)]^{2-}$
Very soluble

Blood Ca^{2+} is replaced by Ca from plaque which dissolves

Iron Chelation Therapy – Treatment of Thallassaemia



Thallassaemia – genetic blood disorder
Thalassemia is caused by variant or missing genes that affect how the body makes haemoglobin - defective synthesis or absence of one or more globin chains in haemoglobin

100,000 babies are born each year with thallassaemia.

It is treated by blood transfusion – if not death occurs within 1 year.

Repeated transfusions however leads to iron overload due to decomposition of transfused blood (pint of blood contains ~200 mg Fe) and tissue damage to the heart, endocrine glands and liver occurs. This causes death within 20 years.

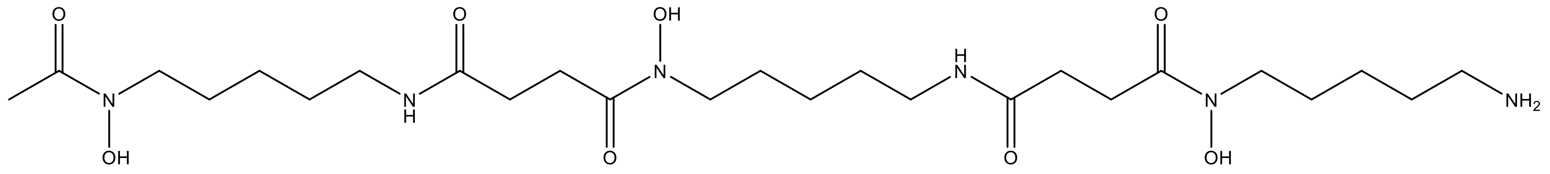
Iron Chelation Therapy – Treatment of Thallassaemia

The healthy body contains 4 – 5 g iron.

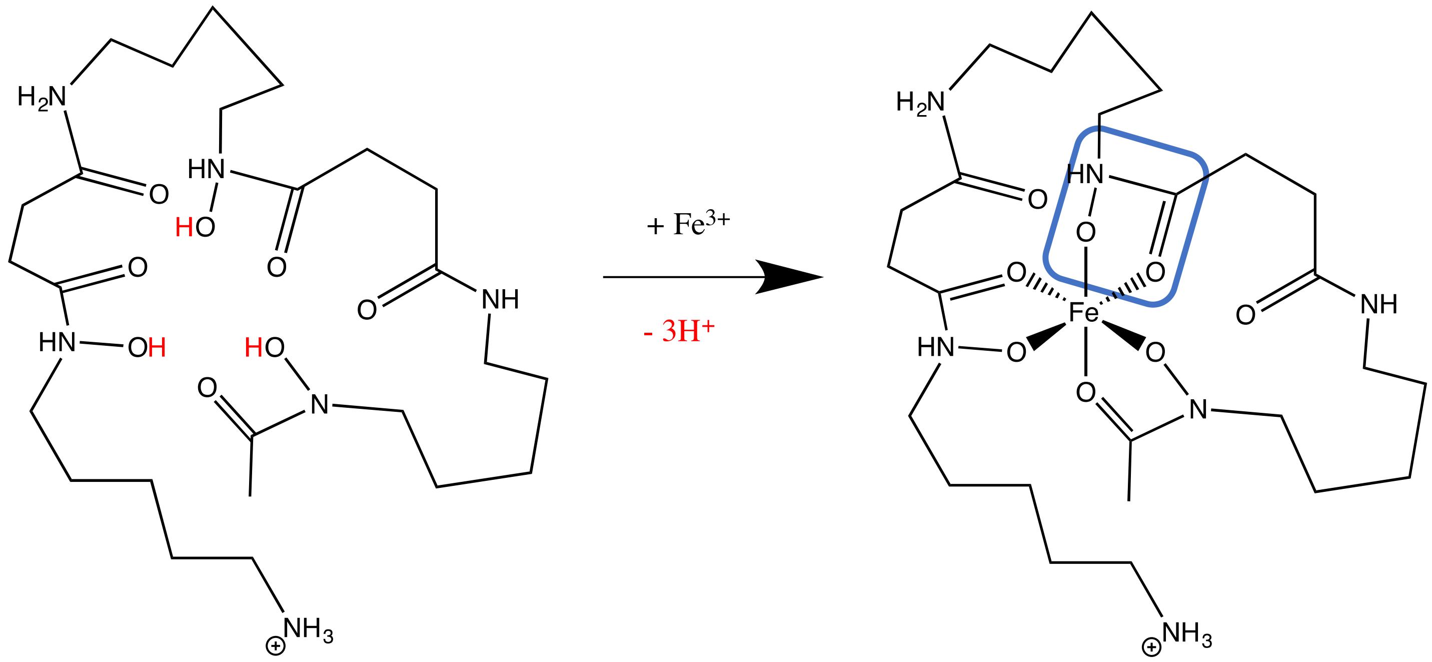
Thalassaemic patients can accumulate 50 – 70 g Fe over a 10 year period as a result of transfusion.

Iron chelation therapy removes excess iron.

Desferrioxamine B (desferal) has until recently been the only drug available for this.
This contains hydroxamic acid groups.



Iron Chelation Therapy – Treatment of Thallassaemia



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- Explain the high stability of a metal-EDTA complex.
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Thank you

FOR MORE INFORMATION PLEASE CONTACT

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