Bioinorganic Chemistry

Biological inorganic chemistry or bioinorganic chemistry is the application of the inorganic elements/compounds in biology. Metal ions, when interacted with biological ligands exhibit properties like ligand binding, catalysis, signalling, regulation, sensing, defence, and structural support.

The elements used in bioinorganic chemistry are oxygen, hydrogen, carbon, nitrogen, phosphorus, sulfur, sodium, magnesium, calcium, and potassium. The trace elements include many d-metals, as well as selenium, iodine, silicon, and boron.

The major binding sites for metal ions are provided by the amino acids that make up protein molecules.

Metalloproteins*, proteins containing metal ions function as catalysts in oxidation and reduction.*
Important elements in metalloproteins are Fe, Mn, Cu, and Mo for reduction, Zn, Fe, Mg, Mn, and Ni for hydrolysis, Co for radical-based rearrangement reactions and methyl-group transfer and Zn for DNA processing.

Metal ion-activated proteins *which alter the conformation/shape of a protein in cell signalling, contain* Ca^{+2} *ions*

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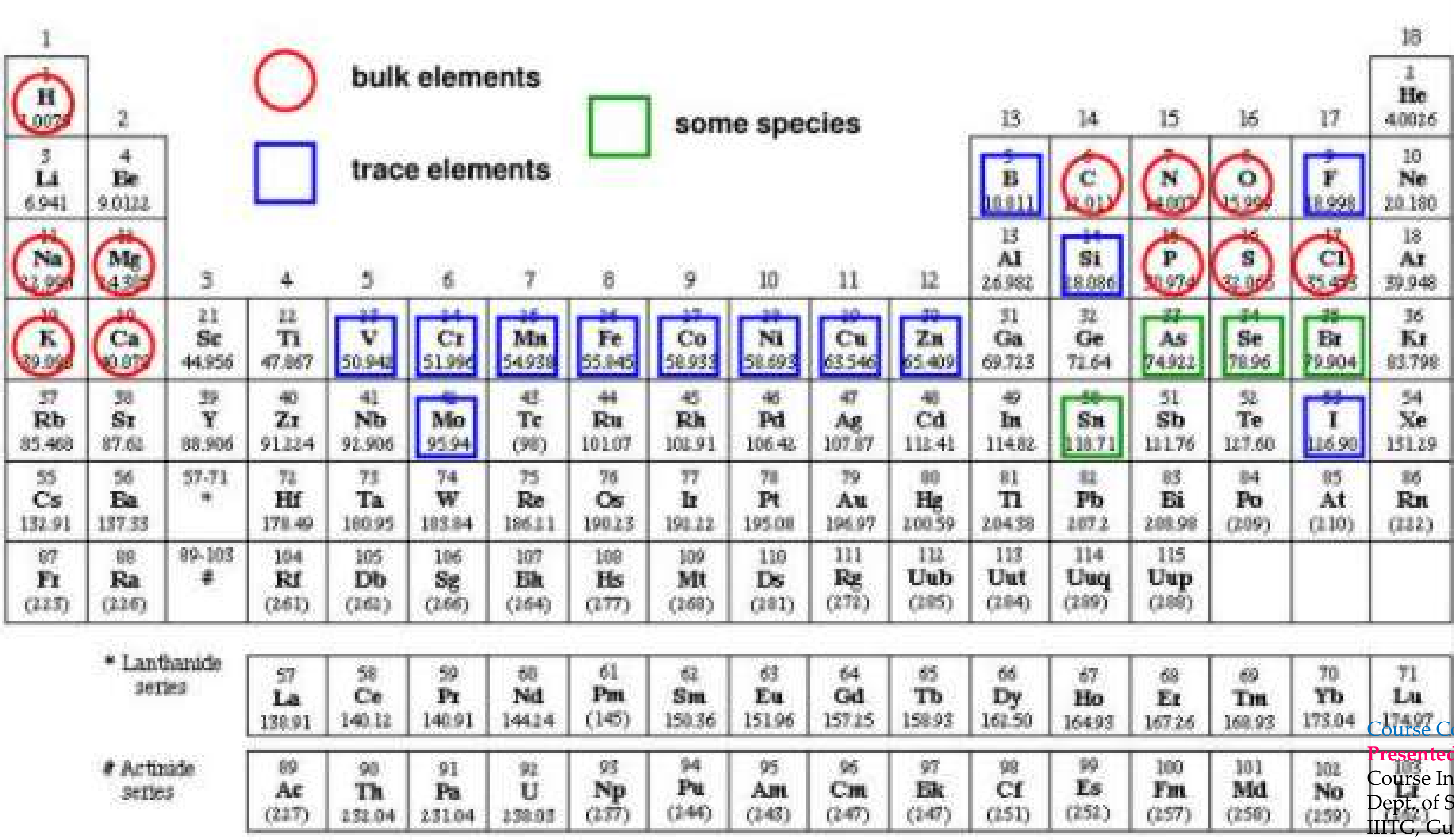
Elements of the living organism:

1. **Elements with large concentration: 11 elements**
   H, C, N, O, Na, Mg, P, S, Cl, K, Ca
2. **Elements with small concentration : 7 elements**
   Mn, Fe, Co, Cu, Zn, I, Mo
3. **Elements of a few species: 7 elements**
   B, F, Si, V, Cr, Se, Sn

- Na, K, Mg, Ca
- V, Cr, Mn, Fe Co, Ni, Cu, Zn
- Mo, W

81 stable elements



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Functions

- Assembly of structures (DNA, biomineralization), endo- and exoskeletons. Ca, Mg, Zn, Si
- Information carriers (muscle contractions, nerve function). Na, K, Ca, Mg
- Activation of enzymes. Mg, Ca
- Formation, metabolism and degradagation of organic compounds by Lewis acid/base catalysis. Zn, Mg
- Transfer of electrons (energy conversion). FeII/FeIII/FeIV, stable due to bioligands
- Uptake, transport, storage and conversion of small molecules
  - $^3O_2$: Fe, Cu (conversion), Mn (generation)
  - N_2: Fe, Mo, V (conversion to ammonia)
  - CO_2: Ni, Fe (reduction to methane)

Na, K: Charge carriers
Osmotic and electrochemical gradients
Nerve function

Mg, Ca: Enzyme activators
Structure promoters
Lewis acids
Mg^{2+}: chlorophyll, photosynthesis
Ca^{2+}: insoluble phosphates

Fe, Cu, Mo: Electron-transfer
Redox proteins and enzymes
Oxygen carrying proteins
Nitrogen fixation

Zn: Metalloenzymes
Structure promoters
Lewis acid
Not a redox catalyst

Cu(I), Cu(II)

Plants, Animals: Electron transfer, O_2-carrying

Protection of DNA from O_2^-

Cu-proteins and enzymes

Cytochrome oxidase	$O_2 \longrightarrow H_2O$
Tyrosinase, phenol oxidase	ox. of phenols
Ceruloplasmin	Fe(II) $\longrightarrow$ Fe(III)
Blue proteins	Electron transfer
Superoxide dismutase	Elimination of O_2^-
Hemocyanin	O_2 transport

human body

75% Hem-iron
- Hemoglobin
- Myoglobin
- Cytochromes
- Oxidases, P-450

25% Non-hem-iron
- Rubredoxins
- Ferredoxins

Fe(II), Fe(III):
- Essential for ALL organisms
- In plants: iron deficiency
- In human body: 4-5 g
- Uptake: ~ 1 mg/day

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Na^+ :

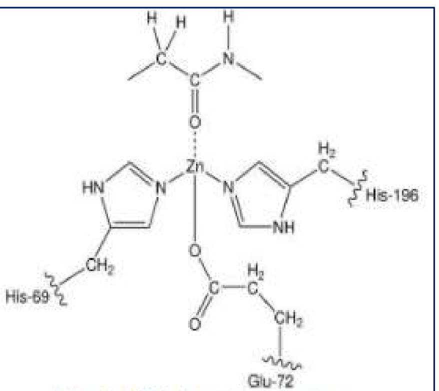
- Extracellular fluid
- Osmotic balance „sodium pump"
- Acid-base balance
- Conformation of { proteins, nucleic acids
- Electrical impulse of nerve system

$$3Na^+_{ic} + 2K^+_{ec} + ATP^{4-} + H_2O \xrightarrow{Mg^{2+}} 3Na^+_{ec} + 2K^+_{ic} + ADP^{3-} + HPO_4^{2-} + H^+$$

Ca^{2+}

- Inhibits Mg^{2+}-activated enzymes
- Extracellular: clotting (10^{-3}M)

$$\text{prothrombin} \xrightarrow{Ca^{2+}} \text{thrombin-fibrinogen-fibrin}$$



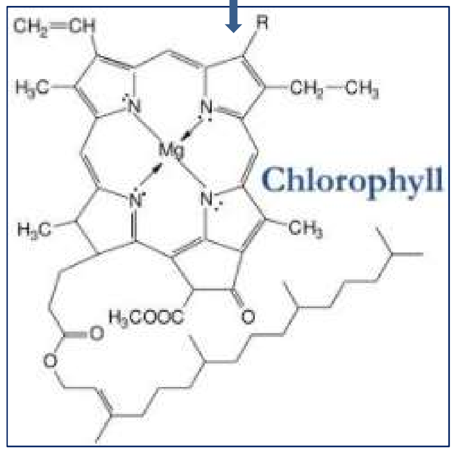
Zink(II) in the active centre of carboxipeptidase-A

K^+

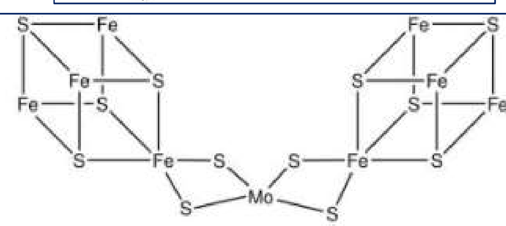
- Enzyme activator
- Conformation of { proteins, RNA (replication)
- Secretion of gastric acid
- Transmembrane potentials

Mg^{2+}

- Plants ⟶ chlorosis
  CHLOROPHYLL
- nervous system (tetany)
- active transport (intracellular)
- enzyme activator (e.g. ATP-ase)
- Ca^{2+} antagonist



Chlorophyll



Supposed structure of Fe-S-Mo cofactor of nitrogenase

Complexes of alkali metals (Na^+, K^+)

Cyclic antibiotics: Valinomycin, Monactin, Nonactin

polyethers, cryptands } synthetic

Zn^{2+} : deficiency:

- disturbances of repr. system
- dwarfism
- skin lesions
- skeletal abnormalities

Function of Zn in metalloenzymes

1. Structure-promoter
2. Substrate binder
3. Lewis acid

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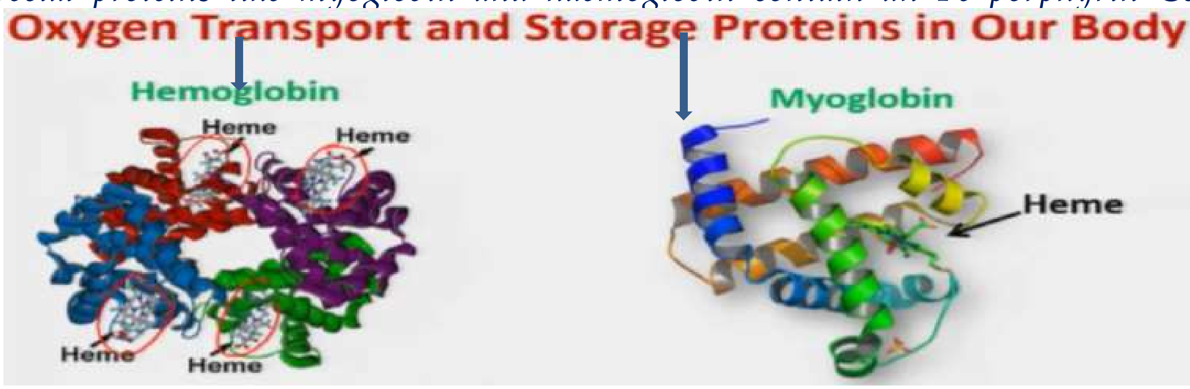
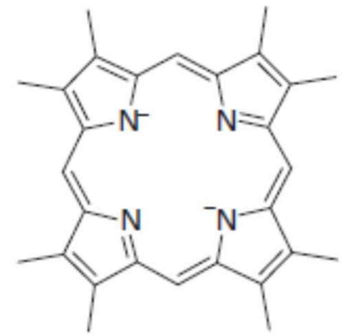
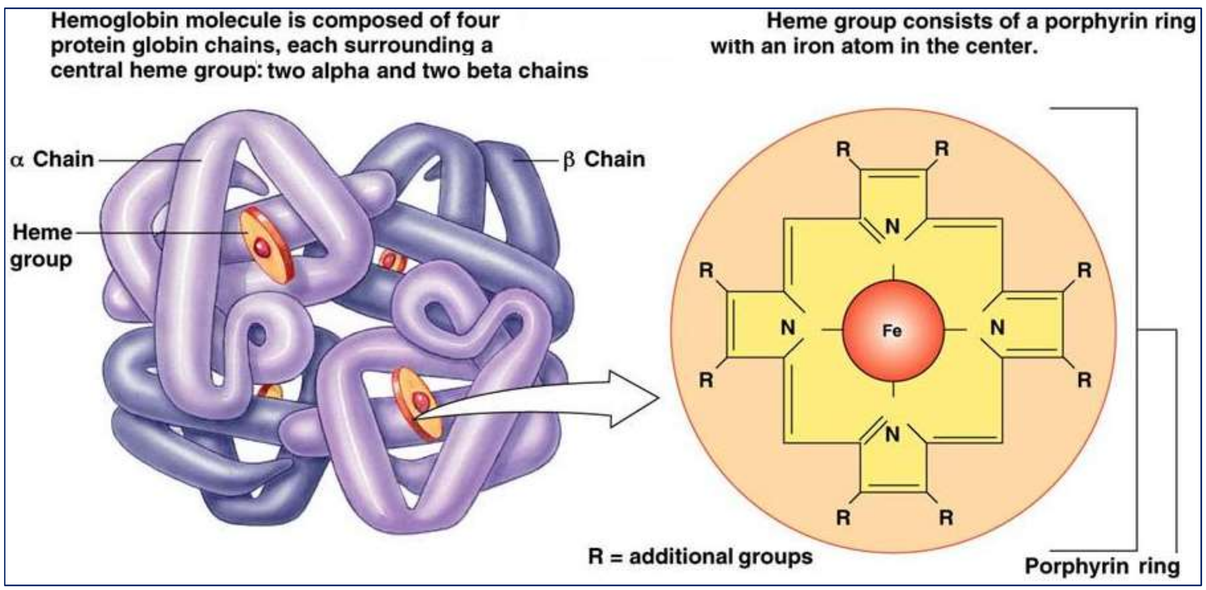
Special types of ligands:

Metal ions are bound in proteins by special organic ligands such as porphyrins and pterin-dithiolenes, as found in haemoglobin which coordinates with Fe. Special proteins like myoglobin and haemoglobin contain an Fe porphyrin Cofactor which functions for oxygen transport and storage.



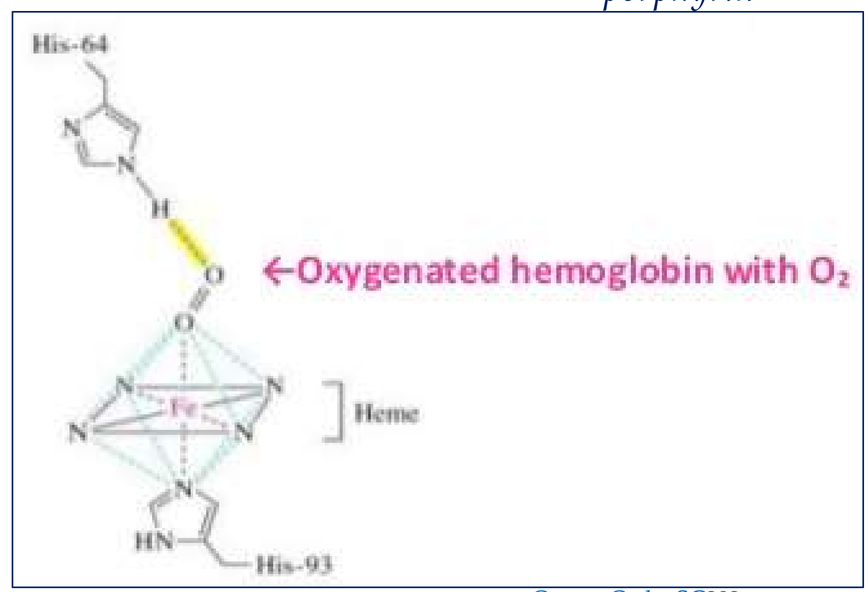


porphyrin



Heme $=Fe^{+3}$ bound to tertapyrrole ring (protoporphyrin IX complex)

Heme non-covalently bound to globin proteins through His residue



O_2 binds non-covalently to heme Fe^{-}, stabilized through H-bonding with another His residue

Heme group in hydrophobic crevice of globin protein

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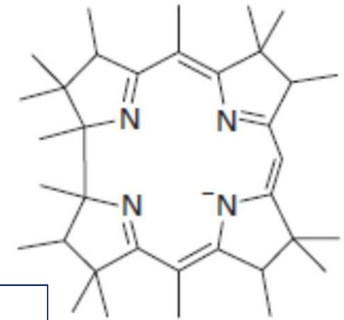
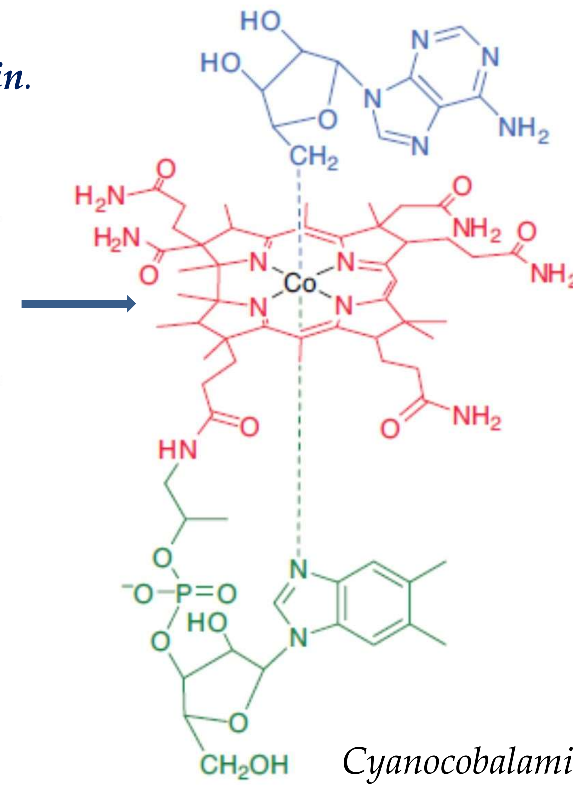
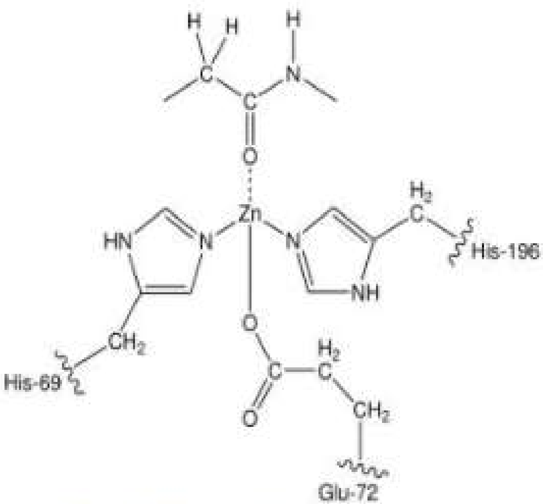
*Corrin coordinates with **Co** in cobalamin to further give the **Vitamin B_{12}, cyanocobalamin**.*



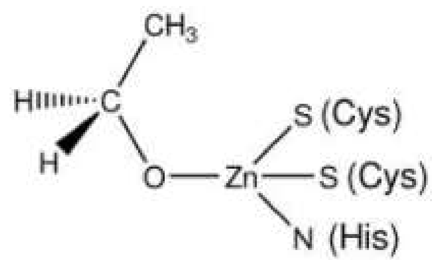
Corrin



Cyanocobalamin



Zinc(II) in the active centre of carboxipeptidase-A



The active centre of the alcohol dehydrogenase

Coordination of Zn to specific histidine and cysteine residues enables the protein to recognize and bind to precise sequences of DNA base pairs and plays a crucial role in transferring information from the gene.

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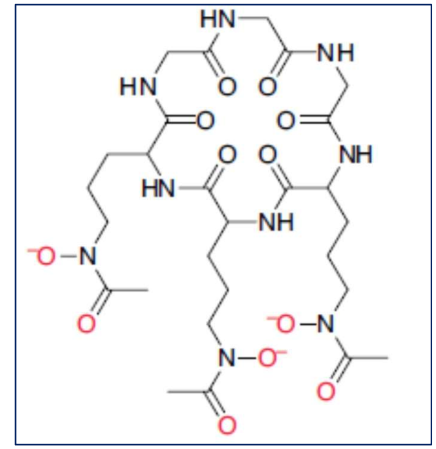
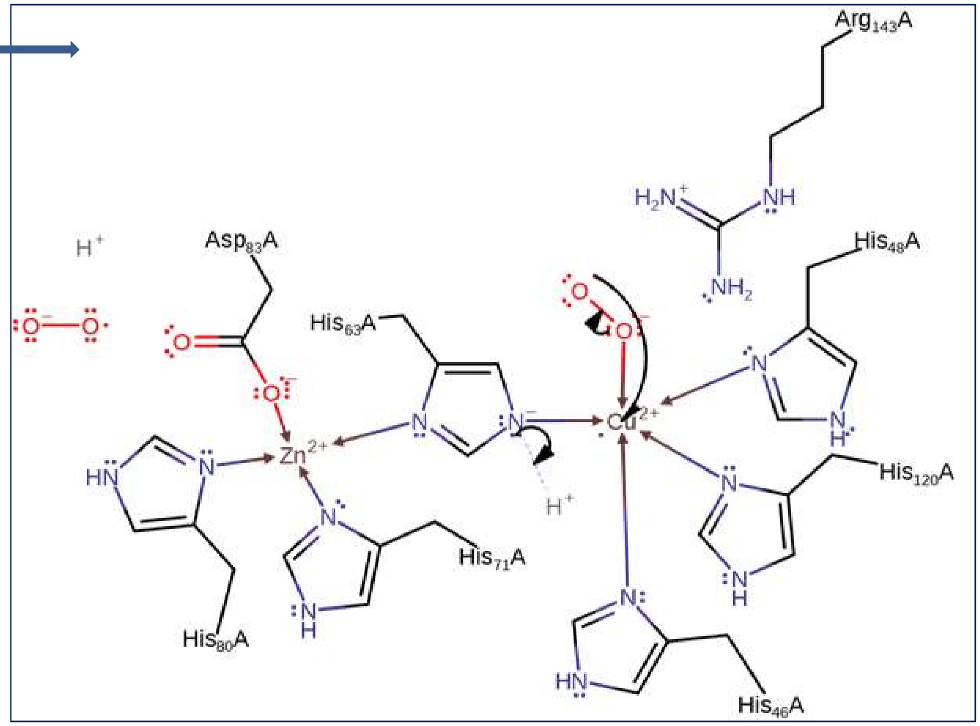
The uptake of Fe into organisms involves special small polydentate ligands known as siderophores. Fe is stored as a protein called ferritin. Ferritins have two components, a 'mineral' core that contains up to 4500 Fe atoms and a protein shell.



Ferrichrome

The ***Cu,Zn superoxide dismutase*** *(SOD1) is an enzyme that converts the toxic superoxide molecule into the less toxic substances of hydrogen peroxide and dioxygen, by the destabilization of the copper(II) metal center due to distorted square pyramid geometry and lability of copper.*



Cu^{2+} is a d^9 metal; therefore, there is an empty orbital for an electron to move up in energy Therefore, d-d transitions can occur when superoxide dismutase is in its reduced form, Cu^{2+}. However, when superoxide dismutase is in its oxidized form, Cu^{1+}, d-d transitions cannot occur. This is because Cu^{1+} is a d^{10} metal. Therefore, all of the orbitals will be filled. Zn^{2+} is a d^{10} metal; all of the orbitals are filled so d-d transitions cannot occur here.

crystal field splitting diagrams for copper metal center is a distorted square pyramid geometry and zinc metal center in a tetrahedron geometry

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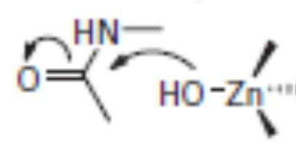
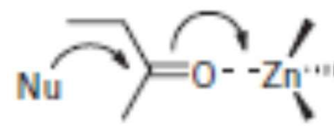
Catalytic processes:

Zinc enzymes catalyse acid–base reactions by exchange of H_2O. Zn is coordinated by three amino acid ligands and one exchangeable H_2O molecule. In the ***Zn-hydroxide mechanism****, the Zn promotes deprotonation of a linked water molecule, thus an OH nucleophile attacks the carbonyl C atom*



In the ***Zn-carbonyl mechanism****, the Zn ion as a Lewis acid accepts an electron pair from the carbonyl O atom*



Zinc is found in the enzyme, carbonic anhydrase or carbon dioxide dehydratase, used for CO_2 hydration. [Zn-hydroxide mechanism]. The enzyme alkaline phosphatase containing Zn centres catalyses the hydrolysis of phosphate monoesters.

$$R - OPO_3^{2-} + H_2O \xrightarrow{\text{cat. Zn}} ROH + HOPO_3^{2-}$$

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Peroxidases catalyse reduction of hydrogen peroxide

$$H_2O_2(aq) + 2e^- + 2H^+(aq) \rightarrow 2H_2O(l)$$

Oxidases are enzymes that catalyse the reduction of O_2 to water or hydrogen peroxide

$$O_2(g) + 4e^- + 8H^+ \rightarrow 2H_2O(l) + 4H^+$$

Oxygenases catalyse the insertion of one or both O atoms derived from O_2 into an organic substrate. They play a crucial role in the metabolism of methane, a greenhouse gas.

$$R-H + O_2 + 2H^+ + 2e^- \rightarrow R-O-H + H_2O$$

Enzymes containing coenzyme B_{12} [cyanocobalamin] catalyse radical-based rearrangements.

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Mo is used to catalyse O atom transfer (O atom is provided by a water molecule), but in more reducing conditions, is catalysed by tungsten W.

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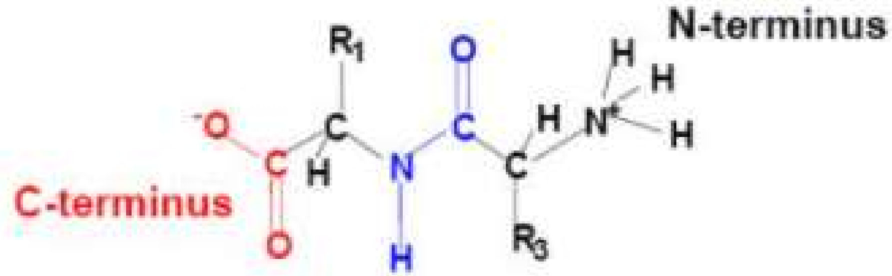
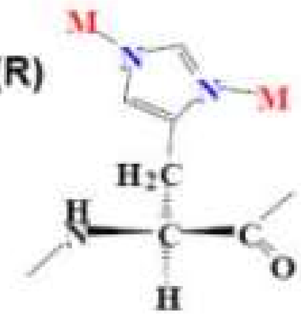
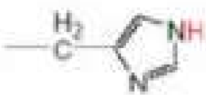
- Proteins consist of α-amino acids, connected via **peptide bonds**



- Metal coordination by functional groups in the side chain (R)

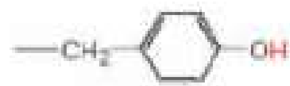


 Histidine (both N atoms available, metal-metal briding possible, pKa ~6)

—$CH_2CH_2SCH_3$ Methionine

—CH_2SH Cysteine (metal-metal bridging, pKa ~ 8)

—CH_2SeH Selenocystein ("non-innocent ligand")

 Tyrosine ("non-innocent ligand")

—CH_2COOH Aspartic acid

—CH_2CH_2COOH Glutamic acid

Aspartic acid, Glutamic acid: pKa ~ 4

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Biomineralization *or crystallization takes place under biological control, has applications in nanotechnology. The formation of biominerals involves the following hierarchy of control mechanisms:*

1. Chemical control (solubility, supersaturation, nucleation).

2. Spatial control (confinement of crystal growth by boundaries such as cells, subcompartments, and even proteins in the case of ferritin.

3. Structural control (nucleation is favoured on a specific crystal face).

4. Morphological control (growth of the crystal is limited by boundaries imposed by organic material that grows with time).

5. Constructional control (interweaving inorganic and organic materials to form a higher order structure, such as bone).

Biominerals can be either ionic salts like calcium carbonate or calcium phosphate, or covalent networks.

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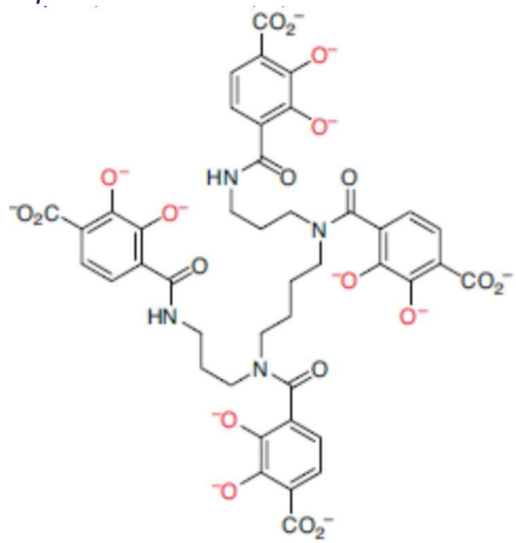
Applications in medicine:

The treatment of **Fe overload** *involves sequestration of Fe by ligands based on or inspired by siderophores.*

Siderophore-like chelating ligands have been developed, such as 3,4,3-LIMACC which contains four catechol groups.



Cancer: *The complex cis-[$PtCl_2(NH_3)_2$] , also called cisplatin, results in the inhibition of DNA replication and prevention of cell division in cancer. Other metal complexes that bind by intercalation within the DNA interior and exhibit better efficacy over Pt drugs include Ru(III) complexes such as fac-[$RuCl_3(NH_3)_3$]. Some Ru complexes selectively interact with DNA, get activated on irradiation, becoming potent oxidizing agents capable of carrying out cleavage of phosphodiester linkages. This method of treating cancers is known as* **phototherapy**.

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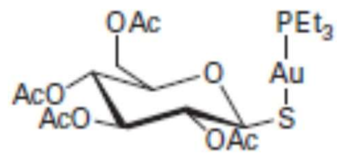
Rheumatoid Arthritis:

Gold drugs are used against rheumatoid arthritis, an inflammatory disease that affects the tissue around joints. Au inhibits the causative factor of rheumatoid arthritis, hydrolytic enzymes in cell compartments known as lysosomes that are associated with the Golgi apparatus. Anti-arthritis drugs are sodium aurothiomalate and sodium aurothioglucose in which Au is in linear coordination. Carbohydrate Au drugs like auranofin are also used.



Imaging:

Certain elements like Technetium, which is an artificial element produced by a nuclear reaction, have an important use as an imaging agent. The active radionuclide of ^{99m}Tc (m for metastable), which decays by γ-emission is used as high-energy γ-rays are less harmful to tissue than α- or β-particles.

$$^{98}\mathrm{Mo} \xrightarrow{\text{neutron capture}} {}^{99}\mathrm{Mo} \xrightarrow{\beta\text{-decay, 90h}} {}^{99m}\mathrm{Tc} \xrightarrow{\gamma\text{-emission, 6 h}}$$

$$^{99}\mathrm{Tc} \xrightarrow{\beta\text{-decay, 200ka}} {}^{99}\mathrm{Ru}$$

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