8. Biological implications of complex combinations

Biological role of metal ions

- Metal ions also play an important role in the organisation, movement and functioning of living matter.

- In the case of transition metal ions, properties such as their small size, complicated electronic structure, large atomic mass, large and variable charge, redox potentials, etc. explain their indispensability for the fundamental biological processes underlying life.

- In living organisms, metal ions are found in the form of chelated complexes, organised in giant structures called macromolecules, such as porphyrins, proteins, lipids, etc.

Biological role of metal ions

- Metal ions in biological systems can have two main roles ***structural*** and ***functional***.
  - ***Structural role***: the metal ion stabilises some structures, especially proteins.
  - ***Functional role***: the metal ion is involved in the reactivity of bio-sites, especially from essential metalloenzymes.

- ***The most important functions*** to which metal ions have been particularly adapted are the following:
  - ***Structural function***
  - ***Load carriers***
  - ***Production, metabolism and degradation of organic compounds***
  - ***Electron transfer***
  - ***Activation of small molecules with high symmetry***
  - ***Organometallic reactivity***

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Lithium	Motor nerve depressant, weakens muscle contraction; not a sodium or potassium antagonist; taken orally only, injectable form causes severe, lethal intoxication. Decreases psychomotor activity in schizophrenia, epilepsy, behavioural disorders.	Gotalitin, in rheumatic diseases; Li2CO3 in neuropsychiatric diseases.
Sodium	Main ionic component in the extracellular environment, influences water distribution in the body. Essential role in membrane electrical processes (sodium influx causes depolarization - contraction, efflux causes repolarization - relaxation). Influences homeostasis, intervening in the hydromineral and acid-base balance, together with Cl^-; increases the bioavailability of sulphonamides, antibiotics and barbiturates by increasing their solubility.	NaCl+NaHCO3 - infusion, used to restore hydromineral and acid-base balance.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Potassium	Major ionic component of the intracellular environment. Contributes to maintaining hydromineral and acid-base balance. Involved in membrane electrical phenomena, in the formation of glycogen from glucose. Anabolism translated by K^+ ion, and catabolism by the removal of K^+. It is a sodium and calcium antagonist.	KCl infusible solution for hydromineral and acid-baserebalancing; to increase bioavailability of drugs, forming soluble compounds; osmotic diuretic.
Magnesium	Component of chlorophyll, red cells, muscle; laxative, cholagogue, antacid, antiseptic; central nervous system (CNS) depressant, anesthetic effect and decreased excitability of the heart. Calcium antagonist.	$MgSO_4$ laxative and cholagogue. MgO, $Mg(OH)_2$ antacid; $MgSO_4$ depressant injectable, hypertensive encephalopathy and paroxysmal tachycardia.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Calcium	Essential component of protoplasm and cell membrane, bones and teeth. Influences phosphorus metabolism, capillary permeability, blood clotting (forming thrombin). Important role in cell division and transmission of nerve impulses; involved in the transfer of sodium and potassium across the membrane. Influences the vegetative nervous system with sympathetic predominance. It is involved in the catalytic activity of some enzymes in the form of citrate or protein complexes. Na antagonist favouring parasympathetic predominance.	Ca-gluconate, lactate, pantothenate, glycerophosphate, phosphate - for calcium intake in pregnancy, lactation, lactation, rickets. $CaCl_2$+ gluconate intravenously to reduce tetanic spasms and allergic protectants. $CaCO_3$+$Ca(OH)_2$ neutralizer and gastric protectant.
Strontium and Barium	Highly toxic, substitutes Ca from bones.	BaSO4 - radio-opaque.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Aluminium	Essential trace element (along with B, Si, Ga, Mn, Mo , etc.). It activates succindehyde-drogenase.	$AlK(SO_4)_2 \cdot 12H_2O$, $AlCl_3$, $Al(CH_3COO)_3$ astringents and antiseptics. $AlPO_4$, $Al(CO_3)OH$ gastric neutralizers.
Gallium	Essential trace element concentrated in bones.	Used as a radioactive preparation in the treatment of some bone cancers.
Tin	Trade element; it is a component of some enzymes.	
Vanadium	Essential trace element. Inhibits cholesterol biosynthesis; favourable effect against tooth decay. Anti-syphilitic properties. It has been tried in the treatment of tuberculosis and diabetes.	All compounds are toxic.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Tellurium	Spirocidal and cytostatic action	Preparations for suppressing night sweats in tuberculosis patients.
Chromium	Important role in carbohydrate metabolism and diabetes.	Chromic acid (0.1-5%) in the treatment of malignant tumours, lupus erythematosus, diphtheria membranes, leukorrhoea. Very toxic Cr(VI).
Molybdenum	Essential trace element for living organisms. Component of xanthine oxidase and aldehyde oxidase. Mo(V)-containing enzymes control nitrite reduction and nitrogen fixation in plants.	

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Manganese	Essential trace element. Activates cozimase, carboxylase, cholinesterase, phosphatase, and luicylpeptidase. It is involved in animal reproduction and growth, calcium and phosphorus metabolism. Mn(II) deficiency leads to animalinfertility and bone malformations.	MnSO4 tonic, robust, in tonic wine. $KMnO_4$ antiseptic. At low concentrations, Mn(II) antagonizes Ba(II)-induced spasm by a direct muscle mechanism. $MnCl_2$ injectable in schizophrenia, furunculosis, acne.
Cobalt	Essential trace element, component of vitamin B12. Stimulates erythropoiesis (in high doses inhibits it). Stimulates iron absorption, in intestinal inflammation.	Fe(II) substitute in the treatment of anaemia. CoCl2 component of neoanemovite (which also contains Fe(II) gluconate and CuCl2).

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Iron	Essential microelement with better studied role. Component of hemoglobin, myoglobin, erythropoietic organs, spleen. Involved in cell metabolism. Has a role in oxygen transport. Component of cytochrome *c* and cytochrome oxidase. Induces haemoglobin synthesis (along with Cu(II), Co(II), Ni(II), Mn(II), Ti(II), Zn(II), etc.). Iron deficiency leads to anaemia. Absorbed in duodenum and intestine as Fe(III) hydroxyphosphate, which with apoferritin, gives ferritin which is deposited in liver, spleen, marrow, kidney, lymph.	Glubifer (iron glutamate) in hypochromic anemias. FeCl3 external use as a haemostatic astringent. Reduced Fe, $FeSO_4$, iron ammonium citrate, $FeCO_3$ in the treatment of anaemia. Some Fe(II) and Fe(III) complexes are also used for the same purpose. In high doses, toxic effects. Ferrum Hausmann intramuscular (maltous iron) or intravenous (saccharide iron), in hypochromic microcytic anemias.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Copper	Component of some oxygen-carrying pigments, some redox enzymes, ceruloplasmin, hemocyanin and turcaine, tyrosinase. Cu(II) participates in the oxidation of glutathione, cysteine, ascorbic acid, influences erythropoiesis (by mobilising Fe from deposits), synthesis of haemoglobin, activates glycolysis. It is distributed in serum, brain, liver, kidneys, bones, striated muscles.	$CuSO_4$, $CuCl_2$ (in tonic syrup, Neoanemovit), in anaemia, asthenia, convalescence. $CuSO_4$ (1%) emetic, in phosphorus poisoning. Astringent and decongestant Cu(II) compounds.
Zinc	An essential trace element, it is found mainly in the pancreas. Component of enzymes such as carbonic anhydrase, carboxypeptidase, alcohol dehydrogenase, glutamate dehydrogenase, muscle lactate dehydrogenase, renal alkaline phosphatase. Activates enolases and lecithinases.	ZnO, $ZnCO_3$, $ZnCl_2$, $ZnSO_4$, solutions or powders, are antiseptic, astringent keratolytic agents used in some skin conditions.

Biological role of metal ions

Metal	Actions in which it is involved	Remarks
Mercury	Not an essential trace element. It is toxic. Hg(II) influences enzyme systems in the renal tubules involved in sodium reabsorption. Antifungal, antiseptic, astringent, germicidal action.	Mercasept, Merbromin, Merthiolat, Mercresol, Nitromersal, antiseptic. Salyrgan, Mercusal, Mercurophylin, Mercaptomerin Poliuren, Eridron, diuretics. Hg_2Cl_2 purgative. $Hg(CN)_2$ antisiphilitic. $HgCl_2$, $Hg(CN)_2$, HgO, $HgNH_2Cl$ in ointments.

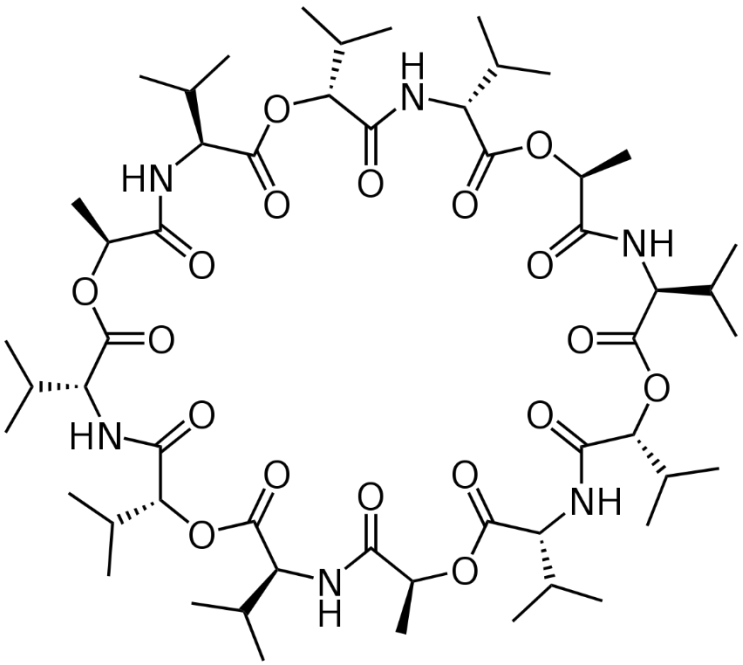
- Other metals such as Tl(I), Tl(III), Pb(II), As(III), Sb(III), Ag(I), Au(I), Au(III), platinum metals and others have toxic effects on the body. Some, such as Ag, Au, Pb, etc., are used in medicinal substances.

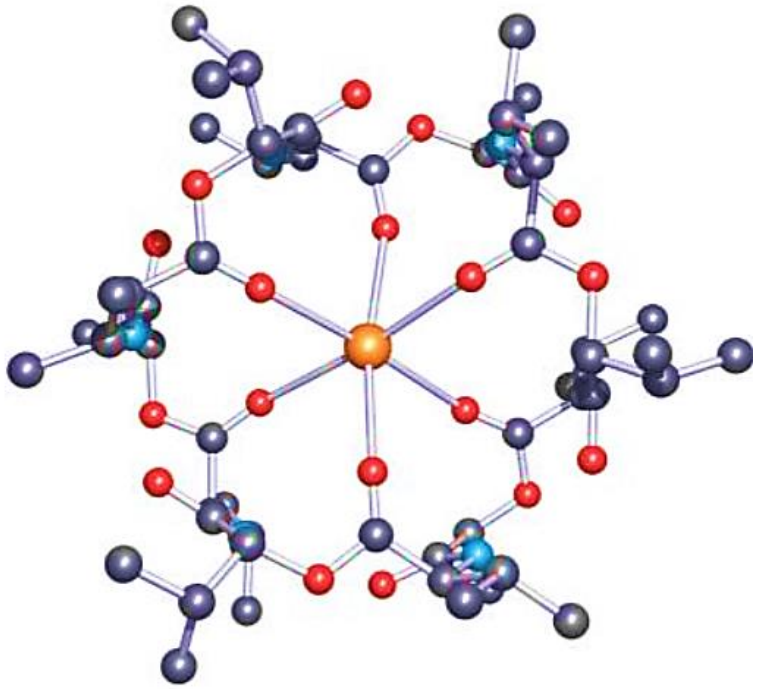
- Metal ions, in the form of chelated complexes of natural biological systems, are involved in the synthesis and degradation of fundamental biological molecules, in the blocking or substitution of functional groups, in oxygen transport to tissues, cellular redox reactions, energy transfer, etc.

Biocoordination systems

Valinomycin-K+

- Valinomycin is a naturally occurring dodecadepsipeptide, obtained from various *Streptomyces*species, used in the transport of potassium ions across the mitochondrial membrane.
- It has a selectivity for K+ ions 10^4 times higher than Na+ ions.
- Valinomycin is also a good antibiotic because of its ability to alter trans-membrane ion balance in bacteria.

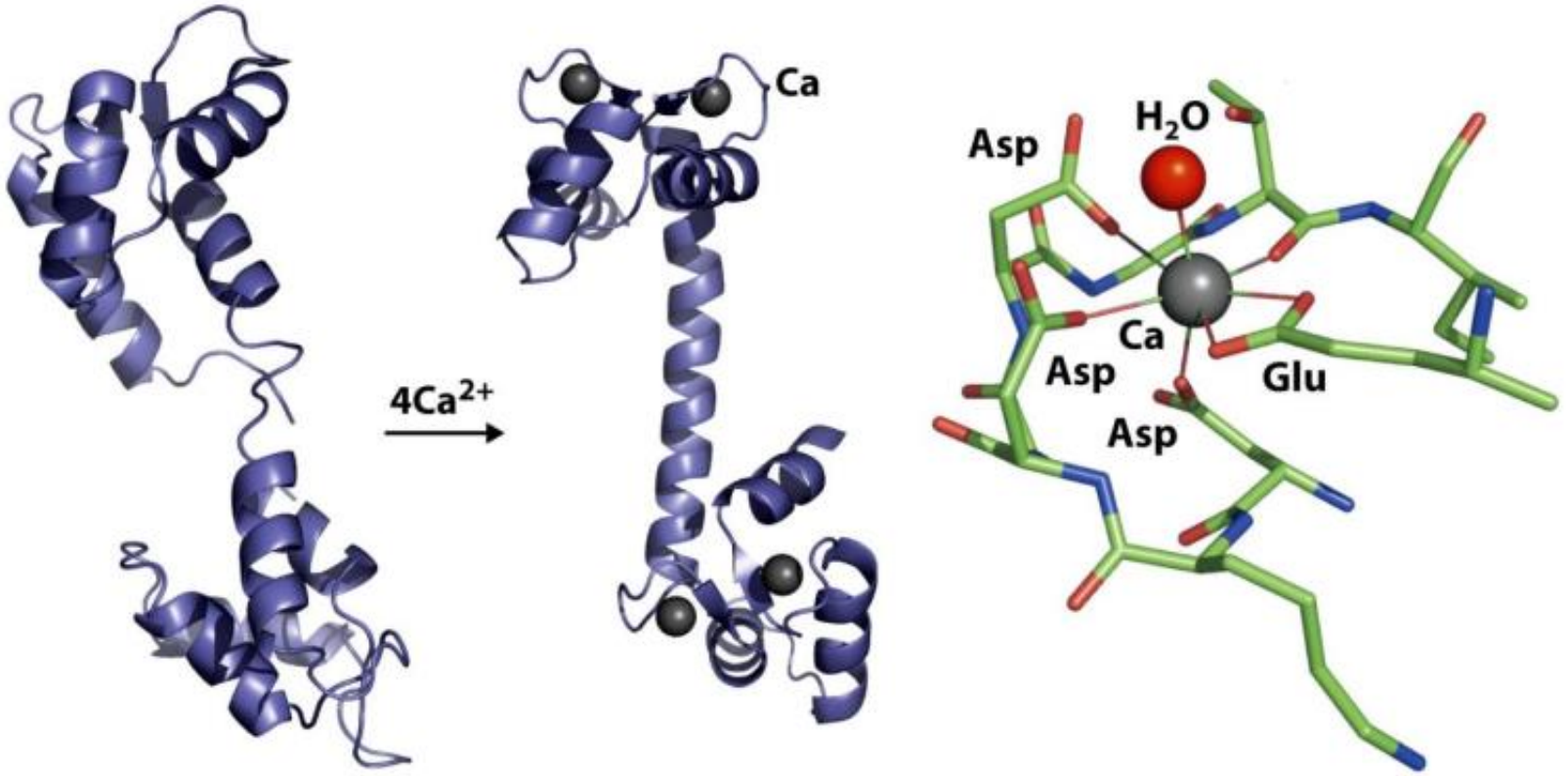




Biocoordination systems

Calmodulin

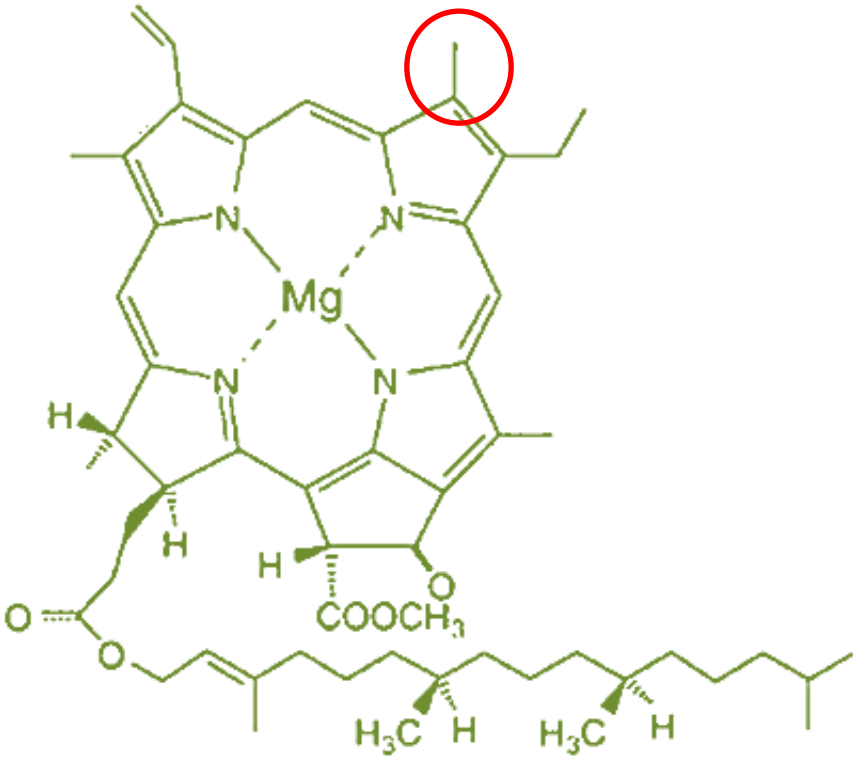
- Calmodulin *(calcium-modulated protein*) is a small protein (ca. 17 kDa) from eukaryotic cells, with amino acid residues **glu** and **asp** binding Ca2+ ions.
- Once bound to Ca2+, calmodulin acts as part of a calcium signaling mechanism by modifying its interactions with various target proteins such as kinases or phosphatases.



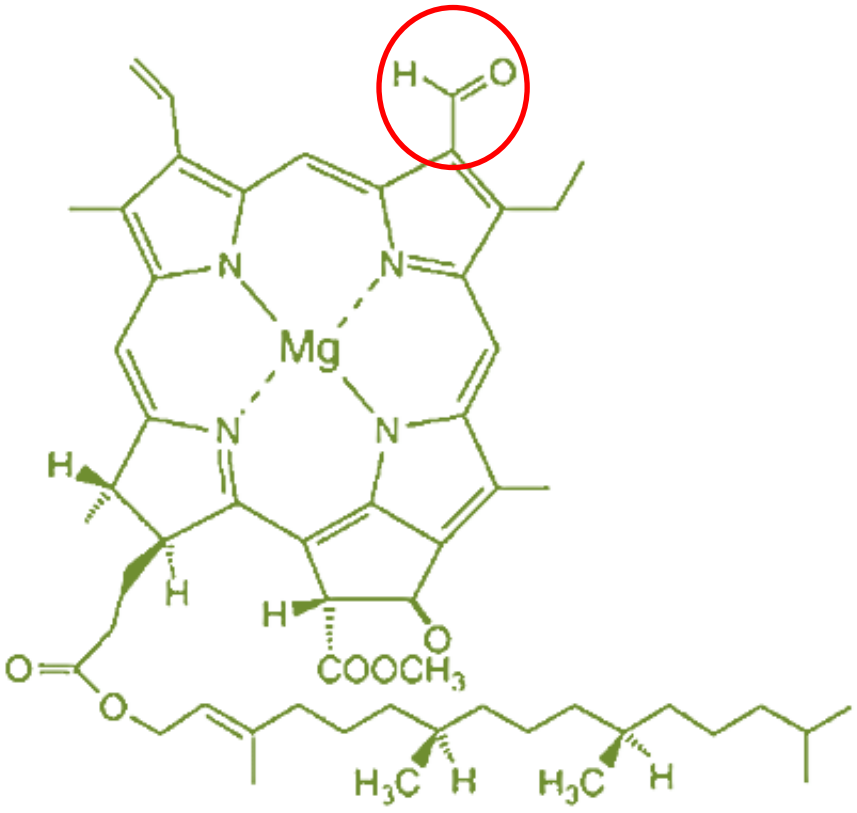
Biocoordination systems

Chlorophyll

- Chlorophyll is the green pigment in the chloroplasts of algae and plants, and in the mesosomes of cyanobacteria.
- It is essential in the process of photosynthesis, allowing plants to absorb the energy of light radiation.



Chlorophyll a

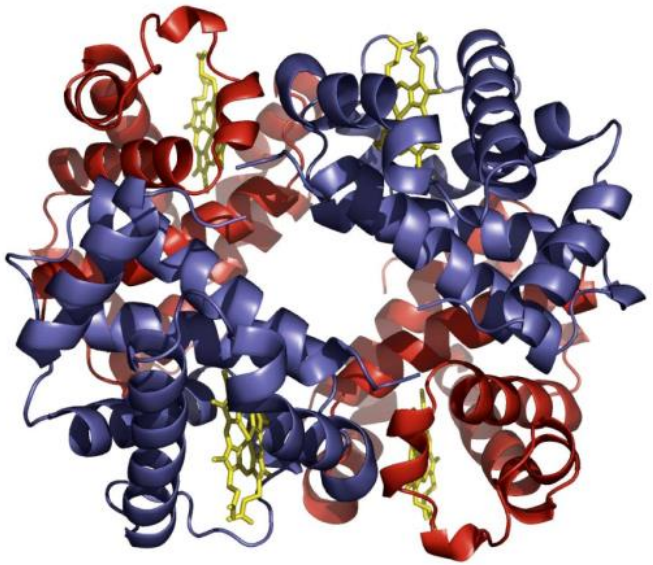


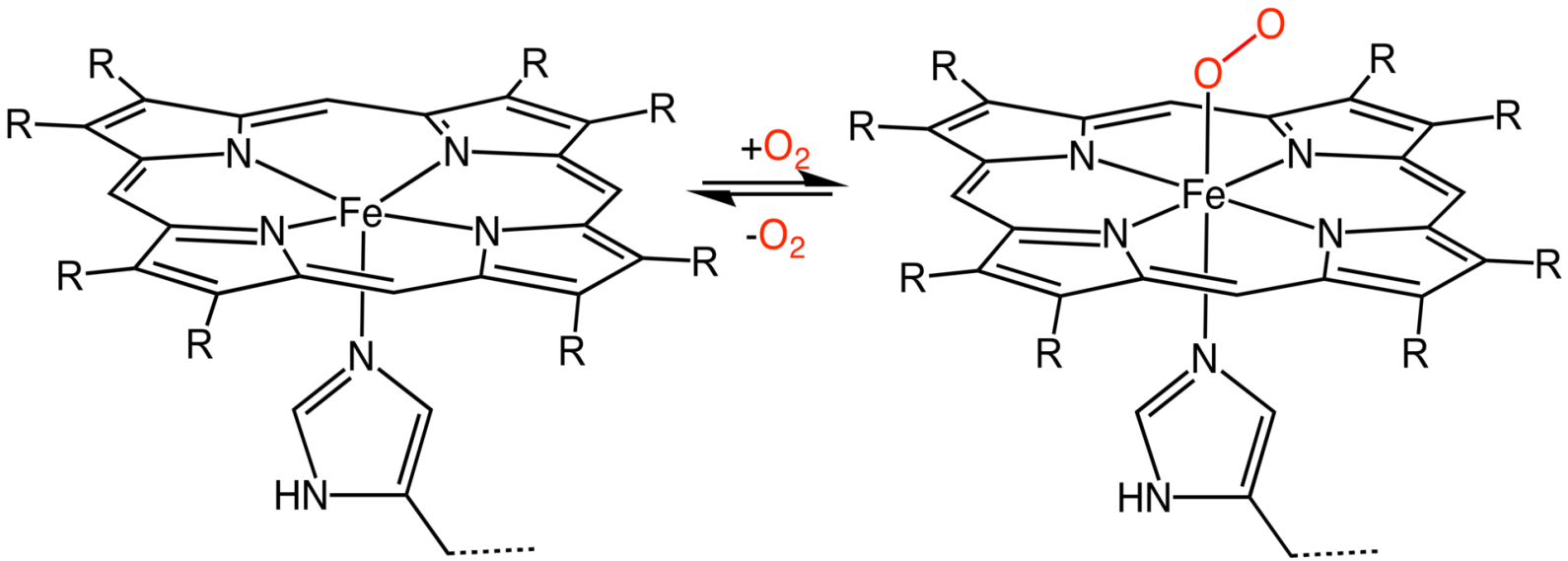
Chlorophyll b

Biocoordination systems

Haema

- Haema (gr. *haima = blood*) is the red pigment of haemoglobin in blood, biosynthesised in both bone marrow and liver. It is also found in other haemoproteins such as myoglobin, cytochromes, catalases and peroxidases.
- It is essential in the process of reversible oxygen uptake during respiration.

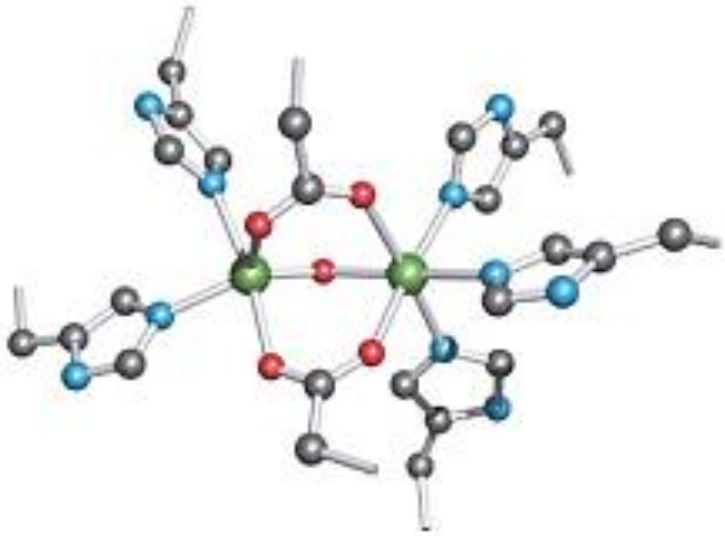


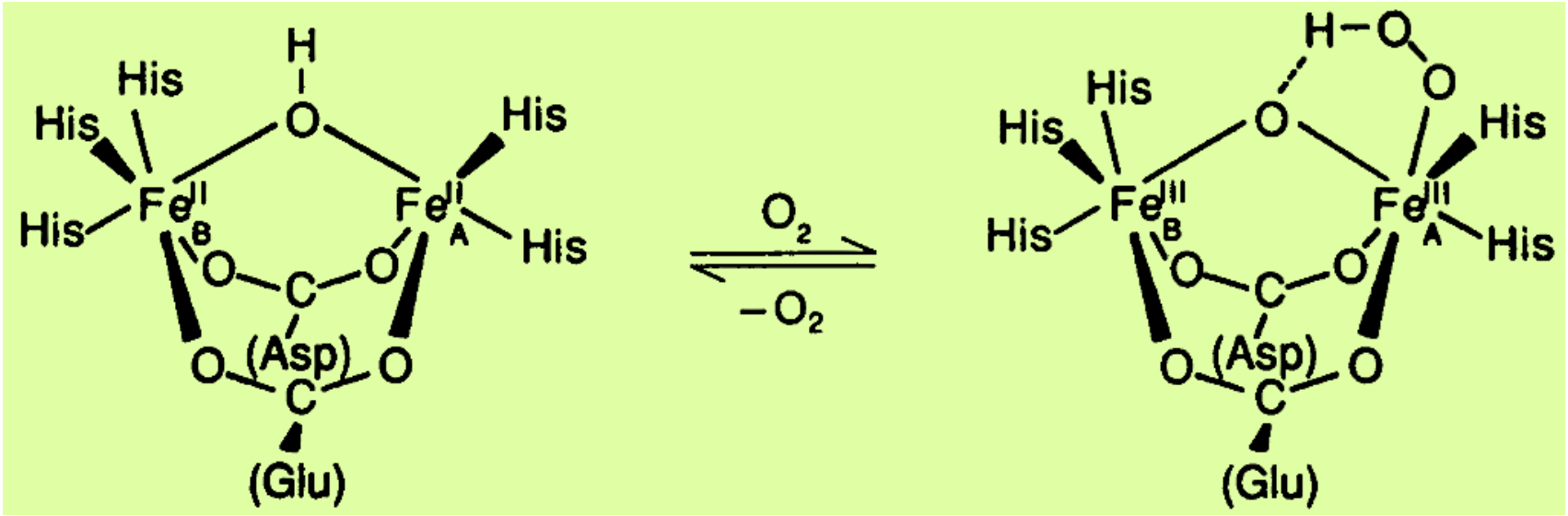


Biocoordination systems

Emeritrine

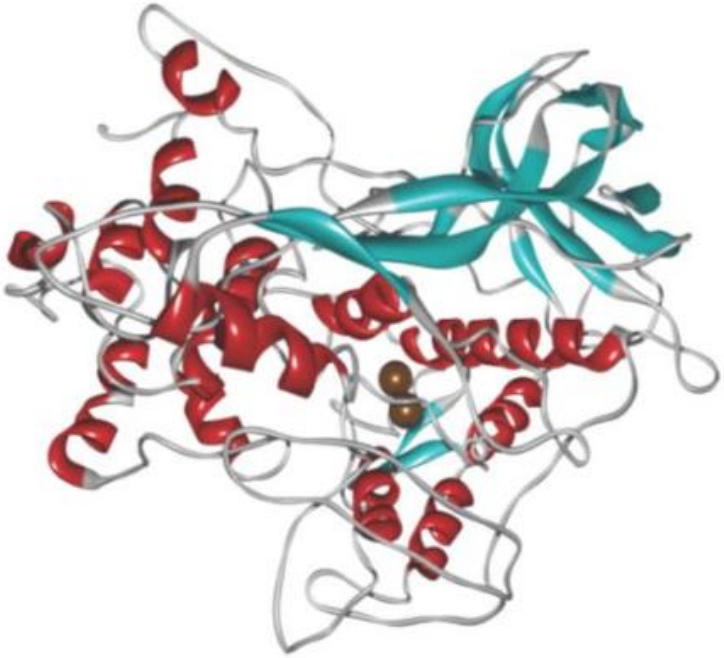
- Some classes of marine invertebrates, molluscs and spiders use non-porphyrin metalloproteins for reversible oxygen uptake.
- One of these is ***emerythrin***, an octameric, mass-like protein. 108 kDa, each subunit consisting of 113 amino acids.



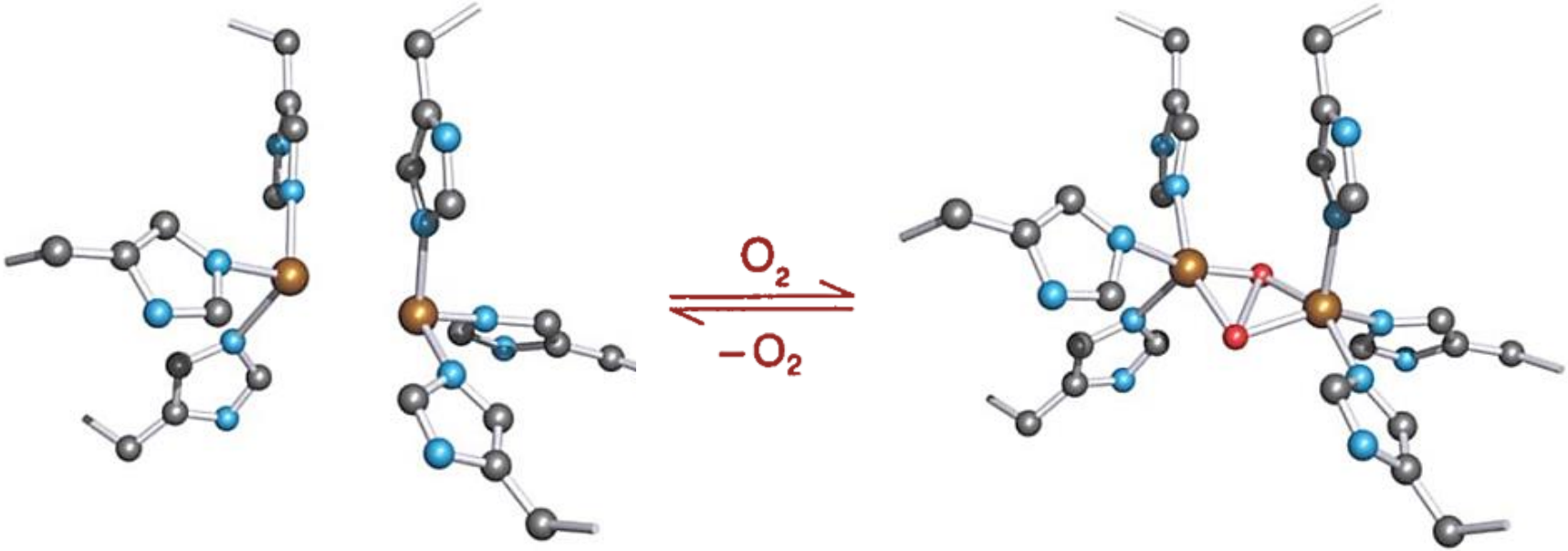


Biocoordination systems

Hemocyanin



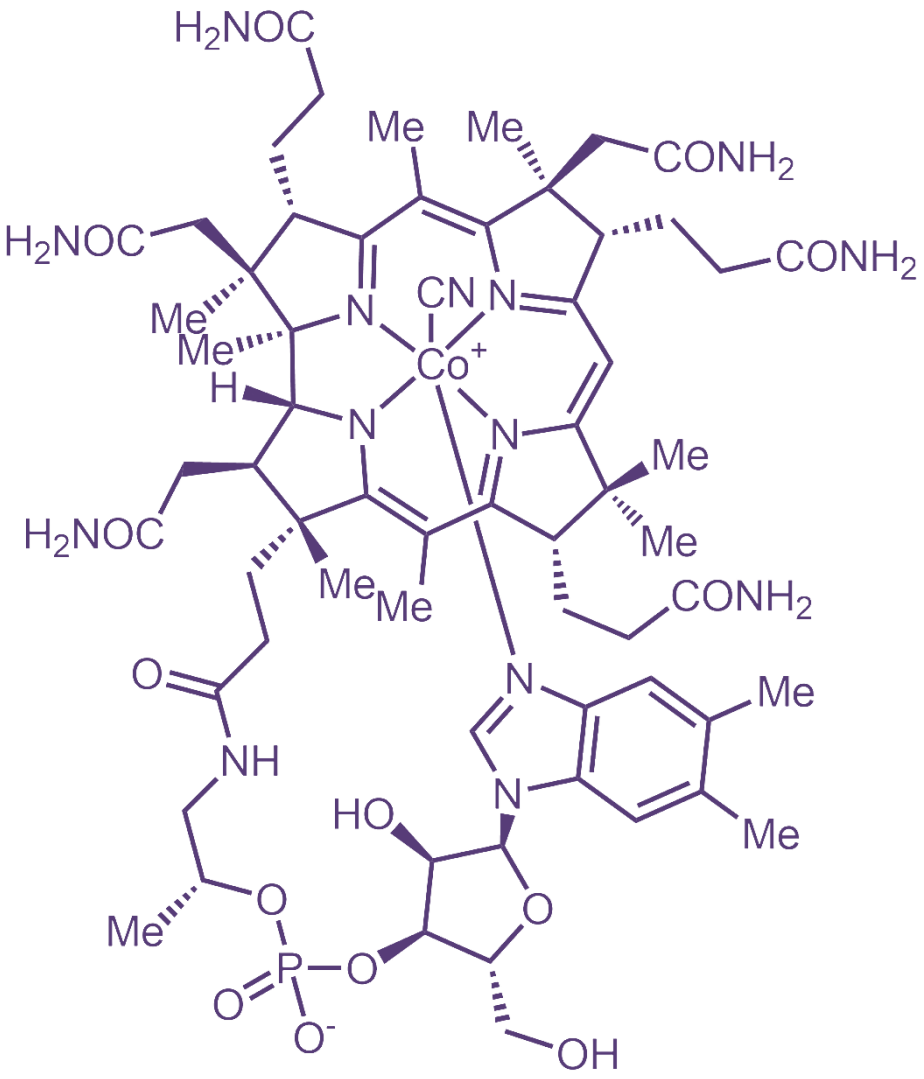
- It is a protein required for oxygen transport in various molluscs and arthropods.
- It is found mainly in organisms living in cold, thin-air environments, conditions in which hemoglobin's efficiency to carry oxygen is lower than that of hemocyanin.



Biocoordination systems

Cyanocobalamin (vitamin B12)

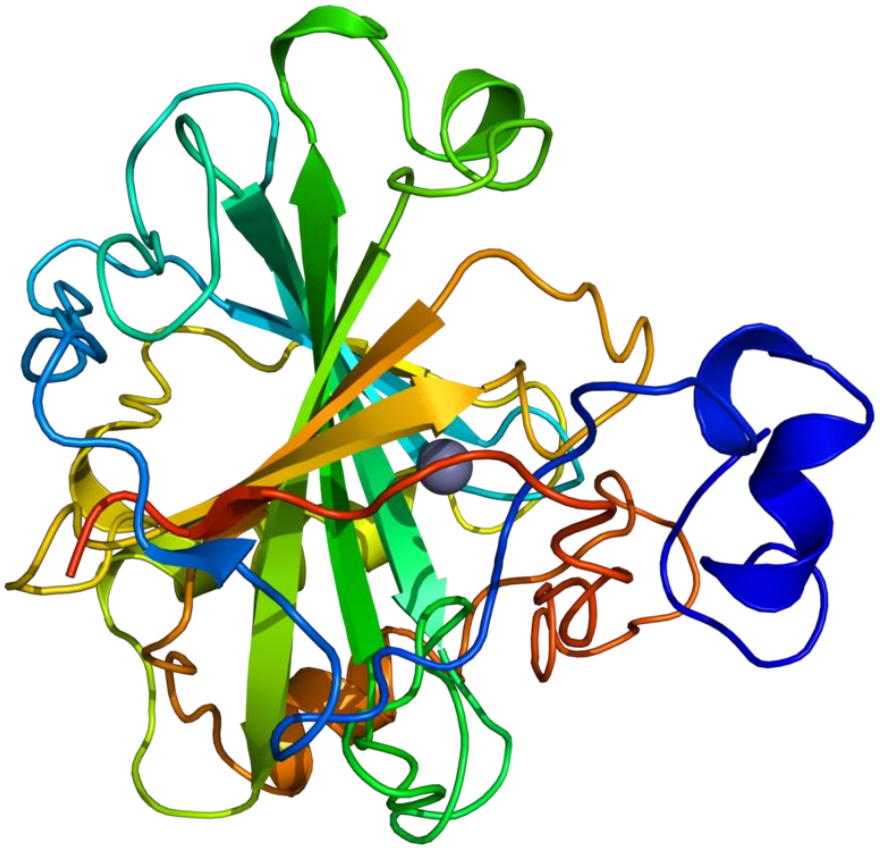
- It is a complex based on Co(III) and chorinic cycle, which must be supplied in the diet, since the human body cannot synthesise it.
- The liver can store enough vitamin B12 for several years.
- The absence of this vitamin leads to pernicious anaemia, a condition in which the body is unable to produce enough healthy red blood cells.
- It is an essential cofactor for many natural enzymes such as methyltransferase and mutagenesis.

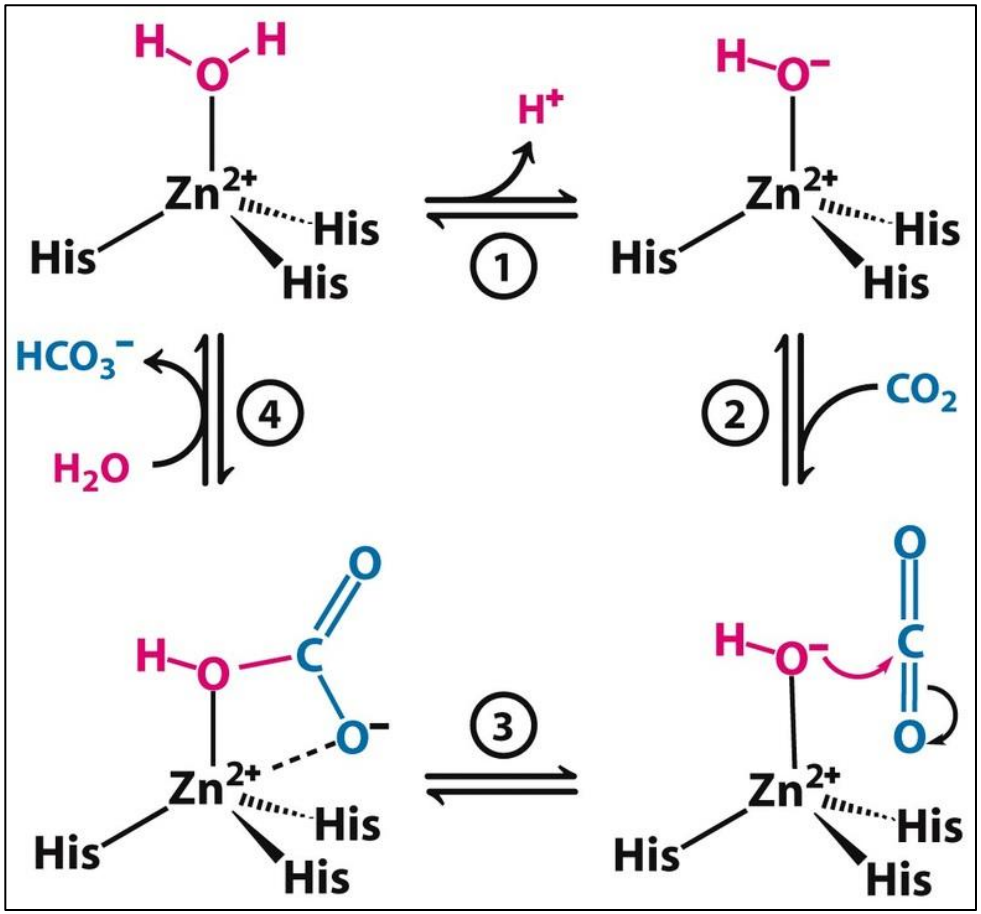


Biocoordination systems

Carbonic anhydrase

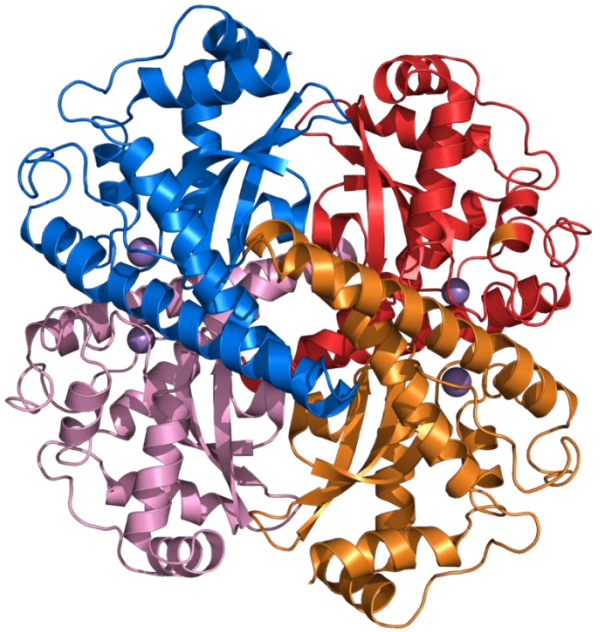
- It is a Zn(II)-based metalloenzyme that catalyses the interconversion between CO_2 and the $HCO3^-$ ion, with an essential role in respiration (rapid removal of CO_2) and in maintaining acid-base balance.



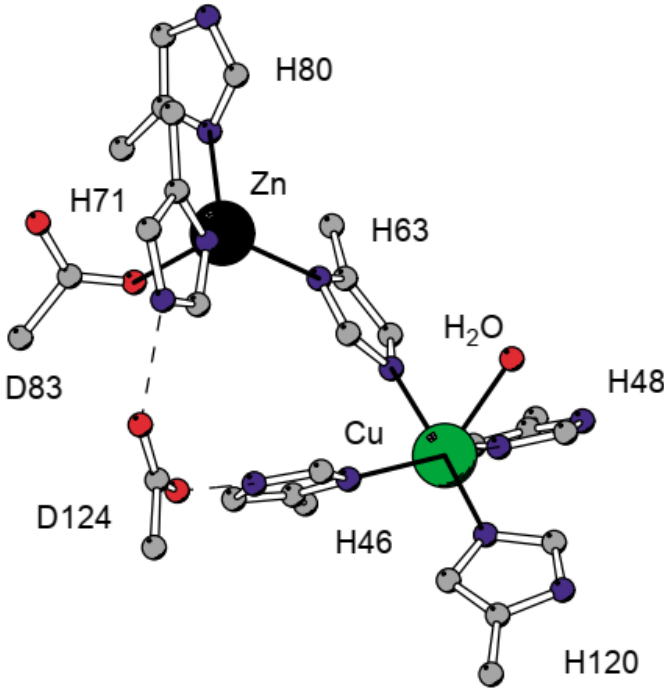


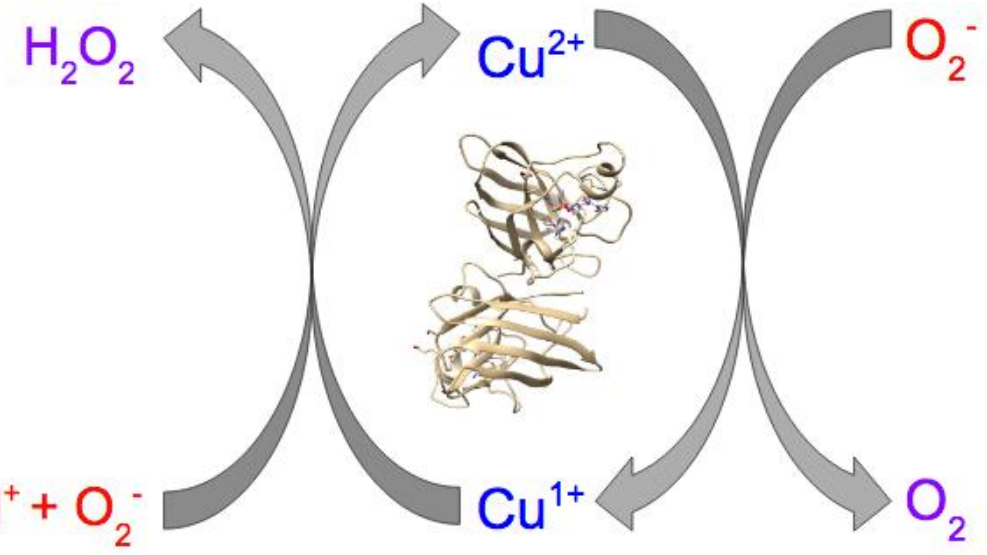
Biocoordination systems

Superoxide dismutase (SOD)



- It is an antioxidant enzyme that catalyzes the superoxide radical dismutation reaction O_2^- to oxygen (O_2) and hydrogen peroxide (H2O2).
- The most important SOD is found in erythrocytes and contains Cu and Zn (there are also SODs containing Fe or Mn in plants or bacteria).





Masking agents in the therapy of heavy metal poisoning

General aspects

- Heavy metal poisoning, i.e. poisoning with heavy metal ions, is usually of an occupational nature, accidental, and less often the result of suicide attempts or murder.

- Often such poisonings are due to excessive pollution of the environment with ions of Pb(II), Cd(II), Hg(II), As(III), As(V), Be(II), etc., as a result of the industrialisation and technicalisation of various sectors of activity.

- Most toxic metal ions are thiolipid, i.e. they have a high affinity for SH groups in proteins and enzymes, which causes displacement of biologically active metal ions and thus deregulation of many normal metabolic processes.

- For the treatment of heavy metal ion poisoning, complexing masking agents are used, usually organic substances of the chelate ligand class.

Masking agents in the therapy of heavy metal poisoning

General aspects

- The effectiveness of treatment with such chelating agents depends on a number of physical-chemical factors as well as on some physiological conditions that the masking agents (antidotes) must fulfil.

- **Among the physical-chemical factors the following can be mentioned:**

1. Structure and physicochemical properties of antidotes.
2. Stability of the complexes that the masking agents form with the metal ions (stability of the complexes must be high).
3. Distribution of metal ions in body fluids and tissues and their binding to biological ligands in the body.
4. The ease with which ligand-antidotes and their complexes can permeate cell membranes.
5. Preference of ligand-antidotes to toxic metal ions, which must be greater than their affinity for essential metal ions.

Masking agents in the therapy of heavy metal poisoning

General aspects

- **Among the physiological conditions that masking agents-antidotes must fulfil are the following:**

1. To be able to reach (diffuse) relatively easily throughout the vascular system to act throughout the intoxicated body.
2. Be slightly toxic, if at all, as overdose is often necessary, in which case toxic ligands cause complications.
3. Prevent the passage of toxic metal ions from the blood into cells.
4. To be able to remove toxic ions from cells if they have already entered the bloodstream.
5. Form soluble, easily excretable complexes with toxic metal ions, because however stable a complex may be, over time it gradually releases the toxic metal ion, even in small quantities.

Masking agents in the therapy of heavy metal poisoning

General aspects

- In the case of radioisotope poisoning it is more difficult to find suitable masking agents, especially if they are deposited in parts of the body that are more difficult to access, such as the bones.

- Although in some cases suitable antidotes have been found, in terms of effectiveness in removing the radioactive toxicant, these antidotes are usually relatively toxic.

- For example, radioactive ^{210}Pb can be removed with 2-mercaptocyclohexyl diacetate or its dimethyl derivative, even more effectively than with EDTA, but both compounds are quite toxic.

- It is also possible to reduce the retention of radioactive ^{90}Sr in bone by treatment with cyclopentanediaminetetraacetic acid, but the effectiveness is too low, as with the use of bis-(dicarboxyaminoethyl)-ether, in which case the retention of radioactive ^{90}Sr is still (in mice) 50% after 24 h.

Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
Zn(II)	Strong local caustic due to protein precipitation or flocculation. Passes into tissues as soluble albuminates. CNS paralysing action, damage to circulatory system and muscles, paralysis of limbs. Death by collapse or glottis oedema.	2,3-dimercapto-propanol (BAL), D-penicillamine, CaEDTA-Na2 (Haussmann calcium)
Cd(II)	Hepato-renal and blood toxicity. Inhibits enzymes by blocking thiolitic groups through complexation. Causes anaemia, asthenia, nasal ulceration, emphysema, chronic discrete nephritis, cadmitic osteosis, bone fissures. In acute intoxications death by respiratory and circulatory failure.	CaEDTA-Na2 No BAL! This is totally ineffective.
Hg(II)	Irritant-corrosive necrotizingaction on the respiratory tract, digestive tract and nervous system, hyperthermia, tendency to collapse. Thiolopriv toxic, blocking SH groups by complexation; blocks enzymes with disulfide groups, causes kidney damage (necrosis, nephritis).	BAL, only in acute intoxications (not in chronic ones!). CaEDTA-Na_2; Rongalite (sodium formaldehyde-hydroxyphosphate).

Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
Cu(II)	Local irritant, toxic to striated muscles and heart muscle (causes paralysis and respiratory arrest or cardiac arrest in diastole). Causes haemolytic anaemia; toxic to liver and kidney. Forms albumin or lipid complexes (last in liver, kidneys, pancreas, nervous system, bones). Liver corrosive.	CaEDTA-Na2
Au(III)	Toxic thioloprovic, inhibits enzymes with SH groups involved in cellular redox processes. Haematotoxic, hepatotoxic and nephrotoxic; depresses haematopoiesis and produces aurostomatitis. Side effects when taking Sanocrysin, Solganal (Tauredon). Accidental acute poisoning by overdose.	BAL
V(II, III, V)	Toxic local irritant (tearing, rhinorrhoea, epistaxis, bronchitis). Digestive and liver toxic.	BAL CaEDTA-Na2

Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
Tl(I)	CNS toxicity (general depression, delirium, epileptiform convulsions, dementia manifestations, thalamic encephalopathy, paralysis of lower limbs). Thiolipid action in cysteine metabolism. Digestive, renal, ocular toxicity. Disorders of genital functions, cessation of menstrual cycle. Alopecifying effect. Collapse or respiratory arrest.	BAL, cysteine, methionine, thioacetamide, CaEDTA-Na2
Pb(II)	Thiolopriv toxic, displacing some metals from metalloenzymes (e.g. those participating in the synthesis of haemoglo-bin). Cardio-circulatory toxicity (vasoconstriction - hypertension, arteriosclerosis). At the cellular level it inhibits the cofactors NADH and NADPH, influencing redox processes. Neurotoxic to CNS and peripheral nerves; nephrotoxic.	CaEDTA-Na_2 Ca-gluconic CaDTPA-Na_2 (DTPA = diethylene triaminpenta-acetate)

Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
As(III,V)	Thioloprivic toxic, inhibiting enzymes with thiol groups (lactic acid dehydrogenase, glycerophosphate dehydrogenase, pyruvate oxidase, cytochrome oxidase, succindehydrogenase, cysteine-cystine systems, reduced glutathione-glutathione oxidase, cellular respiration) blocking carbohydrate and lipid metabolism at the pyruvic acid stage.	BAL, Sodium thiomalate, D-penicillamine, Penicillin, Methionine (which also acts as a hepatoprotector).
Sb(III,V)	Toxic thioloprivic. Action similar to that of arsenic. Stimulation of sympathetic nerves, diarrhea. Elective action on the antitoxic functions of the liver. Intense vasodilation, producing exaggeration of all excretions.	Albumen water, BAL
Be(II)	Local respiratory disorders, painful irritations: acute or recurrentconjunctivitis , acute, chronic bronchopneumopathies, spontaneous pneumothorax, acute dermatitis. Cardiac complications (hypo and asystole). Inhibits amylases and alkaline phosphatase.	Aurintricarboxylic acid

Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
Bi(III)	Passes the digestive barrier, being carried as albuminates. Blocks SH clusters, decreases medullaryhematopoiesis. Toxic to blood (haemorrhages, epistaxis, metrorrhagia, anaemia), nerves (headache, vertigo, asthenia, inhibits cellular respiration), kidneys (polyuria, oliguria, severe nephritis). Allergic action, stomatitis, osteoporosis (Bi has bone tropism); lowers body resistance, favouring infectious diseases. Therapeutic intoxications similar to those with mercury.	BAL, Sodium thiomalate (with caution).
Cr(III,VI)	Local irritant-corrosive toxic, allergenic; especially methemoglobinizing Cr(VI), with asphyxiating symptoms, cyanosis; nephro- and hepatotoxic. Carcinogenic (lung cancer, less commonly nasal and laryngeal cancer). Skin lesions, ulcers, gastroenteritis, oliguria followed by anuria and azotemia. Anaemiant. Severe stomatitis.	CaEDTA-Na_2

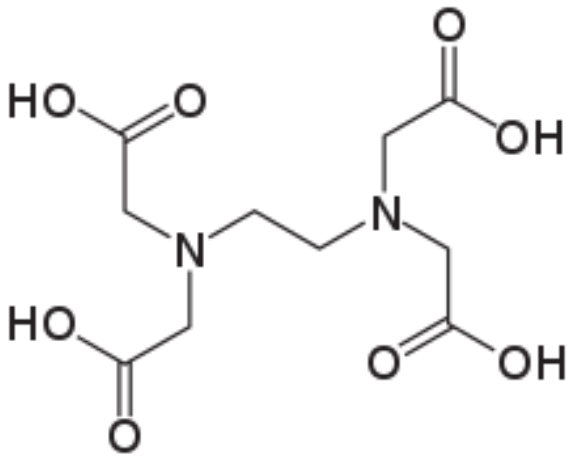
Masking agents in the therapy of heavy metal poisoning

Main toxic ions and corresponding antidotes

Metal ion	Toxic action	Antidotes used
Mn(II,VII)	Cumulative toxic; locally irritating-corrosive. Mn(VII)-methemoglobinizing, cardiac toxic, hepatotoxic, nerve toxic (grey matter damage), vasoplegia and paralysis of lower limbs. Heavy speech, manganic Basedow.	BAL, CaEDTA-Na2, Sodium thiomalate, Rongalit
Ni(II) **$Ni(CO)_4$** **Ni**	Toxic thioloprivic, nerve toxicant acting on the CNS (convulsions, hallucinations, cerebral oedema). Carcinogenic; Ni-powder causes lung and nasal cancer. $Ni(CO)_4$ toxic, choking effect (pulmonary oedema). Acute pulmonary heart failure.	$CaEDTA\text{-}Na_2$, BAL, Diethyl dithiocarbamate
Co(II), **$Co(CO)_8$,** **Co**	Local-irritant toxicity, in blood-forming organs (polycythemia), vasodilator (hypotensive). Nervous toxicity (convulsions, pulmonary asthma). Carcinogenic (lung cancer, osteosarcoma).	BAL, CaEDTA-Na2, Cysteine, Methionine

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of EDTA



- Usually double sodium and calcium salts are used, which have little influence on the calcium concentration in the body, but can exchange Ca(II) for Pb(II), the lead complexonate being more stable:

$$\text{Ca-EDTA-Na}_2 + \text{Pb}^{2+} \rightarrow \text{Pb-EDTA-Na}_2 + \text{Ca}^{2+}$$

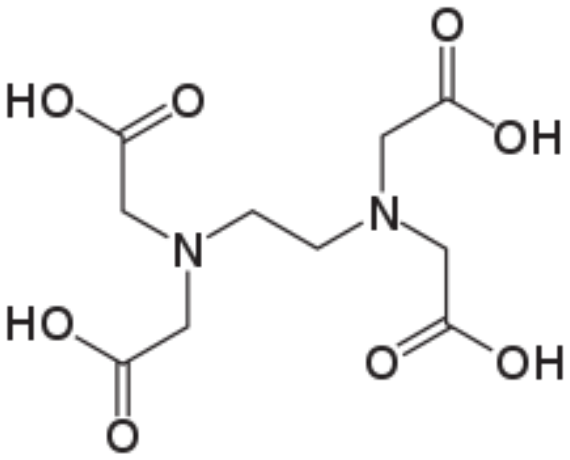
- This chelating agent has the advantage that all of its heavy metal ion complexes are soluble and stable in water, which facilitates their excretion.

- Ca-EDTA-Na2 forms the basis of the standard method of treatment of encephalopathies and is administered intravenously.

- As the toxicity of this antidote is very low, injections of 3g/day intravenously can be given and is well tolerated by the human body.
- In addition, this antidote is excreted as such in the urine, and its metabolism is negligible.

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of EDTA



- In addition to lead, copper and zinc poisoning, Ca-EDTA-Na2 is also used as subcutaneous injections in the therapy of Co(II) poisoning and as intraperitoneal injections in the therapy of Cd(II) poisoning.

- Na2EDTA can be used in the treatment of corneal burns with lime, for Ca(II) removal, or in the treatment of hyperglycaemic patients, also for Ca(II) removal.

- In the form of MgEDTA it can be used to modify the Ca and K ion ratio in digitally determined arithmias according to the exchange reaction:

$$\mathbf{MgEDTA + Ca^{2+} \rightarrow CaEDTA + Mg^{2+}}$$

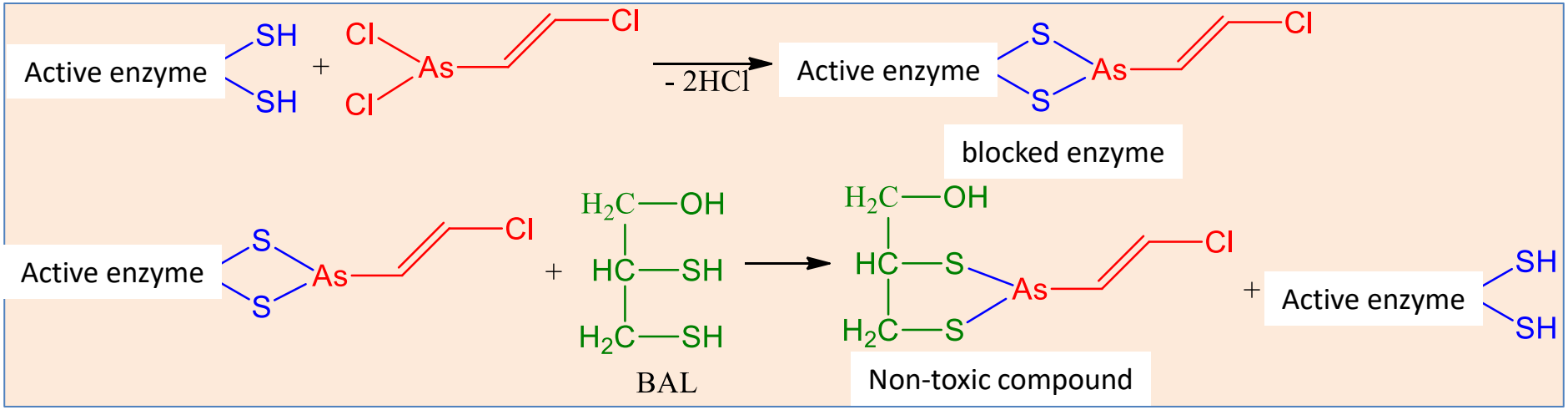
- On the basis of this reaction, the calcium concentration decreases and, therefore, the hypertension.

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of BAL and other thiols

- BAL (British Anti Lewisite), i.e. 2,3-dimercaptopropanol, was used in World War I as an antidote against arsenic poisoning caused by lewizite (dichloro(2-chlorovinyl)arsine).

- In the body, arsenic has a thiolipid action, blocking the thiol groups of some enzymes, which causes serious disruption of important biochemical processes.



- Therefore, the thiol groups of the thiol-enzymes are released under the action of BAL, restoring enzyme activity.

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of BAL and other thiols

- BAL has also proven effective in poisoning with Au, Hg, Sb, Cu, Bi, V etc.

- In BAL therapy, some drawbacks have also been observed, which are generated by: its instability in aqueous medium (it oxidizes), various toxic effects in the body, decrease in blood calcium concentration (by complexing Ca(II) and Mg(II) ions with BAL).

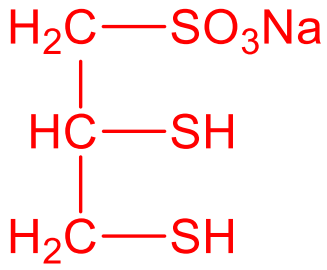
- BAL oily solution is absorbed more slowly, so has a prolonged action, but can cause sedating toxic effects if toxic doses are exceeded. Therefore, BAL is only administered intramuscularly and not intravenously.

- Although the drawbacks accompanying BAL therapy are obvious, it is still the best therapeutic masking agent for arsenic in both animals and humans, including arsenic and auric dermatitis (in the latter cases, BAL is used as an ointment).

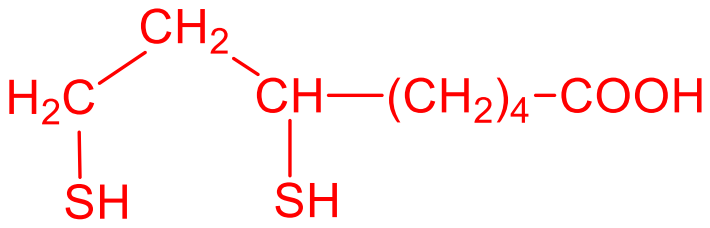
Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of BAL and other thiols

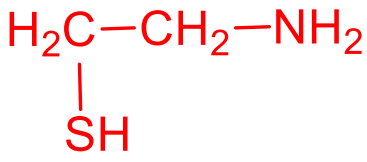
- Apart from BAL, there are numerous other thiols that could be used to mask heavy metal ions:



Sodium dimercaptopropansulphonate



1,3-dithiooctanoic acid



Beta-mercaptoethylamine

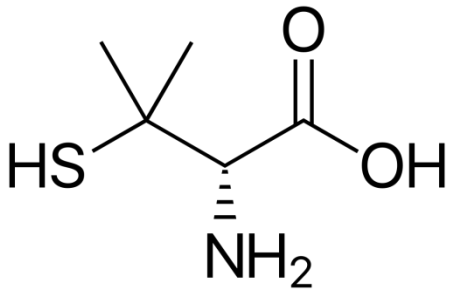
- Of these, β-mercaptoethylamine is less toxic and can be used as an intravenous injection as an antidote in thallium poisoning. Some thiols can also be used as antidotes in mercury poisoning.

- Lately, a less toxic BAL-glucoside-like compound, which can be administered in doses about three times higher than BAL, has been used as a replacement for BAL.

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of D-penicillamine

- D-penicillamine has been used with very good results in the treatment of Wilson's disease, which consists of hepatolenticular degeneration characterised by intracellular copper deposition in the liver and brain.



- It has also been shown to be effective in the therapy of lead poisoning, for which intravenous administration is most effective.

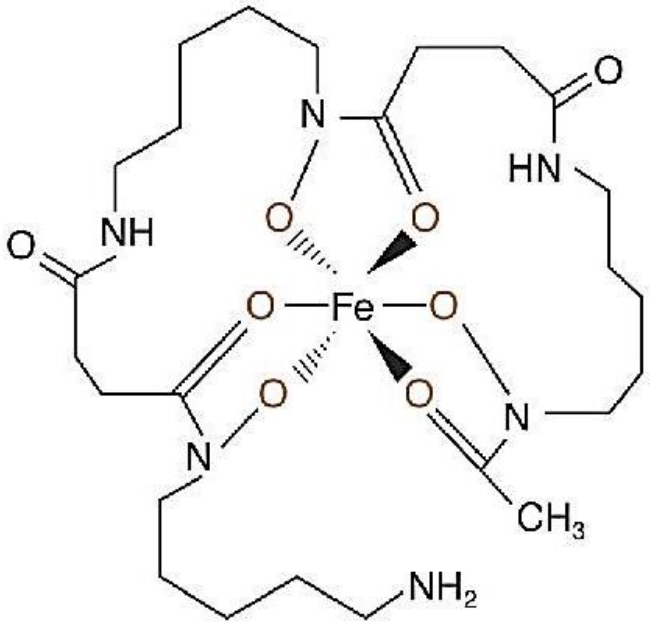
- We use Cuprenil, which contains D-penicillamine, for the treatment of Hg, Cu, Pb poisoning, as well as in Wilson's disease, haemosiderosis, uric lithiasis, macroglobulinaemia, or rheumatoid arthritis.

- In general, the efficacy of D-penicillamine is lower than that of Ca-EDTA-Na2, which is administered as a slow dilute infusion and can relatively easily penetrate cell membranes. In addition, the elimination is slow, so it has a prolonged action.

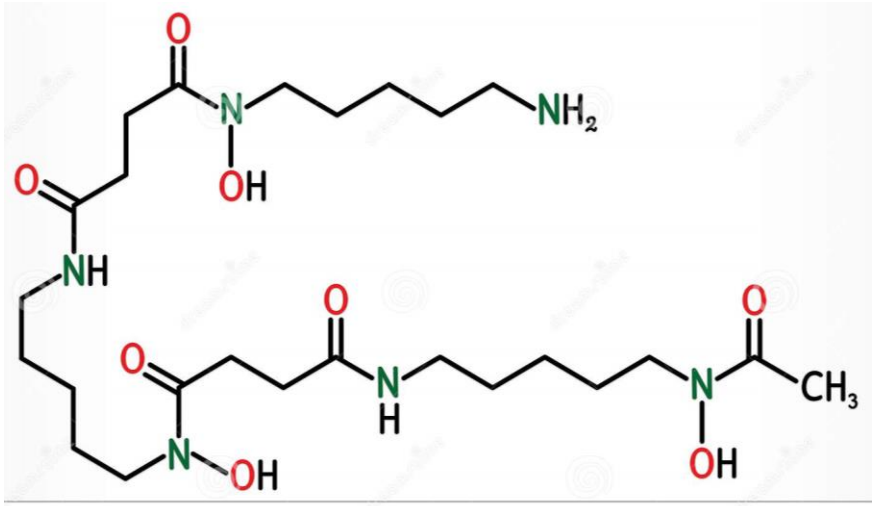
Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of desferioxamine B

- Ferioxamine B, isolated in 1960 from *Streptomyces* cultures, plays an important role in the enzymatic fixation of Fe(III) in the porphyrin skeleton.
- Desferioxamine has a high specificity for Fe(III), which it chelates through strong bonds (octahedral configuration).
- Desferioxamine is used, under the name **desferal**, in hemochromatosis (siderosis) therapy.



Ferioxamine B



Desferioxamine B

Masking agents in the therapy of heavy metal poisoning

Therapeutic applications of Co_2EDTA

- Co_2EDTA is used as a masking agent for the CN^- anion, which causes very serious, even lethal, poisoning.

- The clinical results obtained are very good, but after resolution of the intoxication it is necessary to remove the Co(II) released by Co_2EDTA, which did not react with cyanide.

- For this, Ca-EDTA-Na_2, which chelates cobalt, is administered:

$$\textbf{Ca-EDTA-Na}_2 + \textbf{Co}^{2+} \rightarrow \textbf{CoEDTA-Na}_2 + \textbf{Ca}^{2+}$$

- **Co-desferioxamine** and **aquacobalamin** complexes (which are slightly more effective but less accessible than Co2EDTA), **Co-histidine, Co(II)-dimercaptopropansulphamate**, or **tridosic hexanitrocobaltiate** can also be used to treat cyanide poisoning.

ACTIVE THERAPEUTIC COMPLEXES

Conditioned complexes in pharmaceutical forms

Amino acid complex preparations

- Some amino acid preparations in the form of chelated or unchelated compounds are frequently used, such as: **Aspartase** (double aspartate of magnesium and potassium), **Calciretard** (or Aspara CA, calcium aspartate), **Syderil** (Feraspartyl, divalent iron aspartate), **zinc aspartate**, **Aspara K** (potassium aspartate), etc.

- **Folcysteine U** (containing L-cysteine-HCl, hexamethylenetetramine and folic acid) is used as an SH-group donor for the recovery of SH-group-containing enzymes.

- On the other hand, glutamic acid preparations **(Glubifer** - iron(III) glutamate, **Glutarom** and **Multiglutin -** Na, K and Ca glutamates) play an important role in liver regeneration and are also involved in the metabolism of vitamin B12 and thioamino acids, as well as in ammonium ion fixation (increased concentration in chronic liver diseases).

Calcium and aluminium complex preparations

- **Ca-Doxium**, i.e. **calcium dobesilate**, is used in vascular diseases to normalize vessel permeability.
- **Calcium gluconate ampoules**, in addition to normalising vascular permeability, also plays a plastic role in bone formation, being involved in water metabolism and blood clotting. It is also anti-inflammatory and anti-allergic.

- **Calcium pantothenate** is a factor of the B vitamin group and is used in inflammatory processes of the upper respiratory tract.
- **Calciparine**, a complex of calcium with heparin, is used in the prevention and treatment of thromboembolic disease and thrombogenic conditions.
- Another preparation worth mentioning is **Ca-PAS** *(p-aminosalicylate*calcium*)*, with applications in the treatment of tuberculosis.

- Among the aluminium complexes used in therapy are **aluminium acetotartrate**, which has anti-inflammatory action, and **potassium and ammonium aluminosulphate**, which have antiseptic, emetic and astringent action.

Preparations based on arsenic, stibium and bismuth complexes

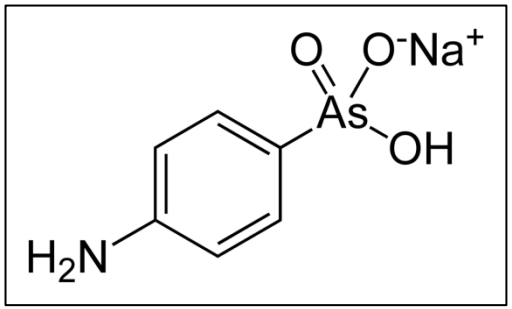
- Although arsenic, stibium and bismuth are toxic to the body, some preparations with these elements have important therapeutic applications.

- Some As(III) complexes such as **Atoxyl**, **Acetarsone**, **Carbarsona** and **Thiocarbarsona** are used in the treatment of some amoebiasis, trypanosomiasis, and **Salvarsan**, **Neosalvarsan** and **Arsfenamine** are used in the treatment of syphilis.

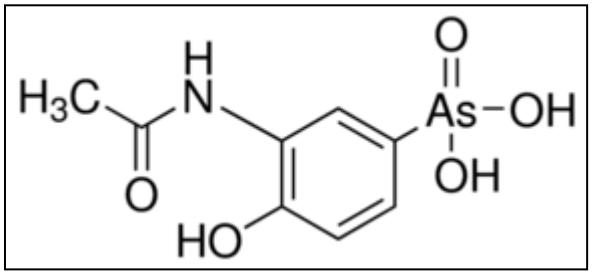
- Of the Sb(III) complexes are used in therapy **Styrofen** *(p-amino-phenylstibonate*), **Anthiomaline** (stybium thiomalate and lithium), **Astiban** (Stybium dithiosuccinate) and others in the treatment of tropical diseases such as leishmaniasis, filariasis and schistosomiasis.

- Of the Bi(III) compounds used **Bismosal** and **Bismuthi subsalicilas** in the treatment of syphilis, and **bismuth-sodium double tartrate** and **potassium dicitrate-bismuthate** are used in the treatment of some oral, gastric and duodenal ulcers.

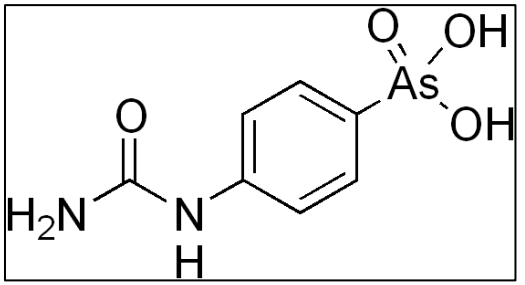
Preparations based on arsenic, stibium and bismuth complexes



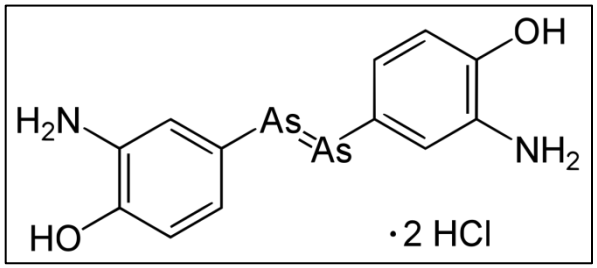
Atoxyl



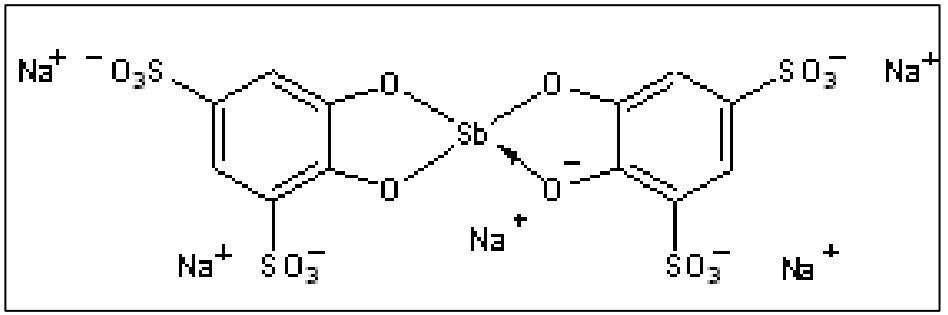
Acetarsone



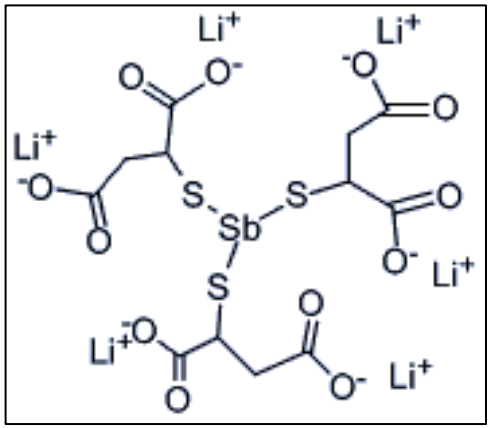
Carbarsone



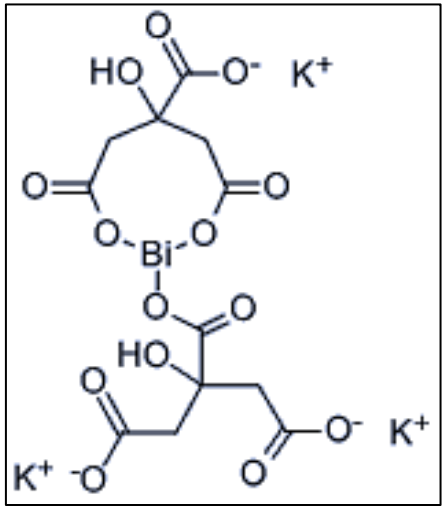
Salvarsan



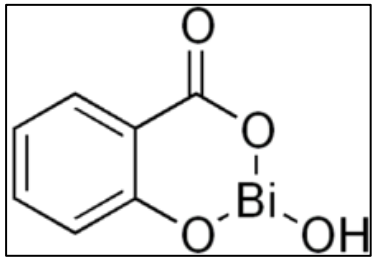
Stybophen



Anthiomaline



potassium dicitrate-bismuthate

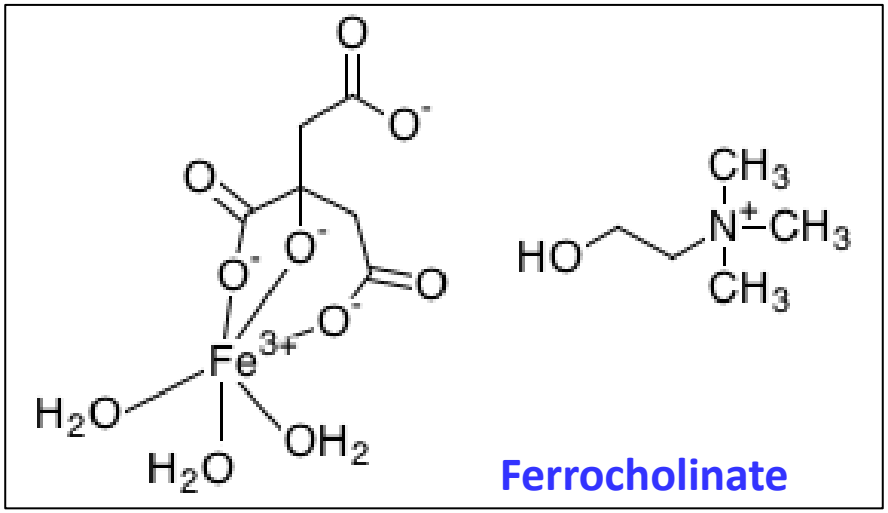


Bismosal

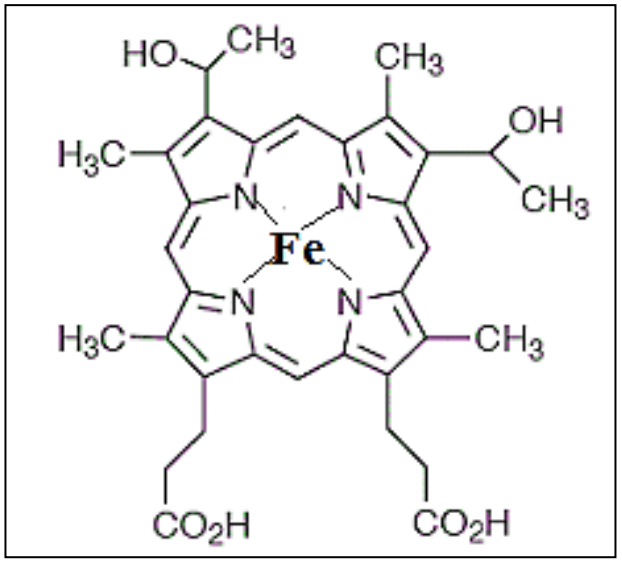
Iron complex preparations

- Of particular therapeutic importance are (usually chelated) Fe(II) complexes, used in the treatment of iron deficiency anaemia or myocytic hypochromasia.
- Among the parenterally administrable iron preparations, one can mention **Fe(II)-polimaltozat, Fe(III)-zaharate, Glubifer or Fe(III)-glutamate, Inferon or Fe(II)-dextran, Ferrocholinate, Fe(II)-rutin, Fe(II)-chlorophyllin-Vit. B_1** etc, which are also lactation, growth, pregnancy and convalescence promoters.
- Also used in the treatment of anaemia are oral preparations such as **Aktiferin** ($FeSO_4$·DL-serine), **Ferronicum Sandoz or Fe(II)-gluconate**, as well as other chelates of Fe(II) with various carboxylic acids and amino acids.
- Complexation of PAS with Fe(II) results in a chelate (2:1 ratio), whereby the tuberculostatic action of PAS is greatly enhanced (the 1:1 complex is inactive).
- Some of the iron complexes have a stimulatory action on the CNS **(haematodin or haematoporphyrin**) or are radioprotective against UV or electron radiation **(Fe(II,III) complexes with mercaptoethylamine and 2-mercaptoethylguanidine**).

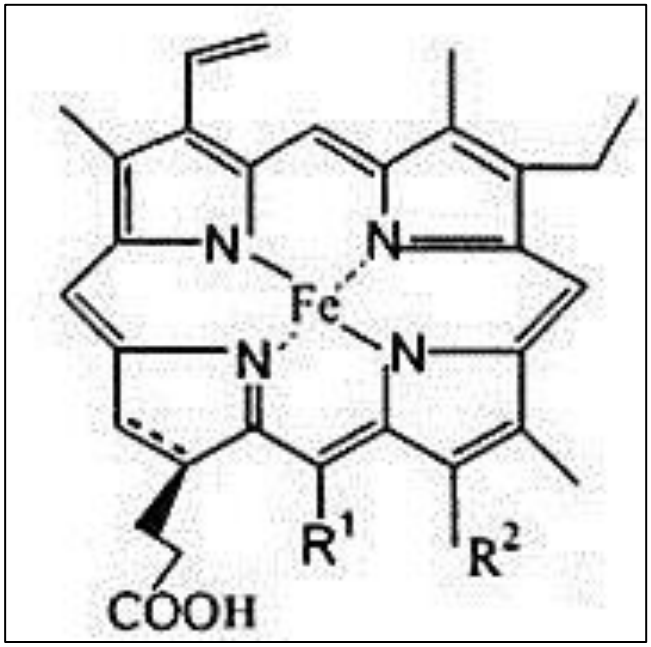
Iron complex preparations



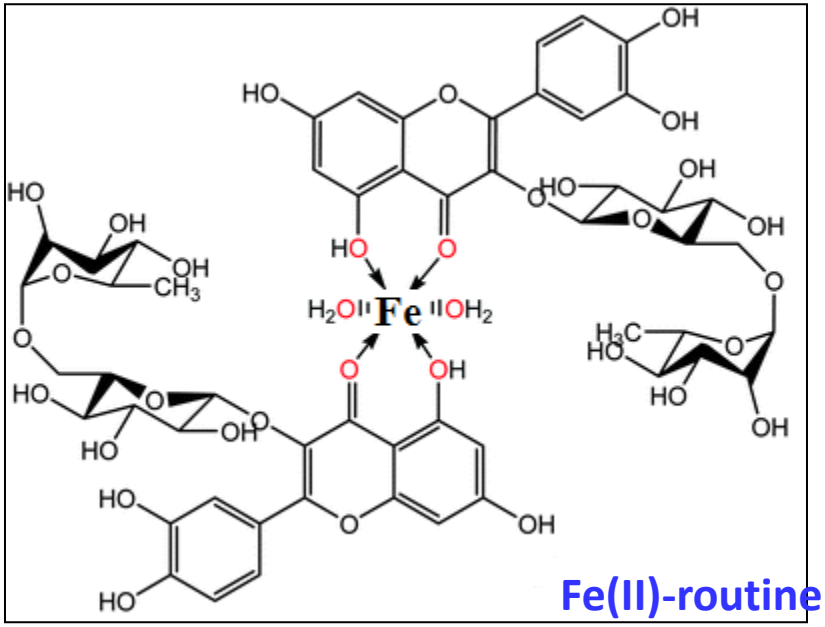
Ferrocholinate



Hematoporphyrin



Fe(II)-chlorophylline



Fe(II)-routine

Preparations based on cobalt complexes

- **Vitamin B12**, which contains the Co(II) ion, is used in the treatment of pernicious anaemia (myocytic hyperchromic anaemia), in addition to other Co(II) chelates with saccharides and amino acids.

- But these complexions have other actions. For example, **Co(II)-histidine**, in low doses, is hypopressor, but in high doses it is myocardio- and coronarotoxic. It follows from this that the use of this complex in therapy should be in small doses under medical supervision.

- **Co(II) complexes with PAS, HIN (isonicotinic acid) and chlorophyllin** have antibiotic and antifungal action, and Co(II) complexes with aromatic Schiff bases have antitumor action, and the one with delta-hydrocortisone has diuretic, hematoforming and anti-inflammatory action.

- However, most of the Co(II) chelators mentioned are used more as models for studying metal-protein interactions and the role of metalloproteins in biochemical reactions.

Silver and gold complex preparations

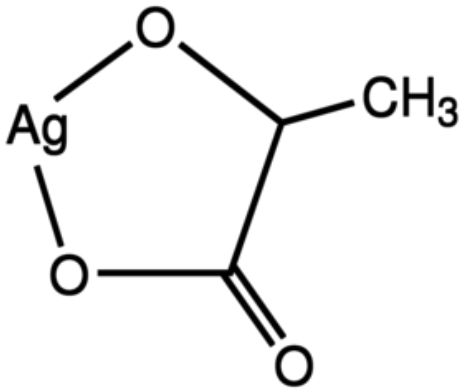
- Some of the Ag(I) complexes, although having an oligodynamic and disinfectant action, also show local irritant-corrosive action. However, a number of Ag(I) protein complexes **(Protargol, Colargol, Argirol**), as well as **Picrargol and silver lactate**, have local disinfectant action and are used in ocular diseases.

- To these complexes are added some complexes of **Ag(I) with sulfonamides, allantoin** with antiseptic action, while **Ag(I**) complexes **with casein** have antitumor action.

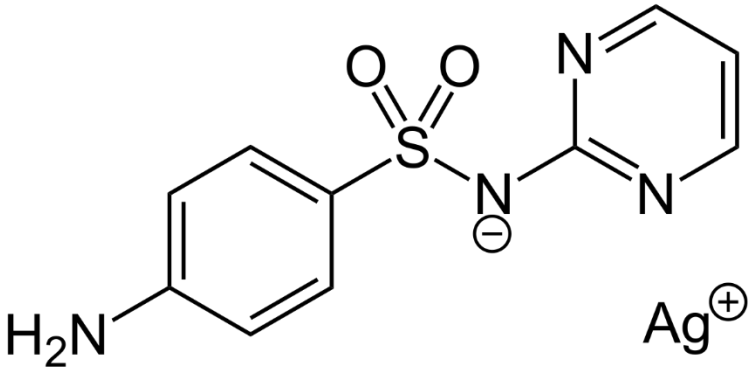
- Some Au(I) and Au(III) complexes are used in the therapy of lupus erythematosus, rheumatoid arthritis or some forms of neoplasm. These include **Solganal or Au(I)-thioglucose**, **Sanocrysin or sodium aurothiosulphate**, **Tauredon or sodium aurothiomalate** , etc.

- Some **Au(I**) complexes **with trialkylphosphines** are also known **(e.g. Auranofin)** which have anti-arthritic action and can be taken orally.

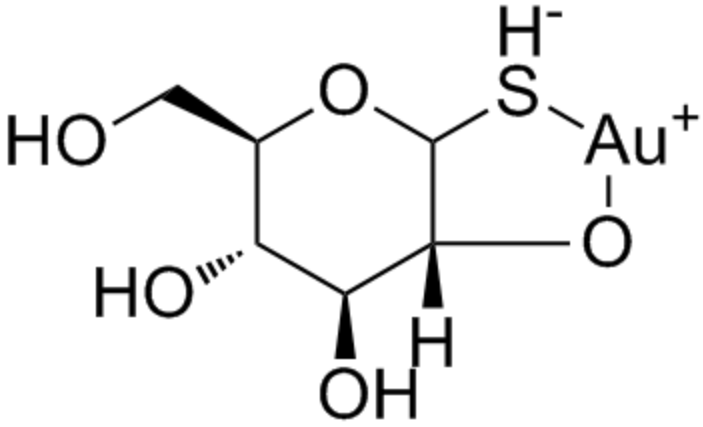
Silver and gold complex preparations



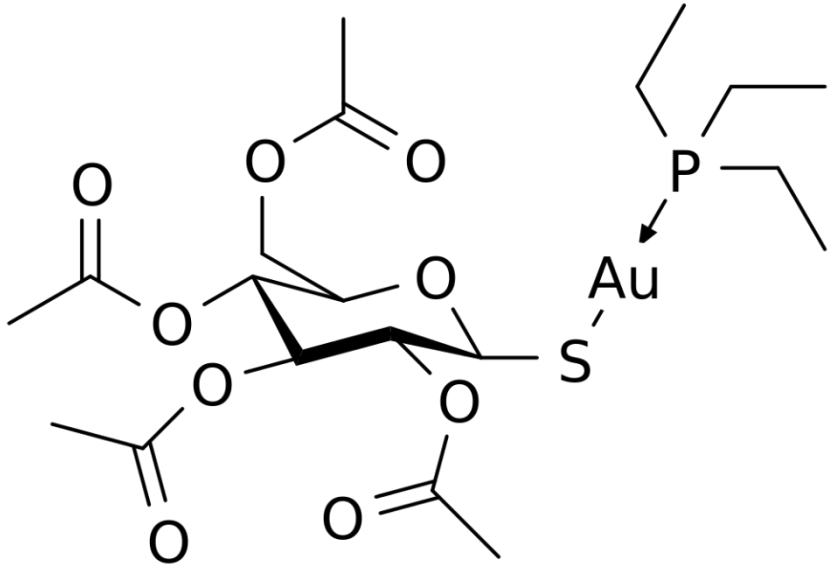
Silver lactate



Ag(I) sulfadiazine



Au(I)-thioglucose



Auranofin

Preparations based on zinc and mercury complexes

- Zinc is found in the body, in addition to the enzymes that contain it, in the **zinc-insulin** complex, a hormone that controls and regulates sugar metabolism.

- Among the preparations with antidiabetic action we can mention **Isofan-Zn-insulin** and **Insulin-Lente-Novo**, both injectable, and among the oral forms, those containing zinc chelates with amino acids. Some zinc chelates with bis(thiosemicarbazone) ligands are also known, with antitumor, antiseptic, antifungal or keratolytic action.

- Among the most important Hg(II) complexes are those with antiseptic action, such as **Phenosept (phenylmercuric borate)**, **Timersal** and **Nitromersal**, and **phenylmercuric acetate**.

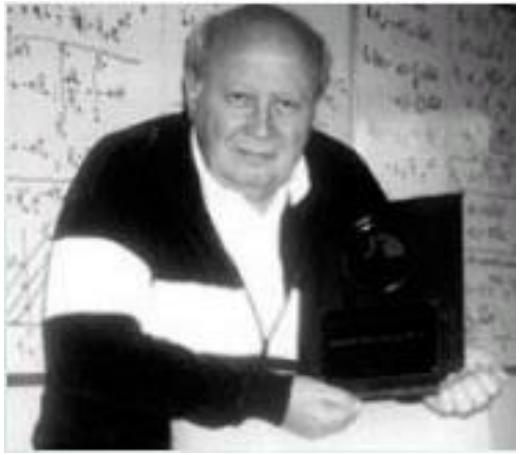
- To these preparations may be added **Mersalyl** or **Salyrgan**, which have a diuretic action, explained by the coordination of mercury to the SH groups in the enzymes acting in the kidney.

Other biologically active complexes

Platinum metal complexes with antitumor action

Metal ion	Complex formula	Tumour test used
Ru(IV) Rh(III)	$K_2[RuCl_6]$; $K_2[RuCl_5(NO)]$ $[RhCl_2(SHth)_4]Cl$ $Na_3[RhCl_2(SHth)_4]$ $(NH_4)_2[RhCl_6]$	Sarcoma in mice Carcinosarcoma Walker 256 (in rat) Ascites Dunning Leukaemia
Pd(II)	*trans*-$[PdCl_2(SHth)_2]$ *cis*-$[PdCl_2(NH_3)_2]$ *cis*-$[PdCl_2(AA)]$ $[Pd\{(RO)_2PS_2\}_2]$	Lewis pulmonary carcinosarcoma Leukaemia P 388 Carcinoma XV (in rabbit)
Pt(II)	cis-$[PtCl_2(NH_3)_2]$ cis-$[PtBr_2(NH_3)_2]$ $[PtCl_2(dat)]$	Sarcoma 180 solid Leukaemia L. 1210 (in mice) Hepatoma (in mice)
Pt(IV)	cis-$[PtCl_4(NH_3)_2]$ cis-$[PtCl_4(en)]$ $(NH_4)_2[PtCl_6]$	Sarcoma 180 solid (in mice) Hamster

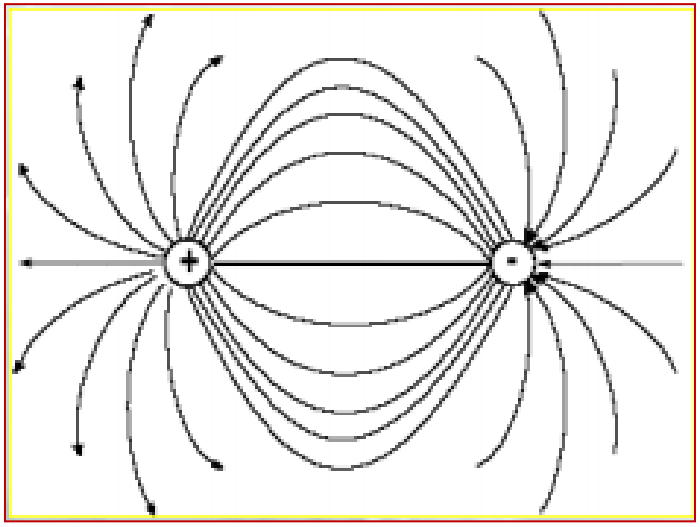
Abbreviations: SHth = 2-mercaptothiazole; AA = amino acid; en = ethylenediamine;
dat = 3,5-diaminotoluene

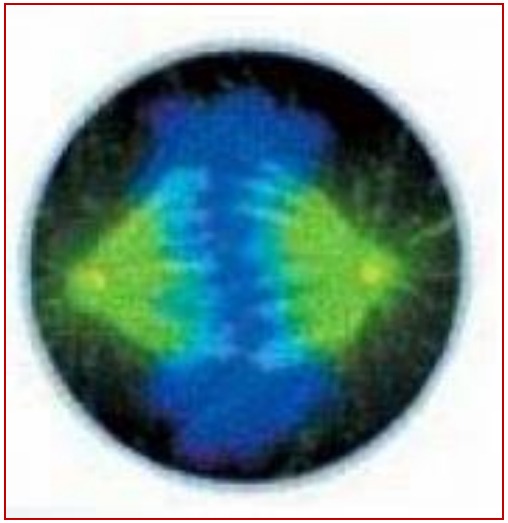


SERENDIPITY

the occurrence and development of events by chance in a happy or beneficial way

Rosenberg had been asked to found a biophysics laboratory at the University of Michigan, USA.



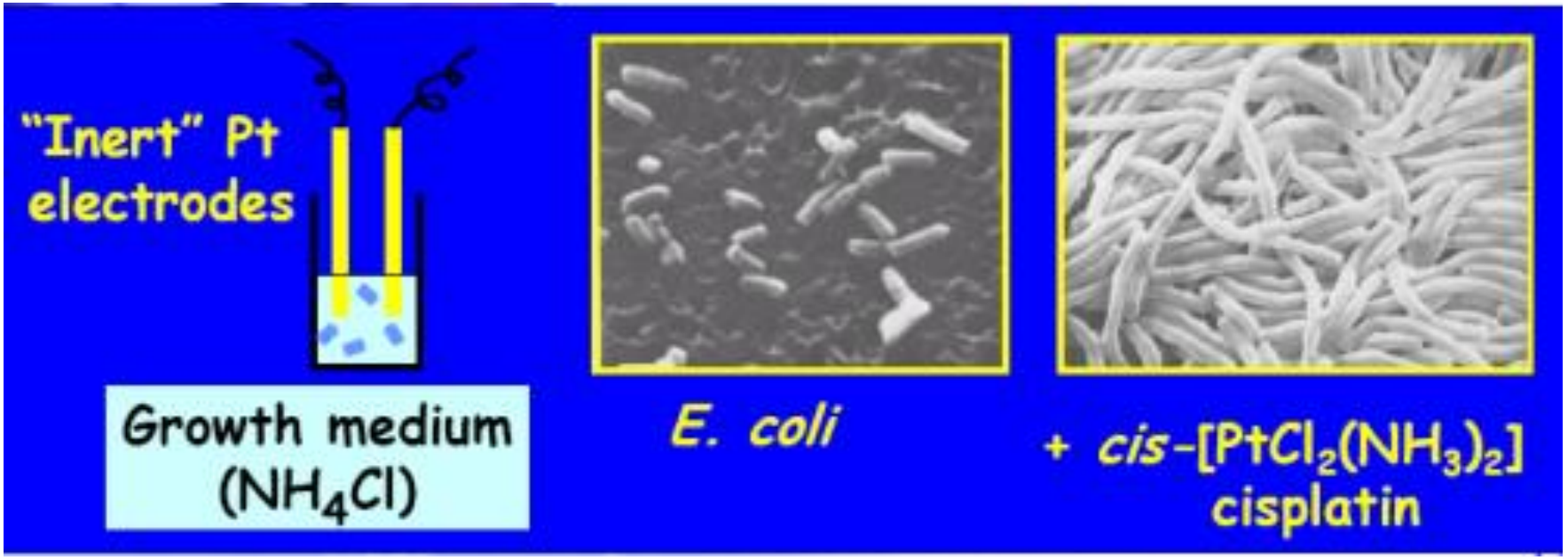


Rosenberg was impressed by the formal analogy between the mitotic spindle (the set of protein filaments governing the separation of duplicate chromosomes and their convergence at opposite poles) and the lines of force of an electric field.

SERENDIPITY

Rosenberg wondered whether cell reproduction could be influenced by an electric field.

The effect of electric field on cell growth

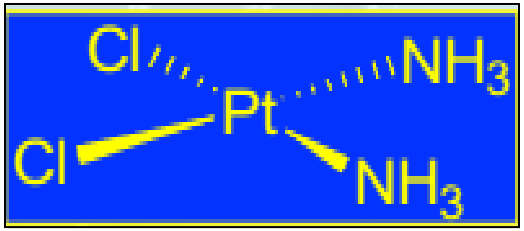


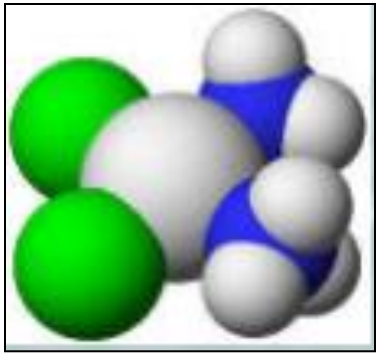
Cis-platinum

Rosenberg used bacterial E. coli cells and, to his surprise, realised that filamentous growth was occurring under experimental conditions. The bacterial cells continued to grow but failed to separate.

It took some time to realize that such a phenomenon was due to the presence of cis-platinum that had formed.

Since 1979 cis-platinum has been widely used as an antitumour agent.





Serious limitations:

- renal and hepatic toxicity limiting its dose.
- nerve toxicity (hearing loss)
- activity limited only to some tumour forms (head, cervix, bladder, ovaries, testicles)
- induced resistance in treated subjects

cis-platinum

The importance of being **cis-**