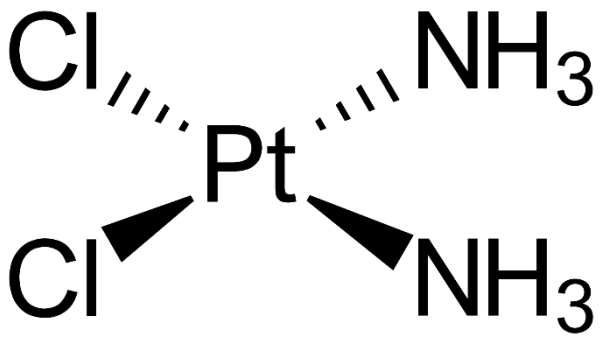
Medicinal Inorganic Chemistry

A relatively young, interdisciplinary research area

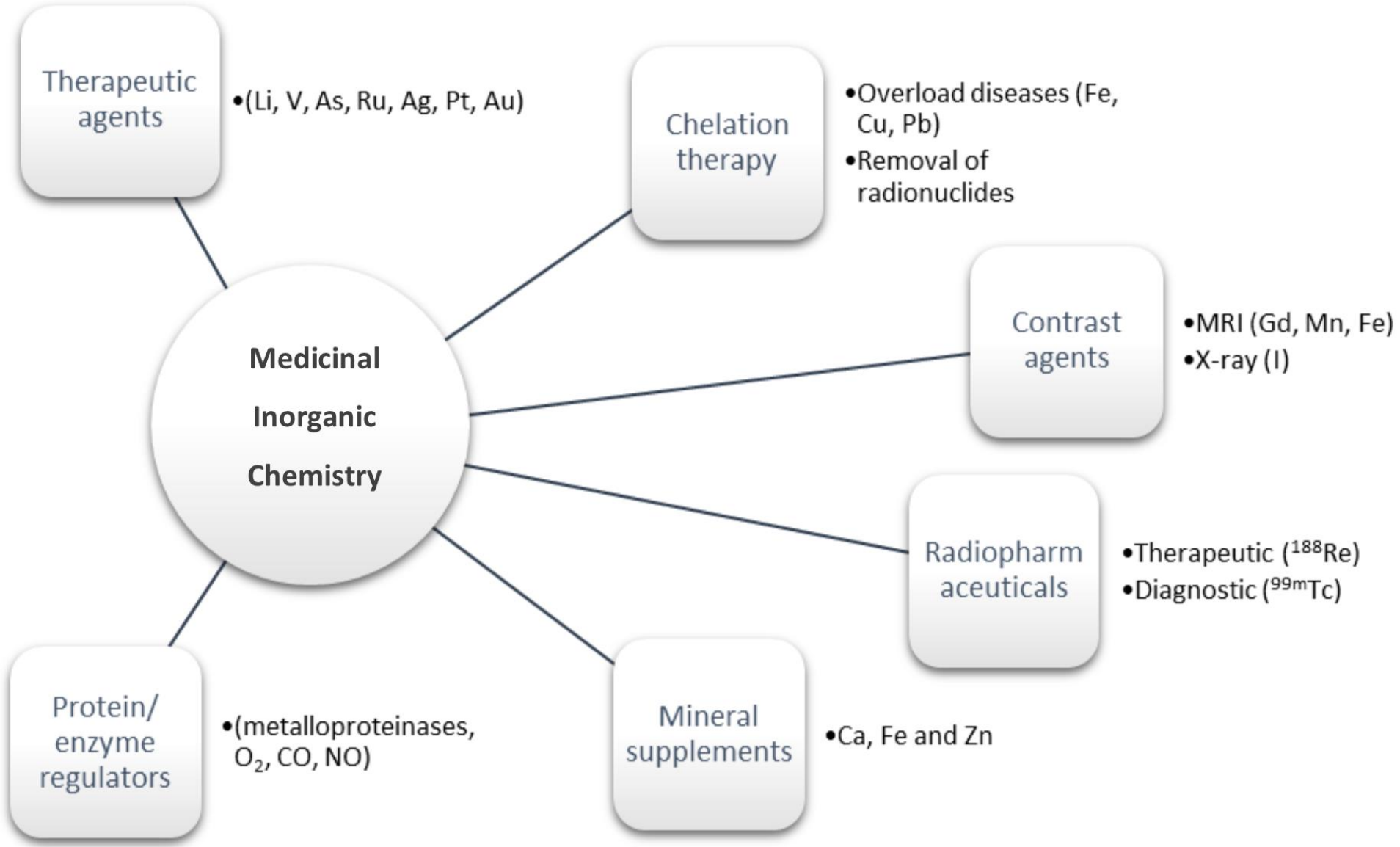
Has grown primarily due to the success of cisplatin, a Pt-based anticancer drug developed in the late 1960s

Also for the development of new analytical techniques



cisplatin

Sectors of interest

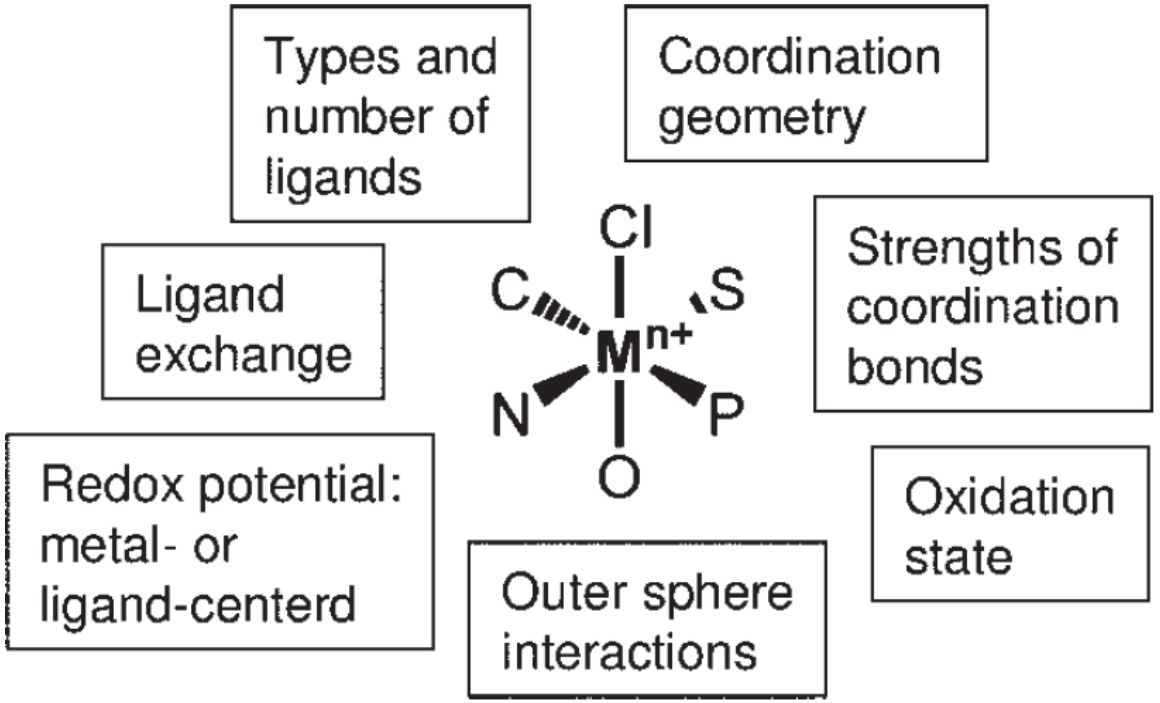


The **rational design of metal-based drugs** is a relatively new concept,

↓

improvements in characterization and imaging techniques

In general a metal complex that is administered is **likely to be a "prodrug"** that undergoes a transformation in vivo before reaching its target site



Feature	Comments (examples)
Coordination number	Full range 2–10; transition metals typically 4–6, can be more variable for main group metals (e.g., Bi) and larger for Ln (e.g., 9)
Geometry	Examples; linear (Au^{I}), square-planar (Pt^{II}), tetrahedral (e.g., Ti^{IV} in $TiCp_2Cl_2$, distorted), trigonal bipyramidal, octahedral (Ti^{IV}, Ru^{III}, Pt^{IV}), possible metal-centered chirality (Co^{III}, Rh^{III})
Oxidation state	Wide range (typically 0–7 in biological media), with different oxidation states favoring different coordination numbers and rates of exchange (e.g., Pt^{IV} vs. Pt^{II})
Ligand type	Wide range of donors, e.g., C, N, O, halides, P, S, Se. Chelating ligands; denticity, e.g., (κ^2) 1,2-diaminoethane, (κ^6), EDTA; hapticity, e.g., η^6 and η^4 binding for benzene
Thermodynamic stability	Wide range of M–L bond strengths (typically 50–150 kJ mol^{-1})
Kinetic stability	Lifetimes of M–L bonds cover wide range (ns–years). Highly dependent on metal oxidation state and other ligands, can be stereospecific, e.g., *trans* effect in Pt^{II}
Properties of ligands	Outer sphere interactions, e.g., H-bonding, hydrophobic interactions (<50 kJ mol^{-1}) for receptor recognition (including use of chirality); may undergo transformation *in vivo*, e.g., by redox, hydrolysis, enzymatic reactions (e.g., by P450 in the liver).
Nuclear stability	Radioactive nuclides can be used to track metabolism of drugs, e.g., ^{195m}Pt ($t_{½}$ = 4 d) and ^{99m}Tc ($t_{½}$ = 6 h). Appropriate nuclide depends on decay pathway (α, β, γ) and half-life

Elucidating the precise mechanisms of action of these new drugs is perhaps the most challenging and complicated aspect of the research.

In fact, it requires both
Knowledge concerning **the reactivity of the metal complex**
And **appreciation of the biochemical pathways** governing cell uptake, metabolism, and excretion

By **appropriate choice of the ligands and metal oxidation state**, it is possible to control the thermodynamic and kinetic properties of metal complexes and to attempt to control **their biological activity**

Antimicrobial Agents

Many metal compounds show appreciable antimicrobial activity, some established examples are based on **silver, bismuth, mercury, and antimony**

Under an inert atmosphere, **silver** has no effect on microorganisms; however, in the **presence of oxygen** it exhibits a **broad spectrum of antimicrobial activities**:

i) Ag^+ **interacts with thiol groups of L-cysteine residues of proteins**, inactivating their enzymatic functions;

(ii) Ag^+ **causes potassium release**;

(iii) Ag^+ **binds to nucleic acids**;

(iv) Ag^+ generates **superoxide (O_2)** intracellularly

This interaction with bacterial proteins and nucleic acids causes structural changes in membranes (blocking respiration), and nucleic acids (blocking transcription).

Morphologically,
treatment of Escherichia coli and Staphylococcus aureus (model strains for Gramnegative and Gram-positive bacteria, respectively) with $AgNO_3$ has been shown to cause **detachment of the bacterial membrane from the cell wall**, **condensation of the nuclear DNA**, and **deposition of S- and Ag-rich granules both around the cell wall and within the cytoplasm**

Simple compounds of silver (e.g., $AgNO_3$) have long been used as antibacterial agents, with particular efficacy in the treatment of burn wounds.

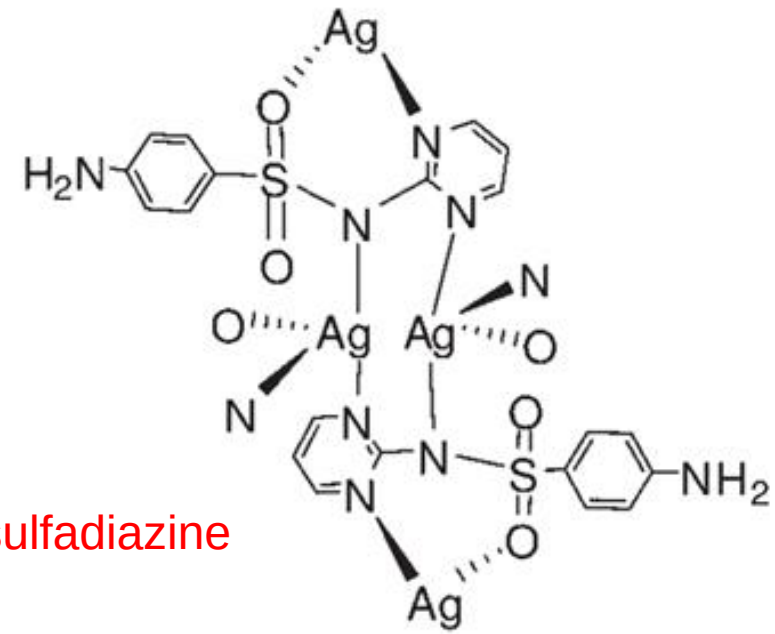
Later on substituted by penicilline

The **combination of silver with a sulfonamide antibiotic** in 1968 produced **silver sulfadiazine (SSD)** cream (an insoluble polymeric Ag^+ compound) a broad spectrum silver-based antibacterial that also exhibits antiviral and antifungal properties.

Wound dressings and materials for medical devices such as catheters are often manufactured with the **incorporation of silver** to improve sterility.

Since silver acts biologically as "Ag^+" the main role of the ligands is to tailor the solubility and pharmacokinetic profile (i.e., release and distribution of Ag^+).

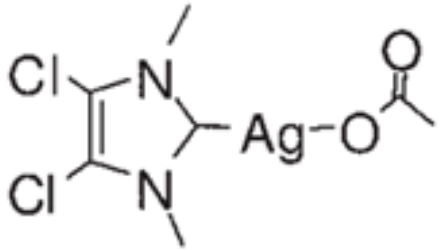
Recent developments in silver-based antimicrobials have focused on **the use of sophisticated ligands (e.g., imidazolium N-heterocyclic carbenes, NHC)** and also on **the potential offered by silver nanoparticles**.



Structures of polymeric silver sulfadiazine

Silver complexes of NHC with electron-withdrawing groups in the 4- and 5-positions
[such as (**1,3-dimethyl-4,5-dichloroimidazole-2-ylidene)silver(I) acetate**]
have demonstrated activity against bacterial strains associated with cystic fibrosis and chronic lung infections.
Typically, NHC-Ag complexes decompose rapidly in aqueous solution, but incorporation of Cl in the 4,5 positions of the imidazole ring withdraws electron density from the carbene carbon, making it less susceptible to attack and slowing the rate of hydrolysis.

(1,3-dimethyl-4,5-dichloroimidazole-2-ylidene)silver(I) acetate

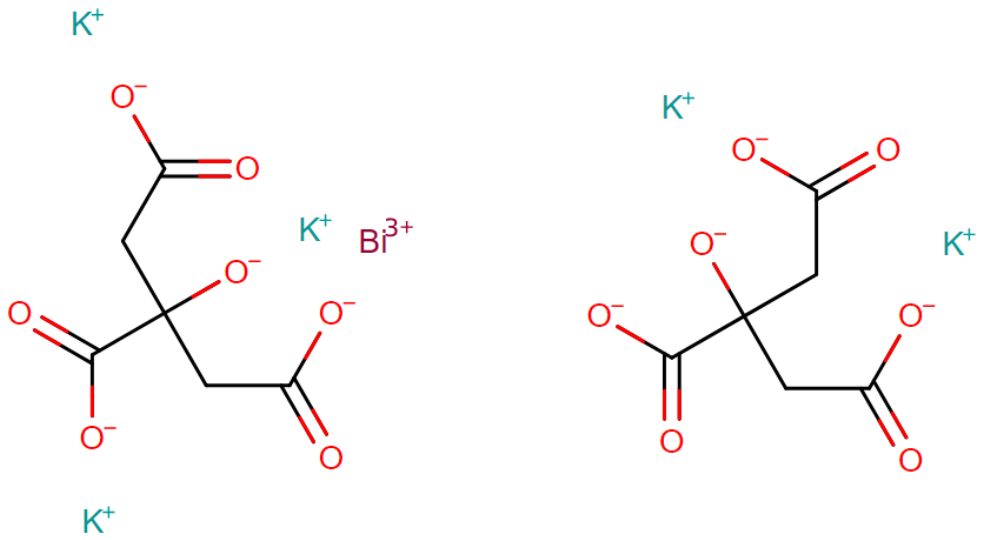


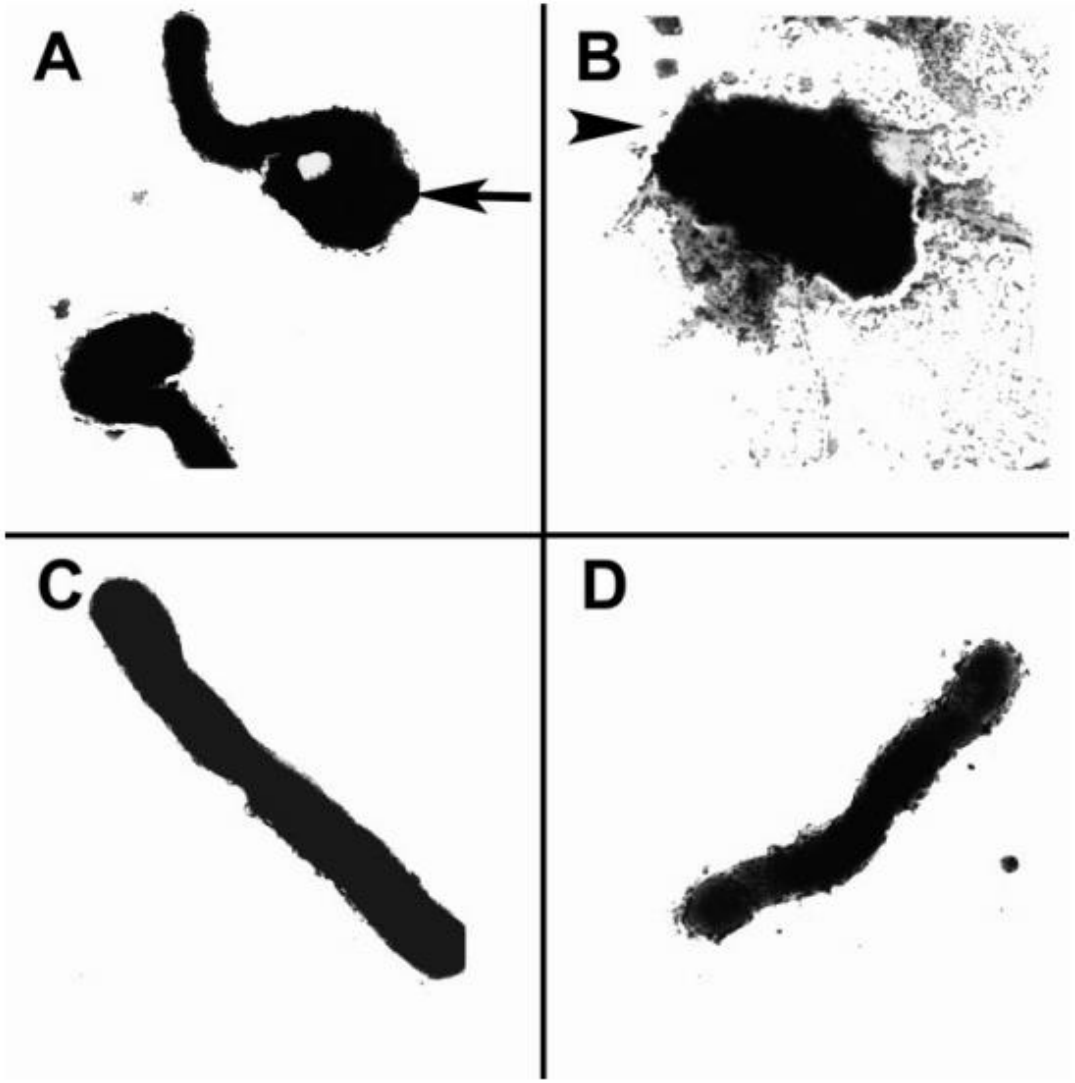
Development of bacterial resistance to silver is thought to be due to increased use of efflux pumps.
Silver toxicity in humans is seen in the form of **argyria** (a permanent blue-tinting of the skin) following administration of particularly high doses.

Bismuth is regarded as a borderline metal and typically exists as Bi(III) in vivo.
Bismuth exhibits variable coordination numbers (3–10) with irregular geometries

Bismuth compounds show low toxicity towards mammalian cells (**protection afforded by the thiol-rich proteins, metallothioneins**) and have been in use for over 200 years as antimicrobial agents, for treating syphilis and other infections, including colitis, gastritis, and diarrhea. Various Bi compounds – **colloidal bismuth sub-citrate**, **ranitidine bismuth citrate**, **bismuth sub-salicyclate (Pepto-Bismol)**, and **ammonium potassium Bi(III) citrate (De-NolTM)** – are used, often in combination therapy with other antibiotics, for the treatment of gastrointestinal disorders caused by Helicobacter pylori.

Colloidal bismuth sub-citrate



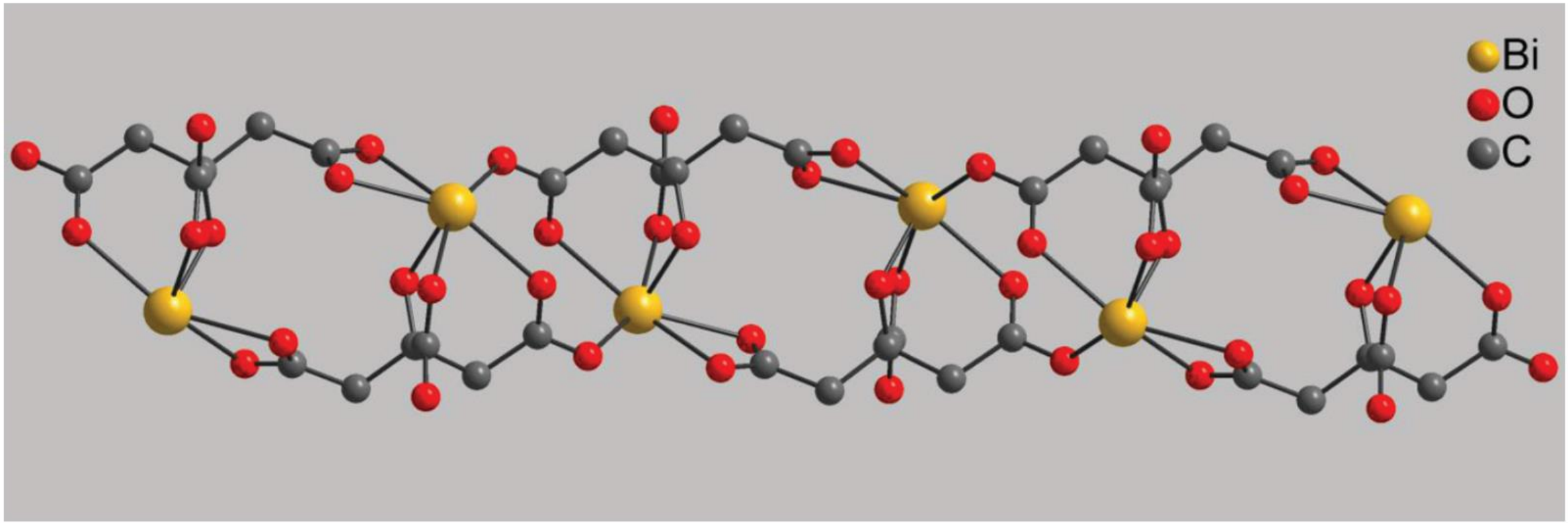


Effects of bismuth (colloidal bismuth subcitrate, CBS) exposure and iron limitation on H. pylori morphology. TEM images (magnification, 28,900) show strain 60190 following growth in 50 M deferoxamine (A), MICCBS (B), MICCBS and protective iron (C), and normal culture conditions (D)

CBS forms colloids in water.

The structures of the *in vivo*-generated compounds are rather speculative, since the coordination number of Bi(III) in its compounds is very flexible and ranges from 3 to 10, exhibiting frequently **irregular polyhedra**.

In vitro studies reveal that polymeric aggregates such as the polyanionic chain $[Bi_2(cit)_2]^{2-}$ (cit^{4-} = citrate tetraanion) are formed, probably covering the surface of the ulcer.



Bismuth salts also show activity against **several other gastrointestinal tract pathogens**, including Escherichia coli, Vibrio cholerae, Campylobacter jejuni, and those of the Yersinia, Salmonella, and Shigella genera.

The major biological targets for Bi(III) are proteins; Bi(III) is **known to bind to both Fe(III)- and Zn(II)-coordination sites of proteins** and, in particular, is thought to **inhibit the nickel-binding protein urease** and **bind to the histidine-rich and cysteine-rich metal-binding domains of heat-shock protein A**, which are both crucial to the survival of *H. pylori* in the gut.

In addition to the **antibacterial action shown by Bi(III),** the **derivatives** formed in the acid environment of the stomach **bind strongly to the proteins in ulcerated tissue to form a protective layer**, allowing it to heal.

They also cause an increase in local prostaglandin levels, which stimulates the production of bicarbonate and mucin thereby protecting the stomach

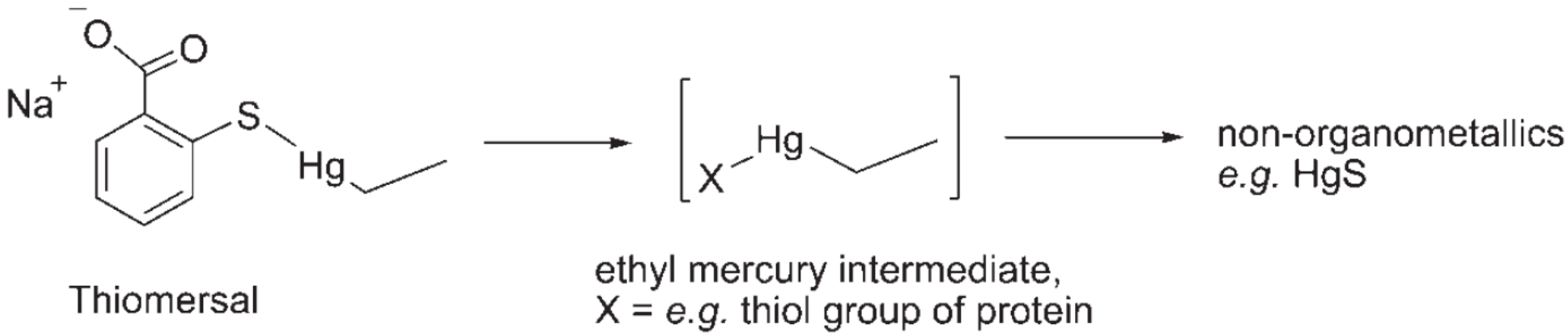
Mercury in medicine

Compounds of mercury show significant variation in bioavailability, bioaccumulation, and metabolism in humans and as such can be divided into three groups: **elemental mercury (Hg), organometallic complexes (i.e., containing at least one Hg—C bond), and non-organometallic (often called "inorganic" complexes, e.g., sulfides).**

The latter two kinds are used in medicine

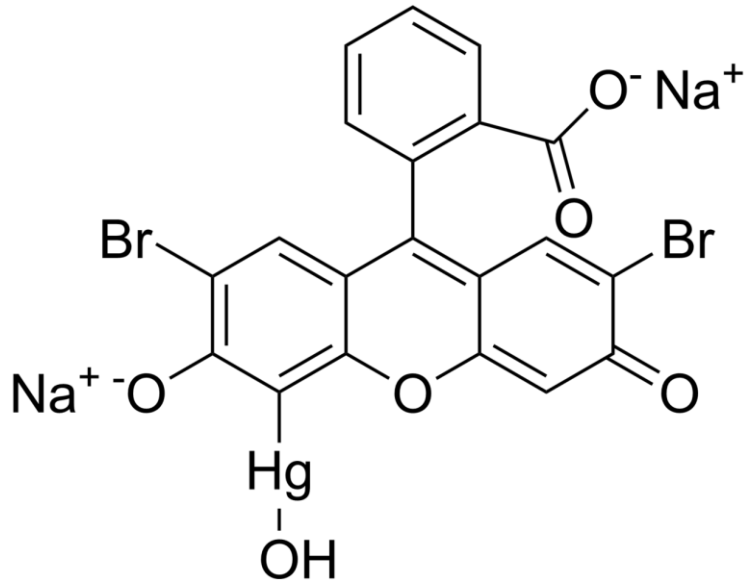
The antibacterial and antifungal properties of organometallic mercurials have resulted in their application as **topical disinfectants** (thiomersal and merbromin), **preservatives in vaccines** (thiomersal), and **grain products** (methyl and ethyl mercurials).

Thiomersal (sodium ethylmercurithiosalicylate) is contained in GlaxoSmithKline's recently released influenza pandemic (swine flu) vaccines Pandemrix and Arepanrix. In Pandemrix, thiomersal is present at 5 mg per 0.5 ml dose, falling well within the World Health Organization (WHO) recommended maximum limit for the similar but more toxic organometallic mercurial compound, methyl mercury (1.6 mg per kg body weight per week)



After injection, **thiomersal rapidly dissociates to produce ethyl mercury**, which binds to the available thiol ligands present in tissue proteins – a mechanism that is corroborated by the fact that the nature of the ligand attached to the ethyl mercury group (thiosalicyclate in the case of thiomersal) makes little difference to the ultimate bodily distribution of mercury.

Merbromin (Mercurochrome) is thought to react in a similar fashion.



Mercurous chloride (calomel, Cl-Hg(I)-Hg(I)-Cl) has been used for centuries as a diuretic, laxative, antiseptic, skin ointment, and to treat vitiligo, although its use has largely been superseded by modern medicines.

The traditional Chinese medicine **Cinnabar**, which is used to achieve sedative and hypnotic effects, **contains mercury sulfide (HgS)**. Since purified mercury sulfide shows poor bioavailability and low absorption from the gastrointestinal tract, it is postulated that **the major medicinal benefit of cinnabar might be due to its interactions with other components of traditional Chinese medicines**.
Once absorbed into the blood, mercury disposition from cinnabar follows the pattern for other inorganic mercury complexes and it is preferentially distributed to the kidneys, with a small portion to the brain.

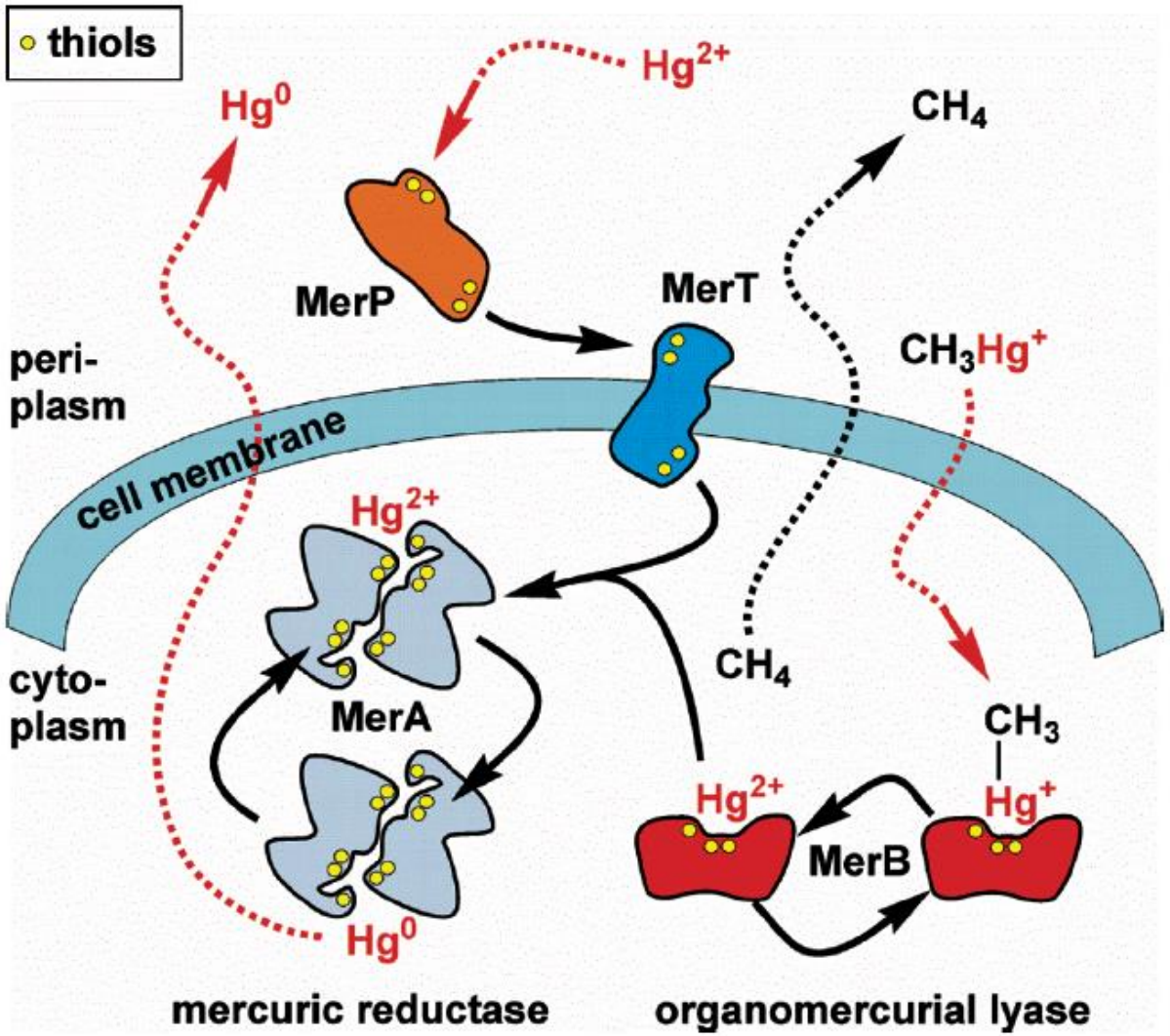
As with silver, **the antibacterial action of mercury is attributed largely, but not exclusively, to the strong affinity of the metal for thiol groups of proteins**. Evidence suggests that mercurials cause structural and functional changes of bacterial cell walls and inhibit membrane bound proteins, interfering with respiration, ATP synthesis, and transport processes.

Bacterial resistance to mercury antimicrobial agents involves induction of enzymes (such as mucuric reductase) that are capable of converting Hg(II) in the cytoplasm into the less toxic and more volatile Hg(0)

The relatively low immediate toxicity of elemental mercury and its volatility have enabled bacteria to develop a resistance mechanism towards soluble Hg compounds

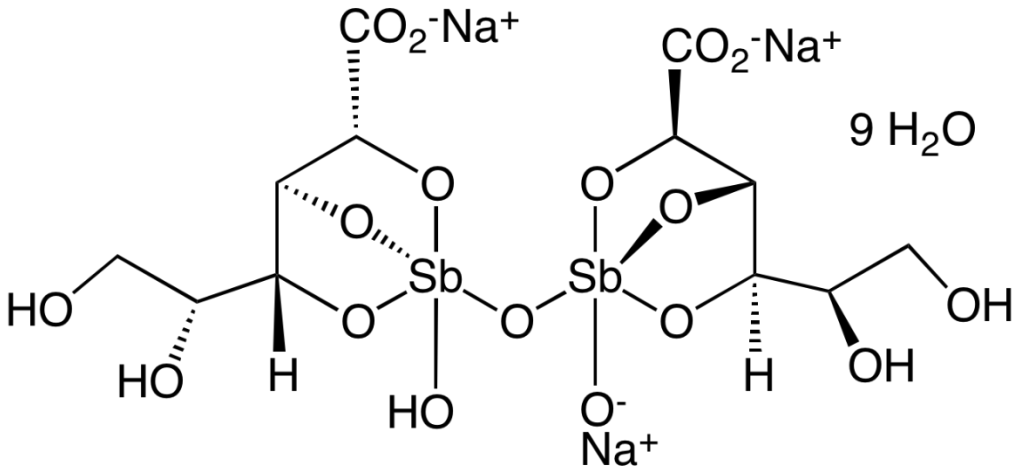
***Mer* system**

The synthesis of the required proteins (*MerA*, *MerB*, *MerP*, *MerT*) is **triggered and controlled by a metal-selective and gene-regulating sensor protein "*MerR*".**

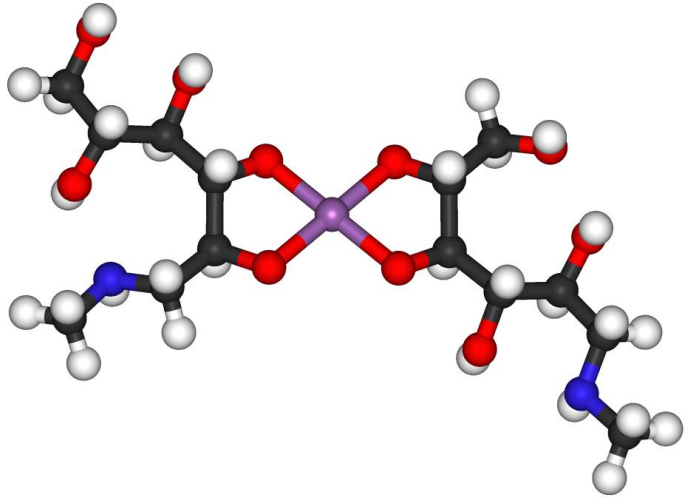


Two "processing" enzymes are especially interesting: a **specific Hg(II) reductase (*MerA*)** and **organomercury** (or organomercurial) **lyase (*MerB*).**

Antimony (Sb(V)) compounds such as sodium stibogluconate (Pentostam) and meglumine antimonite (Glucantime) are used to treat leishmaniasis, a disease caused by a parasite that is transmitted by the bite of a certain species of sand fly.

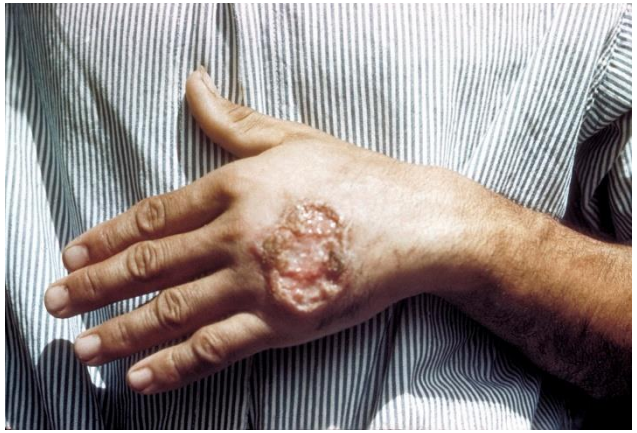


Sodium stibogluconate



Meglumine antimonite

The parasites replicate within mammalian macrophage phagolysosomes, initially causing skin sores, although some forms of the disease exhibit graver effects such as anemia and damage to the spleen and liver, which can be fatal.



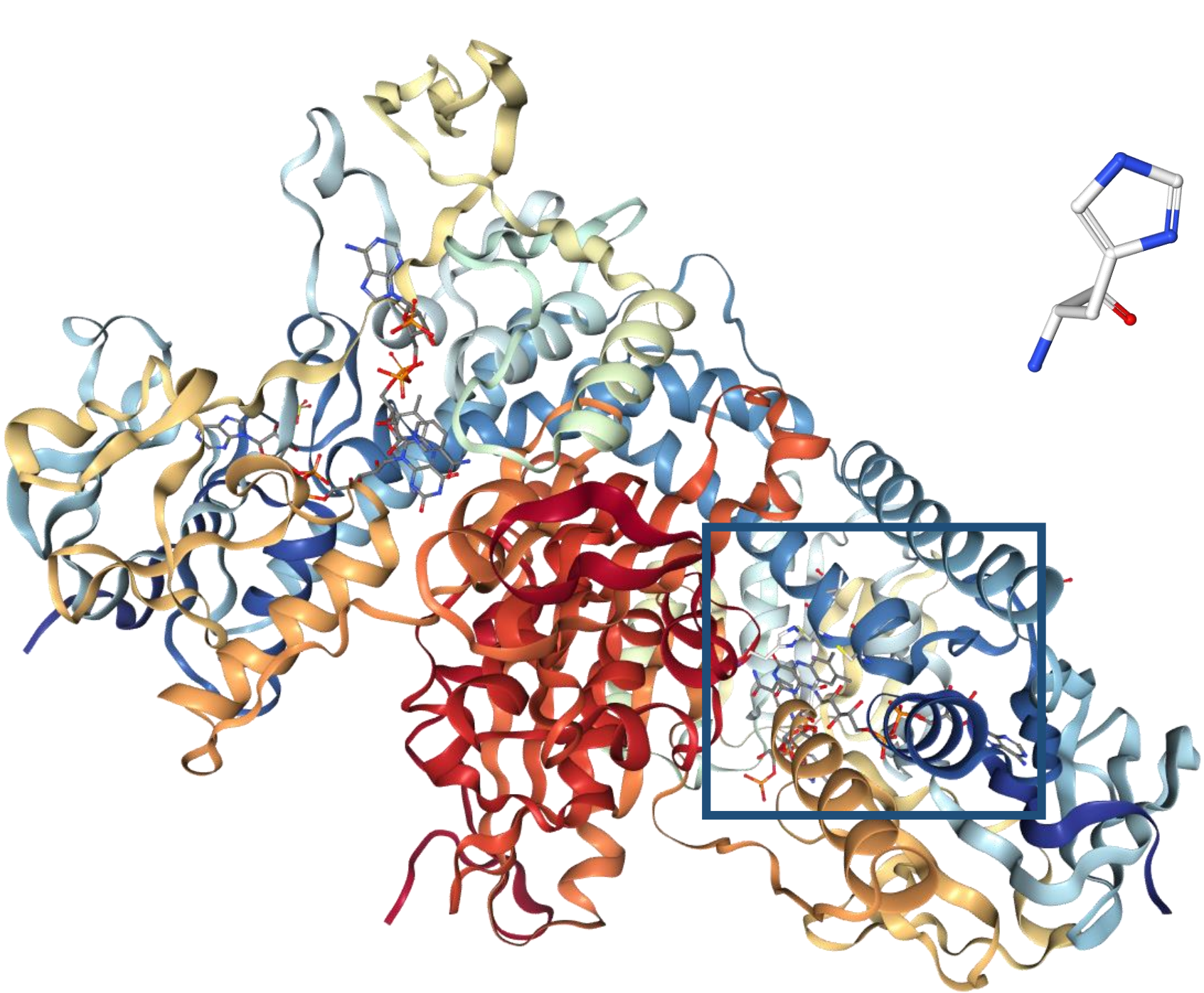
The precise mechanism of action of these Sb_V drugs, which have been in use for 60 years, is still unclear.

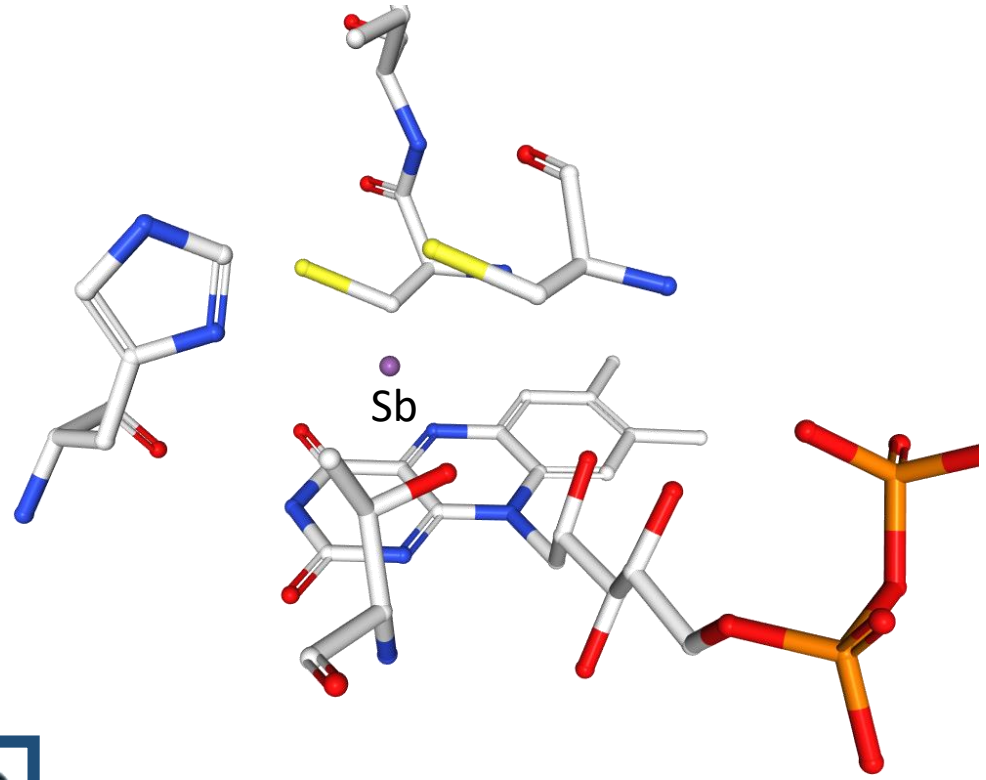
Several effects have been noted:

- **inhibition of glycolysis and fatty acid oxidation**,
- **fragmentation** of parasitic **DNA**,
- **externalization of phosphatidylserine on the outer surface of membranes** via a caspase-independent pathway.

In the parasite, reduced trypanothione $T(SH)_2$ rapidly reduces Sb(V) to Sb(III), which is thought to be the active form.

TR is essential for parasite survival and virulence and is absent from mammalian cells. **Sb(III) is coordinated by the two redox-active catalytic cysteine residues, a threonine residue, and a histidine**, and has been shown to strongly inhibit TR activity, blocking trypanothione reduction

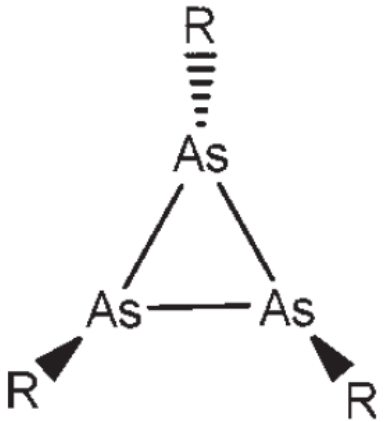


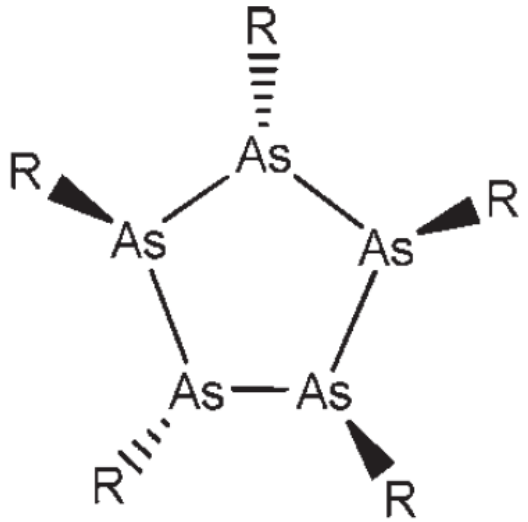


PDB = 2W0H

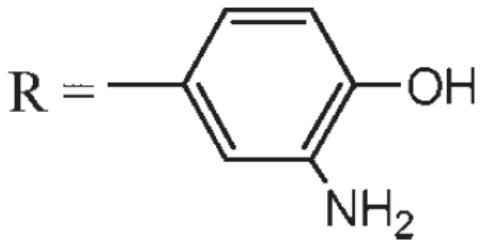
Leishmania infantum Trypanothione reductase in complex with antimony and NADPH

The **arsenic-based antimicrobial** agent Salvarsan ($\{RAs\}_n$, R = 3-amino-4-hydroxyphenyl) was used historically to treat syphilis and trypanosomiasis, although in recent times it has been superseded by penicillin. It is suggested that oxidation in vivo generates the active form of the drug, such that Salvarsan serves as a slow-release source of $RAs(OH)_2$





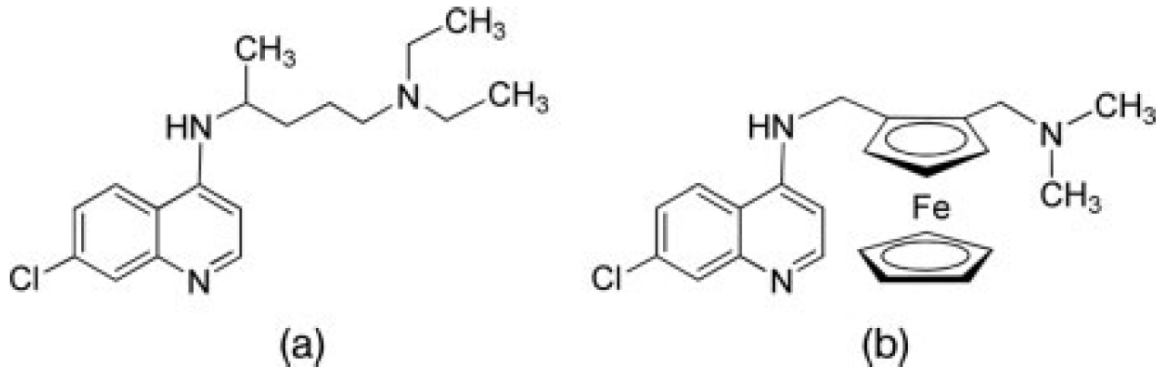
The Structure of 3-amino-4-hydroxyphenylarsenic(III) (Salvarsan) is thought to consist of cyclic species $(AsR)_n$ (R = 3-amino-4-hydroxyphenyl) where n = 3 and n = 5 are the most abundant species.



Malaria is caused by a protozoan parasite of the genus Plasmodium and is responsible for about 2 million deaths per year. The most commonly used antimalarial drug is chloroquine (CQ), which accumulates within the parasite and interferes with the function of its digestive vacuole (where the host hemoglobin is digested).

Metal complexation of established antimalarials shows promise in overcoming resistance.

The ferrocene derivative Ferroquine (FQ) a 4-aminoquinoline antimalarial that contains a quinoline nucleus similar to chloroquine, is being developed by Sanofi-Aventis and has recently entered phase II clinical trials (2007), showing excellent activity against CQ-resistant Plasmodium falciparum, both in vitro and in vivo.



(a) Structure of the antimalarials chloroquine (CQ) and (b) ferroquine.

Gold-containing Drugs Used in the Therapy of Rheumatoid Arthritis

Gold was used for therapeutic purposes in ancient civilizations. For instance, a Chinese prescription dating from the 6th century CE describes in detail the dissolution of metallic gold for use in elixirs aimed at achieving immortality.

Oxidative dissolution of this noble metal involved potassium nitrate, KNO_3, containing iodate, IO^{3-}, as an impurity, which can be reduced to iodide by reductants such as $FeSO_4$ or organic material. In the presence of I^-, the potential for oxidation of gold is lowered by approximately 1 V, and $[AuI_2]^-$ is formed in the process.

In 1924 Mollgaard **applied a thiosulfato complex of monovalent gold in an attempt to cure tuberculosis**, and a few years later **Au(I) thioglucose** was beginning to be **used** in the therapy of **rheumatic fever**.

However, it was only much later that similar compounds were subjected to systematic clinical trials and received proper attention.

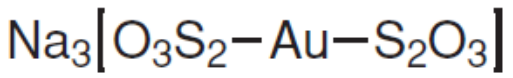
N.B. Only the monovalent form of gold has therapeutic importance in antirheumatic agents, while both Au(I) and Au(III) are found in gold-containing anticancer drugs

The aqua complex of Au(I) is unstable and disproportionates according to:

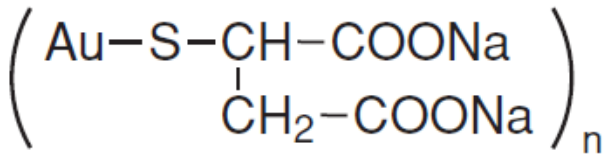
$$3\ Au(I) \leftrightarrow 2\ Au(0) + Au(III)$$

however, **the monovalent state can be stabilized through "soft", polarizable ligands such as CN^-, PR_3 and thiolates, RS^-**, under formation of preferentially linear d^{10} metal complexes.

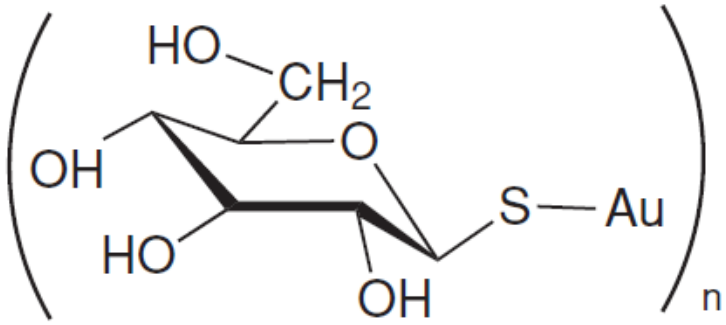
Most of the **Au(I) compounds used as antirheumatic agents contain thiolate ligands**. Au(III) will act as a strong oxidant under such conditions.



trisodiumgold(I)bis(thiosulfate)
("sanocrysin")



disodiumgold(I)thiomalate
("myochrisin")



gold(I)thioglucose

The **linear arrangement** of the sulfur ligands around the two-coordinate metal center **occurs in all cases**, including solganol and myochrisine; in these latter drugs, **sulfurbridged oligomeric species** seem to be present.

Commercial and medicinal preparations of myochrisine are more complex, due to the use of excess thiomalate ligand over the 1 : 1 ratio. In solutions of the drug, tetramers (ESI-MS) and open-chain structures (XAS) have been detected

Solganol and myochrisine are water soluble but are insoluble in hydrophobic environments.

Administered intramuscularly in order to prevent hydrolysis in acidic gastric juice

The lipophilic **auranofin** can be administered orally with about 25% resorption.

After long-term therapy with myochrisine and auranofin, constant levels of 30–50 mg/ml blood are attained; in the blood, myochrisine is mainly bound to albumin in the serum, while auranofin is equally distributed between serum and erythrocytes.

Therapy with **gold compounds to retard active rheumatic processes** has some not uncommon side effects resembling **allergic reactions** on skin and mucous membranes, as well as gastrointestinal and renal problems.
These effects restrictthe gold therapy to only about two-thirds of patients; it is assumed that some are due to the formation of Au(III) compounds.
Since Au(I) forms thermodynamically stable complexes with sulfur ligands, the addition of sulfur-containing chelating agents such as penicillamine or dimercaprol and of antihistamines or adrenocorticosteroids might reduce the toxicity of the gold drugs.

Arthritis is an inflammation of the tissue which surrounds the joints. It is assumed that the damage is caused by the action of hydrolytic enzymes from lysosomes (rheumatoid arthritis as autoimmune reaction).

Examinations of the tissue show that gold is preferentially accumulated in the joints and is stored in the lysosomes of macrophages, forming "**aurosomes**".
Inhibition of the lysosomal enzyme activity can be rationalized by assuming a coordination of gold to the thiolate groups, RS^-, present in the enzymes. *In vitro*, disodiumgold(I) thiomalate (myochrisine) readily reacts with other thiolates, RS^-, under release of thiomalate (similar to linearly coordinated and thus kinetically labile Hg(II) thiolate complexes).

According to a different hypotheses:

Au(I) compounds are able to inhibit the formation of undesired antibodies in the collagen region;

irreversible damage of the joints may result from lipid oxidation with subsequent degradation of proteins by the free radicals formed. Superoxide ions, $O_2^{\bullet-}$, which can be produced by activated phagocytes play an important role in this process. It has been shown that several oxidants can relatively easily convert $O_2^{\bullet-}$ to reactive, not spin-inhibited singlet oxygen, $^1O_2$. In this context, it is important to note that Au(I) compounds should be able to deactivate this excited singlet state of dioxygen, due to the particularly high spin–orbit coupling constant of this heavy element (intersystem crossing).

Lithium in Psychopharmacologic Drugs

For several decades, **manic–depressive (bipolar) psychoses have been treated with lithium** salts, often in the form of exactly measured lithium carbonate. The Li^+ ion is therapeutically valuable because it counteracts both phases in the typically cyclical course of this disorder.

Difficulties in the therapy with lithium compounds result from the relatively **high toxicity of the metal** and the resulting very small therapeutic window.

About 1 mmol Li^+/l (1 mM) blood is necessary for a successful treatment, a 2 mM concentration can cause toxic side effects, particularly in the renal and nervous systems (tremor). Concentrations of 3 mM and higher may eventually be lethal for the patient.

For this reason, **lithium carbonate and other salts of Li^+ are administered orally in several carefully controlled doses per day**. On acute poisoning, the blood should be purified using Na^+-containing dialysis fluids.

Li^+ is relatively **rare in the earth's crust and in sea water**.

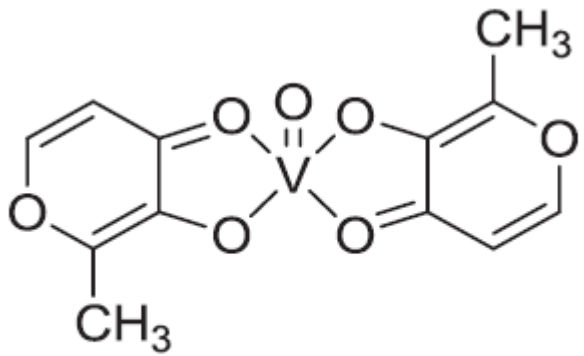
It is also a lighter and, with an ionic radius of 60 pm for the coordination number 4, significantly smaller and thus more polarizing homologue of Na^+, a fact that might directly explain the neurological (side) effects. On the other hand, **Li^+ shares a diagonal relationship and the same physiologically important affinity towards phosphate ligands with the slightly larger Mg^{2+}**.

There are several hypotheses regarding the specific antipsychotic mode of action for lithium in which the effect on the **cellular information system** (via binding to phosphates) is a focal point; **inhibitions of the inositol/phosphate metabolism**, of an **adenyl cyclase** and of a **guanine nucleotide** binding protein, a "G-protein", are under discussion.

Vanadium-containing Insulin Mimetics

Pentavalent vanadium,VV, as vanadate (VO_4^{3-}), and tetravalent V(IV), as vanadyl $[VO]^{2+}$, are in use in insulin-mimetic drugs. They can imitate the function of insulin and stimulate the uptake of glucose.

At the same time, many V-containing compounds exhibit cell toxicity. Vanadium complexes with organic ligands are usually less toxic and exhibit higher lipophilicity. The complex bis(maltolato)oxovanadium(IV) is more effective than $VOSO_4$.

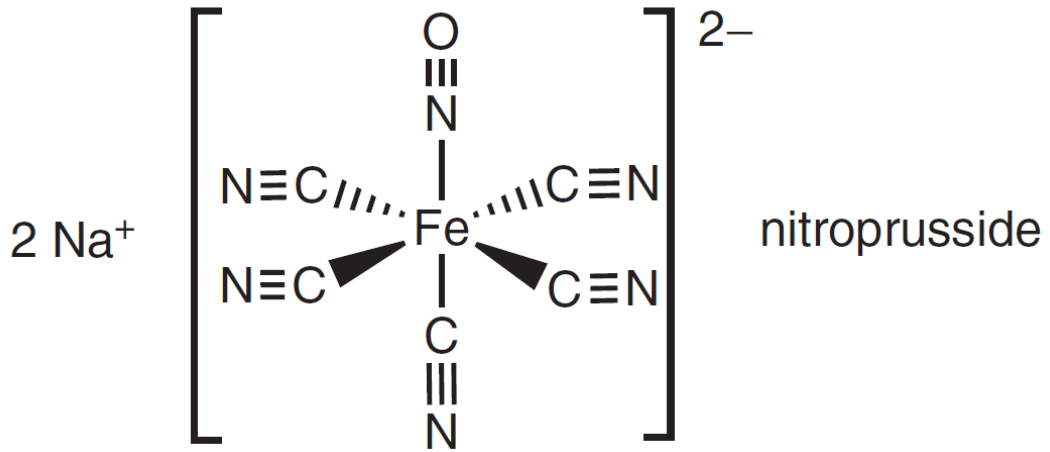


bis(maltolato)oxovanadium(IV)

Sodium Nitroprusside

Sodium nitroprusside (SNP), $Na_2[Fe(CN)_5(NO)] \times 2\ H_2O$, is a nitrosyl complex, long in clinical use.

The low-spin Fe(II) complex is administered in case of suddenly elevated blood pressure (e.g. during surgery) or after myocardial events. After **infusion of the drug, the desired reduction of the blood pressure begins within 1–2 minutes**.



It is assumed that *in vivo* **nitroprusside $[Fe(CN)_5(NO)]^{2-}$ is reduced to $[Fe(CN)_5(NO)]^{3-}$**, which is labile and **loses CN^-**. Subsequently, **$[Fe(CN)_4(NO)]^{2-}$ releases NO**, which leads to a relaxation of the smooth muscles of the blood vessels. This is the reason for the therapeutic effects.