INORGANIC CHEMISTRY II

OBJECTIVES

1. To understand the role of metal ions in biological process.
2. To learn the basic concepts of chemotherapy.
3. To learn the principle of catalysis and reaction mechanisms of organometallics.

UNIT I: General Principles of Bioinorganic Chemistry

Occurrence and availability of inorganic elements in biological systems – biomineralization – control and assembly of advanced materials in biology – nucleation and crystal growth – various biominerals – calcium phosphate – calcium carbonate – amorphous silica, iron biominerals – strontium and barium sulphate.

Function and transport of alkali and alkaline earth metal ions: characterization of K+, Na+, Ca2+ and Mg2+ – complexes of alkali and alkaline earth metal ions with macrocycles – ion channels – ion pumps, catalysis and regulation of bioenergetic processes by the alkaline earth metal ions – Mg2+ and Ca2+.

Metals at the center of photosynthesis – primary processes in photosynthesis – photosystems I and II-light absorption (energy acquisition) – exciton transport (direct energy transfer) – charge separation and electron transport – manganese catalyzed oxidation of water to O2.

UNIT II: Amines, Proteins and Enzymes

Cobalamines: reactions of the alkyl cobalamines – one electron reduction and oxidation – Co-C bond cleavage – coenzyme B12 – alkylation reactions of methylcobalamin.

Heme and non-heme proteins – haemoglobin and myoglobin – oxygen transport and storage – electron transfer and oxygen activation – cytochromes, ferredoxins and rubredoxin – model systems, mononuclear non-heme iron enzymes.

Copper containing proteins – classification and examples – electron transfer – oxygen transport-oxygenation – oxidases and reductases – cytochrome oxidase – superoxide dismutase (Cu, Zn) – nickel containing enzyme: urease.

UNIT III: Medicinal Bioinorganic Chemistry

Bioinorganic chemistry of quintessentially toxic metals – lead, cadmium, mercury, aluminium, chromium, copper and plutonium – detoxification by metal chelation – drugs that act by binding at the metal sites of metalloenzymes.

Chemotherapy – chemotherapy with compounds of certain non-essential elements – platinum complexes in cancer therapy – cisplatin and its mode of

action – cytotoxic compounds of other metals.
Gold containing drugs as anti-rheumatic agents and their mode of action – lithium in psychopharmacological drugs – radiopharmaceuticals – technetium.

UNIT IV: Organometallics

The 18 electron rule – applications and limitations – isolobal concept and its usefulness – uses of typical organometallics such as metal alloys and organometallic hydrides in organic synthesis.
Nitrosyl complexes – bridging and terminal nitrosyls, bent and linear nitrosyls – dinitrogen complexes – metallocene and arene complexes – metal carbenes, carbenes, carboxylate anions.
Classification based on captivity and polarity of M-C bond, organometallic compounds of lanthanides and actinides – fluxional organometallic compounds – organometallics in medicine, agriculture, horticulture and industry.

UNIT V: Reactions and Catalysis by Organometallics

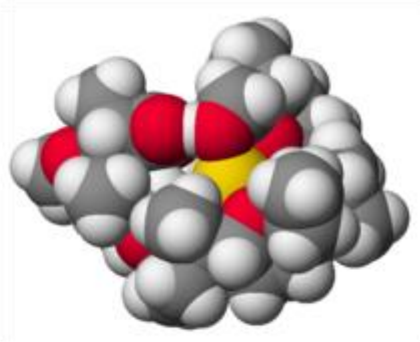
Organometallic reactions – ligand association and dissociation – oxidative addition and reductive elimination – insertion reactions.
Reactions of coordinated ligands in organometallics – hydrogenation, hydroformylation, epoxidation, metathesis.
Polymerization of olefins, olefin oxidation (Wacker process) and carbonylation of methanol.

UNIT I

General Principles of Bioinorganic Chemistry

Occurrence and availability of inorganic elements in biological systems:

Alkali and alkaline earth metals:



The abundant inorganic elements act as ionic electrolytes. The most important ions are sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate. The maintenance of precise gradients across cell membranes maintains osmotic pressure and pH. Ions are also critical for nerves and muscles, as action potentials in these tissues are produced by the exchange of electrolytes between the extracellular fluid and the cytosol.Electrolytes enter and leave cells through proteins in the cell membrane called ion channels. For example, muscle contraction depends upon the movement of calcium, sodium and potassium through ion channels in the cell membrane and T-tubules.

Transition metals:

The transition metals are usually present as trace elements in organisms, with zinc and iron being most abundant.These metals are used in some proteins as cofactors and are essential for the activity of enzymes such as catalase and oxygen-carrier proteins such as hemoglobin.These cofactors are bound tightly to a specific protein; although enzyme cofactors can be modified during catalysis, cofactors always return to their original state after catalysis has taken place. The metal micronutrients are taken up into organisms by specific transporters and bound to storage proteins such as ferritin or metallothionein when not being used.Cobalt is essential for the functioning of vitamin B12.

Main group compounds:

Many other elements aside from metals are bio-active. Sulfur and phosphorus are required for all life. Phosphorus almost exclusively exists as phosphate and its various esters. Sulfur exists in a variety of oxidation states, ranging from sulfate (SO_4^{2-}) down to sulfide (S^{2-}). Selenium is a trace element involved in proteins that are antioxidants. Cadmium is important because of its toxicity.[

Composition of living organisms:

About 99% of mammals' mass are the elements carbon, nitrogen, calcium, sodium, chlorine, potassium, hydrogen, phosphorus, oxygen and sulfur.The organic compounds (proteins, lipids and carbohydrates) contain the majority of the carbon and nitrogen and most of the oxygen and hydrogen is present as water.The entire collection of metal-containing biomolecules in a cell is called the metallome.

Biomineralization:

Biomineralization is the process by which living organisms produce minerals, often to harden or stiffen existing tissues. Such tissues are called mineralized tissues.Examples include silicates in algae and diatoms, carbonates in invertebrates, and calcium phosphates and carbonates in vertebrates. Other examples include copper, iron and gold deposits involving bacteria. Biologically-formed minerals often have special uses such as magnetic sensors in magnetotactic bacteria (Fe_3O_4), gravity sensing devices ($CaCO_3$, $CaSO_4$, $BaSO_4$) and iron storage and mobilization ($Fe_2O_3 \bullet H_2O$ in the protein ferritin). Because extracellular iron is strongly involved in inducing calcification,its control is essential in developing shells; the protein ferritin plays an important role in controlling the distribution of iron.

Control and assembly of advanced materials in biology:

Molecular self-assembly (material)is the process by which molecules adopt a defined arrangement without guidance or management from an outside source. There are two types of self-assembly. These are **intramolecular** self-assembly and **intermolecular** self-assembly. Commonly, the term molecular self-assembly refers to intermolecular self-assembly, while the intramolecular analog is more commonly called folding.

Molecular self-assembly underlies the construction of biologic macromolecular assemblies in living organisms, and so is crucial to the function of cells. It is exhibited in the self-assembly of lipids to form the membrane, the formation of double helical DNA through hydrogen bonding of the individual strands, and the assembly of proteins to form quaternary structures. Molecular self-assembly of incorrectly folded proteins into insoluble amyloid fibers is responsible for infectious prion-related neurodegenerative diseases. Molecular self-assembly of nanoscale structures plays a role in the growth

Nucleation and crystal growth:

Nucleation is the first step in the formation of either a new thermodynamic phase or a new structure via self-assembly or self-organization. Nucleation is typically defined to be the process that determines how long an observer has to wait before the new phase or self-organized structure appears.

For example, if a volume of water is cooled (at atmospheric pressure) below 0 °C, it will tend to freeze into ice, but volumes of water cooled only a few degrees below 0 °C often stay completely free of ice for long periods. At these conditions, nucleation of ice is either slow or does not occur at all

Nucleation is often found to be very sensitive to impurities in the system. These impurities may be too small to be seen by the naked eye, but still can control the rate of nucleation. Because of this, it is often important to distinguish between heterogeneous nucleation and homogeneous nucleation.

The nucleation of crystals

In many cases, liquids and solutions can be cooled down or concentrated up to conditions where the liquid or solution is significantly less thermodynamically stable than the crystal, but where no crystals will form for minutes, hours, weeks or longer. Nucleation of the crystal is then being prevented by a substantial barrier. This has consequences, for example cold high altitude clouds may contain large numbers of small liquid water droplets that are far below 0 °C.

In small volumes, such as in small droplets, only one nucleation event may be needed for crystallisation. In these small volumes, the time until the first crystal appears is usually defined to be the nucleation time. In larger volumes many nucleation events will occur. A simple model for crystallisation in that case, that combines nucleation and growth is the KJMA or Avrami model.

Primary and secondary nucleation

The time until the appearance of the first crystal is also called primary nucleation time, to distinguish it from secondary nucleation times. Primary here refers to the first nucleus to form, while secondary nuclei are crystal nuclei produced from a preexisting crystal. Primary nucleation describes the transition to a new phase that does not rely on the new phase already being present, either because it is the very first nucleus of that phase to form, or because the nucleus forms far from any pre-existing piece of the new phase. Particularly in the study of crystallisation, secondary nucleation can be important. This is the formation of nuclei of a new crystal directly caused by pre-existing crystals.

For example, if the crystals are in a solution and the system is subject to shearing forces, small crystal nuclei could be sheared off a growing crystal, thus increasing the number of crystals in the system. So both primary and secondary nucleation increase the number of crystals in the system but their mechanisms are very different, and secondary nucleation relies on crystals already being present.

Examples of the nucleation of fluids (gases and liquids)

Clouds form when wet air cools (often because the air rises) and many small water droplets nucleate from the supersaturated air.The amount of water vapor that air can carry decreases with lower temperatures. The excess vapor begins to nucleate and to form small water droplets which form a cloud. Nucleation of the droplets of liquid water is heterogeneous, occurring on particles referred to as cloud condensation nuclei. Cloud seeding is the process of adding artificial condensation nuclei to quicken the formation of clouds.

Bubbles of carbon dioxide nucleate shortly after the pressure is released from a container of carbonated liquid.

Nucleation of carbon dioxide bubbles around a finger

Nucleation in boiling can occur in the bulk liquid if the pressure is reduced so that the liquid becomes superheated with respect to the pressure-dependent boiling point. More often, nucleation occurs on the heating surface, at nucleation sites. Typically, nucleation sites are tiny crevices where free gas-liquid surface is maintained or spots on the heating surface with lower wetting properties. Substantial superheating of a liquid can be achieved after the liquid is de-gassed and if the heating surfaces are clean, smooth and made of materials well wetted by the liquid.

Some champagne stirrers operate by providing many nucleation sites via high surface-area and sharp corners, speeding the release of bubbles and removing carbonation from the wine.

The Diet Coke and Mentos eruption offers another example. The surface of Mentos candy provides nucleation sites for the formation of carbon-dioxide bubbles from carbonated soda.

Both the bubble chamber and the cloud chamber rely on nucleation, of bubbles and droplets, respectively.

Examples of the nucleation of crystals

The most common crystallisation process on Earth is the formation of ice. Liquid water does not freeze at 0 °C unless there is ice already present; cooling significantly below 0 °C is required to nucleate ice and so for the water to freeze. For example, small droplets of very pure water can remain liquid down to below -30° C although ice is the stable state below 0 °C.

Many of the materials we make and use are crystalline, but are made from liquids, e.g. crystalline iron made from liquid iron cast into a mold, so the nucleation of crystalline materials is widely studied in industry. It is used heavily in the chemical industry for cases such as in the preparation of metallic ultradispersed powders that can serve as catalysts. For example, platinum deposited onto TiO_2 nanoparticles catalyses the liberation of hydrogen from water.It is an important factor in the semiconductor industry, as the band gap energy in semiconductors is influenced by the size of nanoclusters.

Biominerals – calcium phosphate:

Calcium phosphates (CaP) are one of the most highly researched classes of biominerals, for the reason that the carbonated calcium phosphate apatite crystal is the essential mineral component of both bones and teeth of vertebrates.

The mechanism of CaP nucleation and growth is not fully understood. Based on Cryo-TEM and atomic force microscopy (AFM) studies CaP was suggested to mineralize through complex pathways involving pre-nucleation cluster aggregation, sequential morphological transformations, and finally traversing into the crystalline phase Amorphous calcium phosphate (ACP) has been reported as the transient phase in both in vivo and in vitro studies.

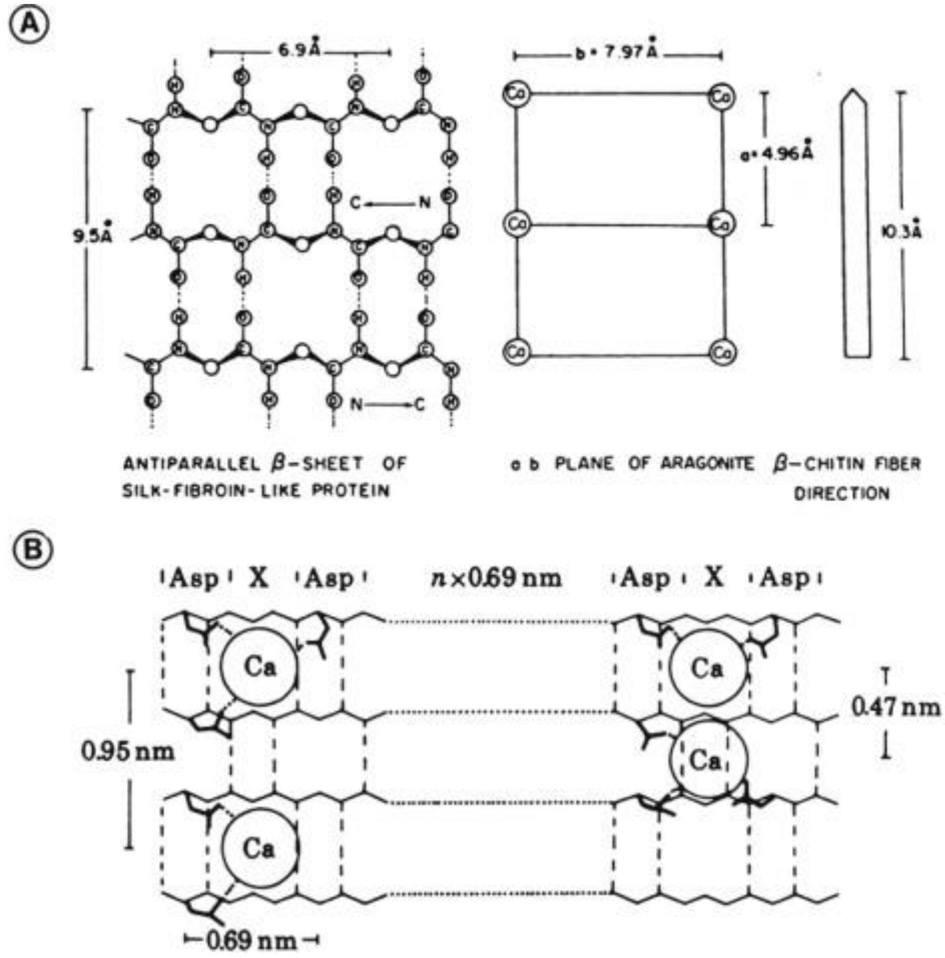
It has been proposed that the existence of ACP pre-nucleation clusters decreases the energy barrier to nucleation and enables biominerals, such as CaP, to mineralize following a non-classical crystal growth process defined as crystallization by particle attachment.

In this process, the pre-nucleation particles, which are regarded as building blocks, are initiated from the solvated state and aggregate with each other to form clusters with chain-like or branched morphology. These pre-nucleation particles could vary from multi-ion complexes to nano-crystals in different mineralization systems.

Calcium-Based Biominerals:

Calcium Carbonates:

Biominerals based on calcium carbonate are found in a very large number of organisms. The shells of molluscs are among the most abundant biogenic minerals, and are composed of 95–99% calcium carbonate crystal and less than 5% organic matrix. Shell layers are formed from calcium carbonate as aragonite or calcite crystal corresponding to different mineral textures (also called microstructures). The organic matrix of the shell is composed of proteins and polysaccharides, which are thought to direct the formation of the calcium carbonate crystal and thus are responsible for the extraordinary properties of the shell. For example, nacre, the aragonite layer of the shell, exhibits a fracture resistance 3000 times higher than that of abiotic aragonite. The different crystal polymorphisms and microstructures of the layers are controlled by proteins secreted from outer epithelial cells in different regions of the mantle.Below Figure shows the molecular correspondence at the inorganic–organic interface in the nacre shell layer of *Nautilus repertus*. There is a close geometric match between the periodicity of the protein β-sheet and the lattice spacings of the aragonite, and it has been suggested that there is molecular complementarity between Ca atoms in the aragonite and aspartic acid residues organized in the sequence As-X-Asp (where X = a neutral residue) along the β-sheet.



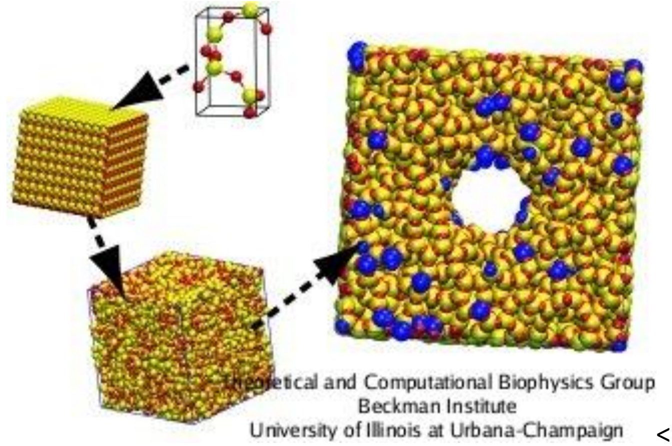
Amorphous silica:

Amorphous silica (SiO_2) is an inorganic material commonly used in semiconductor circuits to isolate different conducting regions.

Due to its mechanical resistance, high dielectric strength, and selectivity for chemical modification, amorphous silica has also become a key material in microelectronics and chromatography.

Because of its unique properties, silica is quintessential for a broad range of applications: chips, optical fibers, and telescope glasses are manufacture on silica. Furthermore, molecular biologists employ silica in resins and optical beads to study the biomacromolecules.

The Body: Silica Structures



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The first compulsory step to perform molecular dynamics simulations is to specify the coordinates and connectivity of each atom of the system. However, due to the amorphous nature of silica, there are no X-ray or NMR structures that can be used as templates.

To obtain amorphous models, crystalline structures are randomized using a set of MD annealing steps that reproduce structural features of actual amorphous silica. The procedure to construct an amorphous silica nanodevice is squematically pictured in the figure on the right side and briefly described in the next paragraph.

First, a cristoballite unit cell is build and replicate it to fill a cubic volume big enough to contain the nanodevice. Then, the crystalline cube is annealed by increasing the temperature to 8000 K .

and then cooling it back slowly to 300 K. The initial high temperature assures the randomization of the crystalline structure. After that, the nanodevice is sculpted by removing atoms from the amorphous cube. To mimic real amorphous silica surfaces, the nanodevice is annealed further, allowing the rearrangement of the surface atoms. Finally, the bonding connectivity is calculated using a cutoff distance of 0.2 nm. The resulting structure can be refined to produce chemically-modified silica forms, by introducing hydroxyl groups or organic molecules at the exposed surface (blue atoms).

Applications of Amorphous Silica:

MaterialsWhere silica fume, fly ash and GGBFS are not readily available, natural pozzolans are used as cement replacement materials and for concrete durability improvement where required. Some of these materials increase concrete water demand. Some materials are used after simply mining and milling them to an appropriate fineness, while others are subjected to ‘calcination’ – heating (to 500 -800°C) to activate certain (clay) minerals. Activated products like meta-kaolin are highly reactive54and are used in both conventional concrete and in the manufacture of geopolymer concrete. In Australia, some research has been carried out on the cementitious efficiency of pitchstone –a glassy mineral found in large outcrops. There are an estimated 100 million tonnes of pitchstone available in North Queensland. This mineral can be mined and milled to a fine powder and behaves as a moderately cementitious material21and has been shown to improve concrete durability.

Low heat Applications:

While silica fume has almost the same contribution to concrete heat of hydration as Portland cement on a unit weight basis, the higher strengths able to be achieved and the consequent lower cementitious content requirements mean silica fume has a role in low heat applications, often in combination with other SCM's like fly ash55.

Sprayed Concrete Applications:

Silica fume is a key ingredient in sprayed concrete (or Shotcrete) which is used particularly for tunnel linings and in mines. Silica fume concrete, alone or with steel fibres included, provides cohesive, high early strength concrete that is particularly suitable for sprayed concrete applications56such as those comprehensively described in the American Concrete Institute "Guide to Shotcrete"57.

Special Amorphous Silica Applications:

One of the main benefits of silica fume is the ability to make very high strength concrete, typically 80-100MPa and above. With these very high strengths comes a high modulus which can be used to advantage in high rise structures in particular58. These performance characteristics allow thinner columns to be used and create additional savings in materials through the need for less concrete and reinforcing steel.High durability performance also makes silica fume concrete the material of choice in projects requiring a long (e.g. 100 year) design life –like Scandinavian bridge structures and tall Middle Eastern tower buildings52.Metakaolin is a suitable raw material for the manufacture of geopolymer concrete59. With its high reactivity it has the potential to impart good strength and durability performance characteristics to this alternative to Portland cement concrete.

Iron Biominerals:

Many structures formed by living organisms are minerals. Examples include apatite [$Ca_2(OH)PO_4$] in bone and teeth, calcite or aragonite ($CaCO_3$) in the shells of marine organisms and in the otoconia (gravity device) of the mammalian ear, silica (SiO_2) in grasses and in the shells of small invertebrates such as radiolara, and iron oxides, such as magnetite (Fe_3O_4) in birds and bacteria (navigational devices) and ferrihydrite FeO(OH) in ferritin of mammals, plants, and bacteria.

Biomineralization is the formation of such minerals by the influence of organic macromolecules, e.g., proteins, carbohydrates, and lipids, on the precipitation of amorphous phases, on the initiation of nucleation, on the growth of crystalline phases, and on the volume of the inorganic material.

Iron oxides, as one of the best-studied classes of biominerals containing transition metals, provide good examples for discussion. One of the most remarkable recent characterizations of such processes is the continual deposition of single-crystal ferric oxide in the teeth of chiton.Teeth of chiton form on what is essentially a continually moving belt, in which new teeth are being grown and moved forward to replace mature teeth that have been abraded.

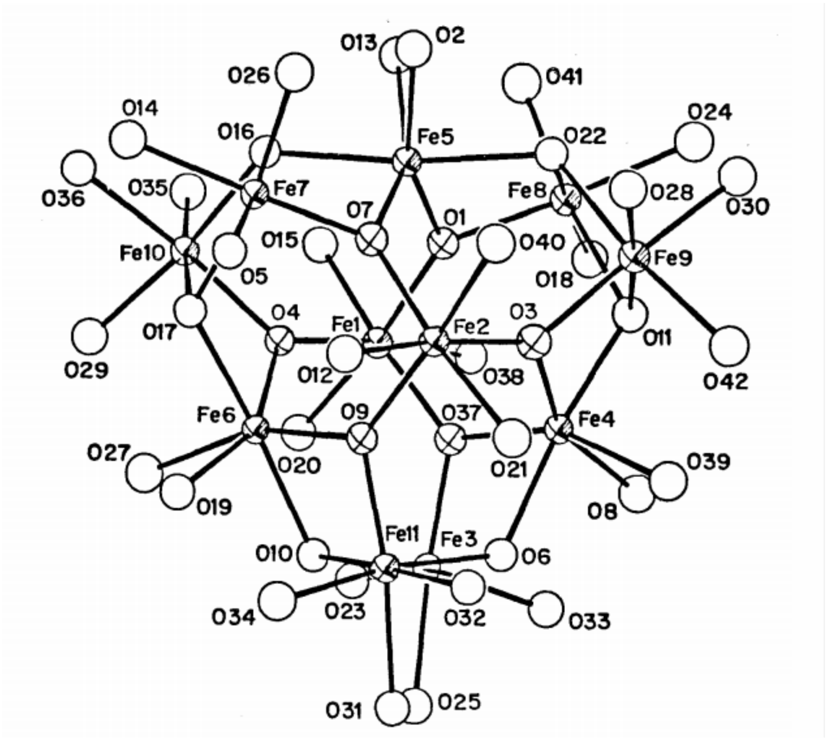
Synthetic iron complexes have provided models for two stages of ferritin iron storage and biomineralization:

1. the early stages, when small numbers of clustered iron atoms are bound to the ferritin protein coat, and
2. the final stages, where the bulk iron is a mineral with relatively few contacts to the protein coat. In addition, models have begun to be examined for the microenvironment inside the protein coat.

Among the models for the early or nucleation stage of iron-core formation are the binuclear Fe(III) complexes with $[Fe_2O(O_2CR_2)]^{2+}$ cores the three other Fe(III) ligands are N.

The μ-oxo complexes, which are particularly accurate models for the binuclear iron centers in hemerythrin, purple acid phosphatases, and, possibly, ribonucleotide reductases, may also serve as models for ferritin, since an apparently transient Fe(II)-O-Fe(III) complex was detected during the reconstitution of ferritin from protein coats and Fe(II).

The facile exchange of (O_2CR) for (O_2PR) in the binuclear complex is particularly significant as a model for ferritin, because the structure of ferritin cores varies with the phosphate content. An asymmetric trinuclear $(Fe_3O)^{7+}$ complex and an $(FeO)_{11}$ complex (Figure) have been prepared; these appear to serve as models for later stages of core nucleation (or growth).



Strontium and Barium Sulphate:

The crystallography and morphology of barium sulphate crystals produced by a range of desmid species have been examined by electron microscopy and electron diffraction. The morphology of the $BaSO_4$ crystals varies between desmid species and water chemistry. Tabular, rhombic crystals are commonly produced by *Closterium lunula* and hexagonal or elliptical crystals by *Micrasterias thomasiana*.

High-resolution transmission electron microscopy (hrtem) has confirmed the single-crystal nature of the biological precipitates. The crystals all lie with their tabular faces perpendicular to the [001] zone axis and are comparable with the typical crystal habit of geological and synthetic barium sulphates, suggesting a limited degree of biological control over precipitation. M^{2+} (Ba^{2+} or Sr^{2+}) : $SO^{2-}{}_4$ ion ratios *in vivo* and *in vitro* have been shown to affect the morphology of the crystals produced. For *Closterium lunula* an M^{2+}: $SO^{2-}{}_4$ ion ratio of less than 1:1 produces rhombic crystals and an ion ratio of more than 10:1 produces hexagonal crystals. For *Micrasterias thomasiana*, an ion ratio of 0.01:1 produces hexagonal crystals; an ion ratio of 1:1 produces a mixture of hexagonal and elliptical crystals, and an ion ratio of more than 10:1 produces elliptical crystals.

Crystal morphologies produced by desmids have been compared with those of synthetic crystals produced at similar ion ratios. The apparently limited extent of biological control and the importance of the ionic environment on the development of crystal morphology are discussed. It is proposed that desmid crystal morphology may provide a diagnostic for the local environment of crystal formation in the cell.

Function and transport of alkali and alkaline earth metal ions_characterization of K+, Na+, Ca2+ and Mg2+:

Potassium $K^{2+:}$

Potassium channels are the most widely distributed type of ion channel and are found in virtually all living organisms.They form potassium-selective pores that span cell membranes. Potassium channels are found in most cell types and control a wide variety of cell functions.

Function

Potassium channels function to conduct potassium ions down their electrochemical gradient, doing so both rapidly (up to the diffusion rate of K^+ ions in bulk water) and selectively (excluding, most notably, sodium despite the sub-angstrom difference in ionic radius).Biologically, these channels act to set or reset the resting potential in many cells. In excitable cells, such as neurons, the delayed counterflow of potassium ions shapes the action potential.

By contributing to the regulation of the action potential duration in cardiac muscle, malfunction of potassium channels may cause life-threatening arrhythmias. Potassium channels may also be involved in maintaining vascular tone.

They also regulate cellular processes such as the secretion of hormones (*e.g.*, insulin release from beta-cells in the pancreas) so their malfunction can lead to diseases

Types

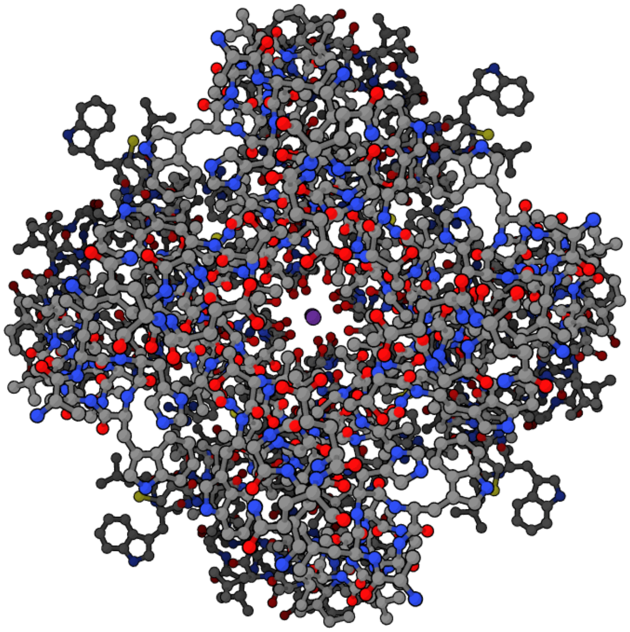
There are four major classes of potassium channels:

- Calcium-activated potassium channel - open in response to the presence of calcium ions or other signalling molecules.
- Inwardly rectifying potassium channel - passes current (positive charge) more easily in the inward direction (into the cell).
- Tandem pore domain potassium channel - are constitutively open or possess high basal activation, such as the "resting potassium channels" or "leak channels" that set the negative membrane potential of neurons.
- Voltage-gated potassium channel - are voltage-gated ion channels that open or close in response to changes in the transmembrane voltage.

For more examples of pharmacological modulators of potassium channels, see potassium channel blocker and potassium channel opener.

Structure

Potassium channels have a tetrameric structure in which four identical protein subunits associate to form a fourfold symmetric (C_4) complex arranged around a central ion conducting pore (i.e., a homotetramer). Alternatively four related but not identical protein subunits may associate to form heterotetrameric complexes with pseudo C_4 symmetry. All potassium channel subunits have a distinctive pore-loop structure that lines the top of the pore and is responsible for potassium selective permeability.



There are over 80 mammalian genes that encode potassium channel subunits. However potassium channels found in bacteria are amongst the most studied of ion channels, in terms of their molecular structure. Using X-ray crystallography,profound insights have been gained into how potassium ions pass through these channels and why (smaller) sodium ions do not.

Sodium Na^{2+}:

Sodium channels are integral membrane proteins that form ion channels, conducting sodium ions (Na^+) through a cell's plasma membrane.[1][2] They belong to the superfamily of cation channels and can be classified according to the trigger that opens the channel for such ions, i.e. either a voltage-change ("voltage-gated", "voltage-sensitive", or "voltage-dependent" sodium channel; also called "VGSCs" or "Nav channel") or a binding of a substance (a ligand) to the channel (ligand-gated sodium channels).

In excitable cells such as neurons, myocytes, and certain types of glia, sodium channels are responsible for the rising phase of action potentials. These channels go through three different states called resting, active and inactive states. Even though the resting and inactive states would not allow the ions to flow through the channels the difference exists with respect to their structural conformation.

Selectivity

Sodium channels are highly selective for the transport of ions across cell membranes. The high selectivity with respect to the sodium ion is achieved in many different ways. All involve encapsulation of the sodium ion in a cavity of specific size within a larger molecule.

Voltage-gated sodium channels

Structure

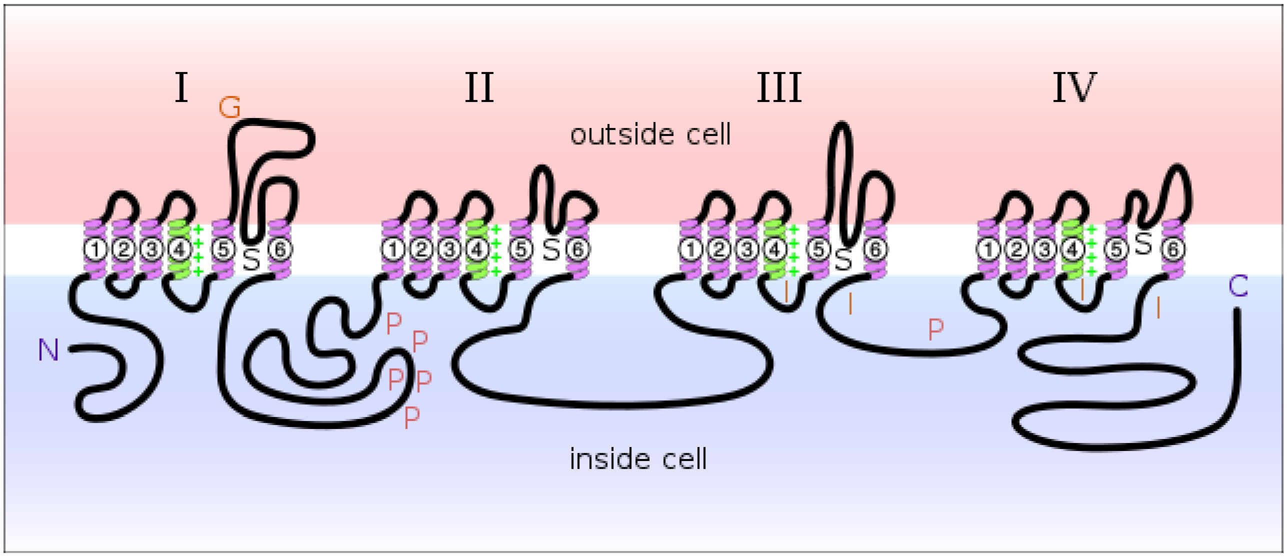


Diagram of a voltage-sensitive sodium channel α-subunit. G – glycosylation, P – phosphorylation, S – ion selectivity, I – inactivation. Positive (+) charges in S4 are important for transmembrane voltage sensing.

Sodium channels consist of large α subunits that associate with proteins, such as β subunits. An α subunit forms the core of the channel and is functional on its own. When the α subunit protein is expressed by a cell, it is able to form channels that conduct Na^+ in a voltage-gated way, even if β subunits or other known modulating proteins are not expressed. When accessory proteins assemble with α subunits, the resulting complex can display altered voltage dependence and cellular localization.

The α-subunit has four repeat domains, labelled I through IV, each containing six membrane-spanning segments, labelled S1 through S6. The highly conserved S4 segment acts as the channel's voltage sensor. The voltage sensitivity of this channel is due to positive amino acids located at every third position. When stimulated by a change in transmembrane voltage, this segment moves toward the extracellular side of the cell membrane, allowing the channel to become permeable to ions. The ions are conducted through a pore, which can be broken into two regions. The more external (i.e., more extracellular) portion of the pore is formed by the "P-loops" (the region between S5 and S6) of the four domains. This region is the most narrow part of the pore and is responsible for its ion selectivity. The inner portion (i.e., more cytoplasmic) of the pore is formed by the combined S5 and S6 segments of the four domains. The region linking domains III and IV is also important for channel function. This region plugs the channel after prolonged activation, inactivating it.

Calcium Ca^{2+}:

Calcium pumps are a family of ion transporters found in the cell membrane of all animal cells. They are responsible for the active transport of calcium out of the cell for the maintenance of the steep Ca^{2+} electrochemical gradient across the cell membrane. Calcium pumps play a crucial role in proper cell signalling by keeping the intracellular calcium concentration roughly 10,000 times lower than the extracellular concentration. Failure to do so is one cause of muscle cramps.

The plasma membrane Ca^{2+} ATPase and the sodium-calcium exchanger are together the main regulators of intracellular Ca^{2+} concentrations

Biological role:

Ca^{2+} has many important roles as an intracellular messenger. The release of a large amount of free Ca^{2+} can trigger a fertilized egg to develop, skeletal muscle cells to contract, secretion by secretory cells and interactions with Ca^{2+} -responsive proteins like calmodulin. To maintain low concentrations of free Ca^{2+} in the cytosol, cells use membrane pumps like calcium ATPase found in the membranes of sarcoplasmic reticulum of skeletal muscle. These pumps are needed to provide the steep electrochemical gradient that allows Ca^{2+} to rush into the cytosol when a stimulus signal opens the Ca^{2+} channels in the membrane. The pumps are also necessary to actively pump the Ca^{2+} back out of the cytoplasm and return the cell to its pre-signal state.

Crystallography of calcium pumps

The structure of calcium pumps found in the sarcoplasmic reticulum of skeletal muscle was elucidated in 2000 by Toyoshima, et al. using microscopy of tubular crystals and 3D microcrystals. The pump has a molecular mass of 110,000 amu, shows three well separated cytoplasmic domains, with a transmembrane domain consisting of ten alpha helices and two transmembrane Ca^{2+} binding sites.

Calcium is an important signaling molecule involved in the regulation of many cellular functions. The large free energy in the Ca^{2+} ion membrane gradients make Ca^{2+} signaling inherently sensitive to the available cellular free energy, primarily in the form of ATP.

In addition, Ca^{2+} regulates many cellular ATP consuming reactions such as muscle contraction, exocytosis, biosynthesis and neuronal signaling. Thus, Ca^{2+} becomes a logical candidate as a signaling molecule to modulate ATP hydrolysis and synthesis during changes in numerous forms of cellular work. Mitochondria are the primary source of aerobic energy production in mammalian cells and also maintain a large Ca^{2+} gradient across their inner membrane providing a signaling potential for this molecule.

The demonstrated link between cytosolic and mitochondrial [Ca^{2+}], identification of transport mechanisms as well as proximity of mitochondria to Ca^{2+} release sites further supports the notion that Ca^{2+} can be an important signaling molecule in the energy metabolism interplay of the cytosol with the mitochondria. Here we review sites within the mitochondria where Ca^{2+} plays a role in the regulation of ATP generation and potentially contributes to the orchestration of the cellular metabolic homeostasis.. Numerous non-invasive approaches monitoring NADH, mitochondrial membrane potential, oxygen consumption and workloads suggest significant Ca^{2+} effects on other elements of NADH generation as well as downstream elements of oxidative phosphorylation including the F_1F_O-ATPase and the cytochrome chain.

These other potential elements of Ca^{2+} modification of mitochondrial energy conversion will be the focus of this review. Though most of specific molecular mechanisms have yet to be elucidated, it is clear that Ca^{2+} provides a balanced activation of mitochondrial energy metabolism which exceeds the alteration of dehydrogenases alone.

Magnesium 2^+:

Magnesium is an essential element **in biological systems**. Magnesium occurs typically as the Mg^{2+} ion. It is an essential mineral nutrient (i.e., element) for life and is present in every cell type in every organism. For example, ATP (adenosine triphosphate), the main source of energy in cells, must bind to a magnesium ion in order to be biologically active. What is called ATP is often actually Mg-ATP. As such, magnesium plays a role in the stability of all polyphosphate compounds in the cells, including those associated with the synthesis of DNA and RNA.

Over 300 enzymes require the presence of magnesium ions for their catalytic action, including *all* enzymes utilizing or synthesizing ATP, or those that use other nucleotides to synthesize DNA and RNA.

In plants, magnesium is necessary for synthesis of chlorophyll and photosynthesis.

Function

A balance of magnesium is vital to the well-being of all organisms. Magnesium is a relatively abundant ion in Earth's crust and mantle and is highly bioavailable in the hydrosphere. This availability, in combination with a useful and very unusual chemistry, may have led to its utilization in evolution as an ion for signaling, enzyme activation, and catalysis. However, the unusual nature of ionic magnesium has also led to a major challenge in the use of the ion in biological systems. Biological membranes are impermeable to magnesium (and other ions), so transport proteins must facilitate the flow of magnesium, both into and out of cells and intracellular compartments.

Chlorophyll in plants converts water to oxygen as O_2. Hemoglobin in vertebrate animals transports oxygen as O_2 in the blood. Chlorophyll is very similar to hemoglobin, except magnesium is at the center of the chlorophyll molecule and iron is at the center of the hemoglobin molecule, with other variations. This process keeps living cells on earth alive and maintains baseline levels of CO_2 and O_2 in the atmosphere.

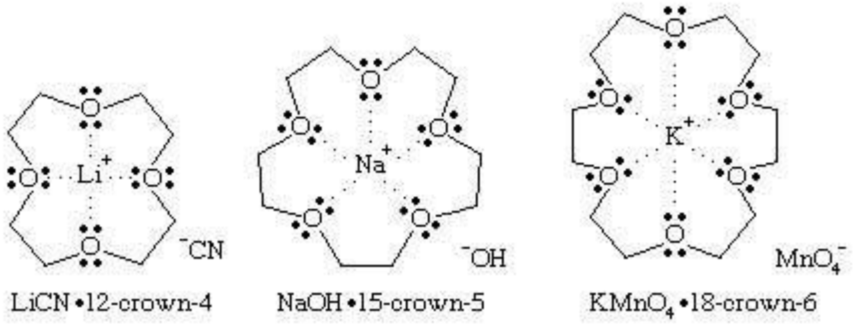
Biological Activity:

Mg^{2+} is the fourth-most-abundant metal ion in cells (per moles) and the most abundant free divalent cation — as a result, it is deeply and intrinsically woven into cellular metabolism. Indeed, Mg^{2+}-dependent enzymes appear in virtually every metabolic pathway: Specific binding of Mg^{2+} to biological membranes is frequently observed, Mg^{2+} is also used as a signalling molecule, and much of nucleic acid biochemistry requires Mg^{2+}, including all reactions that require release of energy from ATP.In nucleotides, the triple-phosphate moiety of the compound is invariably stabilized by association with Mg^{2+} in all enzymatic processes.

Complexes of Alkali and Alkaline Earth Metal Ions With Macrocycles:

There were few complexes of the alkali metal cations with organic molecules. Specialized biological molecules such as valinomycin were known to complex selectively the potassium cation K^+ for transport across cell membranes, but synthetic ionophores (molecules that can form complexes with ions) were rare. All the alkali cations have a charge of +1 and, except for lithium, are chemically similar and rather inert. The only significant difference between one alkali cation and another is the size.

In some cases two crown ether molecules can encapsulate a cation in a “sandwich” fashion. For example, K^+ just fits into the centre of an 18-crown-6 ring (18 atoms in the ring, 12 of which are carbon atoms and 6 are ether oxygen atoms) to form a 1:1 complex (that is, 1 cation:1 crown ether), K^+(18C6). Cs^+ is too large to fit into the ring but can be complexed on one side to form the Cs^+(18C6) complex or can be sandwiched between two 18-crown-6 molecules to form the 1:2 complex, $Cs^+(18C6)_2$. Thus, the selectivity of a crown ether for a particular cation depends on the ring size. Common crown ethers are 12-crown-4, 15-crown-5, and 18-crown-6. These molecules are selective for Li^+, Na^+, and K^+, respectively.



LiCN•12-crown-4 NaOH•15-crown-5 $KMnO_4$•18-crown-6

crown ethers Three crown ethers, each with a complexed alkali metal cation.

These are three-dimensional molecules with an internal cavity or crypt that can completely encapsulate the alkali cation. By synthesizing molecules with different cavity sizes, the selectivity for particular cations over those of the “wrong” size to fit in the cavity can be controlled. It should be noted, however, that these molecules are not rigid and that flexibility of the framework can alter the cavity size to accommodate alkali cations of different sizes, although with differences in the strength of complexation.

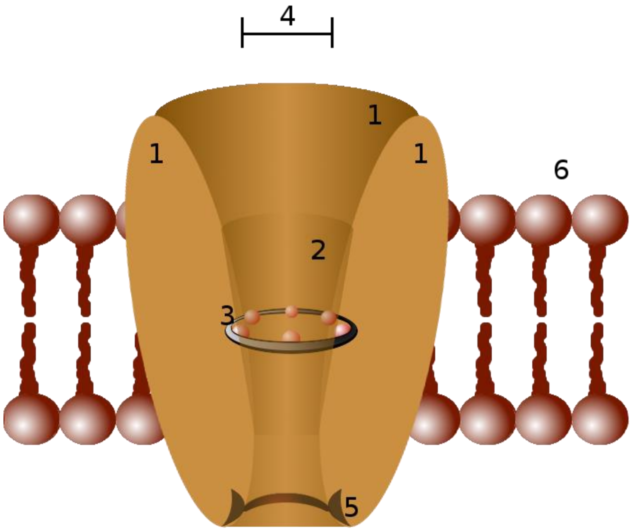
Since the initial syntheses of crown ethers and cryptands, thousands of complexants for cations of various sizes, charges, and geometries have been synthesized. This has led to an entirely new branch of chemistry called supramolecular chemistry.

Ion channel:

Ion channels are pore-forming membrane proteins that allow ions to pass through the channel pore. Their functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. Ion channels are present in the membranes of all cells. Ion channels are one of the two classes of ionophoric proteins, the other being ion transporters.

Biological role

Because channels underlie the nerve impulse and because "transmitter-activated" channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, numerous toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails, and others) work by modulating ion channel conductance and/or kinetics. In addition, ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for new drugs, ion channels are a frequent target.



Classification by type of ions

- Chloride channels: This superfamily of channels consists of approximately 13 members. They include ClCs, CLICs, Bestrophins and CFTRs. These channels are non-selective for small anions; however chloride is the most abundant anion, and hence they are known as chloride channels.
- Potassium channels
  - Voltage-gated potassium channels e.g., Kvs, Kirs etc.
  - Calcium-activated potassium channels e.g., BKCa or MaxiK, SK, etc.
  - Inward-rectifier potassium channels
  - Two-pore-domain potassium channels: This family of 15 members form what is known as leak channels, and they display Goldman-Hodgkin-Katz (open) rectification.
- Sodium channels
  - Voltage-gated sodium channels (NaVs)
  - Epithelial sodium channels (ENaCs)
- Calcium channels (CaVs)
- Proton channels
  - Voltage-gated proton channels
- *Non-selective cation channels*: These non-selectively allow many types of cations, mainly Na^+, K^+ and Ca^{2+}, through the channel.
  - Most transient receptor potential channels

Classification by cellular localization

Ion channels are also classified according to their subcellular localization. The plasma membrane accounts for around 2% of the total membrane in the cell, whereas intracellular organelles contain 98% of the cell's membrane. The major intracellular compartments are endoplasmic reticulum, Golgi apparatus, and mitochondria. On the basis of localization, ion channels are classified as:

- Plasma membrane channels
    - Examples: Voltage-gated potassium channels (Kv), Sodium channels (Nav), Calcium channels (Cav) and Chloride channels (ClC)
- Intracellular channels, which are further classified into different organelles
    - Endoplasmic reticulum channels: RyR, SERCA, ORAi
    - Mitochondrial channels: mPTP, KATP, BK, IK, CLIC5, Kv7.4 at the inner membrane and VDAC and CLIC4 as outer membrane channels.

Other classifications

Some ion channels are classified by the duration of their response to stimuli:

- Transient receptor potential channels: This group of channels, normally referred to simply as TRP channels, is named after their role in *Drosophila* visual phototransduction. This family, containing at least 28 members, is diverse in its mechanisms of activation. Some TRP channels remain constitutively open, while others are gated by voltage, intracellular Ca^{2+}, pH, redox state, osmolarity, and mechanical stretch. These channels also vary according to the ion(s) they pass, some being selective for Ca^{2+} while others are less selective cation channels. This family is subdivided into 6 subfamilies based on homology: canonical TRP (TRPC), vanilloid receptors (TRPV), melastatin (TRPM), polycystins (TRPP), mucolipins (TRPML), and ankyrin transmembrane protein 1 (TRPA).

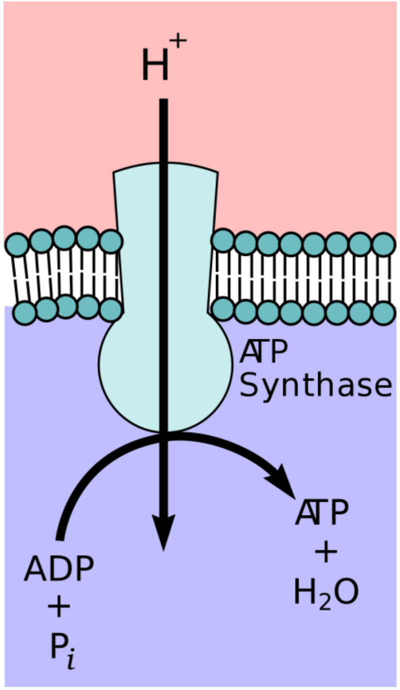
Ion Pump:

In biology, an **ion transporter** (or **ion pump**) is a transmembrane protein that moves ions across a biological membrane against their concentration gradient through active transport. These primary transporters are enzymes that convert energy from various sources—including adenosine triphosphate (ATP), sunlight, and other redox reactions—to potential energy stored in an electrochemical gradient. This potential energy is then used by secondary transporters, including ion carriers and ion channels, to drive vital cellular processes, such as ATP synthesis.

Classification and disambiguation

Ion transporters are classified as a super family of transporters that contain 12 families of transporters.These families are part of the Transport Classification (TC) system that is used by the International Union of Biochemistry and Molecular Biology (IUBMB) and are grouped according to characteristics such as the substrates being transported, the transport mechanism, the energy source used, and also by comparing the DNA sequences making up each protein. The most important unifying factor being the charged nature of the substrate which indicates the transport of an ion and not a neutral species

Ion transporters differ significantly from ion channels. An electrochemical gradient or concentration gradient is a difference in concentration of a chemical molecule or ion in two separate areas.At equilibrium the concentrations of the ion in both areas will be equal, so if there is a difference in concentration the ions will seek to flow "down" the concentration gradient or from a high concentration to low concentration. Ion channels allows the specific ions that will fit into the channel to flow down their concentration gradient, equalizing the concentrations on either side of the cell membrane. Ion channels accomplish this via facilitated diffusion which is a type of passive transport. In contrast, ion transporters perform active transport by moving ions against their concentration gradient. Using energy sources such as ATP, ion transporters are able to move ions against their concentration gradient which can then be used by secondary transporters or other proteins as a source of energy.



Energy source

Primary transport

Primary transporters use energy to transport ions such as Na^+, K^+, and Ca^{2+} across a cells membrane and can create concentration gradients. This transport usually uses ATP as an energy source but can also generate ATP through methods such as the electron transport chain in plants.

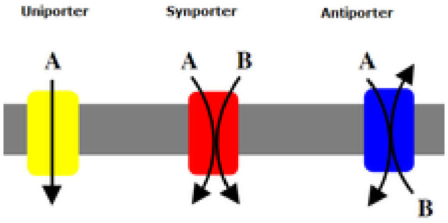
ATP utilizing

Transporters that use ATP convert the energy in ATP into potential energy in the form of a concentration gradient. They use the ATP to transport an ion from a low concentration to a higher concentration. Examples of proteins that use ATP are P-type ATPases that transfer Na^+, K^+, and Ca^{2+} ions by phosphorylation, A-type ATPases that transfer anions, and ABC transporters (ATP binding cassette transporters) that transport a broad set of molecules.Examples of the P-type ATPase include Na^+/K^+-ATPase that is regulated by Janus Kinase-2 as well as Ca^{2+} ATPase which exhibits sensitivity to ADP and ATP concentrations P-glycoprotein is an example of an ABC transport binding protein in the human body.

ATP producing

ATP producing transporters run in the opposite direction of ATP Utilizing transporters. These proteins transport ions from high to low concentration with the gradient but in the process ATP is formed. Potential energy in the form of the concentration gradient is used to generate ATP. In animals, this ATP synthesis takes place in the mitochondria using F- type ATPase otherwise known as ATP synthase. V-type ATPase serves the opposite function as F-type ATPase and is used in plants to hydrolyze ATP to create a proton gradient. Examples of this are lysosomes that use V-type ATPase acidify vesicles or plant vacuoles during process of photosynthesis in the chloroplasts.This process can be regulated through various methods such as pH.

Secondary transport



Secondary transporters also transport ions against the concentration gradient – from low concentration to high concentration - but unlike primary transporters who use ATP to create a concentration gradient, secondary transporters use the potential energy from the concentration gradient created by the primary transporters to transport ions.Symporters such as the Sodium-chloride symporter transport an ion with its concentration gradient, and they couple the transport of a second molecule in the same direction. Antiporters also use the concentration gradient but the coupled molecule is transported in the opposite direction.

Catalysis and Regulation of Bioenergetic Processes By The Alkaline Earth Metal Ions – Mg2+ And Ca2+:

Magnesium $2^{+:}$

Magnesium is an essential element **in biological systems**. Magnesium occurs typically as the Mg^{2+} ion. It is an essential mineral nutrient (i.e., element) for life and is present in every cell type in every organism. For example, ATP (adenosine triphosphate), the main source of energy in cells, must bind to a magnesium ion in order to be biologically active. What is called ATP is often actually Mg-ATP. As such, magnesium plays a role in the stability of all polyphosphate compounds in the cells, including those associated with the synthesis of DNA and RNA.

Over 300 enzymes require the presence of magnesium ions for their catalytic action, including *all* enzymes utilizing or synthesizing ATP, or those that use other nucleotides to synthesize DNA and RNA.

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Catalytic Function

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Calcium2^+:

Calcium is an important signaling molecule involved in the regulation of many cellular functions. The large free energy in the Ca^{2+} ion membrane gradients make Ca^{2+} signaling inherently sensitive to the available cellular free energy, primarily in the form of ATP.

In addition, Ca^{2+} regulates many cellular ATP consuming reactions such as muscle contraction, exocytosis, biosynthesis and neuronal signaling. Thus, Ca^{2+} becomes a logical candidate as a signaling molecule to modulate ATP hydrolysis and synthesis during changes in numerous forms of cellular work. Mitochondria are the primary source of aerobic energy production in mammalian cells and also maintain a large Ca^{2+} gradient across their inner membrane providing a signaling potential for this molecule.

The demonstrated link between cytosolic and mitochondrial $[Ca^{2+}]$, identification of transport mechanisms as well as proximity of mitochondria to Ca^{2+} release sites further supports the notion that Ca^{2+} can be an important signaling molecule in the energy metabolism interplay of the cytosol with the mitochondria. Here we review sites within the mitochondria where Ca^{2+} plays a role in the regulation of ATP generation and potentially contributes to the orchestration of the cellular metabolic homeostasis.. Numerous non-invasive approaches monitoring NADH, mitochondrial membrane potential, oxygen consumption and workloads suggest significant Ca^{2+} effects on other elements of NADH generation as well as downstream elements of oxidative phosphorylation including the F_1F_O-ATPase and the cytochrome chain.

These other potential elements of Ca^{2+} modification of mitochondrial energy conversion will be the focus of this review. Though most of specific molecular mechanisms have yet to be elucidated, it is clear that Ca^{2+} provides a balanced activation of mitochondrial energy metabolism which exceeds the alteration of dehydrogenases alone.

Metals at the center of photosynthesis:

Photosystem II

Photosystem II is the photosystem that generates the two electrons that will eventually reduce $NADP^+$ in ferredoxin-NADP-reductase. Photosystem II is present on the thylakoid membranes inside chloroplasts, the site of photosynthesis in green plants.The structure of photosystem II is remarkably similar to the bacterial reaction center, and it is theorized that they share a common ancestor.

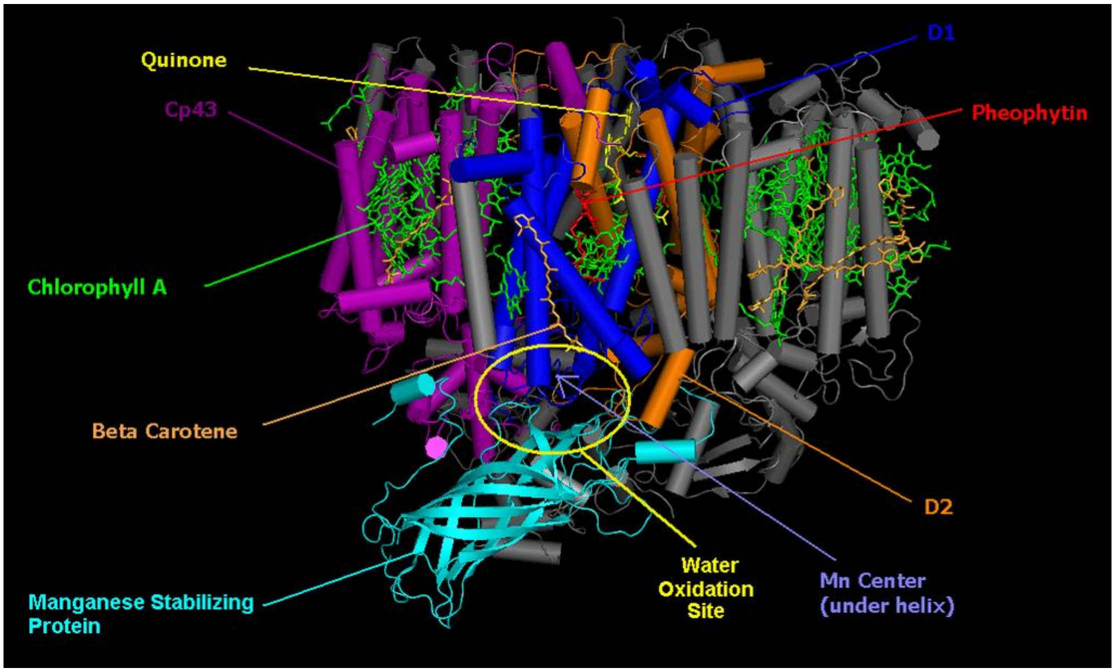
The core of photosystem II consists of two subunits referred to as D1 and D2.

These two subunits are similar to the L and M subunits present in the bacterial reaction center. Photosystem II differs from the bacterial reaction center in that it has many additional subunits that bind additional chlorophylls to increase efficiency. The overall reaction catalysed by photosystem II is:

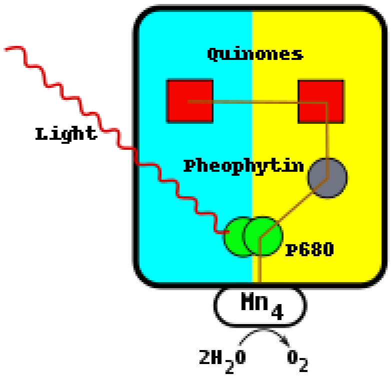
$2Q + 2H_2O + h\nu \rightarrow O_2 + 2QH_2$

Q represents plastoquinone, the oxidized form of Q. QH_2 represents plastoquinol, the reduced form of Q. This process of reducing quinone is comparable to that which takes place in the bacterial reaction center.

Photosystem II obtains electrons by oxidizing water in a process called photolysis. Molecular oxygen is a byproduct of this process, and it is this reaction that supplies the atmosphere with oxygen. The fact that the oxygen from green plants originated from water was first deduced by the Canadian-born American biochemist Martin David Kamen. He used a stable isotope of oxygen, ^{18}O to trace the path of the oxygen from water to gaseous molecular oxygen. This reaction is catalysed by a reactive center in photosystem II containing four manganese ions.



The reaction begins with the excitation of a pair of chlorophyll molecules similar to those in the bacterial reaction center. Due to the presence of chlorophyll *a*, as opposed to bacteriochlorophyll, photosystem II absorbs light at a shorter wavelength. The pair of chlorophyll molecules at the reaction center are often referred to as P680.[1] When the photon has been absorbed, the resulting high-energy electron is transferred to a nearby phaeophytin molecule. This is above and to the right of the pair on the diagram and is coloured grey. The electron travels from the phaeophytin molecule through two plastoquinone molecules, the first tightly bound, the second loosely bound. The tightly bound molecule is shown above the phaeophytin molecule and is coloured red. The loosely bound molecule is to the left of this and is also coloured red. This flow of electrons is similar to that of the bacterial reaction center. Two electrons are required to fully reduce the loosely bound plastoquinone molecule to QH_2 as well as the uptake of two protons.



The difference between photosystem II and the bacterial reaction center is the source of the electron that neutralizes the pair of chlorophyll *a* molecules. In the bacterial reaction center, the electron is obtained from a reduced compound haem group in a cytochrome subunit or from a water-soluble cytochrome-c protein.

Once photoinduced charge separation has taken place, the P680 molecule carries a positive charge. P680 is a very strong oxidant and extracts electrons from two water molecules that are bound at the manganese center directly below the pair. This center, below and to the left of the pair in the diagram, contains four manganese ions, a calcium ion, a chloride ion, and a tyrosine residue. Manganese is adept at these reactions because it is capable of existing in four oxidation states: Mn^{2+}, Mn^{3+}, Mn^{4+} and Mn^{5+}. Manganese also forms strong bonds with oxygen-containing molecules such as water.

Every time the P680 absorbs a photon, it emits an electron, gaining a positive charge. This charge is neutralized by the extraction of an electron from the manganese center, which sits directly below it. The process of oxidizing two molecules of water requires four electrons. The water molecules that are oxidized in the manganese center are the source of the electrons that reduce the two molecules of Q to QH_2. To date, this water-splitting catalytic center has not be reproduced by any man-made catalyst.

Photosystem I

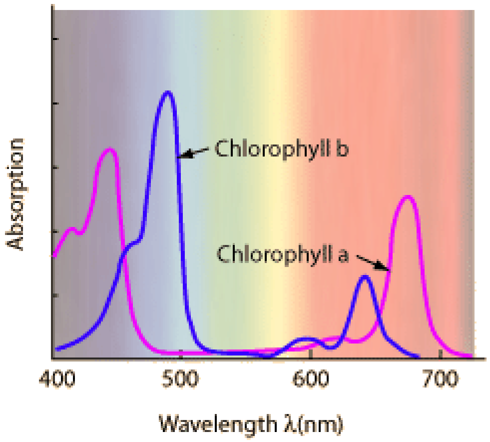
After the electron has left photosystem II it is transferred to a cytochrome b6f complex and then to plastocyanin, a blue copper protein and electron carrier. The plastocyanin complex carries the electron that will neutralize the pair in the next reaction center, photosystem I.

As with photosystem II and the bacterial reaction center, a pair of chlorophyll *a* molecules initiates photoinduced charge separation. This pair is referred to as P700. 700 Is a reference to the wavelength at which the chlorophyll molecules absorb light maximally. The P700 lies in the center of the protein. Once photoinduced charge separation has been initiated, the electron travels down a pathway through a chlorophyll α molecule situated directly above the P700, through a quinone molecule situated directly above that, through three 4Fe-4S clusters, and finally to an interchangeable ferredoxin complex. Ferredoxin is a soluble protein containing a 2Fe-2S cluster coordinated by four cysteine residues. The positive charge left on the P700 is neutralized by the transfer of an electron from plastocyanin. Thus the overall reaction catalysed by photosystem I is:

$$Pc(Cu^{+}) + Fd[ox] + h\nu \rightarrow Pc(Cu^{2+}) + Fd[red]$$

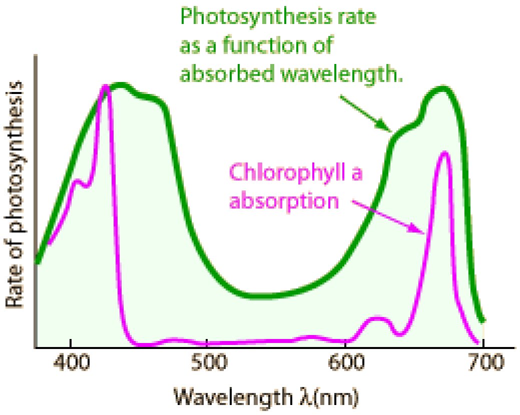
The cooperation between photosystems I and II creates an electron flow from H_2O to $NADP^+$. This pathway is called the 'Z-scheme' because the redox diagram from P680 to P700 resembles the letter z.

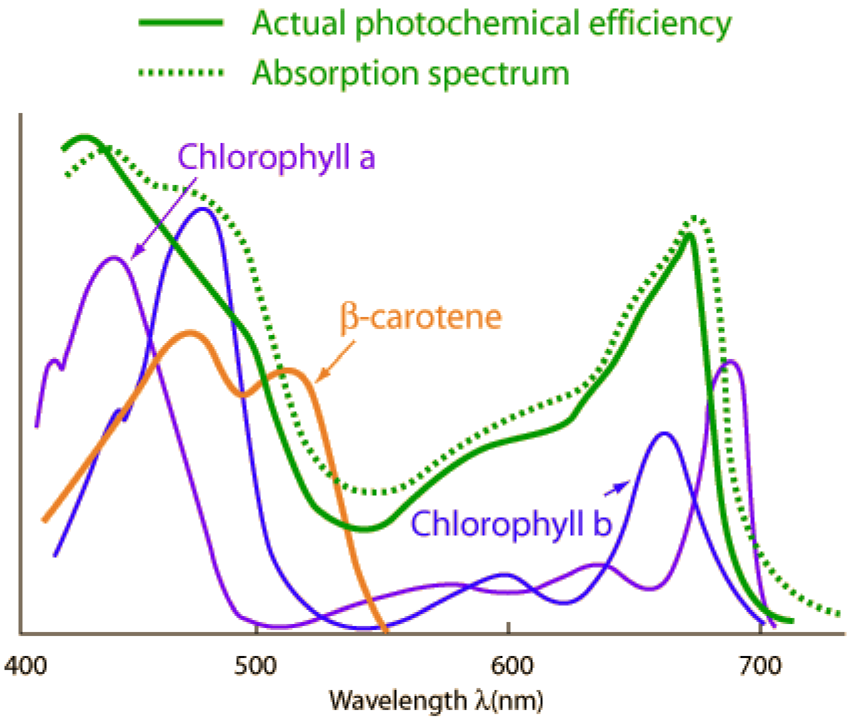
Light Absorption (Energy Acquisition):



Photosynthesis depends upon the absorption of light by pigments in the leaves of plants. The most important of these is chlorophyll-a, but there are several accessory pigments that also contribute.

The measured rate of photosynthesis as a function of absorbed wavelength correlates well with the absorption frequencies of chlorophyll a, but makes it evident that there are some other contributors to the absorption.





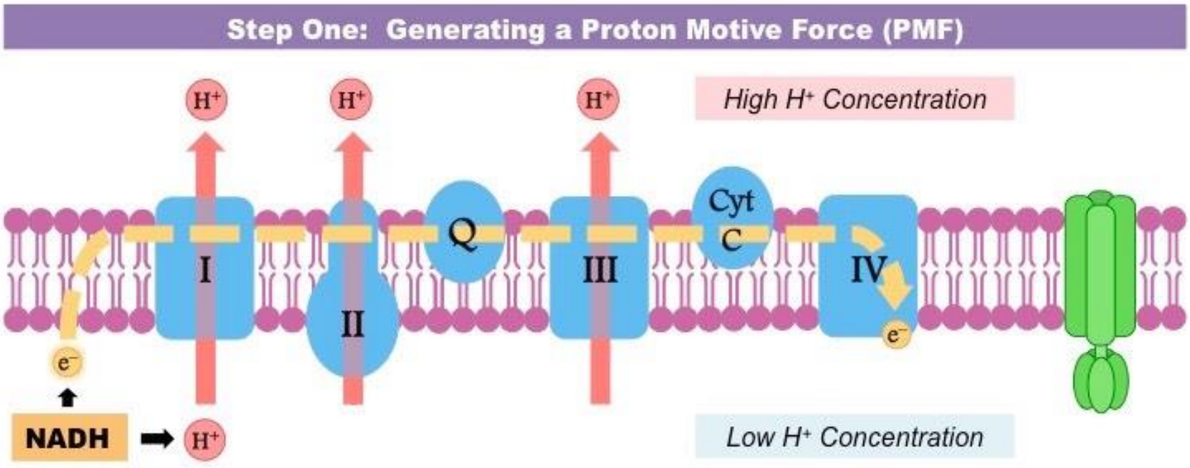
The plot of the absorption spectra of the chlorophylls plus beta carotene correlates well with the observed photosynthetic output. The measure of photochemical efficiency is made by meauring the amount of oxygen produced by leaves following exposure to various wavelengths.

It is evident from these absorption and output plots that only the red and blue ends of the visible part of the electromagnetic spectrum are used by plants in photosynthesis. The reflection and transmission of the middle of the spectrum gives the leaves their green visual color.

Exciton Transport (Direct Energy Transfer) – Charge Separation And Electron Transport:

Step 1: Generating a Proton Motive Force

- The hydrogen carriers (NADH and $FADH_2$) are oxidised and release high energy electrons and protons
- The electrons are transferred to the electron transport chain, which consists of several transmembrane carrier proteins
- As electrons pass through the chain, they lose energy – which is used by the chain to pump protons (H^+ ions) from the matrix
- The accumulation of H^+ ions within the intermembrane space creates an electrochemical gradient (or a proton motive force)

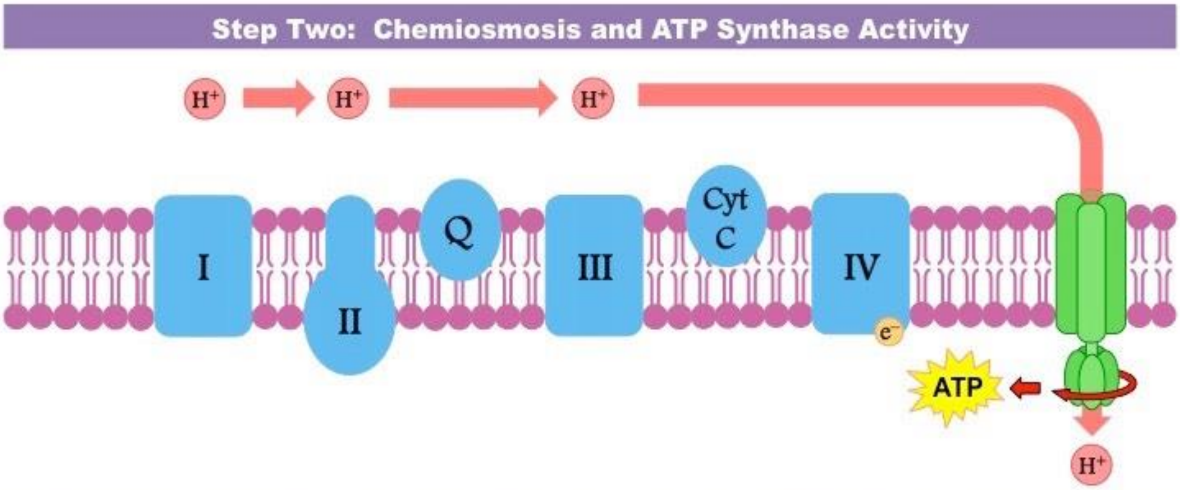


Step One: Generating a Proton Motive Force (PMF)

High energy electrons released by hydrogen carriers are shuttled through the electron transport chain
The released energy is used to translocate H+ ions from the matrix, creating an electrochemical gradient

Step Two: ATP Synthesis via Chemiosmosis

- The proton motive force will cause H^+ ions to move down their electrochemical gradient and diffuse back into matrix
- This diffusion of protons is called *chemiosmosis* and is facilitated by the transmembrane enzyme ATP synthase
- As the H^+ ions move through ATP synthase they trigger the molecular rotation of the enzyme, synthesising ATP



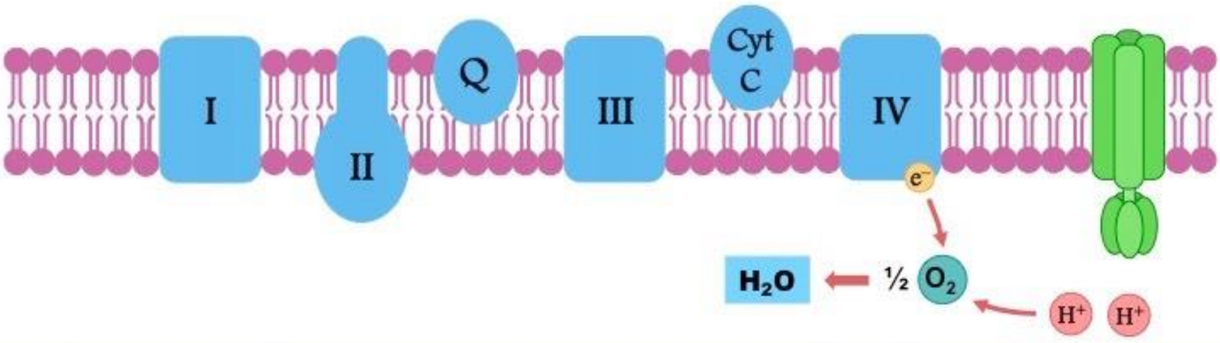
Step Two: Chemiosmosis and ATP Synthase Activity

H+ ions are transported down their electrochemical gradient by ATP synthase (chemiosmosis)
ATP synthase uses this flow of protons back into the matrix to catalyse the synthesis of ATP

Step Three: Reduction of Oxygen

- In order for the electron transport chain to continue functioning, the de-energised electrons must be removed
- Oxygen acts as the final electron acceptor, removing the de-energised electrons to prevent the chain from becoming blocked
- Oxygen also binds with free protons in the matrix to form water – removing matrix protons maintains the hydrogen gradient
- In the absence of oxygen, hydrogen carriers cannot transfer energised electrons to the chain and ATP production is halted

Step Three: Oxygen Acts as the Final Electron Acceptor



Oxygen acts as the final electron acceptor, removing the de-energised electrons from the chain
Oxygen also maintains the electrochemical gradient by binding to H^+ ions in the matrix to form water

Oxidative Phosphorylation

- Hydrogen carriers donate high energy electrons to the electron transport chain (located on the cristae)
- As the electrons move through the chain they lose energy, which is transferred to the electron carriers within the chain

- The electron carriers use this energy to pump hydrogen ions from the matrix and into the intermembrane space
- The accumulation of H^+ ions in the intermembrane space creates an electrochemical gradient (or a proton motive force)
- H^+ ions return to the matrix via the transmembrane enzyme ATP synthase (this diffusion of ions is called chemiosmosis)
- As the ions pass through ATP synthase they trigger a phosphorylation reaction which produces ATP (from ADP + Pi)
- The de-energised electrons are removed from the chain by oxygen, allowing new high energy electrons to enter the chain
- Oxygen also binds matrix protons to form water – this maintains the hydrogen gradient by removing H^+ ions from the matrix

Manganese Catalyzed Oxidation of Water To O_2:

The oxidation of water to molecular oxygen involves thetransfer of four electrons from water to an oxidant, coupledwith the release of four protons.

$2H_2O \rightarrow O_2 + 4H+ + 4e–$

The water oxidation to evolve dioxygen is catalyzed atthe oxygen-evolving center (OEC) in photosystem II (PSII) in photosynthesis.1 Despite recent development on thestructural information of OEC,2 the mechanism of wateroxidation at molecular level still remains unresolvedmystery.3-5 Great efforts have been devoted to develop theOEC model complexes which can be applied to artificialphotosynthetic systems for the splitting of water that couldbe utilized in fuel cells. Such systems would solve not onlythe energy but also environmental problems arising fromcombustion of fossil fuels. However, the catalytic systemscapable of evolving O2 from water are rare, failing toprovide any important mechanistic insight. We report herein a simple and well-defined catalyticsystem of the stoichiometric water oxidation to O_2.

Addition of an outer-sphere one-electron oxidant,Ru(bpy)33+ , to an acetonitrile (MeCN)/H_2O mixed solution(5 :1 v/v) containing a catalytic amount of a manganeseporphyrin, (TMP)Mn(OH) (TMP2- = 5,10,15,20-tetrakis(2,4,6-tri-methylphenyl)porphyrin dianion) resultsin evolution of stoichiometric amount of O2 in the four-electron oxidation of water with Ru(bpy)33+. The two-electron oxidation of (TMP)Mn(OH) by Ru(bpy)33+ toproduce (TMP)Mn=O•+ is shown to be essential for thewater oxidation to O_2. The oxidation rate exhibits asecond-order dependence with respect to the catalystconcentration . This indicates that the rate-determining step for the catalytic water oxidation to O_2

UNIT II

Amines, Proteins and Enzymes

Cobalamines: Reactions of The Alkyl Cobalamines:

Cyanocobalamin is a manufactured form of vitamin B_{12} used to treat vitamin B12 deficiency.The deficiency may occur in pernicious anemia, following surgical removal of the stomach, with fish tapeworm, or due to bowel cancer.It is less preferred than hydroxocobalamin for treating vitamin B12 deficiency. It is used by mouth, by injection into a muscle, or as a nasal spray.

Cyanocobalamin is generally well tolerated. Minor side effects may include diarrhea and itchiness.Serious side effects may include anaphylaxis, low blood potassium, and heart failure.Use is not recommended in those who are allergic to cobalt or have Leber's disease.Vitamin B_{12} is an essential nutrient meaning that it cannot be made by the body but is required for life.

Vitamin B_{12} is the "generic descriptor" name for any vitamers of vitamin B_{12}. Animals, including humans, can convert cyanocobalamin to any one of the active vitamin B_{12} compounds.

Cyanocobalamin is one of the most widely manufactured vitamers in the vitamin B_{12} family (the family of chemicals that function as B_{12} when put into the body), because cyanocobalamin is the most air-stable of the B_{12} forms. It is the easiest to crystallize and therefore easiest to purify after it is produced by bacterial fermentation. It can be obtained as dark red crystals or as an amorphous red powder. Cyanocobalamin is hygroscopic in the anhydrous form, and sparingly soluble in water (1:80).It is stable to autoclaving for short periods at 121 °C (250 °F). The vitamin B_{12} coenzymes are unstable in light. After consumption the cyanide ligand is replaced by other groups (adenosyl, methyl), which are the biologically active forms. The cyanide is converted to thiocyanate and excreted by the kidney.

Chemical reactions

Reduced forms of Cyanocobalamin, with a Co(I) (top), Co(II) (middle), and Co(III) (bottom)

In the cobalamins, cobalt normally exists in the trivalent state, Co(III). However, under reducing conditions, the cobalt center is reduced to Co(II) or even Co(I), which are usually denoted as $B_{12r}$and B_{12s}, for reduced and super reduced, respectively. B_{12r} and B_{12s} can be prepared from cyanocobalamin by controlled potential reduction, or chemical reduction using sodium borohydride in alkaline solution, zinc in acetic acid, or by the action of thiols. Both B_{12r} and B_{12s} are stable indefinitely under oxygen-free conditions. B_{12r} appears orange-brown in solution, while B_{12s} appears bluish-green under natural daylight, and purple under artificial light.

B_{12s} is one of the most nucleophilic species known in aqueous solution.This property allows the convenient preparation of cobalamin analogs with different substituents, via nucleophilic attack on alkyl halides and vinyl halides.

For example, cyanocobalamin can be converted to its analog cobalamins via reduction to B_{12s}, followed by the addition of the corresponding alkyl halides, acyl halides, alkene or alkyne. Steric hindrance is the major limiting factor in the synthesis of the B_{12} coenzyme analogs. For example, no reaction occurs between neopentyl chloride and B_{12s}, whereas the secondary alkyl halide analogs are too unstable to be isolated.This effect may be due to the strong coordination between benzimidazole and the central cobalt atom, pulling it down into the plane of corrin ring. The trans effect determines the polarizability of the Co–C bond so formed. However, once the benzimidazole is detached from cobalt by quaternization with methyl iodide, it is replaced by H_2O or hydroxyl ions. Various secondary alkyl halides are then readily attacked by the modified $B_{12s}$to give the corresponding stable cobalamin analogs.The products are usually extracted and purified by phenol-methylene chloride extraction or by column chromatography.

Cobalamin analogs prepared by this method include the naturally occurring coenzymes methylcobalamin and cobamamide, and other cobalamins that do not occur naturally, such as vinylcobalamin, carboxymethylcobalamin and cyclohexylcobalamin.This reaction is under review for use as a catalyst for chemical dehalogenation, organic reagent and photosensitized catalyst systems.

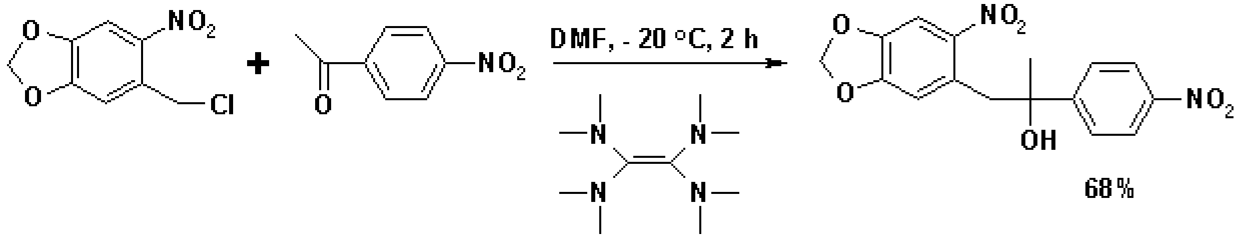
One Electron Reduction And Oxidation:

A **one-electron reduction** - **oxidation** in organic chemistry involves the transfer of an electron from a donor compound to an organic substrate. It serves to differentiate between two electron organic reductions such as hydride transfer reactions.

The first intermediate in a one-electron reduction is often a radical anion, which then engages in secondary reactions. In the Birch reduction, the secondary reaction is proton abstraction from an alcohol. This reaction type is also called a **dissolving metal reduction**. Alkyne reduction to an alkene in the liquid ammonia/sodium system follows the same theme. The first radical anion intermediate abstracts a proton from ammonia to the free radical. A second one-electron transfer leads to the anion, which also abstracts a proton to the neutral alkene.

In the Wurtz reaction, two radical intermediates dimerize in a coupling reaction. Likewise, acetone is converted to pinacol with a magnesium-mercury amalgam in a pinacol coupling reaction. Acyloin condensation couples two carboxylic acids to a α-hydroxyketone. Reactions of this type are also called *reductive couplings*. In the Clemmensen reduction of ketones to alkanes with zinc-mercury amalgam, the intermediate is an organozinc carbenoid.

Electron rich organic molecules like tetrakis(dimethylamino)ethylene (TDAE) are effective reducing agents capable of generating the anion from alkyl halides such as 5-chloromethyl-6-nitrobenzo[1,3]dioxole:



The one-electron reduction potential of a molecule can be used to obtain an electron affinity. For example: The one-electron reduction potential of molecular oxygen gives a value of 1.07eV.

Recently, photoredox catalysis has become a very common way to engage in single electron reduction.

Co-C Bond Cleavage:

The homolytic cleavage of the organometallic Co-C bond in vitamin B12-dependent enzymes is accelerated by a factor of approximately 10(12) in the protein compared to that of the isolated cofactor in aqueous solution.

To understand this much debated effect, we have studied the Co-C bond cleavage in the enzyme glutamate mutase with combined quantum and molecular mechanics methods. We show that the calculated bond dissociation energy (BDE) of the Co-C bond in adenosyl cobalamin is reduced by 135 kJ/mol in the enzyme.

This catalytic effect can be divided into four terms. First, the adenosine radical is kept within 4.2 angstroms of the Co ion in the enzyme, which decreases the BDE by 20 kJ/mol. Second, the surrounding enzyme stabilizes the dissociated state by 42 kJ/mol using electrostatic and van der Waals interactions.

Third, the protein itself is stabilized by 11 kJ/mol in the dissociated state. Finally, the coenzyme is geometrically distorted by the protein, and this distortion is 61 kJ/mol larger in the Co(III) state. This deformation of the coenzyme is caused mainly by steric interactions, and it is especially the ribose moiety and the Co-C5'-C4' angle that are distorted. Without the polar ribose group, the catalytic effect is much smaller, e.g. only 42 kJ/mol for methyl cobalamin. The deformation of the coenzyme is caused mainly by the substrate, a side chain of the coenzyme itself, and a few residues around the adenosine part of the coenzyme.

Coenzyme B_{12}:

Alkylation Reactions of Methyl cobalamin:

The reaction of *n*-alkylcobalamins and of *n*-alkylcobalt derivatives of five different vitamin B_{12} model compounds with a variety of mercaptide ions yields thioethers.

Reaction rates and yields of product are dependent on the size of the alkyl group, the in-plane ligand moiety, and the axial bases of the cobalt complexes. The reaction of methylcobalamin with CH_2S^- affords $(CH_2)_2S$ in near quantitative yield and was shown to follow a second order rate law.

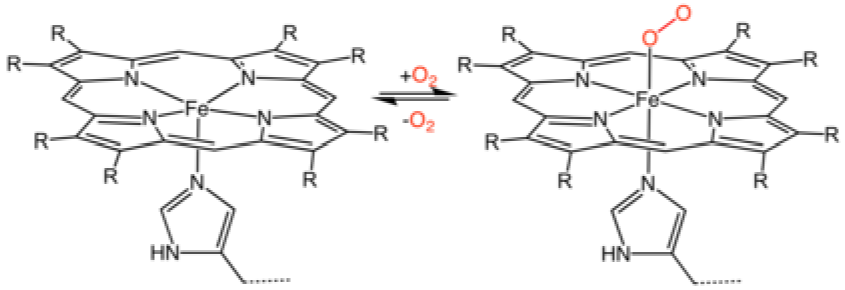
This *S*-methylation reaction provides a model for the terminal step in the biosynthesis of methionine from methylcobalamin and homocysteine by a cobalamin-dependent enzyme of *Escherichia coli*. The reaction of alkylcobalt derivatives of cobaloximes and of several other model compounds with mercaptide ions also yields thioethers, but the yields are lower due to the occurrence of side-reactions (e.g., axial ligation by $R\text{-}S^-$).

The relative rates of the *S*-alkylation reactions nevertheless follow a pattern typical for SN_2 displacement-rather than free radical reactions.

Heme and Non-Heme Proteins:

A **hemeprotein** (or **haemprotein**; also **hemoprotein** or **haemoprotein**), or heme protein, is a protein that contains a heme prosthetic group. They are very large class of metalloproteins. The heme group confers functionality, which can include oxygen carrying, oxygen reduction, electron transfer, and other processes. Heme is bound to the protein either covalently or noncovalently or both.

The heme consists of iron cation bound at the center of the conjugate base of the porphyrin, as well as other ligands attached to the "axial sites" of the iron. The porphyrin ring is a planar dianionic, tetradentate ligand. The iron is typically Fe^{2+} or Fe^{3+}. One or two ligands are attached at the axial sites. The porphyrin ring has 4 nitrogen atoms that bind to the iron, leaving two other coordination positions of the iron available for bonding to the histidine of the protein and a divalent atom.



Roles

- Hemeproteins have diverse biological functions including oxygen transport, which is completed via hemeproteins including hemoglobin, myoglobin, neuroglobin, cytoglobin, and leghemoglobin.
- Some hemeproteins - cytochrome P450s, cytochrome c oxidase, ligninases, catalase. and peroxidases - are enzymes. They often activate O_2 for oxidation or hydroxylation.
- Hemeproteins also enable electron transfer as they form part of the electron transport chain. Cyctochrome a, cytochrome b, and cytochrome c have such electron transfer functions.

The sensory system also relies on some hemeproteins including FixL, an oxygen sensor, CooA, a carbon monoxide sensor, and soluble guanylyl cyclase.

- There are two major sources of food iron: haem iron and non-haem iron.

The two forms of iron in the diet are absorbed with different efficiency

Haem iron

heme iron is derived primarily from hemoglobin and myoglobin in animal protein sources is readily bio-available, since it is absorbed intact within the porphyrin ring and is not influenced by most inhibitory factors in the diet. The non-haem iron in food enters an exchangeable pool that is markedly affected by inhibitory iron-binding ligands

organic (haem) iron must be hydrolysed from any protein to which it is attached and it is then absorbed relatively easily but slowly. The overall absorption of iron from meat may be 20-25%. The most efficient absorption takes place in the duodenum, and is inversely related to the iron store level.

Non haem iron

- **Non-heme iron is found mainly in enriched cereals and pasta, beans, and dark green leafy vegetables**
- Some forms of nonhaem iron, such as ferritin and hemosiderin, only partially enter the exchangeable pool and are poorly absorbed.
- Non-haem iron must be solubilized and hydrolysed before absorption is possible. Hydrochloric acid in the stomach performs this function and also converts any ferric iron in food to its absorbable ferrous state. This reaction is facilitated by ascorbic acid (vitamin C). Other factors enhancing the absorption of inorganic iron include citric acid, lactic acid, fructose and peptides derived from meat. All of these form ligands with the ferrous iron, maintaining its solubility and thus facilitating absorption.

Haemoglobin and Myoglobin:

Hemoglobin

Hemoglobin and myoglobin are examples of hemeproteins that respectively transport and store of oxygen in mammals. Hemoglobin is a quaternary protein that occurs in the red blood cell, whereas, myoglobin is a tertiary protein found the muscle cells of mammals. Although they might differ in location and size, their function are similar. Being hemeproteins, they both contain a heme prosthetic group.

His-F8 of the myoglobin, also known as the proximal histidine, is covalently bonded to the 5th coordination position of the iron. Oxygen interacts with the distal His by way of a hydrogen bond, not a covalent one. It binds to the 6th coordination position of the iron, His-E7 of the myoglobin binds to the oxygen that is now covalently bonded to the iron. The same is true for hemoglobin; however, being a protein with four subunits, hemoglobin contains four heme units in total, allowing four oxygen molecules in total to bind to the protein.

Myoglobin and hemoglobin are globular proteins that serve to bind and deliver oxygen using a prosthetic group. These globins dramatically improve the concentration of molecular oxygen that can be carried in the biological fluids of vertebrates and some invertebrates.

Myoglobin

Myoglobin is found in vertebrate muscle cells. Muscle cells, when put into action, can quickly require a large amount of oxygen for respiration due to their energy requirements. Therefore, muscle cells use myoglobin to accelerate oxygen diffusion and act as localized oxygen reserves for times of intense respiration. Myoglobin also stores the required amount of oxygen and makes it available for the muscle cell mitochondria.

Myoglobin is the primary oxygen-carrying pigment of muscle tissues.High concentrations of myoglobin in muscle cells allow organisms to hold their breath for a longer period of time. Diving mammals such as whales and seals have muscles with particularly high abundance of myoglobin.Myoglobin is found in Type I muscle, Type II A, and Type II B, but most texts consider myoglobin not to be found in smooth muscle.

Myoglobin was the first protein to have its three-dimensional structure revealed by X-ray crystallography.

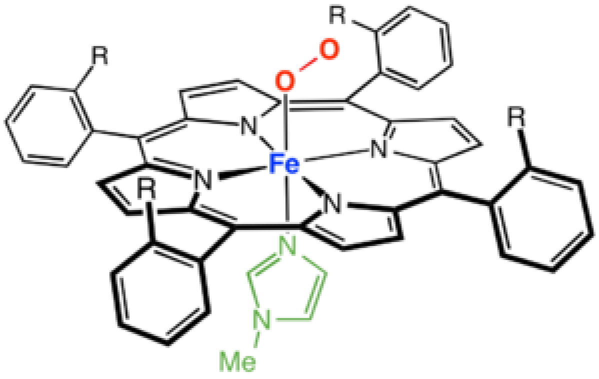
Structure and bonding:

Myoglobin belongs to the globin superfamily of proteins, and as with other globins, consists of eight alpha helices connected by loops. Myoglobin contains 154 amino acids.

Myoglobin contains a porphyrin ring with an iron at its center. A *proximal* histidine group (His-93) is attached directly to iron, and a *distal* histidine group (His-64) hovers near the opposite face.The distal imidazole is not bonded to the iron but is available to interact with the substrate

O_2. This interaction encourages the binding of O_2, but not carbon monoxide (CO), which still binds about 240× more strongly than O_2.

The binding of O_2 causes substantial structural change at the Fe center, which shrinks in radius and moves into the center of N4 pocket. O_2-binding induces "spin-pairing": the five-coordinate ferrous deoxy form is high spin and the six coordinate oxy form is low spin and diamagnetic.



Oxygen Transport and Storage:

Myoglobin can be viable and fertile but show many cellular and physiological adaptations to overcome the loss. Through observing these changes in myoglobin-deplete mice, it is hypothesised that myoglobin function relates to increased oxygen transport to muscle, oxygen storage and as a scavenger of reactive oxygen species

Myoglobin contains hemes, pigments responsible for the colour of red meat. The colour that meat takes is partly determined by the degree of oxidation of the myoglobin. In fresh meat the iron atom is in the ferrous (+2) oxidation state bound to an oxygen molecule (O_2). Meat cooked well done is brown because the iron atom is now in the ferric (+3) oxidation state, having lost an electron. If meat has been exposed to nitrites, it will remain pink because the iron atom is bound to NO, nitric oxide (true of, e.g., corned beef or cured hams). Grilled meats can also take on a pink "smoke ring" that comes from the iron binding to a molecule of carbon monoxide.

Role in disease

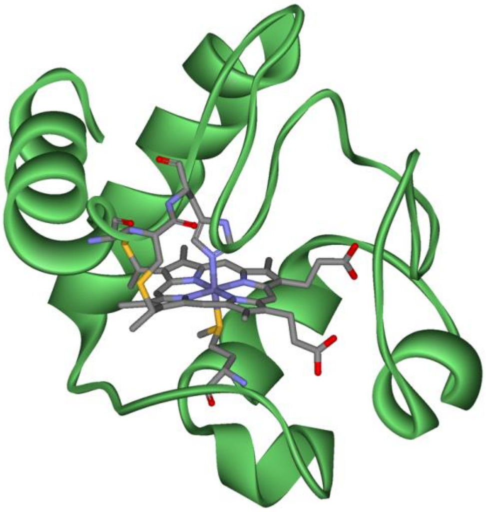
Myoglobin is released from damaged muscle tissue (rhabdomyolysis), which has very high concentrations of myoglobin. The released myoglobin is filtered by the kidneys but is toxic to the renal tubular epithelium and so may cause acute kidney injury.It is not the myoglobin itself that is toxic (it is a protoxin) but the ferrihemate portion that is dissociated from myoglobin in acidic environments (e.g., acidic urine, lysosomes).

Myoglobin is a sensitive marker for muscle injury, making it a potential marker for heart attack in patients with chest pain. However, elevated myoglobin has low specificity for acute myocardial infarction (AMI) and thus CK-MB, cardiac Troponin, ECG, and clinical signs should be taken into account to make the diagnosis.

Electron Transfer and Oxygen Activation:

Cytochromes:

Cytochromes are proteins containing heme as a cofactor. They are classified according to the type of heme and its mode of binding. Four varieties are recognized by the International Union of Biochemistry and Molecular Biology (IUBMB), cytochromes a, cytochromes b, cytochromes c and cytochrome d.Cytochrome function is linked to the reversible redox change from ferrous (Fe(II)) to the ferric (Fe(III)) oxidation state of the iron found in the heme core.



Structure and function

The heme group is a highly conjugated ring system (which allows its electrons to be very mobile) surrounding an iron ion. The iron in cytochromes usually exists in a ferrous (Fe^{2+}) and a ferric (Fe^{3+}) state with a ferroxo (Fe^{4+}) state found in catalytic intermediates.[1] Cytochromes are, thus, capable of performing electron transfer reactions and catalysis by reduction or oxidation of their heme iron. The cellular location of cytochromes depends on their function. They can be found as globular proteins and membrane proteins.

In the process of oxidative phosphorylation, a globular cytochrome cc protein is involved in the electron transfer from the membrane-bound complex III to complex IV. Complex II itself is composed of several subunits, one of which is a b-type cytochrome while another one is a c-type cytochrome. Both domains are involved in electron transfer within the complex. Complex IV contains a cytochrome a/a3-domain that transfers electrons and catalyzes the reaction of oxygen to water. Photosystem II, the first protein complex in the light-dependent reactions of oxygenic photosynthesis, contains a cytochrome b subunit. Cyclooxygenase 2, an enzyme involved in inflammation, is a cytochrome b protein.

Types

Four types of cytochromes are distinguished by their prosthetic groups:

Type	Prosthetic group
Cytochrome a	heme A
Cytochrome b	heme B
Cytochrome c	heme C (covalently bound heme b)
Cytochrome d	heme D (Heme B with γ-spirolactone)[1]

There is no "cytochrome e," but cytochrome f, found in the cytochrome b_6f complex of plants is a c-type cytochrome.

In mitochondria and chloroplasts, these cytochromes are often combined in electron transport and related metabolic pathways:

Cytochromes	Combination
a and a_3	Cytochrome c oxidase ("Complex IV") with electrons delivered to complex by soluble cytochrome c (hence the name)
b and c_1	Coenzyme Q - cytochrome c reductase ("Complex III")
b_6 and *f*	Plastoquinol—plastocyanin reductase

A distinct family of cytochromes is the cytochrome P450 family, so named for the characteristic Soret peak formed by absorbance of light at wavelengths near 450 nm when the heme iron is reduced (with sodium dithionite) and complexed to carbon monoxide. These enzymes are primarily involved in steroidogenesis and detoxification.

Ferredoxins:

Ferredoxins are iron–sulfur proteins that mediate electron transfer in a range of metabolic reactions. The term "ferredoxin" was coined by D.C. Wharton of the DuPont Co. and applied to the "iron protein" first purified in 1962 by Mortenson, Valentine, and Carnahan from the anaerobic bacterium *Clostridium pasteurianum*.

Another redox protein, isolated from spinach chloroplasts, was termed "chloroplast ferredoxin".The chloroplast ferredoxin is involved in both cyclic and non-cyclic photophosphorylation reactions of photosynthesis. In non-cyclic photophosphorylation, ferredoxin is the last electron acceptor thus reducing the enzyme $NADP^+$ reductase. It accepts electrons produced from sunlight-excited chlorophyll and transfers them to the enzyme ferredoxin: $NADP^+$ oxidoreductase .

Ferredoxins are small proteins containing iron and sulfur atoms organized as iron–sulfur clusters. These biological "capacitors" can accept or discharge electrons, with the effect of a change in the oxidation state of the iron atoms between +2 and +3. In this way, ferredoxin acts as an electron transfer agent in biological redox reactions.

Other bioinorganic electron transport systems include rubredoxins, cytochromes, blue copper proteins, and the structurally related Rieske proteins.

Ferredoxins can be classified according to the nature of their iron–sulfur clusters and by sequence similarity.

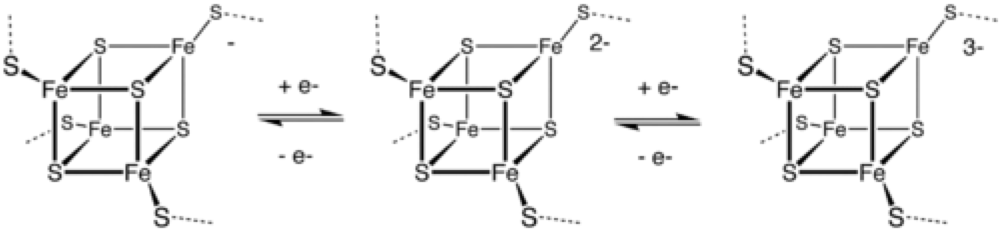
Fe_2S_2 ferredoxins

Members of the 2Fe–2S ferredoxin superfamily have a general core structure consisting of beta(2)-alpha-beta(2), which includes putidaredoxin, terpredoxin, and adrenodoxin.They are proteins of around one hundred amino acids with four conserved cysteine residues to which the 2Fe–2S cluster is ligated. This conserved region is also found as a domain in various metabolic enzymes and in multidomain proteins, such as aldehyde oxidoreductase (*N*-terminal), xanthine oxidase (*N*-terminal), phthalate dioxygenase reductase (*C*-terminal), succinate dehydrogenase iron–sulphur protein (*N*-terminal), and methane monooxygenase reductase (*N*-terminal).

Fe_4S_4 and Fe_3S_4 ferredoxins

The [Fe_4S_4] ferredoxins may be further subdivided into low-potential (bacterial-type) and high-potential (HiPIP) ferredoxins.

Low- and high-potential ferredoxins are related by the following redox scheme:



The formal oxidation numbers of the iron ions can be [$2Fe^{3+}$, $2Fe^{2+}$] or [$1Fe^{3+}$, $3Fe^{2+}$] in low-potential ferredoxins. The oxidation numbers of the iron ions in high-potential ferredoxins can be [$3Fe^{3+}$, $1Fe^{2+}$] or [$2Fe^{3+}$, $2Fe^{2+}$].

Rubredoxin:

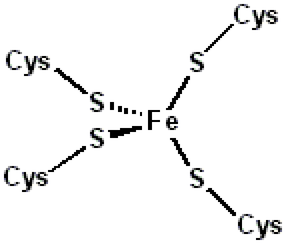
Rubredoxins are a class of low-molecular-weight iron-containing proteins found in sulfur-metabolizing bacteria and archaea. Sometimes rubredoxins are classified as iron-sulfur proteins; however, in contrast to iron-sulfur proteins, rubredoxins do not contain inorganic sulfide. Like cytochromes, ferredoxins and Rieske proteins, rubredoxins participate in electron transfer in biological systems.

Structure

The 3-D structures of a number of rubredoxins have been solved. The fold belongs to the α+β class, with 2 α-helices and 2-3 β-strands. Rubredoxin active site contains an iron ion which is coordinated by the sulfurs of four conserved cysteine residues forming an almost regular tetrahedron. This is sometimes denoted as a [1Fe-0S] or an Fe_1S_0 system, in analogy to the nomenclature for iron-sulfur proteins. While the vast majority of rubredoxins are soluble, there exists a membrane-bound rubredoxin, referred to as rubredoxin A, in oxygenic photoautotrophs.

Rubredoxins perform one-electron transfer processes. The central iron atom changes between the +2 and +3 oxidation states. In both oxidation states, the metal remains high spin, which helps to minimize structural changes. The reduction potential of a rubredoxin is typically in the range +50 mV to -50 mV.

This iron-sulphur protein is an electron carrier, and it is easy to distinguish its metallic centre changes: the oxidized state is reddish (due to a ligand metal charge transfer), while the reduced state is colourless (because the electron transition has an energy of the infrared level, which is imperceptible to the human eye).



Mononuclear Non-Heme Iron Enzymes:

There are two major sources of food iron: haem iron and non-haem iron.

The two forms of iron in the diet are absorbed with different efficiency

Heme iron:

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organic (haem) iron must be hydrolysed from any protein to which it is attached and it is then absorbed relatively easily but slowly. The overall absorption of iron from meat may be 20-25%. The most efficient absorption takes place in the duodenum, and is inversely related to the iron store level.

Non heme iron:

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Copper Containing Proteins:

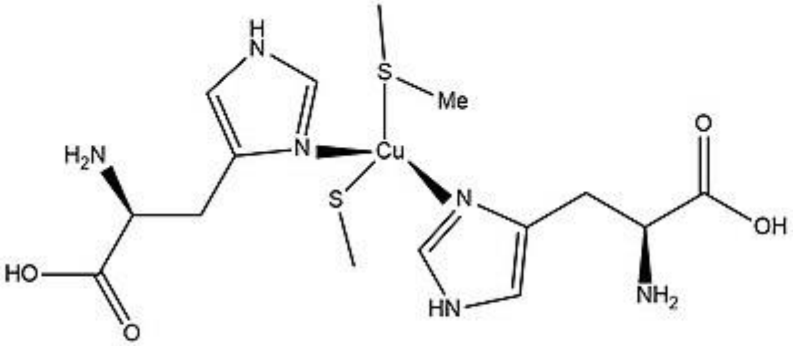
Copper proteins are proteins that contain one or more copper ions as prosthetic groups. Copper proteins are found in all forms of air-breathing life. These proteins are usually associated with electron-transfer with or without the involvement of oxygen (O_2). Some organisms even use copper proteins to carry oxygen instead of iron proteins. A prominent copper proteins in humans is in cytochrome c oxidase (cco). The enzyme cco mediates the controlled combustion that produces ATP.

Blue copper proteins

The blue copper proteins owe their name to their intense blue coloration (Cu(II)). The blue copper protein often called as "moonlighting protein", which means a protein can perform more than one function. They serve as electron transfer agents, with the active site shuttling between Cu(I) and Cu(II). The Cu^{2+} in the oxidized state can accept one electron to form Cu^{1+} in the reduced protein. The geometry of the Cu center has a major impact on its redox properties. The Jahn-Teller distortion does not apply to the blue copper proteins because the copper site has low symmetry that does not support degeneracy in the d-orbital manifold. The absence of large reorganizational changes enhances the rate of their electron transfer. The active site of a type-I blue copper protein. Two 2-histidines, 1 methionine and 1 cysteine present in the coordination sphere. Example for Type-I blue copper protein are plastocyanine , azurin, and nitrite reductase. Thaemocyanin and tyrosinase .

Blue copper protein types structure

Blue Copper Proteins, a class of Type 1 copper proteins, are small proteins containing a cupredoxin fold and a single Type I copper ion coordinated by two histidine N-donors, a cysteine thiolate S-donor and a methionine thioether S-donor. In the oxidized state, the Cu^{+2} ion will form either a trigonal bipyramidal or tetrahedral coordination.The Type 1 copper proteins are identified as blue copper proteins due to the ligand to metal charge transfer an intense band at 600 nm that gives the characteristic of a deep blue colour present in the electron absorption spectrum.[8]

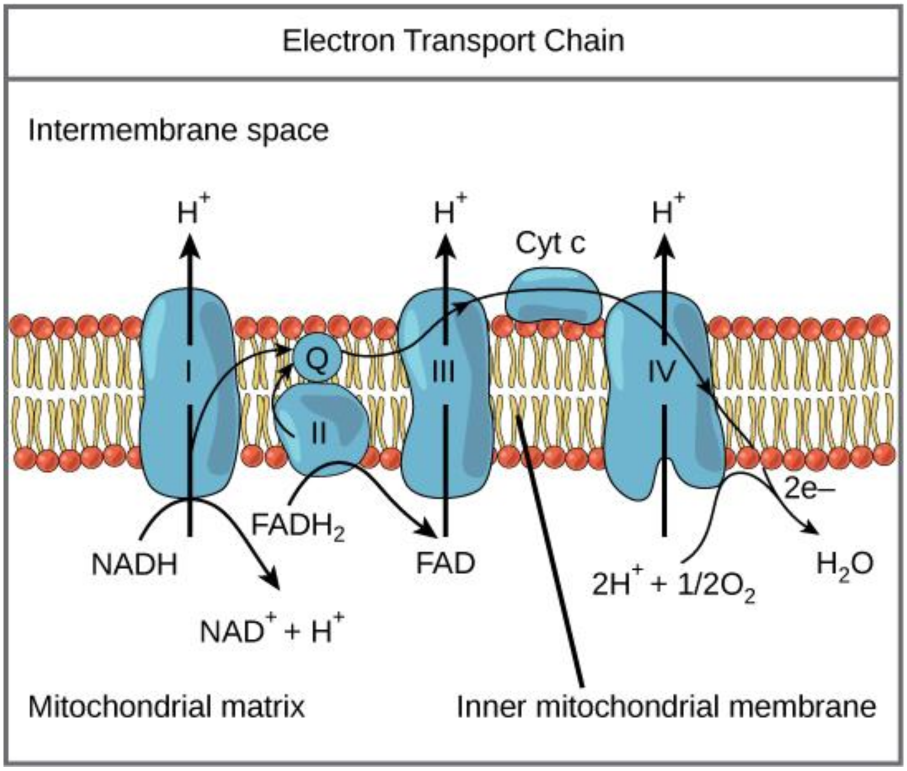


The structure of active site of type 1- blue copper protein.

The protein structure of a Type 1 blue copper protein, amicyanin, is built off of polypeptide folds that are commonly found in blue copper proteins β sandwich structure.The structure is very similar to plastocyanin and azurin as they also identify as Type 1 copper proteins.They are also similar to one another due to the geometry of the copper site of each copper protein. The protein azurin has a trigonal bipyramidal geometry with elongated axial glycine and methoinione sulfur ligands. Plastocyanins have an additional methionine sulfur ligand on the axial position. The main difference of each copper protein is that each protein has different number and species of ligand coordinated to the copper center.

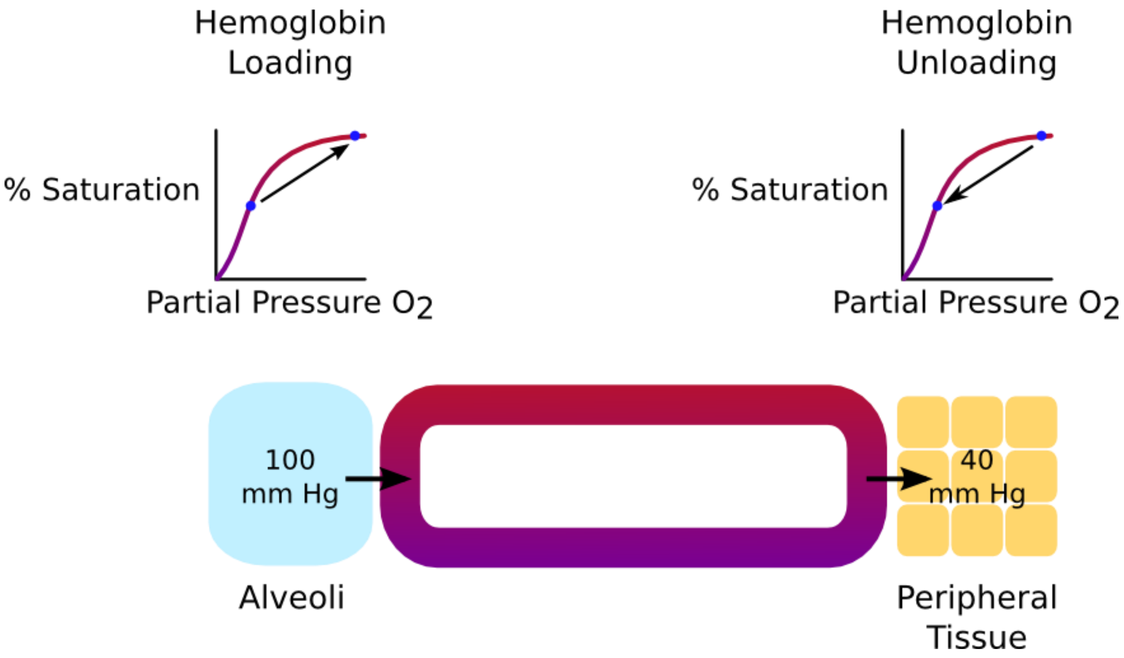
Electron Transfer – Oxygen Transport:

An **electron transport chain** (**ETC**) is a series of complexes that transfer electrons from electron donors to electron acceptors via redox (both reduction and oxidation occurring simultaneously) reactions, and couples this electron transfer with the transfer of protons (H^+ ions) across a membrane. The electron transport chain is built up of peptides, enzymes (which are proteins or protein complexes), and other molecules. The flow of electrons through the electron transport chain is highly exergonic. The energy available, from the redox reactions, creates an electrochemical proton gradient that drives the synthesis of adenosine triphosphate (ATP). In aerobic respiration, the flow of electrons terminates with molecular oxygen being the final electron acceptor. In anaerobic respiration other electron acceptors exist such as sulfate.



Oxygen Transport

- Oxygen is transported within the blood in a simple dissolved form as well as a chemically-bound form associated with hemoglobin (See: Gases in Liquids). Because hemoglobin-associated oxygen accounts for roughly 97% of the oxygen transported, the dynamic relationship between oxygen and hemoglobin is the primary determinant of oxygen transport. Oxygen transport in the body occurs in two basic steps involving the reversible loading and unloading of hemoglobin with oxygen. Hemoglobin is loaded with oxygen as it passes through the pulmonary capillaries and is then transported to the peripheral tissues where the oxygen is unloaded.
- The primary factor determining whether oxygen is loaded or unloaded onto hemoglobin is the surrounding partial pressure of oxygen. The quantitative relationship between oxygen partial pressure and the percent of hemoglobin molecules bound to oxygen is provided by the "Oxygen-Hemoglobin Dissociation Curve" described below. Careful analysis of this dissociation curve can provide valuable insights into how oxygen transport is regulated.



Oxygen is loaded in blood in the pulmonary capillaries where the oxygen tension is 100 mm Hg as a result of alveolar ventilation. Oxygen is unloaded from the blood in the peripheral tissues where the oxygen tension is roughly 40 mm Hg as a result of peripheral tissue oxygen consumption.

Oxygenation:

The addition of oxygen to any system, including the human body. Oxygenation may also refer to the process of treating a patient with oxygen, or of combining a medication or other substance with oxygen.

Hyperbaric oxygenation is an increased amount of oxygen in organs and tissues resulting from the administration of oxygen in a compression chamber at an ambient pressure greater than 1 atmosphere.

The process of taking oxygen from the inspired air and using it to sustain aerobic cellular metabolism throughout the body can be conceptualized as having three steps:

●Oxygenation is the process of oxygen diffusing passively from the alveolus to the pulmonary capillary, where it binds to hemoglobin in red blood cells or dissolves into the plasma. Insufficient oxygenation is termed hypoxemia. This is to be differentiated from hypoxia, which is an abnormally low oxygen content in a tissue or organ.

●Oxygen delivery is the rate of oxygen transport from the lungs to the peripheral tissues.

●Oxygen consumption is the rate at which oxygen is removed from the blood for use by the tissues.

Oxidases and Reductases:

An **oxidoreductase** is an enzyme that catalyzes the transfer of electrons from one molecule, the reductant, also called the electron donor, to another, the oxidant, also called the electron acceptor. This group of enzymes usually utilizes NADP or NAD+ as cofactors. Transmembrane oxidoreductases create electron transport chains in bacteria, chloroplasts and mitochondria, including respiratory complexes I, II and III. Some others can associate with biological membranes as peripheral membrane proteins or be anchored to the membranes through a single transmembrane helix.

Reactions

For example, an enzyme that catalyzed this reaction would be an oxidoreductase:

$$A^{-} + B \rightarrow A + B^{-}$$

In this example, A is the reductant (electron donor) and B is the oxidant (electron acceptor).

In biochemical reactions, the redox reactions are sometimes more difficult to see, such as this reaction from glycolysis:

$$P_i + \text{glyceraldehyde-3-phosphate} + NAD^{+} \rightarrow NADH + H^{+} + \text{1,3-bisphosphoglycerate}$$

In this reaction, NAD^{+} is the oxidant (electron acceptor), and glyceraldehyde-3-phosphate is the reductant (electron donor).

Cytochrome Oxidase:

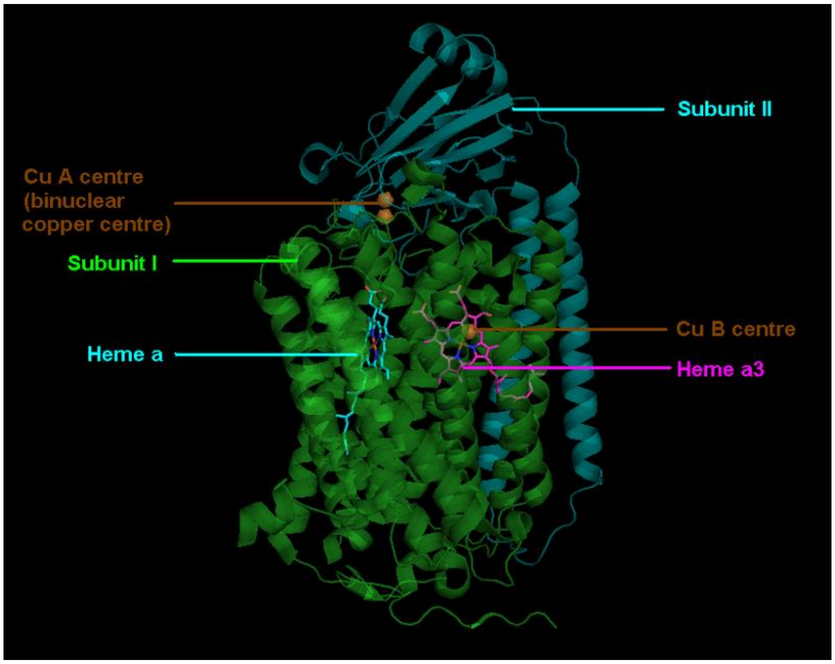
The enzyme **cytochrome c oxidase** or **Complex IV**, is a large transmembrane protein complex found in bacteria, archaea, and in eukaryotes in their mitochondria.

It is the last enzyme in the respiratory electron transport chain of cells located in the membrane. It receives an electron from each of four cytochrome c molecules, and transfers them to one dioxygen molecule, converting the molecular oxygen to two molecules of water. In this process it binds four protons from the inner aqueous phase to make two water molecules, and translocates another four protons across the membrane, increasing the transmembrane difference of proton electrochemical potential which the ATP synthase then uses to synthesize ATP.

Structure

The complex is a large integral membrane protein composed of several metal prosthetic sites and 14 protein subunits in mammals. In mammals, eleven subunits are nuclear in origin, and three are synthesized in the mitochondria. The complex contains two hemes, a cytochrome a and cytochrome a_3, and two copper centers, the Cu_A and Cu_B centers. In fact, the cytochrome a_3 and Cu_B form a binuclear center that is the site of oxygen reduction. Cytochrome c, which is reduced by the preceding component of the respiratory chain (cytochrome bc1 complex, complex III), docks near the Cu_A binuclear center and passes an electron to it, being oxidized back to cytochrome c containing Fe^{3+}. The reduced Cu_A binuclear center now passes an electron on to cytochrome a, which in turn passes an electron on to the cytochrome a_3-Cu_B binuclear center. The two metal ions in this binuclear center are 4.5 Å apart and coordinate a hydroxide ion in the fully oxidized state.

Crystallographic studies of cytochrome c oxidase show an unusual post-translational modification, linking C6 of Tyr(244) and the ε-N of His(240) (bovine enzyme numbering). It plays a vital role in enabling the cytochrome a_3- Cu_B binuclear center to accept four electrons in reducing molecular oxygen to water. The mechanism of reduction was formerly thought to involve a peroxide intermediate, which was believed to lead to superoxide production. However, the currently accepted mechanism involves a rapid four-electron reduction involving immediate oxygen-oxygen bond cleavage, avoiding any intermediate likely to form superoxide.



Reaction:

$$4\ Fe^{2+}\text{-cytochrome } c + 8\ H^{+}_{in} + O_2 \rightarrow 4\ Fe^{3+}\text{-cytochrome } c + 2\ H_2O + 4\ H^{+}_{out}$$

Two electrons are passed from two cytochrome c's, through the Cu_A and cytochrome a sites to the cytochrome a_3- Cu_B binuclear center, reducing the metals to the Fe^{2+} form and Cu^+. The hydroxide ligand is protonated and lost as water, creating a void between the metals that is filled by O_2. The oxygen is rapidly reduced, with two electrons coming from the Fe^{2+}cytochrome a_3, which is converted to the ferryl oxo form ($Fe^{4+}=O$). The oxygen atom close to Cu_B picks up one electron from Cu^+, and a second electron and a proton from the hydroxyl of Tyr(244), which becomes a tyrosyl radical. The second oxygen is converted to a hydroxide ion by picking up two electrons and a proton. A third electron arising from another cytochrome c is passed through the first two electron carriers to the cytochrome a_3- Cu_B binuclear center, and this electron and two protons convert the tyrosyl radical back to Tyr, and the hydroxide bound to Cu_B^{2+} to a water molecule. The fourth electron from another cytochrome c flows through Cu_A and cytochrome a to the cytochrome a_3- Cu_B binuclear center, reducing the $Fe^{4+}=O$ to Fe^{3+}, with the oxygen atom picking up a proton simultaneously, regenerating this oxygen as a hydroxide ion coordinated in the middle of the cytochrome a_3- Cu_B center as it was at the start of this cycle. The net process is that four reduced cytochrome c's are used, along with 4 protons, to reduce O_2 to two water molecules.

Superoxide Dismutase (Cu, Zn):

Superoxide dismutase (**SOD**, is an enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into ordinary molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, causes many types of cell damage. Hydrogen peroxide is also damaging and is degraded by other enzymes such as catalase. Thus, SOD is an important antioxidant defense in nearly all living cells exposed to oxygen. One exception is *Lactobacillus plantarum* and related lactobacilli, which use a different mechanism to prevent damage from reactive O_2^-.

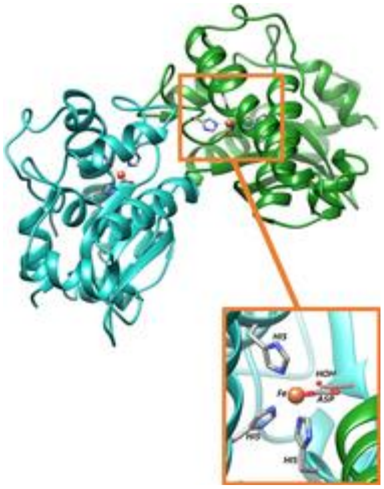
Types

General

There are three major families of superoxide dismutase, depending on the protein fold and the metal cofactor: the Cu/Zn type (which binds both copper and zinc), Fe and Mn types (which bind either iron or manganese), and the Ni type (which binds nickel).

- Copper and zinc – most commonly used by eukaryotes, including humans. The cytosols of virtually all eukaryotic cells contain an SOD enzyme with copper and zinc (Cu-Zn-SOD). For example, Cu-Zn-SOD available commercially is normally purified from bovine red blood cells. The bovine Cu-Zn enzyme is a homodimer of molecular weight 32,500.

The two subunits are tightly joined back-to-back, mostly by hydrophobic and some electrostatic interactions. The ligands of the copper and zinc are six histidine and one aspartate side-chains; one histidine is bound between the two metals.



Active site for iron superoxide dismutase

Iron or manganese – used by prokaryotes and protists, and in mitochondria and chloroplasts

- Iron – Many bacteria contain a form of the enzyme with iron (Fe-SOD); some bacteria contain Fe-SOD, others Mn-SOD, and some (such as *E. coli*) contain both. Fe-SOD can also be found in the chloroplasts of plants. The 3D structures of the homologous Mn and Fe superoxide dismutases have the same arrangement of alpha-helices, and their active sites contain the same type and arrangement of amino acid side-chains. They are usually dimers, but occasionally tetramers.
- Manganese – Nearly all mitochondria, and many bacteria, contain a form with manganese (Mn-SOD): For example, the Mn-SOD found in human mitochondria. The ligands of the manganese ions are 3 histidine side-chains, an aspartate side-chain and a water molecule or hydroxy ligand, depending on the Mn oxidation state (respectively II and III).

Cosmetic uses

SOD may reduce free radical damage to skin—for example, to reduce fibrosis following radiation for breast cancer. Studies of this kind must be regarded as tentative, however, as there were not adequate controls in the study including a lack of randomization, double-blinding, or placebo.Superoxide dismutase is known to reverse fibrosis, possibly through de-differentiation of myofibroblasts back to fibroblasts.

Commercial sources

SOD is commercially obtained from marine phytoplankton, bovine liver, horseradish, cantaloupe, and certain bacteria. For therapeutic purpose, SOD is usually injected locally. There is no evidence that ingestion of unprotected SOD or SOD-rich foods can have any physiological effects, as all ingested SOD is broken down into amino acids before being absorbed. However, ingestion of SOD bound to wheat proteins could improve its therapeutic activity, at least in theory.

Nickel Containing Enzyme: Urease:

Ureases functionally, belong to the superfamily of amidohydrolases and phosphotriesterases. Ureases are found in numerous bacteria, fungi, algae, plants, and some invertebrates, as well as in soils, as a soil enzyme. They are nickel-containing metalloenzymes of high molecular weight.

These enzymes catalyze the hydrolysis of urea into carbon dioxide and ammonia:

$$(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3$$

The hydrolysis of urea occurs in two stages. In the first stage, ammonia and carbamate are produced. The carbamate spontaneously and rapidly hydrolyzes to ammonia and carbonic acid. Urease activity increases the pH of its environment as ammonia is produced, which is basic.

Activity

The k_{cat}/K_m of urease in the processing of urea is 10^{14} times greater than the rate of the uncatalyzed elimination reaction of urea.There are many reasons for this observation in nature. The proximity of urea to active groups in the active site along with the correct orientation of urea allow hydrolysis to occur rapidly. Urea alone is very stable due to the resonance forms it can adopt. The stability of urea is understood to be due to its resonance energy, which has been estimated at 30–40 kcal/mol. This is because the zwitterionic resonance forms all donate electrons to the carbonyl carbon making it less of an electrophile making it less reactive to nucleophilic attack.

Active site

The active site of ureases is located in the α (alpha) subunits. It is a bis-μ-hydroxo dimeric nickel center, with an interatomic distance of ~3.5 Å.[5] > The Ni(II) pair are weakly antiferromagnetically coupled. X-ray absorption spectroscopy (XAS) studies of *Canavalia ensiformis* (jack bean), *Klebsiella aerogenes* and *Sporosarcina pasteurii* (formerly known as *Bacillus pasteurii*) confirm 5–6 coordinate nickel ions with exclusively O/N ligation, including two imidazole ligands per nickel.Urea substrate is proposed to displace aquo ligands.

Water molecules located towards the opening of the active site form a tetrahedral cluster that fills the cavity site through hydrogen bonds. Some amino acid residues are proposed to form mobile flap of the site, which gate for the substrate.Cysteine residues are common in the flap region of the enzymes, which have been determined not to be essential in catalysis, although involved in positioning other key residues in the active site appropriately.In *Sporosarcina pasteurii* urease, the flap was found in the open conformation, while its closed conformation is apparently needed for the reaction.

When compared, the α subunits of *Helicobacter pylori* urease and other bacterial ureases align with the jack bean ureases.

The binding of urea to the active site of urease has not been observed.

Occurrence and potential applications

Urea is found naturally in the environment and is also artificially introduced, comprising more than half of all synthetic nitrogen fertilizers used globally.Heavy use of urea is thought to promote eutrophication, despite the observation that urea is rapidly transformed by microbial ureases, and thus usually does not persist. Environmental urease activity is often measured as an indicator of the health of microbial communities. In the absence of plants, urease activity in soil is generally attributed to heterotrophic microorganisms, although it has been demonstrated that some chemoautotrophic ammonium oxidizing bacteria are capable of growth on urea as a sole source of carbon, nitrogen, and energy.

By promoting the formation of calcium carbonate, ureases are potentially useful for biomineralization-inspired processes. Notably, micro-biologically induced formation of calcium carbonate can be used in making bioconcrete.

UNIT III

Medicinal Bioinorganic Chemistry

Bioinorganic Chemistry of Quintessentially Toxic Metals:

Toxicity

Several metal ions are toxic to humans and other animals. The bioinorganic chemistry of lead in the context of its toxicity has been reviewed.

Toxicity Lead :

Lead poisoning is a type of metal poisoning caused by lead in the body. The brain is the most sensitive. Symptoms may include abdominal pain, constipation, headaches, irritability, memory problems, inability to have children, and tingling in the hands and feet.

It causes almost 10% of intellectual disability of otherwise unknown cause and can result in behavioral problems. Some of the effects are permanent.In severe cases anemia, seizures, coma, or death may occur.

Exposure to lead can occur by contaminated air, water, dust, food,or consumer products.Children are at greater risk as they are more likely to put objects in their mouth such as those that contain lead paint and absorb a greater proportion of the lead that they eat.Exposure at work is a common cause of lead poisoning in adults with certain occupations at particular risk.Diagnosis is typically by measurement of the blood lead level.The Centers for Disease Control (US) has set the upper limit for blood lead for adults at 10 µg/dl (10 µg/100 g) and for children at 5 µg/dl. Elevated lead may also be detected by changes in red blood cells or dense lines in the bones of children as seen on X-ray.

Signs and symptoms

Lead poisoning can cause a variety of symptoms and signs which vary depending on the individual and the duration of lead exposure. Symptoms are nonspecific and may be subtle, and someone with elevated lead levels may have no symptoms. Symptoms usually develop over weeks to months as lead builds up in the body during a chronic exposure, but acute symptoms from brief, intense exposures also occur.

Symptoms from exposure to organic lead, which is probably more toxic than inorganic lead due to its lipid solubility, occur rapidly. Poisoning by organic lead compounds has symptoms predominantly in the central nervous system, such as insomnia, delirium, cognitive deficits, tremor, hallucinations, and convulsions.

Symptoms may be different in adults and children; the main symptoms in adults are headache, abdominal pain, memory loss, kidney failure, male reproductive problems, and weakness, pain, or tingling in the extremities.

Early symptoms of lead poisoning in adults are commonly nonspecific and include depression, loss of appetite, intermittent abdominal pain, nausea, diarrhea, constipation, and muscle pain.Other early signs in adults include malaise, fatigue, decreased libido, and problems with sleep.An unusual taste in the mouth and personality changes are also early signs.

Toxicity cadmium:

Cadmium toxicity occurs when a person breathes in high levels of cadmium from the air, or eats food or drinks water containing high levels of cadmium. Cadmium is a naturally occurring metal. It is usually present in the environment as a mineral combined with other elements like oxygen, chlorine, or sulfur. Either short-term or long-term exposure to cadmium can cause serious health problems. If you suspect you have been exposed to cadmium, contact your doctor right away.

Causes

Most cadmium used in the United States is a by-product of the production of metals like zinc, lead, and copper. It is also found in the following products:

- Cigarettes
- Batteries
- Pigments
- Metal coatings
- Plastics
- Some metal alloys
- Fertilizers
- Bright red, yellow, and orange pigments in some pottery or glassware paint

When cadmium enters the air, it binds to small particles. It falls to the ground or into water in rain or snow, and may contaminate fish, plants, and animals. Improper waste disposal and spills at hazardous waste sites may cause cadmium to leak into nearby water and soil.

Having skin contact with cadmium is not known to cause health problems, but the following exposures to cadmium can cause serious health problems:

- Breathing air that contains high levels of cadmium
- Eating foods contaminated with high levels of cadmium, such as shellfish, liver, kidney, potatoes, and leafy vegetables
- Drinking water contaminated with cadmium
- Breathing in cigarette smoke, which doubles the average daily intake of cadmium

Risk Factors

Anyone can develop cadmium toxicity as a result of cadmium exposure. Factors that increase your chances of being exposed to cadmium include:

- Smoking
- Living near hazardous waste sites or industrial factories that release cadmium into the air
- Working in a metal smelting and/or refining plant
- Working in a plant that produces cadmium products, such as batteries, coatings, plastics, and pigments
- Having a nutritional deficiency in calcium, iron, protein, and/or zinc

Symptoms

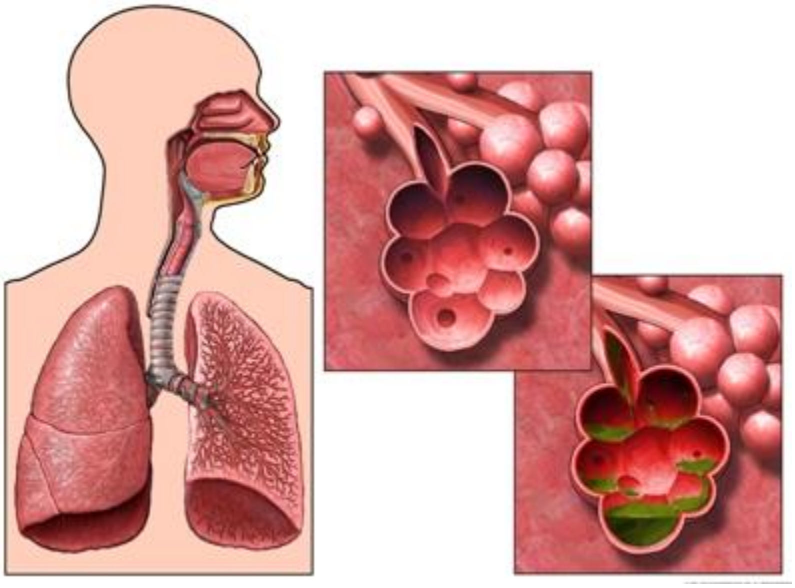
Eating food or drinking water contaminated with high levels of cadmium can result in:

- Nausea and vomiting
- Stomach cramps
- Diarrhea
- Kidney damage
- Fragile bones
- Death

Breathing in cadmium can result in:

- Flu-like symptoms, such as body aches, chills, weakness
- Vomiting
- Diarrhea
- Abdominal pain
- Shortness of breath
- Swelling of the nose, pharynx, and larynx—with chronic inhalation

Lung Damage from Toxic Inhalation



The damaged lung tissue (bottom) has a buildup of green mucus and thickened walls compared to healthy tissue (top).

There is no conclusive evidence that cadmium can cause lung cancer, but as a precaution, the United States Environmental Protection Agency has classified cadmium as a probable carcinogen in humans.

Diagnosis

You will be asked about your symptoms and medical history. A physical exam will be done.

Your fluids and tissues may be tested. This can be done with:

- Blood tests
- Urine tests
- Hair or nail analysis

Treatment

There is no effective treatment for cadmium toxicity. Your treatment will be designed to help manage and relieve your symptoms.

Prevention

To help reduce your chances of cadmium toxicity:

- If you smoke, talk to your doctor about ways to quit. Smoking is the highest source of cadmium intake for most people.
- Identify potential sources of cadmium in and around your home, at work, and where your children play.
- If you maintain a vegetable garden, consider having fertilizers tested for cadmium. Some fertilizers have been found to be high in cadmium, which may then concentrate in your vegetables. Avoid any use of cadmium-containing fungicides near your vegetable gardens.
- Eat a balanced diet that provides enough calcium, iron, protein, and zinc.
- Take inventory of and properly store cadmium-containing products in your home. Keep them out of the reach of children. When in doubt, check the label for cadmium or call the manufacturer to find out if the product contains cadmium.
- Keep nickel-cadmium batteries out of the reach of small children. Find out how to properly dispose of these batteries from your local waste disposal office.
- If you have a water well, have your water tested for cadmium.
- If cadmium is present in your well water, consider using bottled water for drinking or install a water filter that removes cadmium and other metals from drinking water.
- If you work around cadmium, talk to your occupational health and safety officer to find out if you could be bringing cadmium home on your clothing, skin, hair, tools, or other objects.
- Do not allow young children to play in or around hazardous waste sites.

Toxicity Mercury:

Mercury poisoning is a type of metal poisoning due to exposure to mercury. Symptoms depend upon the type, dose, method, and duration of exposure.They may include muscle weakness, poor coordination, numbness in the hands and feet, skin rashes, anxiety, memory problems, trouble speaking, trouble hearing, or trouble seeing. High-level exposure to methylmercury is known as Minamata disease. Methylmercury exposure in children may result in acrodynia (pink disease) in which the skin becomes pink and peels. Long-term complications may include kidney problems and decreased intelligence. The effects of long-term low-dose exposure to methylmercury are unclear.

Forms of mercury exposure include metal, vapor, salt, and organic compound.Most exposure is from eating fish, amalgam based dental fillings, or exposure at work.In fish, those higher up in the food chain generally have higher levels of mercury. Less commonly, poisoning may occur as a method of attempted suicide. Human activities that release mercury into the environment include the burning of coal and mining of gold.Tests of the blood, urine, and hair for mercury are available but do not relate well to the amount in the body.

Prevention includes eating a diet low in mercury, removing mercury from medical and other devices, proper disposal of mercury, and not mining further mercury. In those with acute poisoning from inorganic mercury salts, chelation with either dimercaptosuccinic acid (DMSA) or dimercaptopropane sulfonate (DMPS) appears to improve outcomes if given within a few hours of exposure.Chelation for those with long-term exposure is of unclear benefit.In certain communities that survive on fishing, rates of mercury poisoning among children have been as high as 1.7 per 100.

Signs and symptoms

Common symptoms of mercury poisoning include peripheral neuropathy, presenting as paresthesia or itching, burning, pain, or even a sensation that resembles small insects crawling on or under the skin (formication); skin discoloration (pink cheeks, fingertips and toes); swelling; and desquamation (shedding or peeling of skin).

Mercury irreversibly inhibits selenium-dependent enzymes (see below) and may also inactivate *S*-adenosyl-methionine, which is necessary for catecholamine catabolism by catechol-*O*-methyl transferase. Due to the body's inability to degrade catecholamines (e.g. epinephrine), a person suffering from mercury poisoning may experience profuse sweating, tachycardia (persistently faster-than-normal heart beat), increased salivation, and hypertension (high blood pressure).

Affected children may show red cheeks, nose and lips, loss of hair, teeth, and nails, transient rashes, hypotonia (muscle weakness), and increased sensitivity to light. Other symptoms may include kidney dysfunction (e.g. Fanconi syndrome) or neuropsychiatric symptoms such as emotional lability, memory impairment, or insomnia.

Thus, the clinical presentation may resemble pheochromocytoma or Kawasaki disease. Desquamation (skin peeling) can occur with severe mercury poisoning acquired by handling elemental mercury.

Prevention

Mercury poisoning can be prevented or minimized by eliminating or reducing exposure to mercury and mercury compounds. To that end, many governments and private groups have made efforts to heavily regulate the use of mercury, or to issue advisories about its use. Most countries have signed the Minamata Convention on Mercury.

Toxicity aluminium:

Aluminum toxicity occurs when a person ingests or breathes high levels of aluminum into the body.

Aluminum is the most plentiful metal in the earth’s crust. It is present in the environment combined with other elements such as oxygen, silicon, and fluorine.

Exposure to aluminum is usually not harmful, but exposure to high levels can cause serious health problems. If you think you have been exposed to high levels of aluminum, contact your doctor.

Causes

Because aluminum is found in food, water, air, and soil, people may be exposed to high levels of aluminum when they:

- Drink or ingest substances containing high levels of aluminum
- Breath aluminum dust in workplace air
- Live where aluminum is mined or processed
- Live near certain hazardous waste sites
- Live where aluminum is naturally high

Risk Factors

Anyone can develop this condition, but certain people are more likely to develop aluminum toxicity. The following factors increase your chances of developing aluminum toxicity:

- Diminished kidney function
- Hemodialysis
- Drinking or ingesting substances that are high in aluminum
- Living or working in an environment that contains high levels of aluminum
- Receiving long-term IV nutrition
- Living in dusty environments

Symptoms

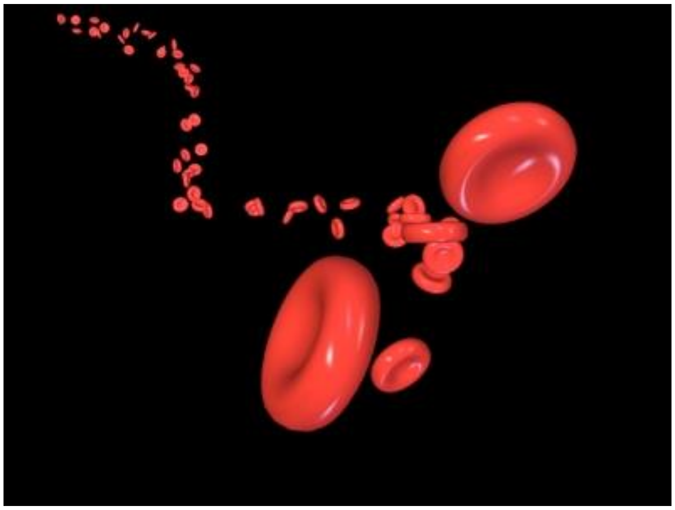
If you have any of the following symptoms, see your doctor, especially if you have kidney disease or are on dialysis :

- Confusion
- Muscle weakness
- Bone pain, deformities, and fractures
- Seizures
- Speech problems
- Slow growth—in children

Complications may include:

- Lung problems
- Nervous system problems causing difficulty with voluntary and involuntary actions
- Bone diseases
- Brain diseases and disorders
- Anemia
- Impaired iron absorption

Red Blood Cells



These vital cells transport oxygen through the body. Symptoms of aluminum toxicity such as anemia and impaired iron absorption decrease the number of red blood cells.

Treatment

Talk with your doctor about the best treatment plan for you. Treatment options include:

Medications

The medication, deferoxamine mesylate, may be given to help eliminate aluminum from your body. This substance works through a procedure known as chelation, which helps the body remove poisonous materials.

Aluminum Avoidance

You will be instructed on how to avoid exposure to excess aluminum from your diet and other sources.

Prevention

To help reduce your chances of getting aluminum toxicity, take steps to avoid the following if they contain aluminum:

- Antacids
- Antiperspirants

Talk to your doctor about your risk of aluminum poisoning from dialysis and total parenteral nutrition solutions.

Toxicity Chromium:

Chromium toxicity refers to any poisonous toxic effect in an organism or cell that results from exposure to specific forms of chromium—especially hexavalent chromium. Hexavalent chromium and its compounds are toxic when inhaled or ingested. Trivalent chromium is a trace mineral that is essential to human nutrition. There is a hypothetical risk of genotoxicity in humans if large amounts of trivalent chromium were somehow able to enter living cells, but normal metabolism and cell function prevent this.

Forms of chromium

Hexavalent chromium and trivalent chromium are chromium ions—they have different numbers of electrons and, therefore, different properties. Trivalent chromium, or chromium(III), is the form of chromium that is essential to human health.Hexavalent chromium, or chromium(VI), is an unequivocally toxic form.

Hexavalent chromium

Hexavalent chromium, also called chromium(VI), is hemotoxic, genotoxic, and carcinogenic.[2] When hexavalent chromium enters the bloodstream, it damages blood cells by causing oxidation reactions. This oxidative damage can lead to hemolysis and, ultimately, kidney and liver failure. Patients might be treated with dialysis.

The median lethal dose of hexavalent chromium is 50–150 mg/kg.The World Health Organization recommends a maximum allowable concentration of 0.05 milligrams per litre of chromium(VI) in drinking water.[5] In Europe, the use of hexavalent chromium is regulated by the Restriction of Hazardous Substances Directive.

Hexavalent chromium can be found in some dyes and paints, as well as in some leather tanning products. Primer paint containing hexavalent chromium is widely used in aerospace and automobile refinishing applications. Metal workers (such as welders)—as well as people with a surgical implant made from cobalt-chromium alloy—may also be exposed to hexavalent chromium.Chromium concentrations in whole blood, plasma, serum, or urine may be measured to monitor for safety in exposed workers, to confirm the diagnosis in potential poisoning victims, or to assist in the forensic investigation in a case of fatal overdosage.

Toxicity copper:

Copper toxicity is a type of metal poisoning caused by an excess of copper in the body. Copperiedus can occur from eating acidic foods cooked in uncoated copper cookware, or from exposure to excess copper in drinking water or other environmental sources.

Signs and symptoms

Acute symptoms of copper poisoning by ingestion include vomiting, hematemesis (vomiting of blood), hypotension (low blood pressure), melena (black "tarry" feces), coma, jaundice (yellowish pigmentation of the skin), and gastrointestinal distress.Individuals with glucose-6-phosphate deficiency may be at increased risk of hematologic effects of copper. Hemolytic anemia resulting from the treatment of burns with copper compounds is infrequent.

Chronic (long-term) copper exposure can damage the liver and kidneys.Mammals have efficient mechanisms to regulate copper stores such that they are generally protected from excess dietary copper levels.

Those same protection mechanisms can cause milder symptoms, which are often misdiagnosed as psychiatric disorders. There is a lot of research on the function of the Cu/Zn ratio in neurological, endocrinological, and psychological conditions.Many of the substances that protect us from excess copper perform important functions in our neurological and endocrine systems, leading to diagnostic difficulties. When they are used to bind copper in the plasma, to prevent it from being absorbed in the tissues, their own function may go unfulfilled. Such symptoms often include mood swings, irritability, depression, fatigue, excitation, difficulty focusing, and feeling out of control. To further complicate diagnosis, some symptoms of excess copper are similar to those of a copper deficit.

Copper in the blood and blood stream exists in two forms: bound to ceruloplasmin (85–95%), and the rest "free", loosely bound to albumin and small molecules. Nutritionally, there is a distinct difference between organic and inorganic copper, according to whether the copper ion is bound to an organic ligand.

Copper poisoning may also cause the following mental and behavioral symptoms:

- feeling anxious or irritable
- having trouble paying attention
- feeling overexcited or overwhelmed
- feeling unusually sad or depressed
- sudden changes in your mood

Long-term copper toxicity can also be fatal or cause:

- kidney conditions
- liver damage or failure
- heart failure
- brain damage

Toxicity Plutonium:

There are two aspects to the harmful effects of plutonium: the radioactivity and the heavy metal poison effects. Isotopes and compounds of plutonium are radioactive and accumulate in bone marrow. Contamination by plutonium oxide has resulted from nuclear disasters and radioactive incidents, including military nuclear accidents where nuclear weapons have burned.[123] Studies of the effects of these smaller releases, as well as of the widespread radiation poisoning sickness and death following the atomic bombings of Hiroshima and Nagasaki, have provided considerable information regarding the dangers, symptoms and prognosis of radiation poisoning, which in the case of the Japanese survivors was largely unrelated to direct plutonium exposure.

During the decay of plutonium, three types of radiation are released—alpha, beta, and gamma. Alpha, beta, and gamma radiation are all forms of ionizing radiation. Either acute or longer-term exposure carries a danger of serious health outcomes including radiation sickness, genetic damage, cancer, and death. The danger increases with the amount of exposure.Alpha radiation can travel only a short distance and cannot travel through the outer, dead layer of human skin. Beta radiation can penetrate human skin, but cannot go all the way through the body. Gamma radiation can go all the way through the body.Even though alpha radiation cannot penetrate the skin, ingested or inhaled plutonium does irradiate internal organs.Alpha particles generated by inhaled plutonium have been found to cause lung cancer in a cohort of European nuclear workers.The skeleton, where plutonium accumulates, and the liver, where it collects and becomes concentrated, are at risk.Plutonium is not absorbed into the body efficiently when ingested; only 0.04% of plutonium oxide is absorbed after ingestion.Plutonium absorbed by the body is excreted very slowly, with a biological half-life of 200 years. Plutonium passes only slowly through cell membranes and intestinal boundaries, so absorption by ingestion and incorporation into bone structure proceeds very slowly.

Plutonium is more dangerous when inhaled than when ingested. The risk of lung cancer increases once the total radiation dose equivalent of inhaled plutonium exceeds 400 mSv.

Detoxification by Metal Chelation:

Having small amounts of some heavy metals, such as iron and zinc, is essential for a healthy body. However, having large amounts of heavy metals can be toxic to the body and the environment.

Certain substances, such as those present in some foods and medications, bind to heavy metals and transport them out of the body. This process is called chelation.

A heavy metal detox aims to remove excess heavy metals from the body.

A substance that binds to heavy metals is known as a chelator, and the process that transports them out of the body is called chelation. People may also refer to a heavy metal detox as chelation therapy.

Doctors use specific chelator medications to treat heavy metal poisoning. Certain foods can also help move heavy metals out of the body.

Heavy metal toxicity can affect the function of organs such as the brain, the liver, and the lungs. Having high levels of heavy metals in the body can also reduce energy levels and affect blood composition.

Long-term exposure to heavy metals can cause the symptoms seen in degenerative conditions, such as Parkinson’s disease and Alzheimer’s disease. In some cases, long-term exposure to some metals may even cause cancer.

Some examples of heavy metals include:

- arsenic
- cadmium
- chromium
- copper
- lead
- nickel
- zinc
- mercury
- aluminum
- iron

Heavy metals can enter our bodies through food and environmental factors. Some sources of heavy metals include:

- soil erosion
- mining
- industrial waste
- fossil fuel emissions
- pesticides on crops
- waste water
- smoking tobacco

Heavy Metal Detoxes Safe

Everyone has a certain amount of heavy metals in their body. For people with a normal amount, chelation has the potential to cause more harm than good.

Chelation therapy can treat heavy metal poisoning under the careful supervision of a healthcare professional. Using chelation therapy for anything other than extreme cases of heavy metal poisoning can be very dangerous and even fatal.

Side effects

Chelation therapy can cause many side effects, including:

- headaches

- a reduction in calcium levels, which can be fatal
- a drop in blood pressure
- permanent kidney damage

Alternatives

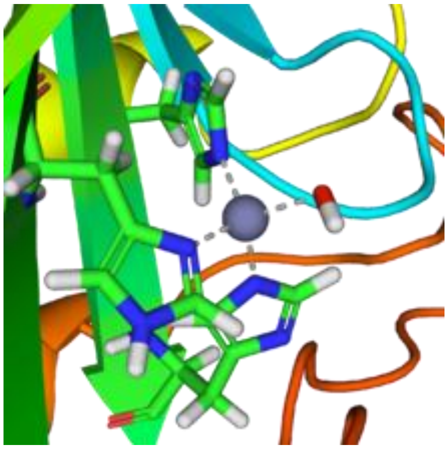
A person may be able to reduce the levels of heavy metals in their body more gradually by making changes to their diet. Certain foods, such as spirulina and cilantro, may help transport excess heavy metals out of the body.

- **Dietary fiber:** Various foods rich in fiber, such as fruit and grains with bran, may help remove heavy metals. Researchers have found fiber to reduce mercury levels in the brain and blood.
- **Chlorella:** Studies have shown that chlorella increases the detoxification of mercury in mice.
- **Foods containing sulfur:** Foods rich in sulfur, such as garlic and broccoli, may be good chelators. Research has suggested that garlic may have prevented kidney damage from cadmium and reduced oxidative damage from lead in rats.
- **Cilantro:** Cilantro may help, but there is currently limited evidence to support this. In an animal study, cilantro decreased absorption of lead into bone. In a trial looking at children with lead exposure, cilantro was as effective as a placebo.

Drugs That Act By Binding at The Metal Sites of Metalloenzymes:

Metalloenzymes all have one feature in common, namely that the metal ion is bound to the protein with one labile coordination site. As with all enzymes, the shape of the active site is crucial. The metal ion is usually located in a pocket whose shape fits the substrate. The metal ion catalyzes reactions that are difficult to achieve in organic chemistry.

Carbonic Anhydrase



Active site of carbonic anhydrase. The three coordinating histidine residues are shown in green, hydroxide in red and white, and the zinc in gray.

In aqueous solution, carbon dioxide forms carbonic acid

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

This reaction is very slow in the absence of a catalyst, but quite fast in the presence of the hydroxide ion

$$CO_2 + OH^- \rightleftharpoons HCO^-_3$$

A reaction similar to this is almost instantaneous with carbonic anhydrase. The structure of the active site in carbonic anhydrases is well known from a number of crystal structures. It consists of a zinc ion coordinated by three imidazole nitrogen atoms from three histidine units. The fourth coordination site is occupied by a water molecule. The coordination sphere of the zinc ion is approximately tetrahedral. The positively-charged zinc ion polarizes the coordinated water molecule, and nucleophilic attack by the negatively-charged hydroxide portion on carbon dioxide (carbonic anhydride) proceeds rapidly. The catalytic cycle produces the bicarbonate ion and the hydrogen ion as the equilibrium

$$H_2CO_3 \rightleftharpoons HCO^-_3 + H^+$$

favours dissociation of carbonic acid at biological pH values.

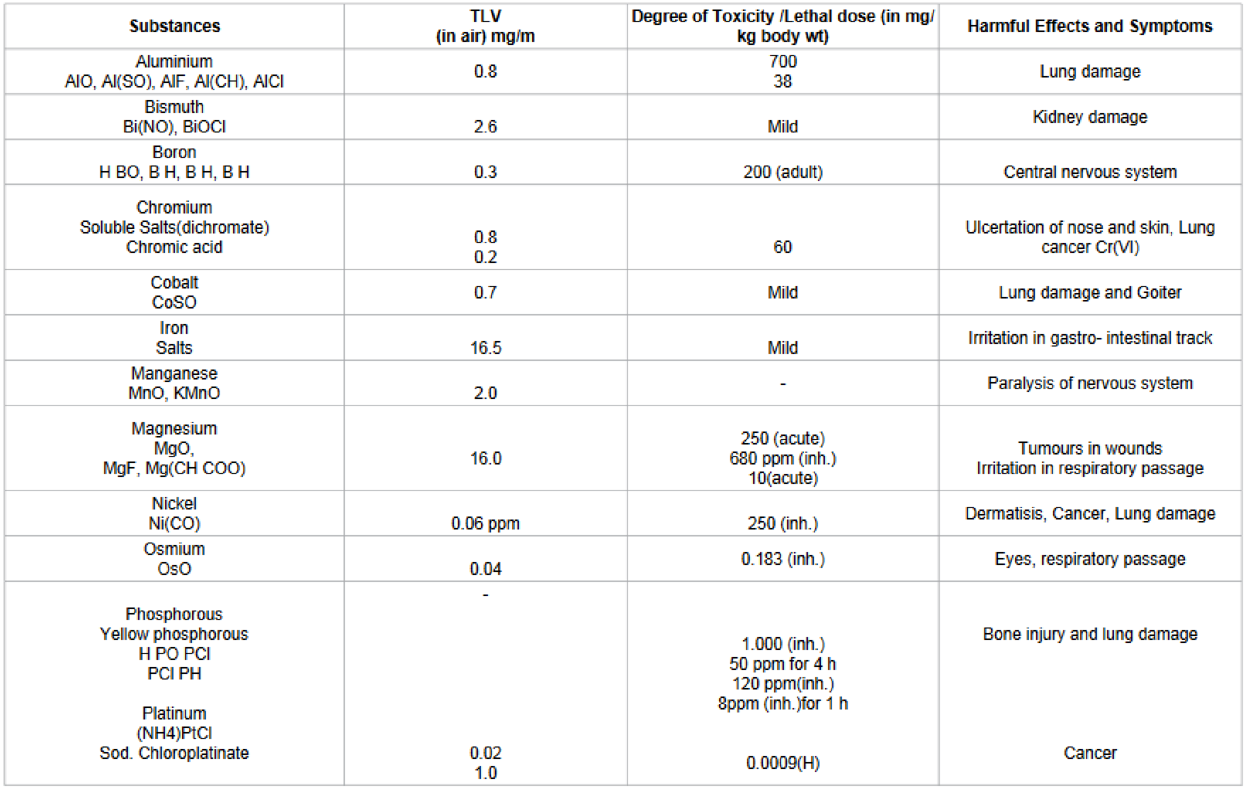
There are two types of carbon monoxide dehydrogenase: one contains iron and molybdenum, the other contains iron and nickel. Parallels and differences in catalytic strategies have been reviewed.

Pb^{2+} (lead) can replace Ca^{2+} (calcium) as, for example, with calmodulin or Zn^{2+} (zinc) as with metallocarboxypeptidases.

CHEMOTHERAPY

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in your body. Chemotherapy is most often used to treat cancer, since cancer cells grow and multiply much more quickly than most cells in the body. Many different chemotherapy drugs are available.

Molecularly targeted and immunotherapies have improved the care of patients with lung cancers. These successes have rallied calls to replace or avoid chemotherapy. Yet, even in this era of precision medicine and exciting advances, cytotoxic chemotherapies remain an essential component of lung cancer treatment. In the setting of locoregional disease, chemotherapy is the only systemic therapy thus far proven to enhance curability when combined with surgery or radiation. In the metastatic setting, chemotherapy can improve the length and quality of life in many patients. Chemotherapy remains the mainstay of care for individuals whose cancers with oncogenic drivers have acquired resistance to targeted agents. Chemotherapy also has the potential to modulate the immune system to enhance the effectiveness of immune checkpoint inhibitors. In this context, chemotherapy should be framed as a critical component of the armamentarium available for optimizing cancer care rather than an unfortunate anachronism. We examine the role of chemotherapy with precision medicine in the current care of patients with lung cancers, as well as opportunities for future integration in combinations with targeted agents, angiogenesis inhibitors, immunotherapies, and antibody drug conjugates.

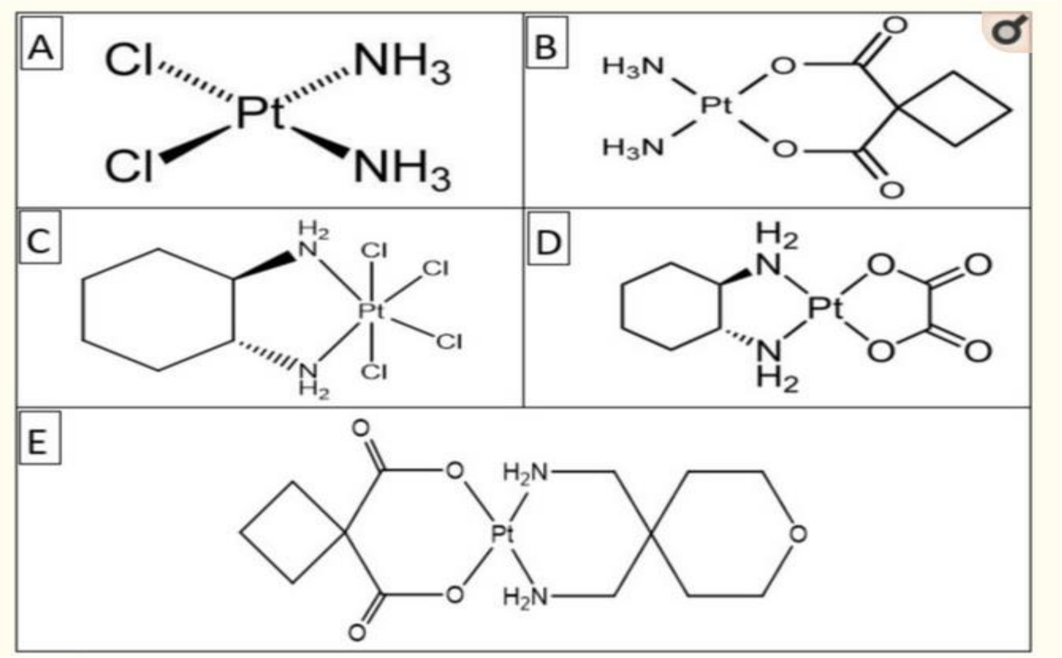


Substances	TLV (in air) mg/m	Degree of Toxicity /Lethal dose (in mg/ kg body wt)	Harmful Effects and Symptoms
Aluminium AlO, Al(SO), AlF, Al(CH), AlCl	0.8	700 38	Lung damage
Bismuth Bi(NO), BiOCl	2.6	Mild	Kidney damage
Boron H BO, B H, B H, B H	0.3	200 (adult)	Central nervous system
Chromium Soluble Salts(dichromate) Chromic acid	0.8 0.2	60	Ulcertation of nose and skin, Lung cancer Cr(VI)
Cobalt CoSO	0.7	Mild	Lung damage and Goiter
Iron Salts	16.5	Mild	Irritation in gastro- intestinal track
Manganese MnO, KMnO	2.0	-	Paralysis of nervous system
Magnesium MgO, MgF, Mg(CH COO)	16.0	250 (acute) 680 ppm (inh.) 10(acute)	Tumours in wounds Irritation in respiratory passage
Nickel Ni(CO)	0.06 ppm	250 (inh.)	Dermatisis, Cancer, Lung damage
Osmium OsO	0.04	0.183 (inh.)	Eyes, respiratory passage
Phosphorous Yellow phosphorous H PO PCl PCl PH	-	1.000 (inh.) 50 ppm for 4 h 120 ppm(inh.) 8ppm (inh.)for 1 h	Bone injury and lung damage
Platinum (NH4)PtCl Sod. Chloroplatinate	0.02 1.0	0.0009(H)	Cancer

Platinum complexes cisplatin is used in treatment of cancer

Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum (II), is a well-known chemotherapeutic drug. It has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers. It is effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells. However, because of drug resistance and numerous undesirable side effects such as severe kidney problems, allergic reactions, decrease immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients, other platinum-containing anti-cancer drugs such as carboplatin, oxaliplatin and others, have also been used. Furthermore, combination therapies of cisplatin with other drugs have been highly considered to overcome drug-resistance and reduce toxicity. This comprehensive review highlights the physicochemical properties of cisplatin and related platinum-based drugs, and discusses its uses (either alone or in combination with other drugs) for the treatment of various human cancers. A special attention is given to its molecular mechanisms of action, and its undesirable side effects.

Since the early seminal work in the preclinical and clinical development of cisplatin, several thousand analogues have been synthesized and tested for properties that would enhance its therapeutic index. About 13 of these analogues have been evaluated in clinical trials, but only one (carboplatin) has provided definite advantage over cisplatin and achieved worldwide approval. Nine platinum analogues are currently in clinical trials around the world ormaplatin (tetraplatin), oxaliplatin, DWA2114R, enloplatin, lobaplatin, CI-973 (NK-121), 254-S, JM-216, and liposome-entrapped cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) (LNDDP)]Figure 1 presents the chemical structures of cisplatin and four of its analogs including carboplatin, oxaliplatin, ormaplatin and enloplatin



Cisplatin and Lung Cancer

Lung cancer remains one of the most common types of fatal malignancies Small cell lung cancers (SCLCs) represent 15% of all lung cancers At present, platinum based treatments are key drugs for SCLC . Cisplatin and carboplatin are two of the most common types of platinum based treatments used in SCLC chemotherapy (In clinical trials, cisplatin is often selected due to its strong antitumor activity, but its adverse effects include renal toxicity, nausea and vomiting Therefore, to avoid renal toxicity, urine volumes should be monitored and large-dose infusion is mandatory in cisplatin based chemotherapy. In clinical practice, carboplatin has been considered to be a substitute for cisplatin without any apparent loss of therapeutic efficacy since aggressive hydration is often problematic.

The standard of care for localized non-small-cell lung cancer (NSCLC) is surgery followed by, in case of stage II and III disease, adjuvant cisplatin-based chemotherapy. The Lung Adjuvant Cisplatin Evaluation program, a pooled analysis of the five largest trials, recently showed an absolute 5-year survival benefit of 5.3%with adjuvant chemotherapy as well as the NSCLC meta-analysis

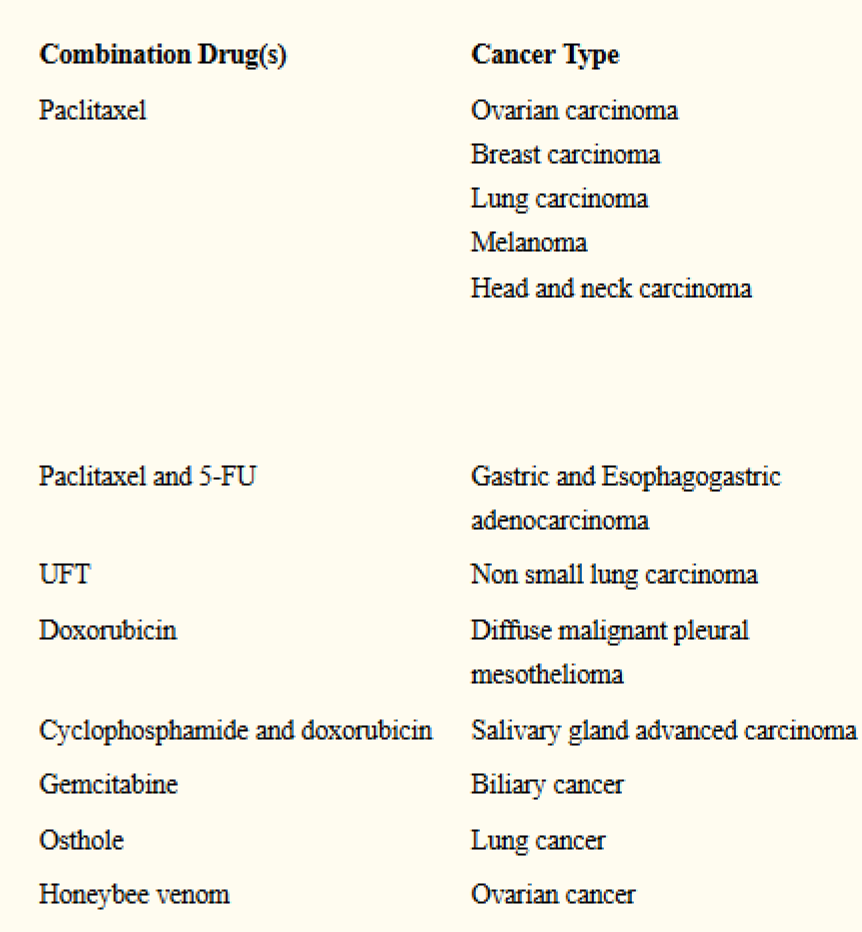
CD133, a surface glycoprotein linked to organ-specific stem cells, has been described as a marker of cancer-initiating cells in different tumor types. It has also been reported that a CD133$^+$, epithelial-specific antigen-positive (CD133$^+$ESA$^+$) population is increased in primary non-small cell lung cancer (NSCLC) compared with normal lung tissue

Cisplatin and Ovarian Cancer

Ovarian cancer has the highest mortality among gynecologic cancers. Most patients with ovarian cancer are diagnosed at late stages due to lack of effective screening strategies and specific symptoms associated with early-stage disease. Conventional treatment for late stages of ovarian cancers is surgical excision followed by platinum/ taxane combination chemotherapy. Although this treatment regime is effective as the first-line treatment, recurrence occurs in up to 75% of ovarian cancer patients. Patients with recurrent ovarian cancer ultimately develop resistance to chemotherapy and eventually succumb to the disease . About 90% of ovarian cancers arise originally from ovaries with an unknown reason, while the remainder has hereditary background, or are associated with breast and colon cancers . Cisplatin derivatives are used as the mainline treatment of ovarian cancer, despite their severe side effects and development of resistance. Cisplatin is used in combination with other chemical agents or compounds to treat ovarian cancer in both the resistant and sensitive cell lines. For example Cisplatin is used along with honey venom , withaferin trichostatin A or 5-aza-2′-deoxycytidine overcoming chemotherapy resistance of ovarian cancer cells by liposomal Cisplatin

Combination Therapy of Cisplatin with Other Cancer Drugs

Cisplatin combination chemotherapy is the basis of treatment of many cancers. Platinum responsiveness is high primarily but many cancer patients will ultimately relapse with cisplatin-resistant disease. Hence, drug resistance has been observed in many patients who have relapsed from cisplatin treatment. The proposed mechanisms of cisplatin resistance include changes in cellular uptake and efflux of cisplatin, increased biotransformation and detoxification in the liver, and increase in DNA repair and anti-apoptotic mechanisms . To overcome resistance, cisplatin is commonly used in combination with some other drugs in treating ovarian cancer, biliary tract cancer, lung cancer (diffuse malignant pleural mesothelioma), gastric cancer, carcinoma of salivary gland origin, breast, colon, lung, prostate, melanoma and pancreatic cancer cell lines, squamous cell carcinoma of male genitial tract, urothelial bladder cancer, and cervical cancer. Table 1 presents a synopsis of Cisplatin combination therapy with other cancer drugs and targeted cancers.



Combination Drug(s)	Cancer Type
Paclitaxel	Ovarian carcinoma Breast carcinoma Lung carcinoma Melanoma Head and neck carcinoma
Paclitaxel and 5-FU	Gastric and Esophagogastric adenocarcinoma
UFT	Non small lung carcinoma
Doxorubicin	Diffuse malignant pleural mesothelioma
Cyclophosphamide and doxorubicin	Salivary gland advanced carcinoma
Gemcitabine	Biliary cancer
Osthole	Lung cancer
Honeybee venom	Ovarian cancer

Cytotoxicity

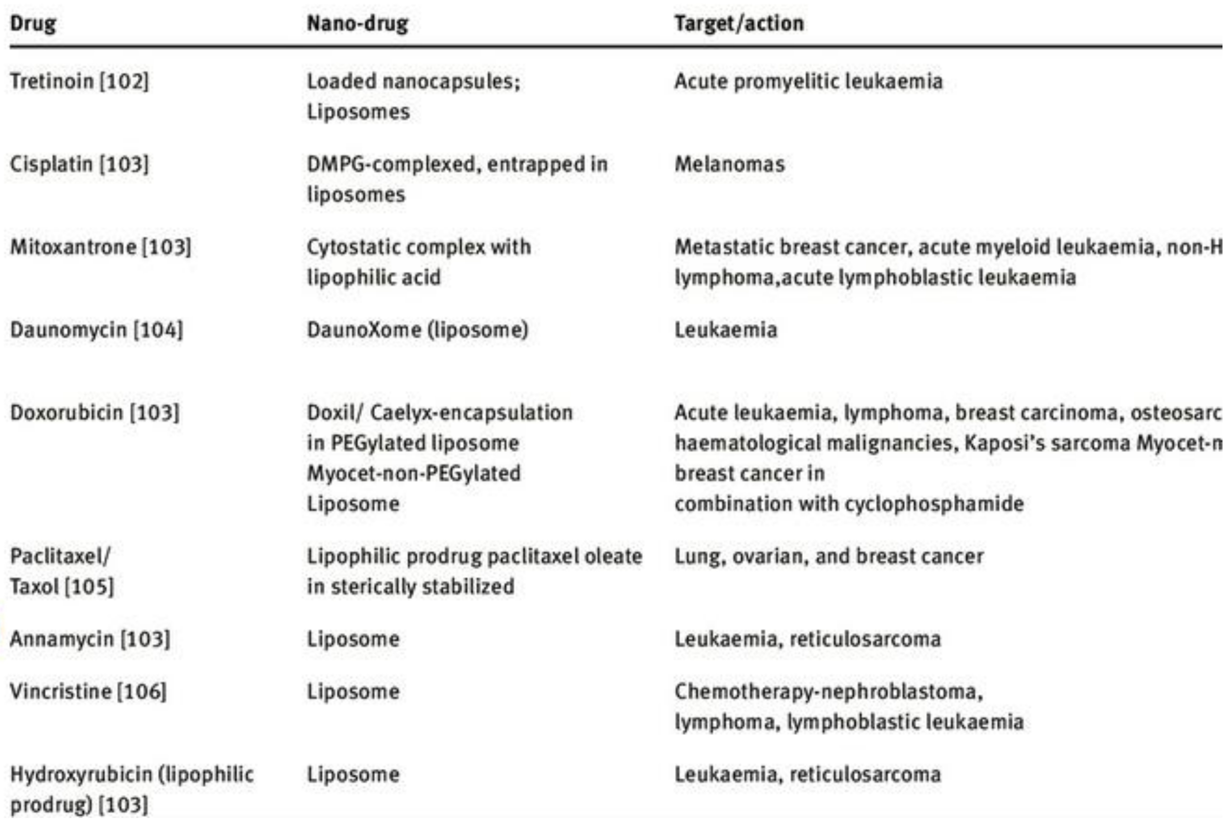
Cytotoxicity is the quality of being toxic to cells. Examples of toxic agents are an immune cell or some types of venom,

Immune system

Antibody-dependent cell-mediated cytotoxicity (ADCC) describes the cell-killing ability of certain lymphocytes, which requires the target cell being marked by an antibody. Lymphocyte-mediated cytotoxicity, on the other hand, does not have to be mediated by antibodies; nor does complement-dependent cytotoxicity (CDC), which is mediated by the complement system.

Three groups of cytotoxic lymphocytes are distinguished:

- Cytotoxic T cells
- Natural killer cells
- Natural killer T cells



Drug	Nano-drug	Target/action
Tretinoin [102]	Loaded nanocapsules; Liposomes	Acute promyelitic leukaemia
Cisplatin [103]	DMPG-complexed, entrapped in liposomes	Melanomas
Mitoxantrone [103]	Cytostatic complex with lipophilic acid	Metastatic breast cancer, acute myeloid leukaemia, non-H lymphoma,acute lymphoblastic leukaemia
Daunomycin [104]	DaunoXome (liposome)	Leukaemia
Doxorubicin [103]	Doxil/ Caelyx-encapsulation in PEGylated liposome Myocet-non-PEGylated Liposome	Acute leukaemia, lymphoma, breast carcinoma, osteosarc haematological malignancies, Kaposi's sarcoma Myocet-n breast cancer in combination with cyclophosphamide
Paclitaxel/ Taxol [105]	Lipophilic prodrug paclitaxel oleate in sterically stabilized	Lung, ovarian, and breast cancer
Annamycin [103]	Liposome	Leukaemia, reticulosarcoma
Vincristine [106]	Liposome	Chemotherapy-nephroblastoma, lymphoma, lymphoblastic leukaemia
Hydroxyrubicin (lipophilic prodrug) [103]	Liposome	Leukaemia, reticulosarcoma

GOLD CONTAINING DRUGS AS ANTI-RHEUMATIC AGENT AND ITS MODE OF ACTION

Three new findings are reviewed that help to understand the mechanisms of action of anti-rheumatic gold drugs, such as disodium aurothiomalate (Na2Au(I)TM): i) We found that Na2Au(I)TM selectively inhibits T-cell receptor-mediated antigen recognition by murine CD4+ T-cell hybridomas specific for antigenic peptides containing at least two cysteine residues. Presumably, Au(I) acts as a chelating agent forming linear complexes (Cys-Au(I)-Cys) which prevents correct antigen-processing and/or peptide recognition by the T-cell receptor, ii) We were able to show that Au(I) is oxidized to Au(III) in mononuclear phagocytes, such as macrophages. Because Au(III) rapidly oxidizes protein and itself is re-reduced to Au(I), this may introduce an Au(I)/Au(III) redox system into phagocytes which scavenges reactive oxygen species, such as hypochlorous acid (HOCl) and inactivates lysosomal enzymes, iii) Pretreatment with Au(III) of a model protein antigen, bovine ribonuclease A (RNase A), induced novel antigenic determinants recognized by CD4+ T lymphocytes. Analysis of the fine specificity of these "Au(III)-specific" T-cells revealed that they react to RNase peptides that are not presented to T-cells when the native protein, i.e., not treated with Au(III), is used as antigen. The T-cell recognition of these cryptic peptides did not require the presence of gold. This finding has important implications founderstanding the pathogenesis of allergic and autoimmune responses induced by gold drugs. Taken together, our findings indicate that Au(I) and Au(III) each exert specific effects on several distinct functions of macrophages and the activation of T-cells. These effects may explain both the desired anti-inflammatory and the adverse effects of antirheumatic gold drugs.

lithium in psychopharmacological drugs

Lithium compounds, also known as **lithium salts**, are primarily used as a psychiatric medication. It is primarily used to treat bipolar disorder and treat major depressive disorder that does not improve following the use of antidepressants. In these disorders, it reduces the risk of suicide. Lithium is taken by mouth.

Common side effects include increased urination, shakiness of the hands, and increased thirst. Serious side effects include hypothyroidism, diabetes insipidus, and lithium toxicity. Blood level monitoring is recommended to decrease the risk of potential toxicity. If levels become too high, diarrhea, vomiting, poor coordination, sleepiness, and ringing in the ears may occur.[2] If used during pregnancy, lithium can cause problems in the baby. It appears to be safe to use while breastfeeding.[1] Lithium salts are classified as mood stabilizers. How lithium works is not specifically known.

Medical uses

Lithium is used primarily for bipolar disorder It is sometimes used when other treatments are not effective in a number of other conditions, including major depression, schizophrenia, disorders of impulse control, and some psychiatric disorders in children. In mood disorders, of which bipolar disorder is one, it decreases the risk of suicide This benefit is not seen with other medications.

Bipolar disorder

Lithium carbonate treatment was previously considered to be unsuitable for children; however, more recent studies show its effectiveness for treatment of early-onset bipolar disorder in children as young as eight. The required dosage is slightly less than the toxic level (representing a low therapeutic index), requiring close monitoring of blood levels of lithium carbonate during treatment. A limited amount of evidence suggests lithium carbonate may contribute to treatment of substance use disorders for some people with bipolar disorder.

Schizophrenic disorders

Lithium is recommended for the treatment of schizophrenic disorders only after other antipsychotics have failed and it has limited effectiveness when used alone. The results of different clinical studies of the efficacy of combining lithium with antipsychotic therapy for treating schizophrenic disorders have varied.

Adverse effects

Hypothyroidism

The rate of hypothyroidism is around six times higher in people who take lithium. Low thyroid hormone levels in turn increase the likelihood of developing depression. People taking lithium thus should routinely be assessed for hypothyroidism and treated with synthetic thyroxine if necessary.[30]

Because lithium competes with the receptors for the antidiuretic hormone in the kidney, it increases water output into the urine, a condition called nephrogenic diabetes insipidus. Clearance of lithium by the kidneys is usually successful with certain diuretic medications, including amiloride and triamterene.[33] It increases the appetite and thirst ("polydypsia") and reduces the activity of thyroid hormone (hypothyroidism).[34][35] The latter can be corrected by treatment with thyroxine and does not require the lithium dose to be adjusted. Lithium is also believed to permanently affect renal function[although this does not appear to be common.

Pregnancy and breast feeding

Lithium is a teratogen, causing birth defects in a small number of newborn babiesCase reports and several retrospective studies have demonstrated possible increases in the rate of a congenital heart defect known as Ebstein's anomaly, if taken during a woman's pregnancy. As a consequence, fetal echocardiography is routinely performed in pregnant women taking lithium to exclude the possibility of cardiac anomalies. Lamotrigine seems to be a possible alternative to lithium in pregnant women for the treatment of acute bipolar depression or for the management of bipolar patients with normal mood[Gabapentin and clonazepamare also indicated as antipanic medications during the childbearing years and during pregnancy. Valproic acid and carbamazepine also tend to be associated with teratogenicity.

While it appears to be safe to use while breastfeeding a number of guidelines list it as a contraindication] including the British National Formulary.

Kidney damage

Lithium has been associated with several forms of kidney injury It is estimated that impaired urinary concentrating ability is present in at least 50% of individuals on chronic lithium therapy, a condition called lithium-induced nephrogenic diabetes insipidus. Continued use of lithium can lead to more serious kidney damage in an aggravated form of diabetes insipidus and chronic kidney failure. Chronic kidney disease is found in about one-third of people undergoing long-term lithium treatment, according to one study. Some forms of lithium-caused kidney damage may be progressive and lead to end-stage kidney failure.

Hyperparathyroidism

Lithium-associated hyperparathyroidism is the leading cause of hypercalcemia in lithium-treated patients. Lithium may lead to exacerbation of pre-existing primary hyperparathyroidism or cause an increased set-point of calcium for parathyroid hormone suppression, leading to parathyroid hyperplasia.

Radiopharmaceuticals

Radiopharmaceuticals, or **medicinal radiocompounds**, are a group of pharmaceutical drugs containing radioactive isotopes. Radiopharmaceuticals can be used as diagnostic and therapeutic agents. Radiopharmaceuticals emit radiation themselves, which is different from contrast media which absorb or alter external electromagnetism or ultrasound. Radiopharmacology is the branch of pharmacology that specializes in these agents.

The main group of these compounds are the radiotracers used to diagnose dysfunction in body tissues. While not all medical isotopes are radioactive, radiopharmaceuticals are the oldest and still most common such drugs.

Specific radiopharmaceuticals

A list of **nuclear medicine radiopharmaceuticals** follows. Some radioisotopes are used in ionic or inert form without attachment to a pharmaceutical; these are also included. There is a section for each radioisotope with a table of radiopharmaceuticals using that radioisotope. The sections are ordered alphabetically by the English name of the radioisotope. Sections for the same element are then ordered by atomic mass number.

Production

Production of a radiopharmaceutical involves two processes:

- The production of the radionuclide on which the pharmaceutical is based.
- The preparation and packaging of the complete radiopharmaceutical.

Radionuclides used in radiopharmaceuticals are mostly radioactive isotopes of elements with atomic numbers less than that of bismuth, that is, they are radioactive isotopes of elements that also have one or more stable isotopes. These may be roughly divided into two classes:

- Those with more neutrons in the nucleus than those required for stability are known as **proton-deficient**, and tend to be most easily produced in a nuclear reactor. The majority of radiopharmaceuticals are based on proton deficient isotopes, with technetium-99m being the most commonly used medical isotope, and therefore nuclear reactors are the prime source of medical radioisotopes.[2]
- Those with fewer neutrons in the nucleus than those required for stability are known as **neutron-deficient**, and tend to be most easily produced using a proton accelerator such as a medical cyclotron.

Drug nomenclature for radiopharmaceuticals

- As with other pharmaceutical drugs, there is standardization of the drug nomenclature for radiopharmaceuticals, although various standards coexist. The International Nonproprietary Name (INN) gives the base drug name, followed by the radioisotope (as mass number, no space, element symbol) in parentheses with no superscript, followed by the ligand (if any). It is common to see square brackets and superscript superimposed onto the INN name, because chemical nomenclature (such as IUPAC nomenclature) uses those. The United States Pharmacopeia (USP) name gives the base drug name, followed by the radioisotope (as element symbol, space, mass number) with no parentheses, no hyphen, and no superscript, followed by the ligand (if any). The USP style is not the INN style, despite their being described as one and the same in some publications (e.g., *AMA*,[4] whose style for radiopharmaceuticals matches the USP style). The United States Pharmacopeial Convention is a sponsor organization of the USAN Council, and the USAN for a given drug is often the same as the USP name.

International Nonproprietary Name (INN)	United States Pharmacopeia (USP)	Comments
technetium (99mTc) sestamibi	technetium Tc 99m sestamibi	
fludeoxyglucose (18F)	fludeoxyglucose F 18	
sodium iodide (125I)	sodium iodide I 125	
indium (111In) altumomab pentetate	indium In 111 altumomab pentetate	

TECHNETIUM

Technetium is a chemical element with the symbol **Tc** and atomic number 43. It is the lightest element whose isotopes are all radioactive; none are stable other than the fully ionized state of ^{97}Tc.[

Physical properties

Technetium is a silvery-gray radioactivemetal with an appearance similar to platinum, commonly obtained as a gray powder. The crystal structure of the pure metal is hexagonal close-packed. Atomic technetium has characteristic emission lines at wavelengths of 363.3 nm, 403.1 nm, 426.2 nm, 429.7 nm, and 485.3 nm.

The metal form is slightly paramagnetic, meaning its magnetic dipoles align with external magnetic fields, but will assume random orientations once the field is removed.] ure, metallic, single-crystal technetium becomes a type-II superconductor at temperatures below 7.46 K Below this temperature, technetium has a very high magnetic penetration depth, greater than any other element except niobium.

Pertechnetate and derivatives

The most prevalent form of technetium that is easily accessible is sodium pertechnetate, $Na[TcO_4]$. The majority of this material is produced by radioactive decay from $[^{99}MoO_4]^{2-}$:

$$[^{99}MoO_4]^{2-} \rightarrow [^{99}TcO_4]^{-} + \gamma$$

Pertechnetate (tetroxidotechnetate) TcO^- behaves analogously to perchlorate, both of which are tetrahedral. Unlike permanganate (MnO^- it is only a weak oxidizing agent.

Related to pertechnetate is heptoxide. This pale-yellow, volatile solid is produced by oxidation of Tc metal and related precursors:

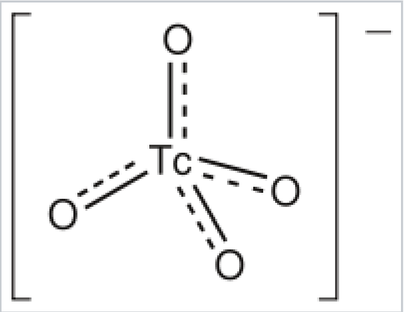
$$4\,Tc + 7\,O_2 \rightarrow 2\,Tc_2O_7$$

It is a very rare example of a molecular metal oxide, other examples being OsO_4 and RuO_4. It adopts a centrosymmetric structure with two types of Tc−O bonds with 167 and 184 pm bond lengths.

Technetium heptoxide hydrolyzes to pertechnetate and pertechnetic acid, depending on the pH:

$$Tc_2O_7 + 2\,OH^- \rightarrow 2\,TcO_4^- + H_2O$$
$$Tc_2O_7 + H_2O \rightarrow 2\,HTcO_4$$

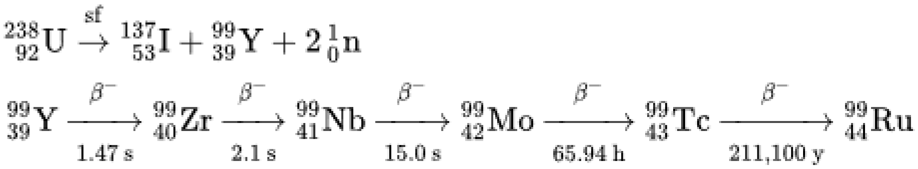
$HTcO_4$ is a strong acid. In concentrated sulfuric acid, $[TcO_4]^-$ converts to the octahedral form $TcO_3(OH)(H_2O)_2$, the conjugate base of the hypothetical triaquo complex $[TcO_3(H_2O)_3]^+$.



Pertechnetate is one of the most available forms of technetium. It is structurally related to permanganate.

Fission product for commercial use

The metastable isotope technetium-99m is continuously produced as a fission product from the fission of uranium or plutonium in nuclear reactors:



$$^{238}_{92}\mathrm{U} \overset{\mathrm{sf}}{\rightarrow} {}^{137}_{53}\mathrm{I} + {}^{99}_{39}\mathrm{Y} + 2\,{}^{1}_{0}\mathrm{n}$$

$$^{99}_{39}\mathrm{Y} \xrightarrow[1.47\,\mathrm{s}]{\beta^-} {}^{99}_{40}\mathrm{Zr} \xrightarrow[2.1\,\mathrm{s}]{\beta^-} {}^{99}_{41}\mathrm{Nb} \xrightarrow[15.0\,\mathrm{s}]{\beta^-} {}^{99}_{42}\mathrm{Mo} \xrightarrow[65.94\,\mathrm{h}]{\beta^-} {}^{99}_{43}\mathrm{Tc} \xrightarrow[211{,}100\,\mathrm{y}]{\beta^-} {}^{99}_{44}\mathrm{Ru}$$

Because used fuel is allowed to stand for several years before reprocessing, all molybdenum-99 and technetium-99m is decayed by the time that the fission products are separated from the major actinides in conventional nuclear reprocessing. The liquid left after plutonium–uranium extraction (PUREX) contains a high concentration of technetium as TcO_4^- but almost all of this is technetium-99, not technetium-99m

The vast majority of the technetium-99m used in medical work is produced by irradiating dedicated highly enriched uranium targets in a reactor, extracting molybdenum-99 from the targets in reprocessing facilities, and recovering at the diagnostic center the technetium-99m produced upon decay of molybdenum-99. Molybdenum-99 in the form of molybdate MoO_4^{2-} is adsorbed onto acid alumina (Al_2O_3) in a shielded column chromatograph inside a technetium-99m generator ("technetium cow", also occasionally called a "molybdenum cow"). Molybdenum-99 has a half-life of 67 hours, so short-lived technetium-99m (half-life: 6 hours), which results from its decay, is being constantly produced. The soluble pertechnetate TcO_4^- can then be chemically extracted by elution using a saline solution. A drawback of this process is that it requires targets containing uranium-235, which are subject to the security precautions of fissile materials.

The first technetium-99m generator, unshielded, 1958. A Tc-99m pertechnetate solution is being eluted from Mo-99 molybdate bound to a chromatographic substrate

Applications

Nuclear medicine and biology

Technetium-99m ("m" indicates that this is a metastable nuclear isomer) is used in radioactive isotope medical tests. For example, Technetium-99m is a radioactive tracer that medical imaging equipment tracks in the human body. It is well suited to the role because it emits readily detectable 140 keV gamma rays, and its half-life is 6.01 hours (meaning that about 94% of it decays to technetium-99 in 24 hours). The chemistry of technetium allows it to be bound to a variety of biochemical compounds, each of which determines how it is metabolized and deposited in the body, and this single isotope can be used for a multitude of diagnostic tests. More than 50 common radiopharmaceuticals are based on technetium-99m for imaging and functional studies of the brain, heart muscle, thyroid, lungs, liver, gall bladder, kidneys, skeleton, blood, and tumors.

The longer-lived isotope, technetium-95m with a half-life of 61 days, is used as a radioactive tracer to study the movement of technetium in the environment and in plant and animal systems.

Industrial and chemical

Technetium-99 decays almost entirely by beta decay, emitting beta particles with consistent low energies and no accompanying gamma rays. Moreover, its long half-life means that this emission decreases very slowly with time. It can also be extracted to a high chemical and isotopic purity from radioactive waste. For these reasons, it is a National Institute of Standards and Technology (NIST) standard beta emitter, and is used for equipment calibration.] Technetium-99 has also been proposed for optoelectronic devices and nanoscale nuclear batteries.

Like rhenium and palladium, technetium can serve as a catalyst. In processes such as the dehydrogenation of isopropyl alcohol, it is a far more effective catalyst than either rhenium or palladium. However, its radioactivity is a major problem in safe catalytic applications.

When steel is immersed in water, adding a small concentration (55 ppm) of potassium pertechnetate(VII) to the water protects the steel from corrosion, even if the temperature is raised to 250 °C (523 K).] For this reason, pertechnetate has been used as an anodic corrosion inhibitor for steel, although technetium's radioactivity poses problems that limit this application to self-contained systems. While (for example) CrO_4^{2-} can also inhibit corrosion, it requires a concentration ten times as high. In one experiment, a specimen of carbon steel was kept in an aqueous solution of pertechnetate for 20 years and was still uncorroded. The mechanism by which pertechnetate prevents corrosion is not well understood, but seems to involve the reversible formation of a thin surface layer (passivation). One theory holds that the pertechnetate reacts with the steel surface to form a layer of technetium dioxide which prevents further corrosion; the same effect explains how iron powder can be used to remove pertechnetate from water. The effect disappears rapidly if the concentration of pertechnetate falls below the minimum concentration or if too high a concentration of other ions is added.

As noted, the radioactive nature of technetium (3 MBq/L at the concentrations required) makes this corrosion protection impractical in almost all situations. Nevertheless, corrosion protection by pertechnetate ions was proposed (but never adopted) for use in boiling water reactors.

UNIT IV: ORGANOMETALLICS

18 Electron Rules

Jump to search

The 18-electron rule is a rule used primarily for predicting and rationalizing formulas for stable metal complexes, especially organometallic compounds. The rule is based on the fact that the valence shells of transition metals consist of nine valence orbitals (one s orbital, three p orbitals and five d orbitals), which collectively can accommodate 18 electrons as either bonding or nonbonding electron pairs. This means that the combination of these nine atomic orbitals with ligand orbitals creates nine molecular orbitals that are either metal-ligand bonding or non-bonding. When a metal complex has 18 valence electrons, it is said to have achieved the same electron configuration as the noble gas in the period. The rule and its exceptions are similar to the application of the octet rule to main group elements. The rule is not helpful for complexes of metals that are not transition metals, and *interesting or useful transition metal complexes will violate the rule* because of the consequences deviating from the rule bears on reactivity.

Applicability

The rule usefully predicts the formulas for low-spin complexes of the Cr, Mn, Fe, and Co triads. Well-known examples include ferrocene, iron pentacarbonyl, chromium carbonyl, and nickel carbonyl.

Ligands in a complex determine the applicability of the 18-electron rule. In general, complexes that obey the rule are composed at least partly of π-acceptor ligands (also known as π-acids). This kind of ligand exerts a very strong ligand field, which lowers the energies of the resultant molecular orbitals so that they are favorably occupied. Typical ligands include olefins, phosphines, and CO. Complexes of π-acids typically feature metal in a low-oxidation state. The relationship between oxidation state and the nature of the ligands is rationalized within the framework of π backbonding.

Consequences for reactivity

Compounds that obey the 18-electron rule are typically "exchange inert". Examples include $[Co(NH_3)_6]Cl_3$, $Mo(CO)_6$, and $[Fe(CN)_6]^{4-}$. In such cases, in general ligand exchange occurs via dissociative substitution mechanisms, wherein the rate of reaction is determined by the rate of dissociation of a ligand. On the other hand, 18-electron compounds can be highly reactive toward electrophiles such as protons, and such reactions are associative in mechanism, being acid-base reactions.

Complexes with fewer than 18 valence electrons tend to show enhanced reactivity. Thus, the 18-electron rule is often a recipe for non-reactivity in either a stoichiometric or a catalytic sense.

Duodectet rule

Current computational findings suggest valence p-orbitals on the metal participate in metal-ligand bonding, albeit weakly.[3] Some new theoretical treatments do not count the metal p-orbitals in metal-ligand bonding,[4] although these orbitals are still included as polarization functions. This results in a duodectet (12-electron) rule for one s-orbital and five d-orbitals only, but the modified rule has yet to be adopted by the general chemistry community.

Exceptions

π-donor or σ-donor ligands with small interactions with the metal orbitals lead to a weak ligand field which increases the energies of t_{2g} orbitals. These molecular orbitals become non-bonding or weakly anti-bonding orbitals (small Δ_{oct}). Therefore, addition or removal of electron has little effect on complex stability. In this case, there is no restriction on the number of d-electrons and complexes with 12–22 electrons are possible. Small Δ_{oct} makes filling e_g* possible (>18 e^-) and π-donor ligands can make t_{2g} antibonding (<18 e^-). These types of ligand are located in the low-to-medium part of the spectrochemical series. For example: $[TiF_6]^{2-}$ (Ti(IV), d^0, 12 e^-), $[Co(NH_3)_6]^{3+}$ (Co(III), d^6, 18 e^-), $[Cu(OH_2)_6]^{2+}$ (Cu(II), d^9, 21 e^-).

In terms of metal ions, Δ_{oct} increases down a group as well as with increasing oxidation number. Strong ligand fields lead to low-spin complexes which cause some exceptions to the 18-electron rule.

Bulky ligands

Bulky ligands can preclude the approach of the full complement of ligands that would allow the metal to achieve the 18 electron configuration. Examples:

- $Ti(neopentyl)_4$ (8 e^-)
- $Cp^*_2Ti(C_2H_4)$ (16 e^-)
- $V(CO)_6$ (17 e^-)
- $Cp^*Cr(CO)_3$ (17 e^-)
- $Pt(P^tBu3)_2$ (14 e^-)
- $Co(norbornyl)_4$ (13 e^-)
- $[FeCp_2]^+$ (17 e^-)

Sometimes such complexes engage in agostic interactions with the hydrocarbon framework of the bulky ligand. For example:

- $W(CO)_3[P(C_6H_{11})_3]_2$ has 16 e^- but has a short bonding contact between one C–H bond and the W center.
- $Cp(PMe_3)V(CHCMe_3)$ (14 e^-, diamagnetic) has a short V–H bond with the 'alkylidene-H', so the description of the compound is somewhere between $Cp(PMe_3)V(CHCMe_3)$ and $Cp(PMe_3)V(H)(CCMe_3)$.

High-spin complexes

High-spin metal complexes have singly occupied orbitals and may not have any empty orbitals into which ligands could donate electron density. In general, there are few or no π-acidic ligands in the complex. These singly occupied orbitals can combine with the singly occupied orbitals of radical ligands (e.g., oxygen), or addition of a strong field ligand can cause electron-pairing, thus creating a vacant orbital that it can donate into. Examples:

- $CrCl_3(THF)_3$ (15 e^-)
- $[Mn(H_2O)_6]^{2+}$ (17 e^-)
- $[Cu(H_2O)_6]^{2+}$ (21 e^-, see comments below)

Complexes containing strongly π-donating ligands often violate the 18-electron rule. These ligands include fluoride (F^-), oxide (O^{2-}), nitride (N^{3-}), alkoxides (RO^-), and imides (RN^{2-}). Examples:

- $[CrO_4]^{2-}$ (16 e^-)
- $Mo(=NR)_2Cl_2$ (12 e^-)

In the latter case, there is substantial donation of the nitrogen lone pairs to the Mo (so the compound could also be described as a 16 e^- compound). This can be seen from the short Mo–N bond length, and from the angle Mo–N–C(R), which is nearly 180°. Counter-examples:

- *trans*-$WO_2(Me_2PCH_2CH_2PMe_2)_2$ (18 e^-)
- Cp^*ReO_3 (18 e^-)

In these cases, the M=O bonds are "pure" double bonds (i.e., no donation of the lone pairs of the oxygen to the metal), as reflected in the relatively long bond distances.

π-donating ligands

Ligands where the coordinating atom bear nonbonding lone pairs often stabilize unsaturated complexes. Metal amides and alkoxides often violate the 18e rule.

Combinations of effect

The above factors can sometimes combine. Examples include

- Cp^*VOCl_2 (14 e^-)
- $TiCl_4$ (8 e^-)

Higher electron counts

Some complexes have more than 18 electrons. Examples:

- Cobaltocene (19 e^-)
- Nickelocene (20 e^-)

- The hexaaquacopper(II) ion $[Cu(H_2O)_6]^{2+}$ (21 e^-)
- *TM*$(CO)_8^-$ (*TM* = Sc, Y, La) (20 e^-)

Often, cases where complexes have more than 18 valence electrons are attributed to electrostatic forces – the metal attracts ligands to itself to try to counterbalance its positive charge, and the number of electrons it ends up with is unimportant. In the case of the metallocenes, the chelating nature of the cyclopentadienyl ligand stabilizes its bonding to the metal. Somewhat satisfying are the two following observations: cobaltocene is a strong electron donor, readily forming the 18-electron cobaltocenium cation; and nickelocene tends to react with substrates to give 18-electron complexes, e.g. $CpNiCl(PR_3)$ and free CpH.

In the case of nickelocene, the extra two electrons are in orbitals which are weakly metal-carbon antibonding; this is why it often participates in reactions where the M–C bonds are broken and the electron count of the metal changes to 18

The 20-electron systems $TM(CO)_8^-$ (TM = Sc, Y, La) have a cubic (O_h) equilibrium geometry and a singlet ($^1A_{1g}$) electronic ground state. There is one occupied valence MO with a_{2u} symmetry, which is formed only by ligand orbitals without a contribution from the metal AOs. But the adducts $TM(CO)_8^-$ (TM=Sc, Y, La) fulfill the 18-electron rule when one considers only those valence electrons, which occupy metal–ligand bonding orbitals

Isolobal concept

The isolobal principle (also known **as isolobal analogy**) is way to predict bonding properties of organometallic compounds. In organometallic chemistry, it relates the structure of organic ligands that can bind to inorganic molecular fragments. Roald Hoffmann described molecular fragments as isolobal "if the number, symmetry properties, approximate energy and shape of the frontier orbitals and the number of electrons in them are similar – not identical, but similar One can predict the bonding and reactivity of a lesser-known pieces from that of a better-known pieces if the two molecular fragments have similar frontier orbitals, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Isolobal compounds are analogs to isoelectronic compounds that share the same number of valence electrons and structure. A graphic representation of isolobal structures, with the isolobal pairs connected through a double-headed arrow with half an orbital below, is found in Figure 1.

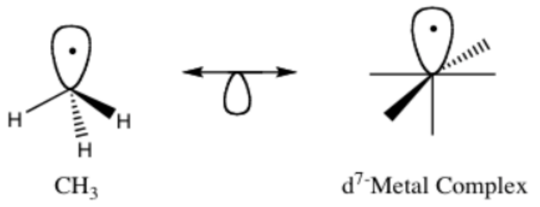
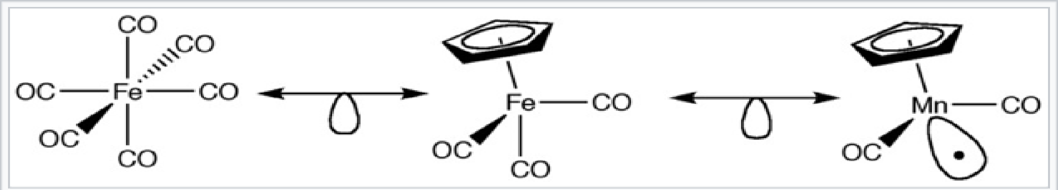


Figure 1: Basic example of the isolobal analogy.

Ligands

Typical ligands used in the isolobal analogy are two-electron donors such as phosphines, halogens or carbonyls. However, other types of ligands can be employed. If ligands donate multiple pairs of electrons, they will occupy multiple coordination sites. For example, the cyclopentadienyl anion is a six-electron donor, so it occupies three coordination sites. Polydentate ligands can also be used in the analogy, such as ethylenediamine, a bidentate ligand, or triethylenetetramine, a tetradentate ligand.



Isoelectronic fragments

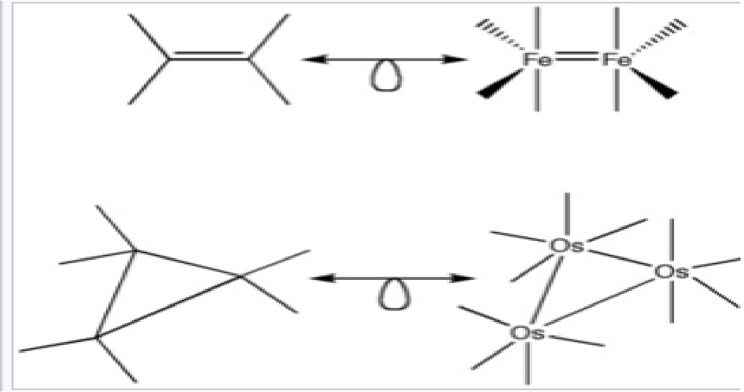
The isolobal analogy can also be used with isoelectronic fragments having the same coordination number, which allows charged species to be considered. For example, $Re(CO)_5$ is isolobal with CH_3 and therefore, $[Ru(CO)_5]^+$ and $[Mo(CO)_5]^-$ are also isolobal with CH_3. Any 17-electron metal complex would be isolobal in this example.

In a similar sense, the addition or removal of electrons from two isolobal fragments results in two new isolobal fragments. Since $Re(CO)_5$ is isolobal with CH_3, $[Re(CO)_5]^+$ is isolobal with CH^+

Non-octahedral complexes

The analogy applies to other shapes besides tetrahedral and octahedral geometries. The derivations used in octahedral geometry are valid for most other geometries. The exception is square-planar because square-planar complexes typically abide by the 16-electron rule. Assuming ligands act as two-electron donors the metal center in square-planar molecules is d^8. To relate an octahedral fragment, ML_n, where M has a d^x electron configuration to a square planar analogous fragment, the formula ML_{n-2} where M has a d^{x+2} electron configuration should be followed.

Further examples of the isolobal analogy in various shapes and forms are shown in Fig



Applications and examples

Uses of the isolobal analogy include providing a shortcut to understanding electronic structure, predicting reactivity and reaction mechanisms, and a method of classifying molecules. Applications are typically utilized to make connections between well-known systems and less familiar systems. For example, the possibility of unsynthesized compounds can be imagined from those of known molecular conformations. The isolobal analogy does not guarantee these products are capable of being produced, but only proposes a possibility. Consider the molecule $Fe(CO)_3$ complexed with cyclobutadiene.$Fe(CO)_3$ is isolobal with CH^+. Therefore, one can predict that CH^+ will coordinate with cyclobutadiene in a similar fashion that $Fe(CO)_3$ will. Thus the molecule $C_5H^+_5$ can be envisioned regardless of its actual existence.

Predicting the reactivity of complexes can also be accomplished using the isolobal analogy. From the simple expectation of two CH_3 radicals reacting to form ethane one can use the analogy to predict M–C or M–M bonding such as $(CH_3)M(CO)_5$ and $M_2(CO)_{10}$, where M is d^7.

Another application of the isolobal analogy is assisting in predicting reaction mechanisms. As in the other applications the mechanisms of well-known reactions can be used to help predict mechanistic pathways of lesser-known reactions. There is no limit on the potential comparisons between organic and inorganic complexes. The analogy can flow in either direction (organic to inorganic) or within each division (organic to organic).

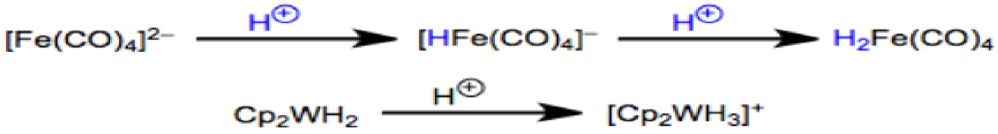
Arteaga Müller et al. utilize the isolobal analogy to relate imido half-sandwich complexes with isoelectronic dicyclopentadienyl complexes. The isolobal relationship of the imido and the cyclopentadienyl ligands is the key to this comparison. The study found the reactivity of these two types of complexes to be similar although their catalytic abilities differed in some respects. This study shows that the isolobal analogy does not make perfect predictions between two isolobal fragments, as Hoffman warned in his Nobel Lecture.

ORGANOMETALLIC HYDRIDES IN ORGANIC SYNTHESIS

Synthesis

Here we'll discuss four ways to make hydrides: metal protonation, oxidative addition of H2, addition of nucleophilic main-group hydrides (borohydrides, aluminum hydrides, and silanes), and β-hydride elimination.

Just as in organic chemistry, the basicity of an organometallic complex is inversely related to the acidity of its conjugate base. Furthermore, charges have a predictable effect on the basicity of organometallic complexes: negatively charged complexes lacking π-acidic ligands are highly basic. Even neutral complexes containing strong donor ligands, like the tungsten complex below, can be protonated effectively. Notice that protonation is actually a kind of oxidative addition—the oxidation state of Fe in the first reaction below goes from -2 to 0 to +2! All coordination events of isolated electrophiles can also be viewed in this light. Reactions of this type are sometimes called **oxidative ligations** to distinguish them from oxidative addition reactions, which involve the addition of two ligands to the metal center with oxidation.

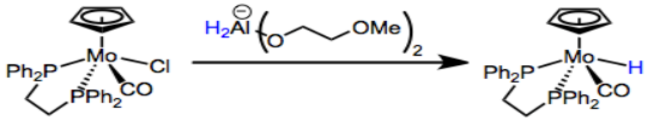


Metal protonation reactions involve the metal center as a base.

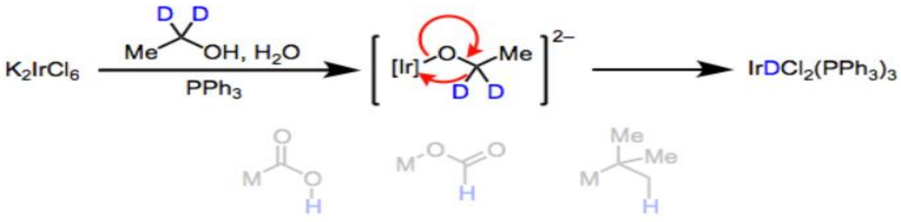
Contrast oxidative ligation with the **oxidative addition** of dihydrogen (H2), a second method for the synthesis of hydride complexes. A key requirement here is that the starting metal center is at least d2—two electrons are formally lost from the metal center, and metals can't possess a negative number of d electrons. An open coordination site on the starting material must also be present (or possible through ligand dissociation). The reaction below is a standard example of the addition of H2 to Vaska's complex, but there are some funky variations on this theme. These riffs include third-order homolytic cleavage of H2 by two metal radicals, and oxidative addition followed by deprotonation by the starting complex (apparent heterolytic cleavage).

Oxidative addition of dihydrogen for the synthesis of metal hydrides.

Main-group hydrides like borohydrides and aluminum hydrides are great sources of H– for organometallic complexes. These reactions seem more natural than metal protonations, since we often think of metals as electropositive or electrophilic species. Indeed, the combination of main-group sources of nucleophilic hydride with complexes containing metal–leaving group bonds is a very general method for the synthesis of metal hydride complexes. Check out the reaction below—what's the most likely mechanism? Is associative or dissocative substitution more likely? Hint: count electrons!



β-hydride elimination forms metal hydride complexes and double bonds within organic ligands. Alkoxide ligands are commonly used for this purpose—elimination to form the hydride complex and aldehyde is more favorable than the reverse, migratory insertion of C=O into the M–H bond. Since the unsaturated byproduct is thrown away, it's desirable to make it something small, cheap, and gaseous. Hydroxycarbonyl, formate, and tert-butyl ligands have been applied successfully with this goal in mind…what are the byproducts?



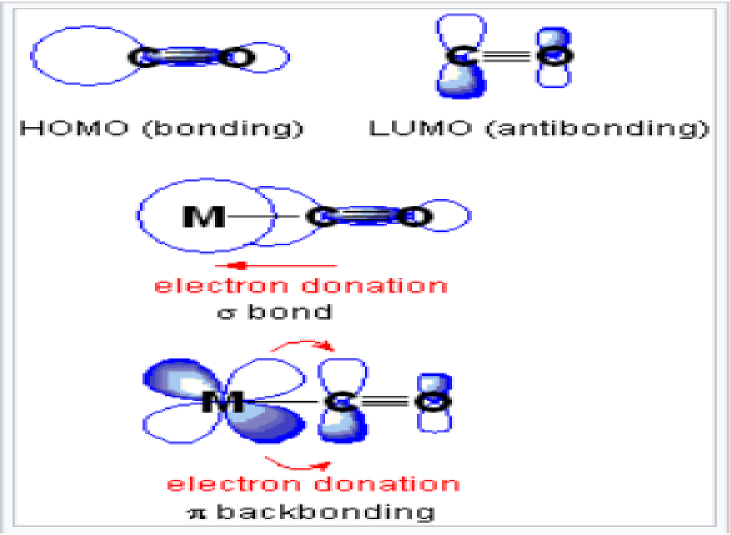
Beta-hydride elimination for the synthesis of metal hydrides.

NITROSYL COMPOUNDS

Metal nitrosyl complexes are complexes that contain nitric oxide, NO, bonded to a transition metal. Many kinds of nitrosyl complexes are known, which vary both in structure and coligand

Bonding and structure

Most complexes containing the NO ligand can be viewed as derivatives of the nitrosyl cation, NO^+. The nitrosyl cation is isoelectronic with carbon monoxide, thus the bonding between a nitrosyl ligand and a metal follows the same principles as the bonding in carbonyl complexes. The nitrosyl cation serves as a two-electron donor to the metal and accepts electrons from the metal via back-bonding. The compounds $Co(NO)(CO)_3$ and $Ni(CO)_4$ illustrate the analogy between NO^+ and CO. In an electron-counting sense, two linear NO ligands are equivalent to three CO groups. This trend is illustrated by the isoelectronic pair $Fe(CO)_2(NO)_2$ and $[Ni(CO)_4]$. These complexes are isoelectronic and, incidentally, both obey the 18-electron rule. The formal description of nitric oxide as NO^+ does not match certain measureable and calculated properties. In an alternative description, nitric oxide serves as a 3-electron donor, and the metal-nitrogen interaction is a triple bond.

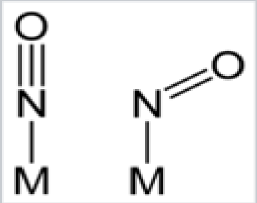


Linear vs bent nitrosyl ligands

The M-N-O unit in nitrosyl complexes is usually linear, or no more than 15° from linear. In some complexes, however, especially when back-bonding is less important, the M-N-O angle can strongly deviate from 180°. Linear and bent NO ligands can be distinguished using infrared spectroscopy. Linear M-N-O groups absorb in the range 1650–1900 cm^{-1}, whereas bent nitrosyls absorb in the range 1525–1690 cm^{-1}. The differing vibrational frequencies reflect the differing N-O bond orders for linear (triple bond) and bent NO (double bond).

The bent NO ligand is sometimes described as the anion, NO^{-}. Prototypes for such compounds are the organic nitroso compounds, such as nitrosobenzene. A complex with a bent NO ligand is *trans*-$[Co(en)_2(NO)Cl]^{+}$.

The adoption of linear vs bent bonding can be analyzed with the Enemark-Feltham notation. In their framework, the factor that determines the bent vs linear NO ligands is the sum of electrons of pi-symmetry. Complexes with "pi-electrons" in excess of 6 tend to have bent NO ligands. Thus, $[Co(en)_2(NO)Cl]^{+}$, with seven electrons of pi-symmetry (six in t_{2g} orbitals and one on NO), adopts a bent NO ligand, whereas $[Fe(CN)_5(NO)]^{3-}$, with six electrons of pi-symmetry, adopts a linear nitrosyl. In a further illustration, the {MNO} d-electron count of the $[Cr(CN)_5NO]^{3-}$ anion is shown. In this example, the cyanide ligands are "innocent", i.e., they have a charge of −1 each, −5 total. To balance the fragment's overall charge, the charge on {CrNO} is thus +2 (−3 = −5 + 2). Using the neutral electron counting scheme, Cr has 6 d electrons and NO· has one electron for a total of 7. Two electrons are subtracted to take into account that fragment's overall charge of +2, to give 5. Written in the Enemark-Feltham notation, the d electron count is $\{CrNO\}^{5}$. The results are the same if the nitrosyl ligand were considered NO^{+} or NO^{-}.



linear and bent M-NO bonds

Bridging nitrosyl ligands

Nitric oxide can also serve as a bridging ligand. In the compound $[Mn_3(\eta^5C_5H_5)_3$ $(\mu_2\text{-}NO)_3$ $(\mu_3\text{-}NO)]$, three NO groups bridge two metal centres and one NO group bridge to all three.

Preparation

Nitrosyl complexes are typically prepared by treating reduced metal complexes with nitric oxide. The nitrosylation of cobalt carbonyl is illustrative:

$Co_2(CO)_8 + 2\ NO \rightarrow 2\ CoNO(CO)_3 + 2\ CO$

From nitrosonium sources

Replacement of ligands by the nitrosyl cation may be accomplished using nitrosyl tetrafluoroborate, $[NO]BF_4$. When applied to the hexacarbonyls of molybdenum and tungsten, the NO binds to the metal:

$M(CO)_6 + 4\ MeCN + 2\ NOBF_4 \rightarrow [M(NO)_2(MeCN)_4](BF_4)_2$

Nitrosyl chloride and molybdenum hexacarbonyl react to give $[Mo(NO)_2Cl_2]_n$.[8] Diazald is also used as an NO source.

Other methods

Other indirect methods are indirect with the NO group deriving from some other species, often accompanied by oxidation and reduction reactions. A classic example is provided by the brown ring test in which the nitrate ion is the source of a nitric oxide ligand.

Reactions

An important reaction is the acid/base equilibrium:

$[L_nMNO]^{2+} + 2OH^- \rightleftharpoons L_nMNO_2 + H_2O$

This equilibrium serves to confirm that the linear nitrosyl ligand is, formally, NO^+, with nitrogen in the oxidation state +3

$NO^+ + 2\ OH^- \rightleftharpoons NO_2^- + H_2O$

Since nitrogen is more electronegative than carbon, metal-nitrosyl complexes tend to be more electrophilic than related metal carbonyl complexes. Nucleophiles often add to the nitrogen.[1] The nitrogen atom in bent metal nitrosyls is basic, thus can be oxidized, alkylated, and protonated, e.g.:

$(Ph_3P)_2(CO)ClOsNO + HCl \rightarrow (Ph_3P)_2(CO)ClOsN(H)O$

In rare cases, NO is cleaved by metal centers:

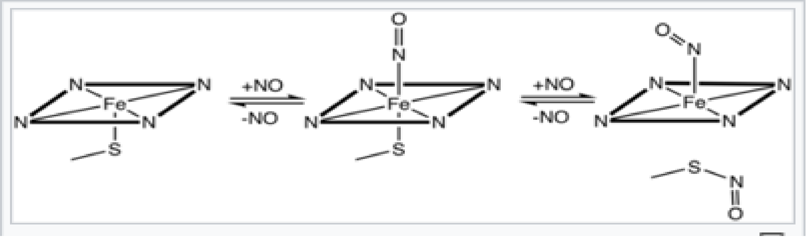
$Cp_2NbMe_2 + NO \rightarrow Cp_2(Me)Nb(O)NMe$

$2\ Cp_2(Me)Nb(O)NMe \rightarrow 2\ Cp_2Nb(O)Me + ½MeN{=}NMe$

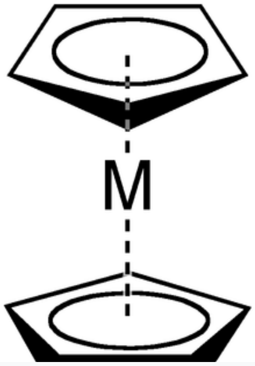
Applications

Metal-nitrosyls are assumed to be intermediates in catalytic converters, which reduce the emission of NOx from internal combustion engines. This application has been described as “one of the most successful stories in the development of catalysts.

Metal-catalyzed reactions of NO are not often useful in organic chemistry. In biology and medicine, nitric oxide is however an important signalling molecule in nature and this fact is the basis of the most important applications of metal nitrosyls. The nitroprusside anion, $[Fe(CN)_5NO]^{2-}$, a mixed nitrosyl cyano complex, has pharmaceutical applications as a slow release agent for NO. The signalling function of NO is effected via its complexation to haeme proteins, where it binds in the bent geometry. Nitric oxide also attacks iron-sulfur proteins giving dinitrosyl iron complexes.



Metallocene



General chemical structure of a metallocene compound, where M is a metal cation

A metallocene is a compound typically consisting of two cyclopentadienyl anions ($C_5H^-_5$, abbreviated Cp) bound to a metal center (M) in the oxidation state II, with the resulting general formula $(C_5H_5)_2M$. Closely related to the metallocenes are the metallocene derivatives, e.g. titanocene dichloride, vanadocene dichloride. Certain metallocenes and their derivatives exhibit catalytic properties, although metallocenes are rarely used industrially. Cationic group 4 metallocene derivatives related to $[Cp_2ZrCH_3]^+$ catalyze olefin polymerization.

Classification

here are many (η^5-C_5H_5)–metal complexes and they can be classified by the following formulas:

Formula	Description
$[(\eta^5\text{-}C_5H_5)_2M]$	Symmetrical, classical 'sandwich' structure
$[(\eta^5\text{-}C_5H_5)_2ML_x]$	Bent or tilted Cp rings with additional ligands, L
$[(\eta^5\text{-}C_5H_5)ML_x]$	Only one Cp ligand with additional ligands, L ('piano-stool' structure)

Metallocene complexes can also be classified by type:

1. Parallel
2. Multi-decker
3. Half-sandwich compound
4. Bent metallocene or tilted
5. More than two Cp ligands

Synthesis

Using a metal salt and cyclopentadienyl reagents

Sodium cyclopentadienide (NaCp) is the preferred reagent for these types of reactions. It is most easily obtained by the reaction of molten sodium and dicyclopentadiene. Traditionally, the starting point is the cracking of dicyclopentadienyl, the dimer of cyclopentadiene. Cyclopentadiene is deprotonated by strong bases or alkali metals.

$MCl_2 + 2\ NaC_5H_5 \rightarrow (C_5H_5)_2M + 2\ NaCl$ (M = V, Cr, Mn, Fe, Co; solvent = THF, DME, NH_3)

$CrCl_3 + 3\ NaC_5H_5 \rightarrow [(C_5H_5)_2Cr] + \frac{1}{2}\ "C_{10}H_{10}" + 3\ NaCl$

NaCp acts as a reducing agent and a ligand in this reaction.

Using a metal and cyclopentadiene

This technique provides using metal atoms in the gas phase rather than the solid metal. The highly reactive atoms or molecules are generated at a high temperature under vacuum and brought together with chosen reactants on a cold surface.

$M + C_5H_6 \rightarrow MC_5H_5 + \frac{1}{2} H_2$ (M = Li, Na, K)
$M + 2\ C_5H_6 \rightarrow [(C_5H_5)_2M] + H_2$ (M = Mg, Fe

Structure

A structural trend for the series MCp_2 involves the variation of the M-C bonds, which elongate as the valence electron count deviates from 18.

$M(C_5H_5)_2$	$r_{M–C}$ (pm)	Valence electron count
Fe	203.3	18
Co	209.6	19
Cr	215.1	16
Ni	218.5	20
V	226	15

In metallocenes of the type $(C_5R_5)_2M$, the cyclopentadienyl rings rotate with very low barriers. Single crystal X-ray diffraction studies reveal both eclipsed or staggered rotamers. For non-substituted metallocenes the energy difference between the staggered and eclipsed conformations is only a few kJ/mol. Crystals of ferrocene and osmocene exhibit eclipsed conformations at low temperatures, whereas in the related bis(pentamethylcyclopentadienyl) complexes the rings usually crystallize in a staggered conformation, apparently to minimize steric hindrance between the methyl groups.

Applications

Many derivatives of early metal metallocenes are active catalysts for olefin polymerization. Unlike traditional and still dominant heterogeneous Ziegler–Natta catalysts, metallocene catalysts are homogeneous. Early metal metallocene derivatives, e.g. Tebbe's reagent, Petasis reagent, and Schwartz's reagent are useful in specialized organic synthetic operations.

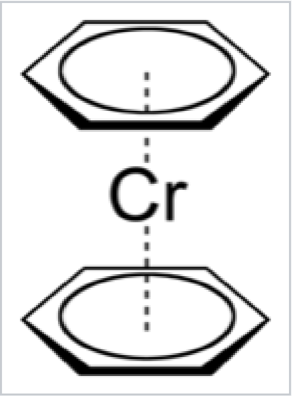
Potential application

The ferrocene/ferrocenium biosensor has been discussed for determining the levels of glucose in a sample electrochemically through a series of connected redox cycles.

Metallocene dihalides [Cp_2MX_2] (M = Ti, Mo, Nb) exhibit anti-tumor properties, although none have proceeded far in clinical trials

arene complex

Metal arene complexes are organometallic compounds of the formula $(C_6R_6)_xML_y$. Common classes of are of the type $(C_6R_6)ML_3$ and $(C_6R_6)_2M$. These compounds are reagents in inorganic and organic synthesis. The principles that describe arene complexes extend to related organic ligands such as many heterocycles (e.g. thiophene) and polycyclic aromatic compounds (e.g. naphthalene).



Structure of $Cr(\eta^6\text{-}C_6H_6)_2$.

Direct synthesis

By metal vapor synthesis, metal atoms co-condensed with arenes react to give complexes of the type M(arene)$_2$. $Cr(C_6H_6)_2$ can be produced by this method.

$Cr(CO)_6$ reacts directly with benzene and other arenes to give the piano stool complexes $Cr(C_6R_6)(CO)_3$. The carbonyls of Mo and W behave comparably. The method works particularly well with electron-rich arenes (e.g., anisole, mesitylene). The reaction has been extended to the synthesis of $[Mn(C_6R_6)(CO)_3]^+$:

$$BrMn(CO)_5 + Ag^+ + C_6R_6 \rightarrow [Mn(C_6R_6)(CO)_3]^+ + AgBr + 2\ CO$$

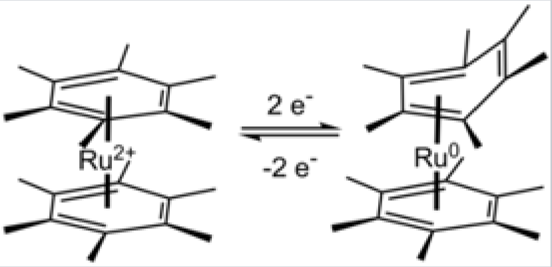
Structure

In most of its complexes, arenes bind in an η^6 mode, with six nearly equidistant M-C bonds. The C-C-C angles are unperturbed vs the parent arene, but the C-C bonds are elongated by 0.2 Å. In some complexes, the arene binds through four carbons (η^4 bonding), in which case the arene is no longer planar. A well studied example is $[Ru(\eta^6\text{-}C_6Me_6)(\eta^4\text{-}C_6Me_6)]^0$, formed by the reduction of $[Ru(\eta^6\text{-}C_6Me_6)_2]^{2+}$.

In the fullerene complex $Ru_3(CO)_9(C_{60})$, the fullerene binds to the triangular face of the cluster.

Reactivity

When bound in the η^6 manner, arenes often function as unreactive spectator ligands, as illustrated by several homogeneous catalysts used for transfer hydrogenation, such as $(\eta^6\text{-}C_6R_6)Ru(TsDPEN)$. In cationic arene complexes or those supported by several CO ligands, the arene is susceptible to attack by nucleophiles to give cyclohexadienyl derivatives.



Hapticity change for bis(hexamethylbenzene)ruthenium.

Particularly from the perspective of organic synthesis, the decomplexation of arenes is of interest. Decomplexation can often be induced by treatment with excess of ligand (MeCN, CO, etc).

Metal carbene

A transition metal carbene complex is an organometallic compound featuring a divalent organic ligand. The divalent organic ligand coordinated to the metal center is called a carbene. Carbene complexes for almost all transition metals have been reported. Many methods for synthesizing them and reactions utilizing them have been reported. The term carbene ligand is a formalism since many are not derived from carbenes and almost none exhibit the reactivity characteristic of carbenes. Described often as $M{=}CR_2$, they represent a class of organic ligands intermediate between alkyls ($-CR_3$) and carbynes ($\equiv CR$). They feature in some catalytic reactions, especially alkene metathesis, and are of value in the preparation of some fine chemicals.

Classification

Metal carbene complexes are often classified into two types. The Fischer carbenes named after Ernst Otto Fischer feature strong π-acceptors at the metal and being electrophilic at the carbene carbon atom. Schrock carbenes, named after Richard R. Schrock, are characterized by more nucleophilic carbene carbon centers, these species typically feature higher valent metals. *N*-Heterocyclic carbenes (NHCs) were popularlized following Arduengo's isolation of a stable free carbene in 1991. Reflecting the growth of the area, carbene complexes are now known with a broad range of different reactivities and diverse substituents. Often it is not possible to classify a carbene complex with regards to its electrophilicity or nucleophilicity.

Fischer carbenes

Fischer carbenes are found with:

- low oxidation state metal center
- middle and late transition metals Fe(0), Mo(0), Cr(0)
- π-acceptor metal ligands
- π-donor substituents on the carbene atom such as alkoxy and alkylated amino groups.

The chemical bonding (*Scheme 1*) is based on σ-type electron donation of the filled lone pair orbital of the carbene atom to an empty metal d-orbital, and π back bonding of a filled metal d-orbital to the empty p-orbital on carbon. An example is the complex $(CO)_5Cr=C(NR_2)Ph$.

Fischer carbenes can be likened to ketones, with the carbene carbon being electrophilic, much like the carbonyl carbon of a ketone. Like ketones, Fischer carbene species can undergo aldol-like reactions. The hydrogen atoms attached to the carbon α to the carbene carbon are acidic, and can be deprotonated by a base such as *n*-butyllithium, to give a nucleophile which can undergo further reaction.

This carbene is the starting material for other reactions such as the Wulff-Dötz reaction.

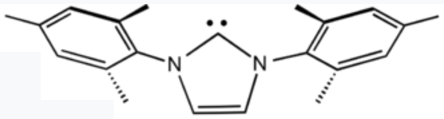
Schrock carbenes

Schrock carbenes do not have π-accepting ligands. These complexes are nucleophilic at the carbene carbon atom. Schrock carbenes are typically found with:

- high oxidation state metal center
- early transition metals Ti(IV), Ta(V)
- π-donor ligands
- hydrogen and alkyl substituents on carbenoid carbon.

Bonding in such complexes can be viewed as the coupling of a triplet state metal and triplet carbene. These bonds are polarized towards carbon and therefore the carbene atom is a nucleophile. An example of a Schrock carbene is the compound $Ta(=C(H)Bu^t)(CH_2Bu^t)_3$, with a tantalum(V) center doubly bonded to a neopentylidene ligand as well as three neopentyl ligands. An example of interest in organic synthesis is Tebbe's reagent.

N-Heterocyclic carbenes



IMes is a common NHC ligand.

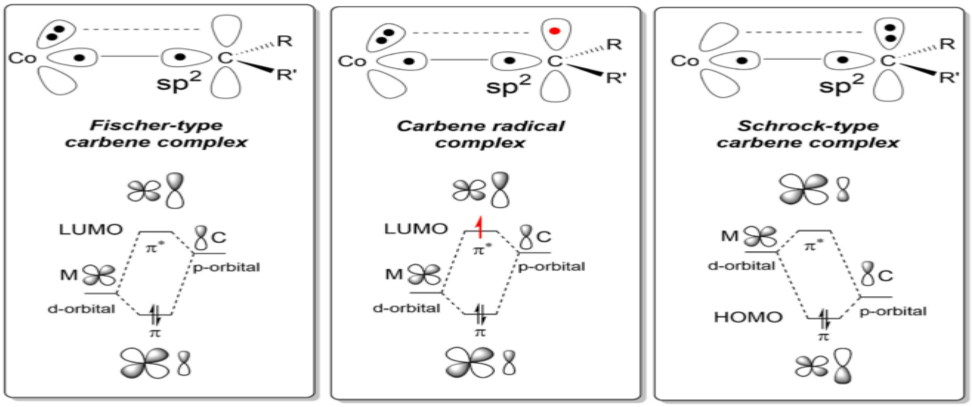
N-Heterocyclic carbenes (NHCs) are particularly common carbene ligands. They are popular because they are more readily prepared than Schrock and Fischer carbenes. In fact many NHCs are isolated as the free ligand, since they are persistent carbenes. Being strongly stabilized by π-donating substituents, NHCs are powerful σ-donors but π-bonding with the metal is weak. For this reason, the bond between the carbon and the metal center is often represented by a single dative bond, whereas Fischer and Schrock carbenes are usually depicted with double bonds to metal. Continuing with this analogy, NHCs are often compared with trialkylphosphine ligands. Like phosphines, NHCs serve as spectator ligands that influence catalysis through a combination of electronic and steric effects, but they do not directly bind substrates. Carbenes without a metal ligand have been produced in the lab.

Carbene radicals

Carbene radicals are long-lived reaction intermediates found with:

low oxidation state metal center with singly occupied dz2 orbital

- middle and late transition metal, e.g. Co(II)
- σ-donor and π-acceptor ligand
- π-acceptor substituents on the ligand such as carbonyl or sulfonyl groups. The chemical bond present in carbene radicals is described as aspects of both Fischer and Schrock carbenes.



Applications of carbene complexes

The main applications of metal carbenes involves none of the above classes of compounds, but rather heterogeneous catalysts used for alkene metathesis in the Shell higher olefin process. A variety of related reactions are used to interconvert light alkenes, e.g. butenes, propylene, and ethylene. Carbene-complexes are invoked as intermediates in the Fischer–Tropsch route to hydrocarbons. A variety of soluble carbene reagents, especially the Grubbs' and molybdenum-imido catalysts have been applied to laboratory-scale synthesis of natural products and materials science. In the nucleophilic abstraction reaction, a methyl group can be abstracted from a Fischer carbene for further reaction.

Diazo compounds like methyl phenyldiazoacetate can be used for cyclopropanation or to insert into C-H bonds of organic substrates. These reactions are catalyzed by dirhodium tetraacetate or related chiral derivatives. Such catalysis is assumed to proceed via the intermediacy of carbene complexes.

carboxylate anion

A carboxylate is the conjugate base of a carboxylic acid. Carboxylate salts have the general formula $M(RCOO)_n$, where M is a metal and n is 1, 2,...; carboxylate esters have the general formula RCOOR′ (or RCO_2R'). R and R′ are organic groups; R′ ≠ H.

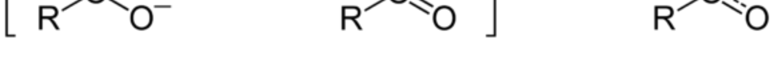
Synthesis

A carboxylate can be easily made by deprotonation of carboxylic acids. Most of them have a pK_a of approximately 5, which means that they can be deprotonated by many bases, such as sodium hydroxide or sodium bicarbonate

$$RCO_2H + NaOH \longrightarrow RCO_2Na + H_2O$$

Resonance stabilization of the carboxylate ion

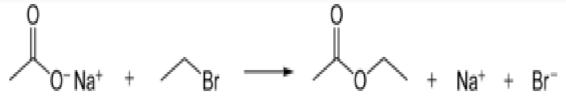
Carboxylic acids easily dissociate into a carboxylate anion and a positively charged hydrogen ion (proton), much more readily than alcohols do (into an alkoxide ion and a proton), because the carboxylate ion is stabilized by resonance. The negative charge that is left after deprotonation of the carboxyl group is delocalized between the two electronegative oxygen atoms in a resonance structure. If the R group is an electron-withdrawing group (such as $-CF_3$), the basicity of the carboxylate will be further weakened.



This delocalization of the electron cloud means that both of the oxygen atoms are less strongly negatively charged; the positive proton is therefore less strongly attracted back to the carboxylate group once it has left; hence, the carboxylate ion is more stable. In contrast, an alkoxide ion, once formed, would have a strong negative charge on the oxygen atom, which would make it difficult for the proton to escape. Carboxylic acids thus have a lower pKa values than alcohols. For example, the pKa value of ethanol is 16 while acetic acid has a pKa of 4.9. Hence acetic acid is a much stronger acid than ethanol. the higher the number of protons in solution, the lower the pH.

Reactions

Carboxylate ions are good nucleophiles. They react with alkyl halides to form ester. The following reaction shows the reaction mechanism.

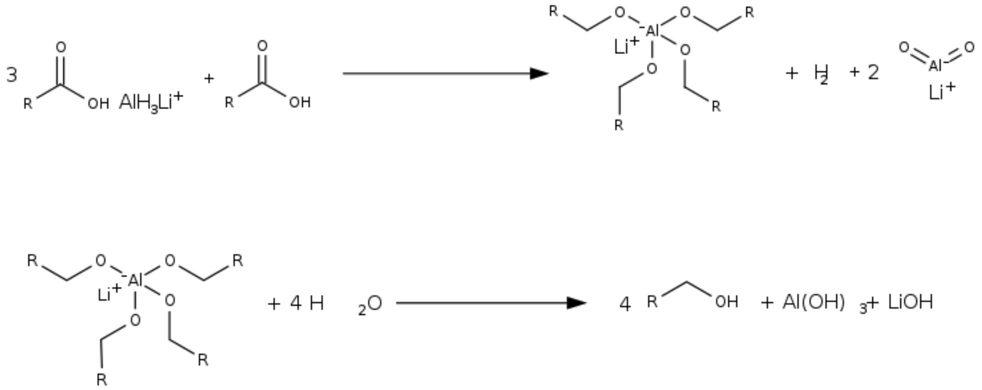


The S_N2 reaction between sodium acetate and bromoethane. The products are ethyl acetate and sodium bromide.

The nucleophilicity of carboxylate ions are much weaker than that of hydroxide and alkoxide ions, but stronger than halide anions (in a polar aprotic solvent, though there are other effects such as solubility of the ion)

Reduction

Unlike the reduction of ester, the reduction of carboxylate is different, due to the lack of the leaving group and the relatively electron-rich carbon atom (due to the negative charge on the oxygen atoms) . With small amount of acid, the reaction occurs with lithium aluminium hydride by changing the LAH into a Lewis acid, AlH_3 in the process, converting the oxyanion to 4 Al-O bonds.



Lanthanide Organometallics

Organometallic Chemistry

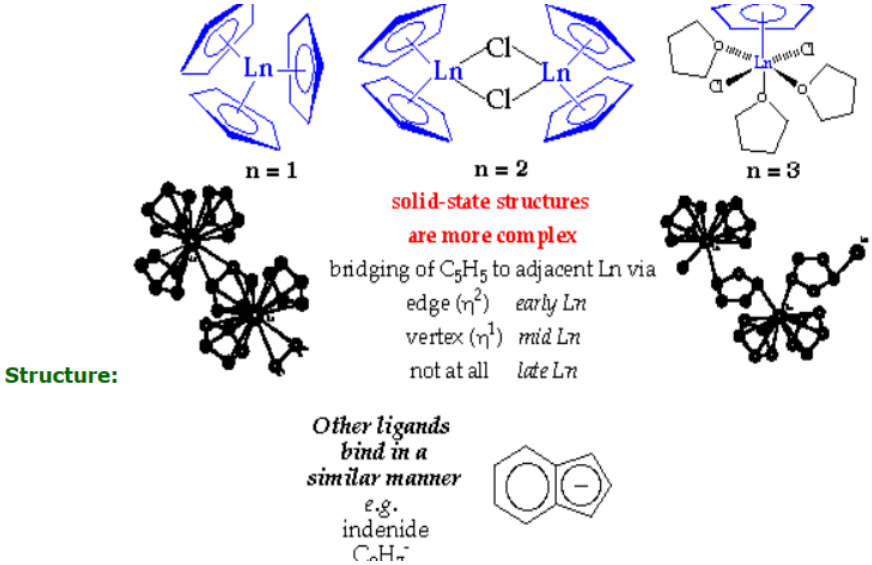
- Organolanthanide chemistry is not as extensive as organotransition metal chemistry,
- Currently receiving a lot of attention, especially in *C-H Bond Activation* studies
- Primarily ionic in their bonding □ contracted nature of the 4f valence orbitals
- Lanthanides cannot act as □-bases □ Ln-CO compounds are not stable
- Organolanthanides are extremely air & moisture sensitive

~ reflects highly carbanionic character of organic ligand & oxophilicity of $Ln^{2+/3+}$

Cyclopentadienides ($C_5H_5^-$ ligand)

$$LnCl_3 + nNa(C_5H_5) \xrightarrow{THF} \mathbf{LnCl_{3-n}(C_5H_5)_n} + nNaCl$$

Preparation:



Alkyls & Aryls

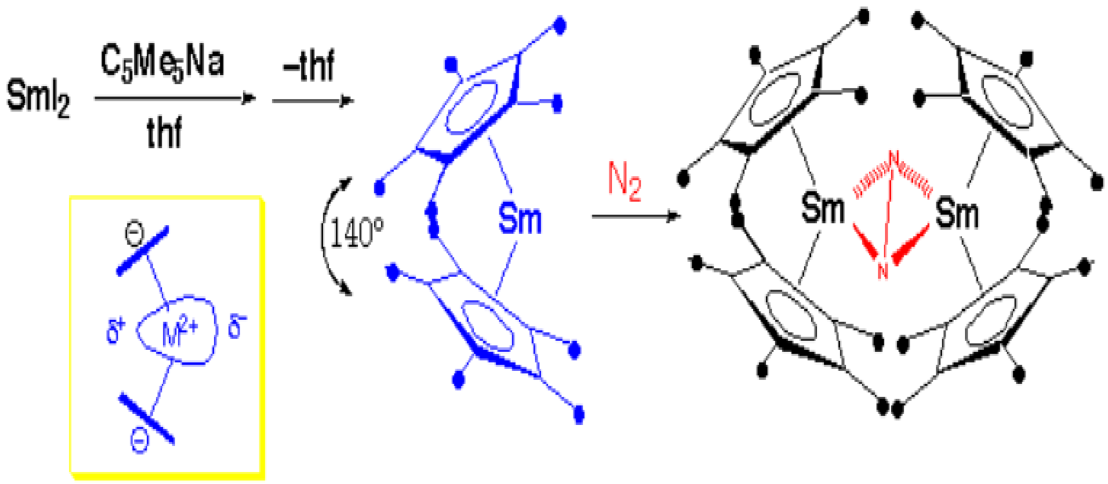
- □-bonded alkyls & aryls
- from metathesis in ether/thf $LnCl_3 + 3LiR \xrightarrow{THF} \mathbf{LnR_3} + 3LiCl$
    - R = phenyl probably polymeric

    - R = CH_2CMe_3 stable as $LnR_3(thf)_2$
- $[LnMe_6]^{3-}$ have been isolated for most Ln

Mixed Alkyl Cyclopentadienides

- C_5Me_5 (*Pentamethyl-cyclopentadienyl*) is a common organo-Ln ligand
    - large bulk□□ only 2 C_5Me_5 may be bound to Ln
    - causes major change in structural & chemical properties
    - especially novel chemistry in mixed alkyl cyclopentadienides

Also in **+2 Oxidation State**

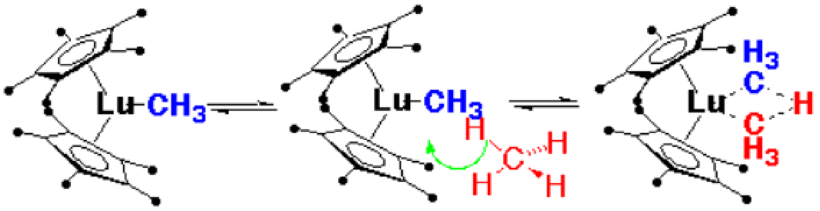


e.g. **$(C_5Me_5)_2LuCH_3$**

∅ catalyzes **alkene polymerization** (Ziegler-Natta chemistry)

∅ **reacts with C-H bonds** of extremely low acidity *e.g.* CH_4 !!

Mechanism of Methane Activation?

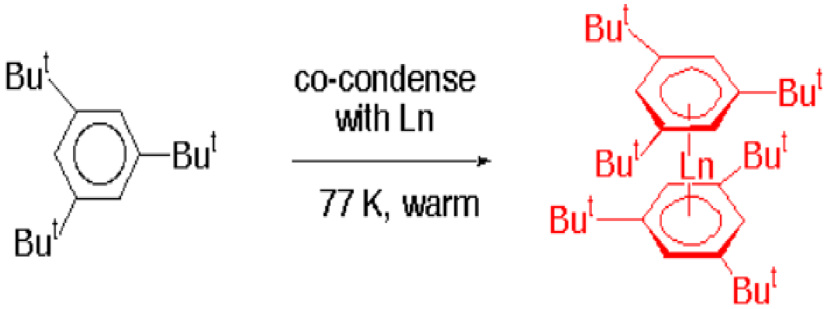


Cycloctatetraenide $M^{3+}(C_8H_8^{2\&endash;})_2$ Sandwich Compounds

Arenes

Lanthanide Bis-Arene 'sandwich' compounds

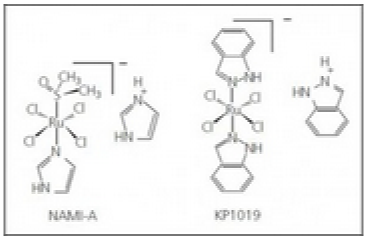
- prepared by metal vapour synthesis (**MVS**) techniques
- **stable** at ambient temperature



- **Ln^0** - such compounds could not be expected for Ln^{III} with contracted 4f orbitals

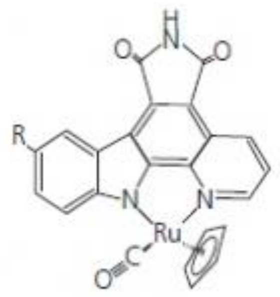
Medicinal Organometallic Chemistry

The medicinal organometallic complexes of iron, titanium, technetium and gold among other metals; however, this review will focus on those chapters featuring the platinum group metals (pgms). The discovery of the anticancer properties of cisplatin was arguably one of the major discoveries for anticancer chemotherapy in the twentieth century and now platinum anticancer drugs feature in multiple chemotherapy regimens (1). Though cisplatin is a simple inorganic complex (*cis*-$PtCl_2(NH_3)_2$), it has had a major impact on all aspects of inorganic medicinal chemistry including organometallic medicinal chemistry. The mechanism of action of cisplatin is believed to be the formation of DNA intrastrand crosslinks. Much of the early work on metal-based compounds focused on their interaction with DNA. However, it is now increasingly apparent that many metal complexes with potential anti-tumor activity do not behave like cisplatin, and it has been proposed that we should move away from the 'platinum paradigm' by developing drugs based on other metals such as ruthenium which have a different mechanism of action (2, 3) (Figure 1). Another apparent misconception is that organometallic compounds are too unstable to be useful as drugs, but many organometallic compounds are now being developed that are stable under physiological conditions. These concepts are exemplified by many of the contributions in this book.



Various ruthenium complexes have demonstrated antitumour activity in preclinical studies and it is apparent that for many of these the primary biological target is not DNA. Angela Casini *et al*. (École Polytechnique Fédérale de Lausanne, Switzerland) describe in the third chapter the biological target of Ru-arene compounds with the formula $[Ru(\eta^6\text{-arene})Cl_2(pta)]$ (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane), named RAPTA compounds. Interestingly, in mouse cancer models these compounds are able to inhibit tumour metastasis without affecting the growth of the primary tumour. This has led to a search for alternative biological targets, with a focus on two enzymes: thioredoxin reductase and cathepsin B, both of which contain cysteine in their active site. Though in general RAPTA compounds were found to be weak inhibitors of thioredoxin reductase, they were able to inhibit cathepsin B by coordination of the Ru(II) to the cysteine in the active site.

Protein phosphorylation by kinase enzymes is a major regulatory mechanism for protein activity and transmission of intracellular signals. There is a growing trend towards targeted therapy in which cancer drugs are aimed at specific molecular targets such as kinases. An excellent example is the drug imatinib which is targeted at the gene fusion protein breakpoint cluster region-Abelson (bcr-abl) tyrosine kinase and has changed the landscape for chronic myeloid leukemia therapy. Seann Mulcahy and Eric Meggers (Philipps-Universität Marburg, Germany) describe in the sixth chapter the ability of metal-containing compounds to form rigid 3D structures which can then be used as structurally diverse, unique scaffolds for the design of specific enzyme inhibitors. Staurosporine, an indolocarbazole alkaloid, is a relatively non-selective protein kinase inhibitor. By using cyclopentadienyl half-sandwich Ru complexes as a structural scaffold for staurosporine mimetics, and combining features of the indolocarbazole within the half-sandwich complex, highly potent and specific protein kinase inhibitors have been identified for the protein kinases Pim1, MSK1 and glycogen synthase kinase (GSK3α). These kinases are all potential targets for anticancer drugs (**Figure 3**).



R = H or OH

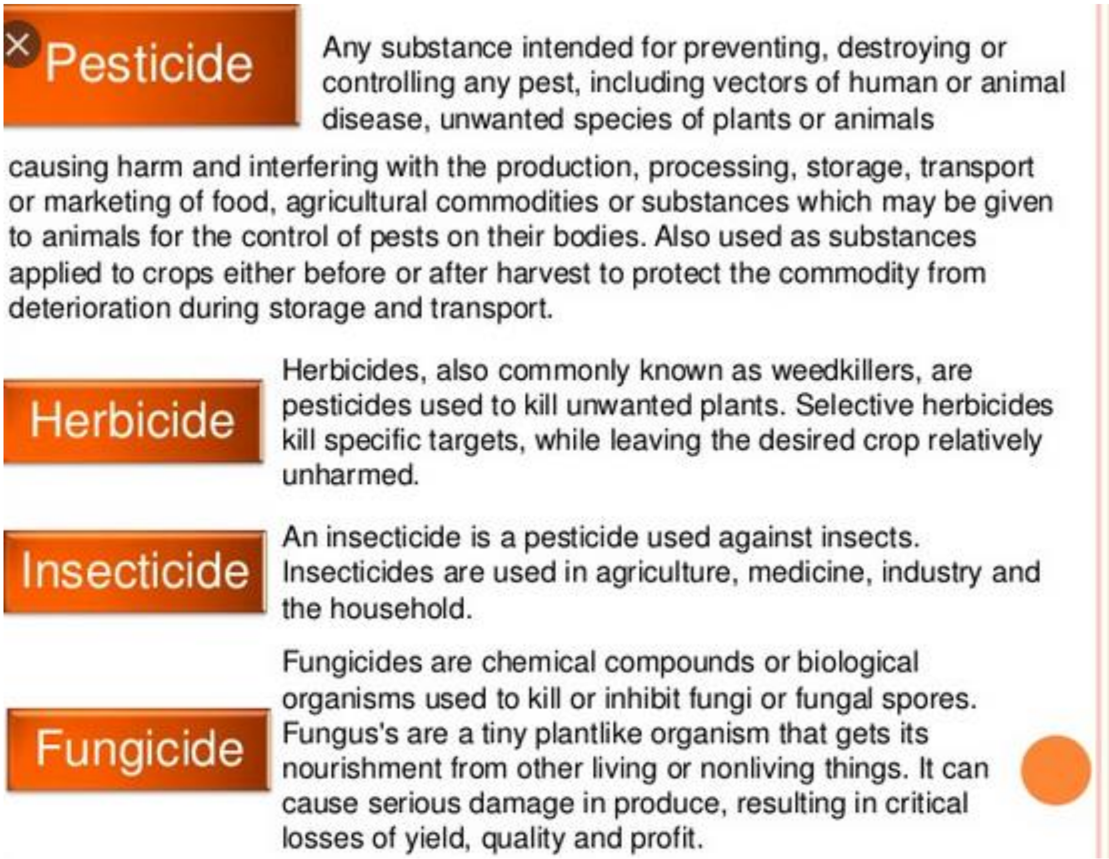
Ru-indolocarbazole

Agricultural and biocidal applications of organometallics

Organometallic Compounds have a broad range of applications in the field of chemistry. Some of them are given below-

- In some of the commercial chemical reactions, organometallic compounds are used as homogeneous catalysts.
- These compounds are used as stoichiometric reagents in both industrial and research-oriented chemical reactions.
- These compounds are also used in the manufacture of some of the semiconductors, which require the use of compounds such as trimethylgallium, trimethylaluminum, trimethylindium, and trimethyl antimony.
- They are also used in the production of light emitting diodes (or LEDs).
- These compounds are employed in bulk hydrogenation processes such as the production of margarine.
- These compounds are used as catalysts and reagents during the synthesis of some organic compounds.
- The complexes formed from organometallic compounds are useful in the facilitation of the synthesis of many organic compounds.

The points given above emphasize the importance of organometallic compounds. However, they are also the cause of many environmental concerns due to the highly toxic nature of some of these types of compounds.

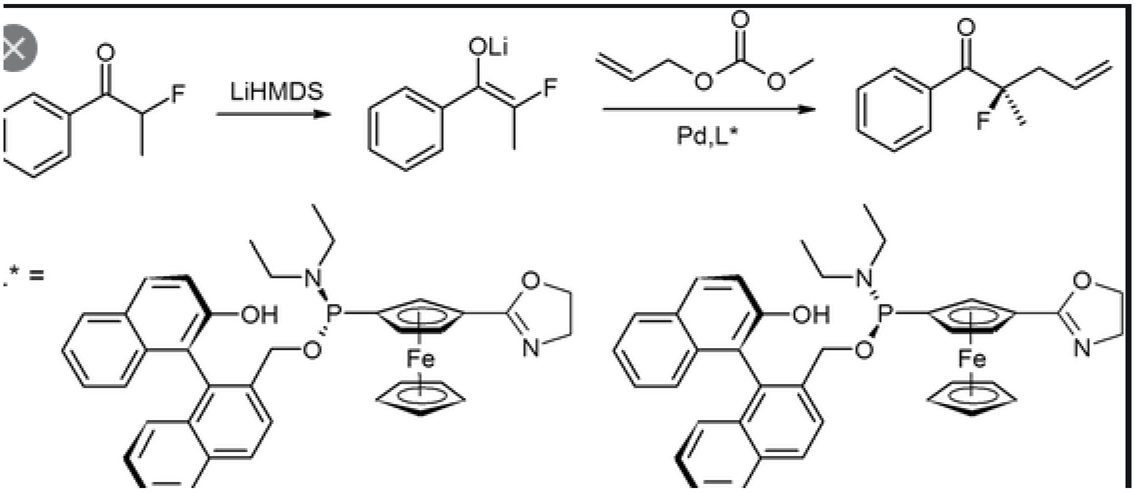


Pesticide Any substance intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm and interfering with the production, processing, storage, transport or marketing of food, agricultural commodities or substances which may be given to animals for the control of pests on their bodies. Also used as substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

Herbicide Herbicides, also commonly known as weedkillers, are pesticides used to kill unwanted plants. Selective herbicides kill specific targets, while leaving the desired crop relatively unharmed.

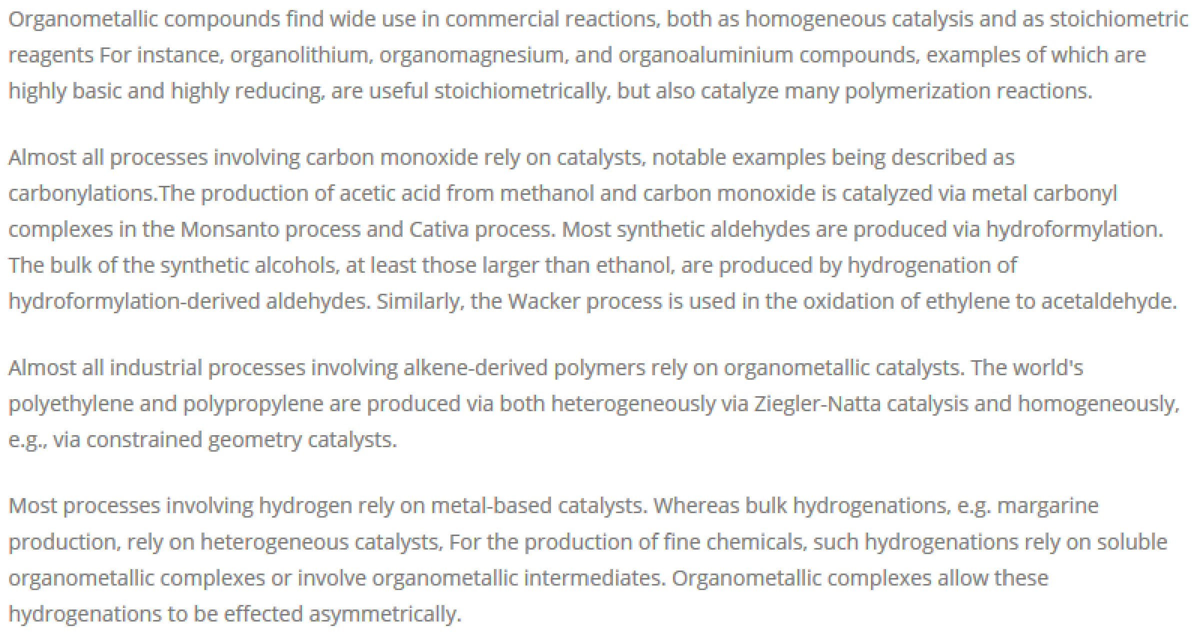
Insecticide An insecticide is a pesticide used against insects. Insecticides are used in agriculture, medicine, industry and the household.

Fungicide Fungicides are chemical compounds or biological organisms used to kill or inhibit fungi or fungal spores. Fungus's are a tiny plantlike organism that gets its nourishment from other living or nonliving things. It can cause serious damage in produce, resulting in critical losses of yield, quality and profit.



applications of organometallic compounds in industry

Organometallic compounds are widely used both stoichiometrically in research and **industrial** chemical reactions, as well as in the role of catalysts to increase the rates of such reactions (e.g., as in uses of homogeneous catalysis), where target molecules include polymers, pharmaceuticals



Organometallic compounds find wide use in commercial reactions, both as homogeneous catalysis and as stoichiometric reagents For instance, organolithium, organomagnesium, and organoaluminium compounds, examples of which are highly basic and highly reducing, are useful stoichiometrically, but also catalyze many polymerization reactions.

Almost all processes involving carbon monoxide rely on catalysts, notable examples being described as carbonylations.The production of acetic acid from methanol and carbon monoxide is catalyzed via metal carbonyl complexes in the Monsanto process and Cativa process. Most synthetic aldehydes are produced via hydroformylation. The bulk of the synthetic alcohols, at least those larger than ethanol, are produced by hydrogenation of hydroformylation-derived aldehydes. Similarly, the Wacker process is used in the oxidation of ethylene to acetaldehyde.

Almost all industrial processes involving alkene-derived polymers rely on organometallic catalysts. The world's polyethylene and polypropylene are produced via both heterogeneously via Ziegler-Natta catalysis and homogeneously, e.g., via constrained geometry catalysts.

Most processes involving hydrogen rely on metal-based catalysts. Whereas bulk hydrogenations, e.g. margarine production, rely on heterogeneous catalysts, For the production of fine chemicals, such hydrogenations rely on soluble organometallic complexes or involve organometallic intermediates. Organometallic complexes allow these hydrogenations to be effected asymmetrically.

UNIT V: REACTION AND CATALYSIS BY ORGANOMETALLICS

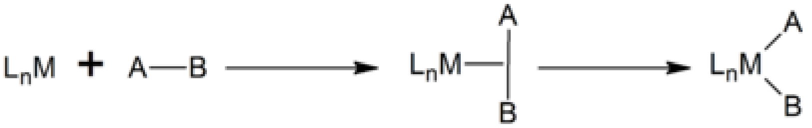
Oxidative addition

Oxidative addition and **reductive elimination** are two important and related classes of reactions in organometallic chemistry. Oxidative addition is a process that increases both the oxidation state and coordination number of a metal centre. Oxidative addition is often a step in catalytic cycles, in conjunction with its reverse reaction, reductive elimination

Mechanisms of oxidative addition

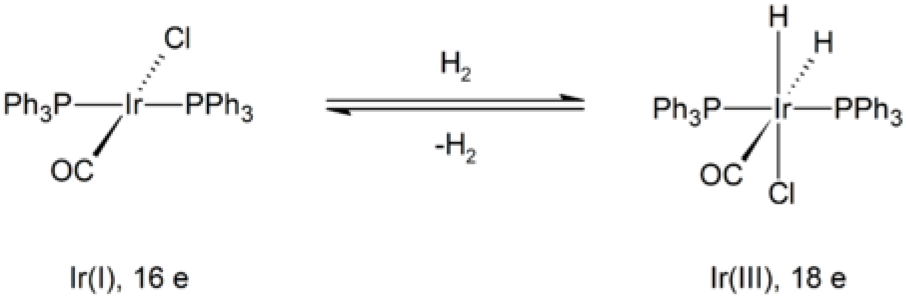
Concerted pathway

Oxidative additions of nonpolar substrates such as hydrogen and hydrocarbons appear to proceed via concerted pathways. Such substrates lack π-bonds, consequently a three-centered σ complex is invoked, followed by intramolecular ligand bond cleavage of the ligand (probably by donation of electron pair into the sigma* orbital of the inter ligand bond) to form the oxidized complex. The resulting ligands will be mutually *cis*, although subsequent isomerization may occur.



This mechanism applies to the addition of homonuclear diatomic molecules such as H_2. Many C–H activation reactions also follow a concerted mechanism through the formation of an M–(C–H) agostic complex.

A representative example is the reaction of hydrogen with Vaska's complex, *trans*-IrCl(CO)[P(C_6H_5)$_3$]$_2$. In this transformation, iridium changes its formal oxidation state from +1 to +3. The product is formally bound to three anions: one chloride and two hydride ligands. As shown below, the initial metal complex has 16 valence electrons and a coordination number of four whereas the product is a six-coordinate 18 electron complex.

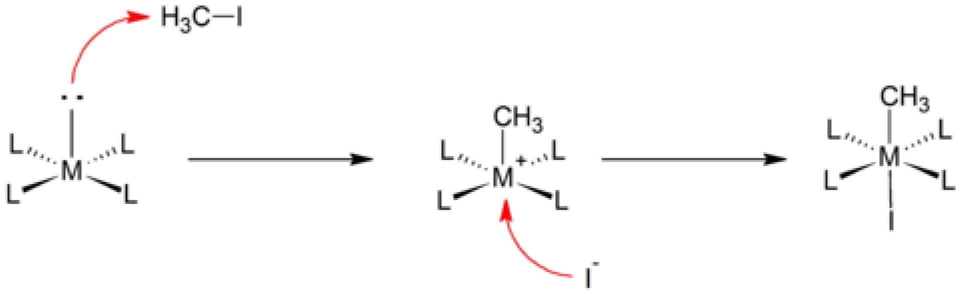


Formation of a trigonal bipyramidal dihydrogen intermediate is followed by cleavage of the H–H bond, due to electron back donation into the H–H σ*-orbital. This system is also in chemical equilibrium, with the reverse reaction proceeding by the elimination of hydrogen gas with simultaneous reduction of the metal center

The electron back donation into the H–H σ*-orbital to cleave the H–H bond causes electron-rich metals to favor this reaction. The concerted mechanism produces a *cis* dihydride, while the stereochemistry of the other oxidative addition pathways do not usually produce *cis* adducts.

S_N2-type

Some oxidative additions proceed analogously to the well known bimolecular nucleophilic substitution reactions in organic chemistry. Nucleophillic attack by the metal center at the less electronegative atom in the substrate leads to cleavage of the R–X bond, to form an $[M–R]^+$ species. This step is followed by rapid coordination of the anion to the cationic metal center. For example, reaction of a square planar complex with methyl iodide:



This mechanism is often assumed in the addition of polar and electrophilic substrates, such as alkyl halides and halogens.

Radical

In addition to undergoing S_N2-type reactions, alkyl halides and similar substrates can add to a metal center via a radical mechanism, although some details remain controversial.[2] Reactions which are generally accepted to proceed by a radical mechanism are known however. One example was proposed by Lednor and co-workers.

Initiation

$[(CH_3)_2C(CN)N]_2 \rightarrow 2\ (CH_3)_2(CN)C^\bullet + N_2$

$(CH_3)_2(CN)C^\bullet + PhBr \rightarrow (CH_3)_2(CN)CBr + Ph^\bullet$

Propagation

$Ph^\bullet + [Pt(PPh_3)_2] \rightarrow [Pt(PPh_3)_2Ph]^\bullet$

$[Pt(PPh_3)_2Ph]^\bullet + PhBr \rightarrow [Pt(PPh_3)_2PhBr] + Ph^\bullet$

Applications

Oxidative addition and reductive elimination are invoked in many catalytic processes both in homogeneous catalysis (i.e., in solution) such as the Monsanto process and alkene hydrogenation using Wilkinson's catalyst. It is often suggested that oxidative addition-like reactions are also involved in mechanisms of heterogeneous catalysis, e.g. hydrogenation catalyzed by platinum metal. Metals are however characterised by band structures, so oxidation states are not meaningful. Oxidative addition is also needed in order for nucleophilic addition of an alkyl group to occur. Oxidative insertion is also a crucial step in many cross-coupling reactions like the Suzuki coupling, Negishi coupling, and the Sonogashira coupling.

Reductive elimination

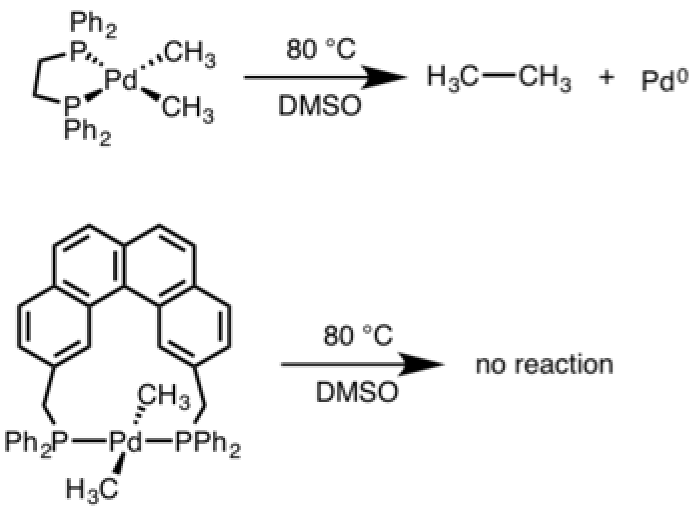
Reductive elimination is an elementary step in organometallic chemistry in which the oxidation state of the metal center decreases while forming a new covalent bond between two ligands. It is the microscopic reverse of oxidative addition, and is often the product-forming step in many catalytic processes. Since oxidative addition and reductive elimination are reverse reactions, the same mechanisms apply for both processes, and the product equilibrium depends on the thermodynamics of both directions.

Reductive elimination is often seen in higher oxidation states, and can involve a two-electron change at a single metal center (mononuclear) or a one-electron change at each of two metal centers (binuclear, dinuclear, or bimetallic).

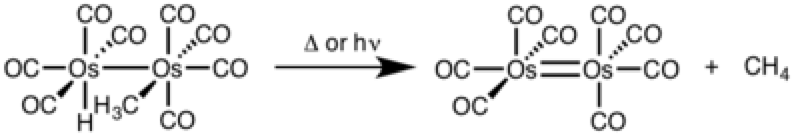
General Reductive Elimination.png

For mononuclear reductive elimination, the oxidation state of the metal decreases by two, while the d-electron count of the metal increases by two. This pathway is common for d8 metals Ni(II), Pd(II), and Au(III) and d6 metals Pt(IV), Pd(IV), Ir(III), and Rh(III). Additionally, mononuclear reductive elimination requires that the groups being eliminated must be cis to one another on the metal center.[3]

Cis vs. Trans.png



For binuclear reductive elimination, the oxidation state of each metal decreases by one, while the d-electron count of each metal increases by one. This type of reactivity is generally seen with first row metals, which prefer a one-unit change in oxidation state, but has been observed in both second and third row metals.

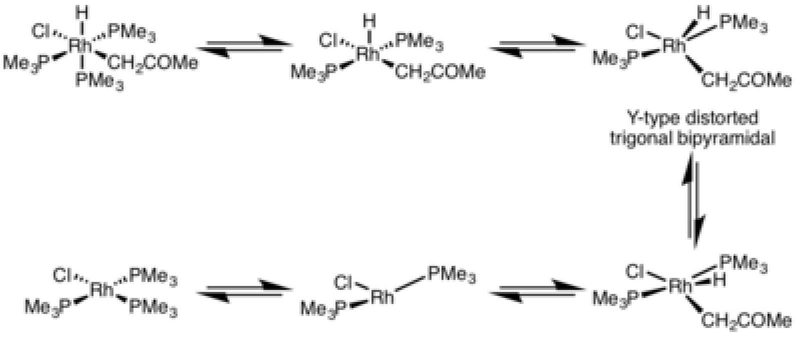


Mechanisms

As with oxidative addition, several mechanisms are possible with reductive elimination. The prominent mechanism is a concerted pathway, meaning that it is a nonpolar, three-centered transition state with retention of stereochemistry. In addition, an SN2 mechanism, which proceeds with inversion of stereochemistry, or a radical mechanism, which proceeds with obliteration of stereochemistry, are other possible pathways for reductive elimination.

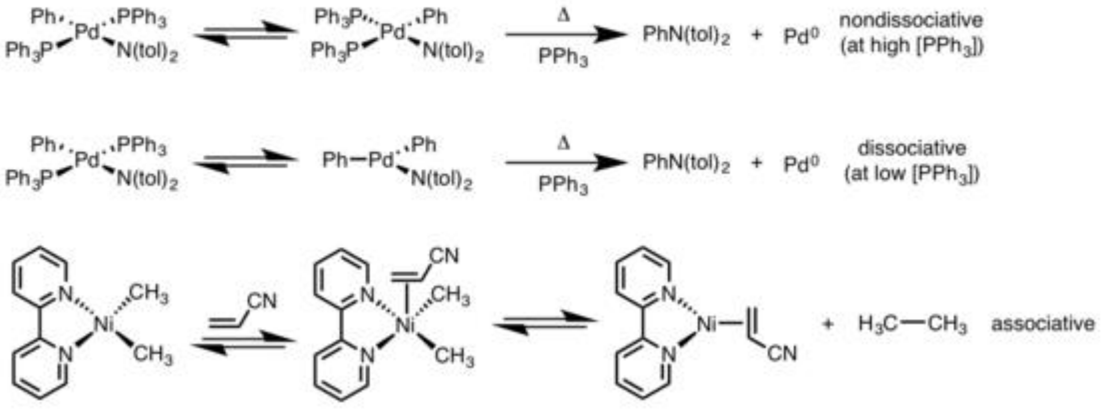
Octahedral complexes

The rate of reductive elimination is greatly influenced by the geometry of the metal complex. In octahedral complexes, reductive elimination can be very slow from the coordinatively saturated center, and often, reductive elimination only proceeds via a dissociative mechanism, where a ligand must initially dissociate to make a five-coordinate complex. This complex adopts a Y-type distorted trigonal bipyramidal structure where a π-donor ligand is at the basal position and the two groups to be eliminated are brought very close together. After elimination, a T-shaped three-coordinate complex is formed, which will associate with a ligand to form the square planar four-coordinate complex



Square planar complexes

Reductive elimination of square planar complexes can progress through a variety of mechanisms: dissociative, nondissociative, and associative. Similar to octahedral complexes, a dissociative mechanism for square planar complexes initiates with loss of a ligand, generating a three-coordinate intermediate that undergoes reductive elimination to produce a one-coordinate metal complex. For a nondissociative pathway, reductive elimination occurs from the four-coordinate system to afford a two-coordinate complex. If the eliminating ligands are trans to each other, the complex must first undergo a trans to cis isomerization before eliminating. In an associative mechanism, a ligand must initially associate with the four-coordinate metal complex to generate a five-coordinate complex that undergoes reductive elimination synonymous to the dissociation mechanism for octahedral complexes.



Applications

Reductive elimination has found widespread application in academia and industry, most notable being hydrogenation, the Monsanto acetic acid process,hydroformylation,and cross-coupling reactions.In many of these catalytic cycles, reductive elimination is the product forming step and regenerates the catalyst; however, in the Heck reaction and Wacker process,[18] reductive elimination is involved only in catalyst regeneration, as the products in these reactions are formed via β–hydride elimination.

Trans metalation

Transmetalation (alt. spelling: transmetallation) is a type of organometallic reaction that involves the transfer of ligands from one metal to another. It has the general form:

M1–R + M2–R′ → M1–R′ + M2–R

where R and R′ can be, but are not limited to, an alkyl, aryl, alkynyl, allyl, halogen, or pseudo-halogen group. The reaction is usually an irreversible process due to thermodynamic and kinetic reasons. Thermodynamics will favor the reaction based on the electronegativities of the metals and kinetics will favor the reaction if there are empty orbitals on both metals.[1] There are different types of trans metalation including redox-trans metalation and redox-trans metalation/ligand exchange. During trans metalation the metal-carbon bond is activated, leading to the formation of new metal-carbon bonds.[2] Trans metalation is commonly used in catalysis, synthesis of main group complexes, and synthesis of transition metal complexes.

Types of trans metalation

There are two main types of transmetalation, redox-transmetalation (RT) and redox-transmetalation/ligand-exchange (RTLE). Below, M_1 is usually a 4d or 5d transition metal and M_2 is usually a main group or 3d transition metal. By looking at the electronegativities of the metals and ligands, one can predict whether the RT or RTLE reaction will proceed and what products the reaction will yield. For example, one can predict that the addition of 3 $HgPh_2$ to 2 Al will yield 3 Hg and 2 $AlPh_3$ because Hg is a more electronegative element than Al.

Redox-transmetalation

$$M_1^{n+}–R + M_2 \rightarrow M_1 + M_2^{n+}–R.$$

In redox-transmetalation a ligand is transferred from one metal to the other through an intermolecular mechanism. During the reaction one of the metal centers is oxidized and the other is reduced. The electronegativities of the metals and ligands is what causes the reaction to go forward. If M_1 is more electronegative than M_2, it is thermodynamically favorable for the R group to coordinate to the less electronegative M_2.

Redox-transmetalation/ligand-exchange

$$M_1–R + M_2–X \rightarrow M_1–X + M_2–R.$$

In redox-transmetalation/ligand exchange the ligands of two metal complexes switch places with each other, bonding with the other metal center. The R ligand can be an alkyl, aryl, alkynyl, or allyl group and the X ligand can be a halogen, pseudo-halogen, alkyl, or aryl group. The reaction can proceed by two possible intermediate steps. The first is an associative intermediate, where the R and X ligands bridge the two metals, stabilizing the transition state. The second and less common intermediate is the formation of a cation where R is bridging the two metals and X is anionic. The RTLE reaction proceeds in a concerted manner. Like in RT reactions, the reaction is driven by electronegativity values. The X ligand is attracted to highly electropositive metals. If M_1 is a more electropositive metal than M_2, it is thermodynamically favorable for the exchange of the R and X ligands to occur.

Applications

Cross-coupling reactions

Transmetalation is often used as a step in the catalytic cycles of cross-coupling reactions. Some of the cross-coupling reactions that include a transmetalation step are Stille cross-coupling, Suzuki cross-coupling, Sonogashira cross-coupling, and Negishi cross-coupling. The most useful cross-coupling catalysts tend to be ones that contain palladium. Cross-coupling reactions have the general form of $R'–X + M–R \rightarrow R'–R + M–X$ and are used to form C–C bonds. R and R′ can be any carbon fragment. The identity of the metal, M, depends on which cross-coupling reaction is being used. Stille reactions use tin, Suzuki reactions use boron, Sonogashira reactions use copper, and Negishi reactions use zinc. The transmetalation step in palladium catalyzed reactions involve the addition of an R–M compound to produce an R′–Pd–R compound. Cross-coupling reactions have a wide range of applications in synthetic chemistry including the area of medicinal chemistry. The Stille reaction has been used to make an antitumor agent, (±)-*epi*-jatrophone; the Suzuki reaction has been used to make an antitumor agent, oximidine II the Sonogashira reaction has been used to make an anticancer drug, eniluracil; and the Negishi reaction has been used to make the carotenoid β-carotene via a transmetalation cascade.

Lanthanides

Lanthanide organometallic complexes have been synthesized by RT and RTLE. Lanthanides are very electropositive elements.

Organomercurials, such as $HgPh_2$, are common kinetically inert RT and RTLE reagents that allow functionalized derivatives to be synthesized, unlike organolithiums and Grignard reagents. Diarylmercurials are often used to synthesize lanthanide organometallic complexes. $Hg(C_6F_5)_2$ is a better RT reagent to use with lanthanides than $HgPh_2$ because it does not require a step to activate the metal. However, phenyl-substituted lanthanide complexes are more thermally stable than the pentafluorophenyl complexes. The use of $HgPh_2$ led to the synthesis of a ytterbium complex with different oxidation states on the two Yb atoms

$$Yb(C_{10}H_8)(THF)_2 + HgPh_2 \rightarrow Yb^{II}Yb^{III}Ph_5(THF)_4$$

In the $Ln(C_6F_5)_2$ complexes, where Ln = Yb, Eu, or Sm, the Ln–C bonds are very reactive, making them useful in RTLE reactions. Protic substrates have been used as a reactant with the $Ln(C_6F_5)_2$ complex as shown: $Ln(C_6F_5)_2 + 2LH \rightarrow Ln(L)_2 + 2C_6F_5H$. It is possible to avoid the challenges of working with the unstable $Ln(C_6F_5)_2$ complex by forming it in situ by the following reaction:

$$Ln + HgR_2 + 2\ LH \rightarrow Ln(L)_2 + Hg + 2\ RH$$

Organotins are also kinetically inert RT and RTLE reagents that have been used in a variety of organometallic reactions. They have applications to the synthesis of lanthanide complexes, such as in the following reaction:

$$Yb + Sn(N(SiMe_3)_2)_2 \rightarrow Yb(N(SiMe_3)_2)_2 + Sn$$

Actinides

RT can be used to synthesize actinide complexes. RT has been used to synthesize uranium halides using uranium metal and mercury halides as shown:

$$U + HgX \rightarrow UX + Hg \qquad (X = Cl, Br, I)$$ [11]

This actinide RT reaction can be done with multiple mercury compounds to coordinate ligands other than halogens to the metal:

$$2\ U + 3\ (C_5H_5)_2Hg + HgCl_2 \rightarrow 2\ (C_5H_5)_3UCl + 4\ Hg$$

Alkaline earth metals

Alkaline earth metal complexes have been synthesized by RTLE, employing the same methodology used in synthesizing lanthanide complexes. The use of diphenylmercury in alkaline-earth metal reactions leads to the production of elemental mercury. The handling and disposal of elemental mercury is challenging due to its toxicity to humans and the environment. This led to the desire for an alternative RTLE reagent that would be less toxic and still very effective. Triphenylbismuth, $BiPh_3$, was discovered to be a suitable alternative. Mercury and bismuth have similar electronegativity values and behave similarly in RTLE reactions. $BiPh_3$ has been used to synthesize alkaline-earth metal amides and alkaline-earth metal cyclopentadienides. The difference between $HgPh_2$ and $BiPh_3$ in these syntheses was that the reaction time was longer when using $BiPh_3$.

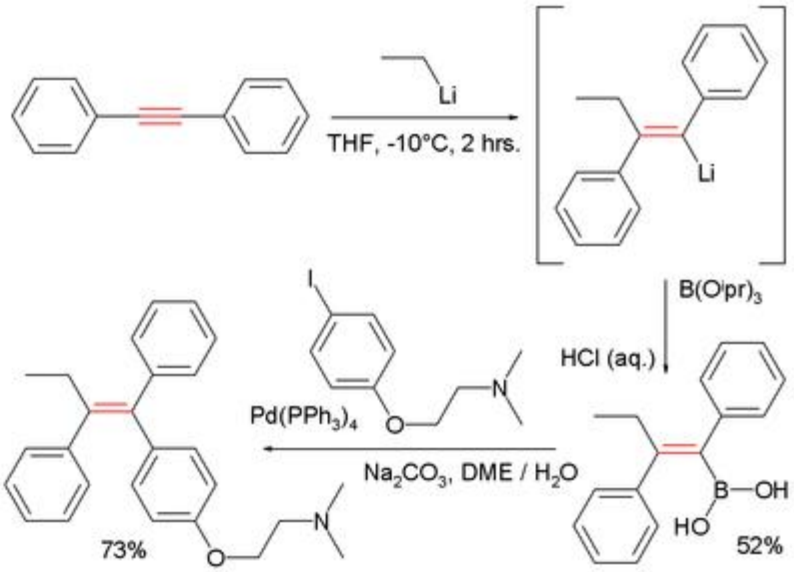
Carbometallation

A **carbometalation** is any reaction where a carbon-metal bond reacts with a carbon-carbon π-bond to produce a new carbon-carbon σ-bond and a carbon-metal σ-bond. The resulting carbon-metal bond can undergo further carbometallation reactions (oligomerization or polymerization see Ziegler-Natta Polymerization) or it can be reacted with a variety of electrophiles including halogenating reagents, carbonyls, oxygen, and inorganic salts to produce different organometallic reagents. Carbometalations can be performed on alkynes and alkenes to form products with high geometric purity or enantioselectivity, respectively. Some metals prefer to give the *anti*-addition product with high selectivity and some yield the syn-addition product. The outcome of *syn* and *anti*- addition products is determined by the mechanism of the carbometalation.

Carbolithiation

Carbolithiation is the addition of an organolithium reagent across a carbon-carbon pi-bond. The organolithium reagents used in this transformation can be commercial (such as n-butyllithium) or can be generated through deprotonation or lithium halogen exchange. Both inter- and intramolecular examples of carbolithiation exist and can be used in synthesis to generate complexity. Organolithiums are highly reactive chemicals and often the resulting organolithium reagent generated from the carbolithiation can continue to react with electrophiles or remaining starting material (resulting in polymerization). This reaction has been rendered enantioselective[6][7] through the use of sparteine, which can chelate the lithium ion and induce chirality.[4] Today, this is not a common strategy due to a shortage of natural sparteine.

Another demonstration of this reaction type is an alternative route to tamoxifen starting from diphenylacetylene and ethyllithium The capturing electrophile here is triisopropyl borate forming the boronic acid $R–B(OH)_2$. The second step completing tamoxifen is a Suzuki reaction.



As a consequence of the high reactivity of organolithiums as strong bases and strong nucleophiles, the substrate scope of the carbolithiation is generally limited to chemicals that do not contain acidic or electrophilic functional groups.

Insertion reaction

An **insertion reaction** is a chemical reaction where one chemical entity (a molecule or molecular fragment) interposes itself into an existing bond of typically a second chemical entity *e.g.*:

$$A + B\text{–}C \rightarrow B\text{–}A\text{–}C$$

The term only refers to the result of the reaction and does not suggest a mechanism. Insertion reactions are observed in organic, inorganic, and organometallic chemistry. In cases where a metal-ligand bond in a coordination complex is involved, these reactions are typically organometallic in nature and involve a bond between a transition metal and a carbon or hydrogen.[1] It is usually reserved for the case where the coordination number and oxidation state of the metal remain unchanged.[2] When these reactions are reversible, the removal of the small molecule from the metal-ligand bond is called extrusion or elimination.

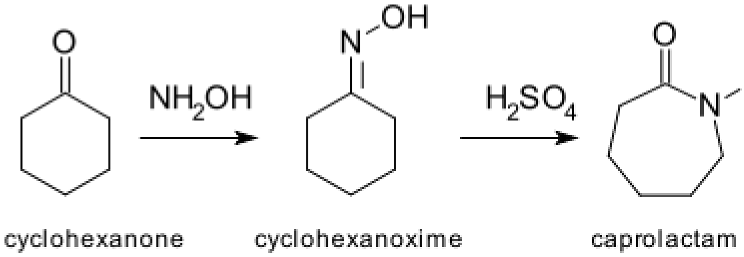
$$\mathrm{M{-}L + X{-}Y \longrightarrow M{-}\overset{\displaystyle Y}{\overset{|}{X}}{-}L} \qquad \text{(a)}$$

$$\mathrm{M{-}L + X{-}Y \longrightarrow M{-}X{-}Y{-}L} \qquad \text{(b)}$$

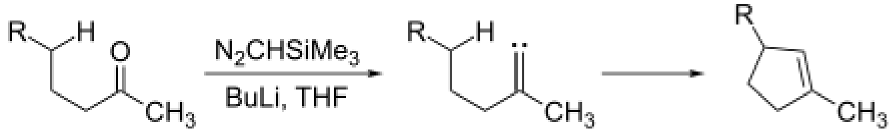
Examples of type 1,1 (a) and 1,2 (b) resulting geometries for insertion reactions

There are two common insertion geometries— 1,1 and 1,2 (pictured above). Additionally, the inserting molecule can act either as a nucleophile or as an electrophile to the metal complex. These behaviors will be discussed in more detail for CO, nucleophilic behavior, and SO_2, electrophilic behavior

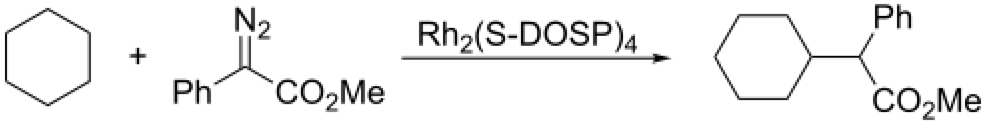
The Beckmann rearrangement is another example of a ring expanding reaction in which a heteroatom is inserted into a carbon-carbon bond. The most important application of this reaction is the conversion of cyclohexanone to its oxime, which is then rearranged under acidic conditions to provide ε-caprolactam, the feedstock for the manufacture of Nylon 6. Annual production of caprolactam exceeds 2 billion kilograms.



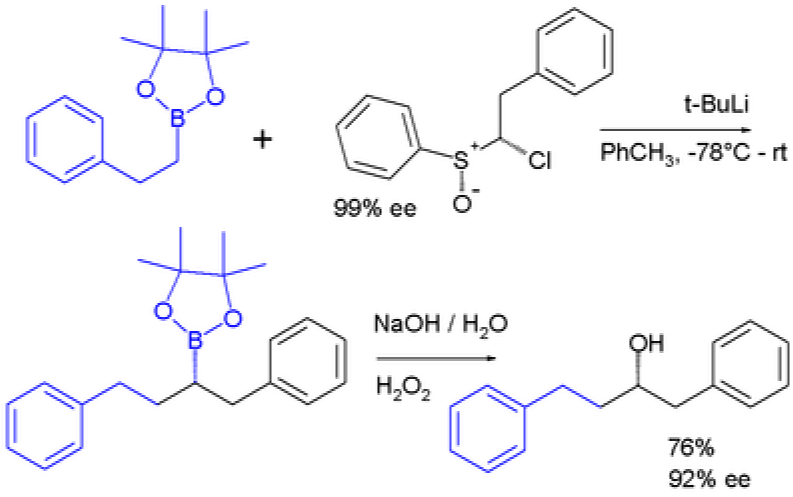
Carbenes undergo both intermolecular and intramolecular insertion reactions. Cyclopentene moieties can be generated from sufficiently long-chain ketones by reaction with trimethylsilyldiazomethane, $(CH_3)_3Si–CHN_2$:



Here, the carbene intermediate inserts into a carbon-hydrogen bond to form the carbon-carbon bond needed to close the cyclopentene ring. Carbene insertions into carbon-hydrogen bonds can also occur intermolecularly:



Carbenoids are reactive intermediates that behave similarly to carbenes.[19] One example is the chloroalkyllithium carbenoid reagent prepared *in situ* from a sulfoxide and *t*-BuLi which inserts into the carbon-boron bond of a pinacol boronic ester:



Carbonylation

Carbonylation refers to reactions that introduce carbon monoxide into organic and inorganic substrates. Carbon monoxide is abundantly available and conveniently reactive, so it is widely used as a reactant in industrial chemistry. The term carbonylation also refers to oxidation of protein side chains

Several industrially useful organic chemicals are prepared by carbonylations, which can be highly selective reactions. Carbonylations produce organic carbonyls, i.e., compounds that contain the C=O functional group such as aldehydes, carboxylic acids, and esters.[1][2] Carbonylations are the basis of many types of reactions, including hydroformylation and Reppe Chemistry. These reactions require metal catalysts, which bind and activate the CO.[3] Much of this theme was developed by Walter Reppe.

Hydroformylation

Hydroformylation entails the addition of both carbon monoxide and hydrogen to unsaturated organic compounds, usually alkenes. The usual products are aldehydes:

$$RCH{=}CH_2 + H_2 + CO \rightarrow RCH_2CH_2CHO$$

The reaction requires metal catalysts that bind CO, forming intermediate metal carbonyls. Many of the commodity carboxylic acids, i.e. propionic, butyric, valeric, etc, as well as many of the commodity alcohols, i.e. propanol, butanol, amyl alcohol, are derived from aldehydes produced by hydroformylation. In this way, hydroformylation is a gateway from alkenes to oxygenates.

Decarbonylation

Many organic carbonyls undergo decarbonylation. A common transformation involves the conversion of aldehydes to alkanes, usually catalyzed by metal complexes:[4]

$$RCHO \rightarrow RH + CO$$

Few catalysts are highly active or exhibit broad scope.

Acetic acid and acetic anhydride

Large-scale applications of carbonylation are the Monsanto and Cativa processes, which convert methanol to acetic acid. In another major industrial process, Acetic anhydride is prepared by a related carbonylation of methyl acetate.

Oxidative carbonylation

Dimethyl carbonate and dimethyl oxalate are produced industrially using carbon monoxide and an oxidant, in effect as a source of CO^{2+}.[1]

$$2\ CH_3OH + 1/2\ O_2 + CO \rightarrow (CH_3O)_2CO + H_2O$$

The oxidative carbonylation of methanol is catalyzed by copper(I) salts, which form transient carbonyl complexes. For the oxidative carbonylation of alkenes, palladium complexes are used.

Hydrocarboxylation and hydroesterification

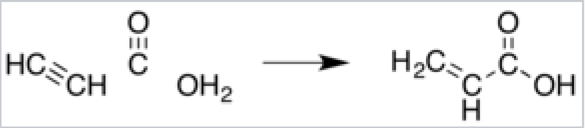
In **hydrocarboxylation**, alkenes and alkynes are the substrates. This method is used industrially to produce propionic acid from ethylene using nickel carbonyl as the catalyst:[1]

$$RCH{=}CH_2 + H_2O + CO \rightarrow RCH_2CH_2CO_2H$$

In the industrial synthesis of ibuprofen, a benzylic alcohol is converted to the corresponding arylacetic acid via a Pd-catalyzed carbonylation:[1]

$$ArCH(CH_3)OH + CO \rightarrow ArCH(CH_3)CO_2H$$

Acrylic acid was once mainly prepared by the hydrocarboxylation of acetylene.



Synthesis of acrylic acid using "Reppe chemistry". A metal catalyst is required.

Hydroformylation

Hydroformylation, also known as **oxo synthesis** or **oxo process**, is an industrial process for the production of aldehydes from alkenes. This chemical reaction entails the net addition of a formyl group (CHO) and a hydrogen atom to a carbon-carbon double bond. This process has undergone continuous growth since its invention: Production capacity reached 6.6×10^6 tons in 1995. It is important because aldehydes are easily converted into many secondary products. For example, the resulting aldehydes are hydrogenated to alcohols that are converted to detergents. Hydroformylation is also used in speciality chemicals, relevant to the organic synthesis of fragrances and drugs. The development of hydroformylation is one of the premier achievements of 20th-century industrial chemistry.

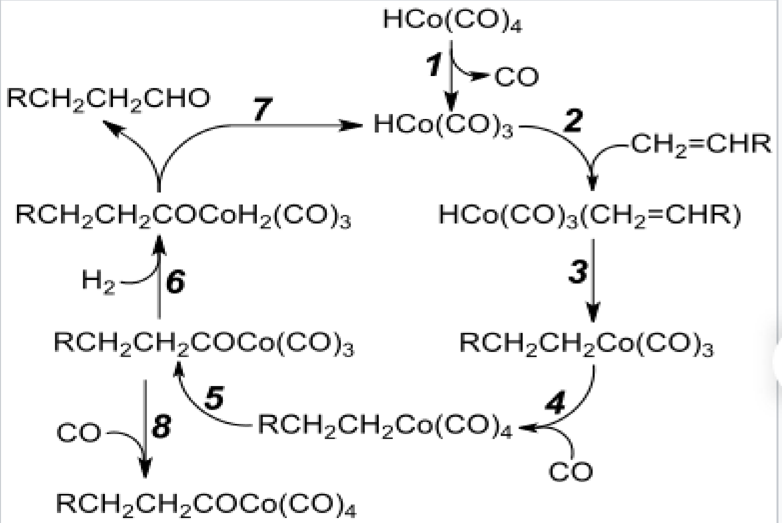
The process entails treatment of an alkene typically with high pressures (between 10 and 100 atmospheres) of carbon monoxide and hydrogen at temperatures between 40 and 200 °C. Transition metal catalysts are required. Invariably, the catalyst dissolves in the reaction medium, i.e. hydroformylation is an example of homogeneous catalysis

Mechanism

A key consideration of hydroformylation is the "normal" vs. "iso" selectivity. For example, the hydroformylation of propylene can afford two isomeric products, butyraldehyde or isobutyraldehyde:

$H_2 + CO + CH_3CH{=}CH_2 \rightarrow CH_3CH_2CH_2CHO$ ("normal")
vs.
$H_2 + CO + CH_3CH{=}CH_2 \rightarrow (CH_3)_2CHCHO$ ("iso")

These isomers reflect the regiochemistry of the insertion of the alkene into the M–H bond. Since both products are not equally desirable (normal is more stable than iso), much research was dedicated to the quest for catalyst that favored the normal isomer.



Mechanism of cobalt-catalyzed hydroformylation. The process begins with dissociation of CO from cobalt tetracarbonyl hydride to give the 16-electron species (step **1**). Subsequent binding of alkene gives an 18e species (step **2**). In step **3**, the olefin inserts to give the 16e alkyl tricarbonyl. Coordination of another equivalent of CO give alkyl tetracarbonyl (step **4**).[6] Migratory insertion of CO gives the 16e acyl in step **5**. In step **6**, oxidative addition of hydrogen gives a dihydrido complex, which in step **7** releases aldehyde by reductive elimination.[10] Step **8** is unproductive and reversible.

POLYMERIZARION OF OLEFINS

α-olefins are often polymerized in the presence of stereospecific catalysts such as metallocenes or Ziegler-Natta catalysts. These catalysts are able to restict the addition of monomer molecules to a specific regular orientation (tacticity). In the case of isotactic orientation, all alkyl groups are positioned at the same side of the molecule with respect to the polymer backbone, and in the case of syndiotactic orientation the position of the alkyl groups alters.

The coordination polymerization of olefins has many advantages over conventional polymerization. For example, it allows for excellent control of the molecular weight (MW), tacticity, and comonomer incorporation and results in narrow MW distribution. Usually, only very small quantities of catalyst is required.

The most important α-olefin is propylene; it is the second most widely used commercial polymer today and almost exclusively produced via stereospecific polymerization. Compared to conventional polypropylene, it shows very little creep at room temperature under load even if of comparatively low molecular weight. It is also more crystalline due to the regular structure and has a higher heat deflection temperature and thus a higher service temperature.

The mechanism of α-olefin polymerization using stereoselective catalysts includes initiation, propagation, transfer and termination reactions:

Initiation: The polymerization reaction starts when the olefin monomer coordinates to the transitional metal atom bearing a positive charge followed by insertion.

Propagation: The insertion of monomer molecules into the ionic Me–C bond at each active center results in the formation of long polymer chains:

$$Cp_2Me^+\text{-}R' + n\ CH_2{=}CHR \rightarrow Cp_2Me^+\underline{\text{-}(CH_2\text{-}CHR)_n\text{-}R'}$$

The instant polymerization rate is

$$R_p = k_p \cdot [\mathrm{Cat}] \cdot [\mathrm{M}]$$

where [Cat] is the concentration of active propagation centers, [M] is the concentration of monomers and k_p is the rate constant which is usually very high for most transition metal catalysts.

Elimination: Polymerization stops when the polymer chain is disengaged from the active center. The most common termination reaction is the *β-hydride elimination*:

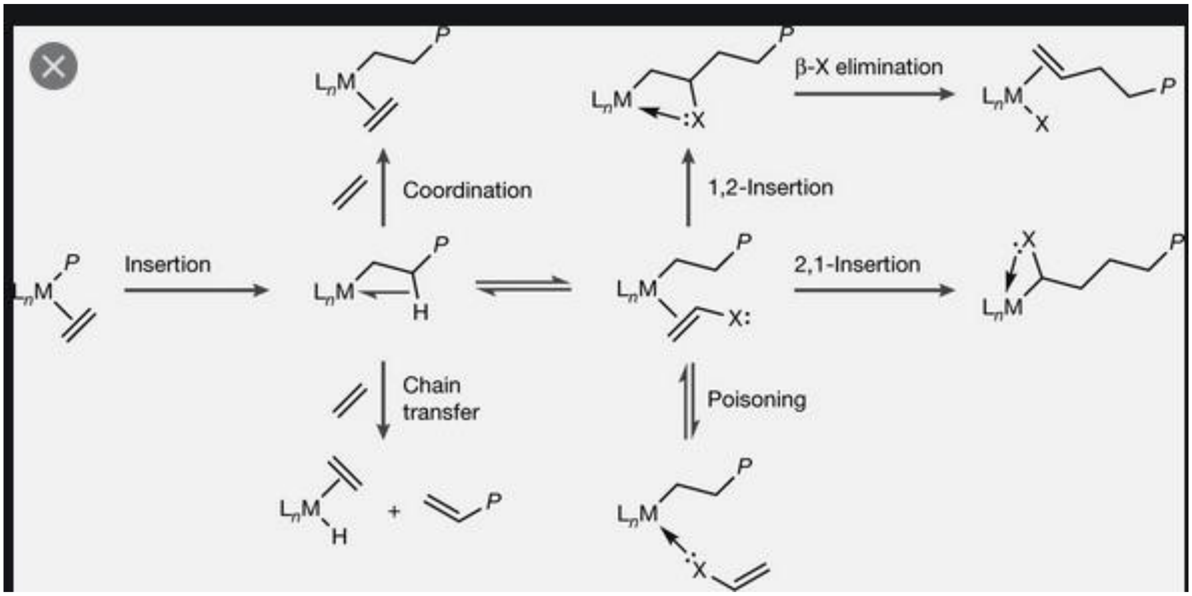
$$Cp_2Me^+\text{-}(CH_2\text{--}CHR)_n\text{-}R' + CH_2{=}CHR \rightarrow Cp_2Me^+\text{-}H + CH_2{=}CHR\text{-Polymer}$$

Depending on the charge distribution, the metal hydride can often initiate a new polymerization reaction (*β-hydride transfer reaction*). In fact, chain termination reactions are usually very unlikely events in Ziegler–Natta and metallocene catalytic polymerization resulting in too high molecular weights. To control the molecular weight, quenching agents are often added. For example, the catalyst can be deactivated by contact with water or alcohol.

The stereoselctivity in α-olefin polymerization depends on many factors. The most important factor is the stability of the chemisorbed catalytic complex. Its stability is affected by the ion radius of the metal atoms linked to the metalorganic compound, irregularities of the catalyst, and surface energy of the crystall lattice. Another important factor is the polymerization temperature. In general, the degree of tacticity decreases with increasing temperature.

Regulation of the average molecular weight is of great importance in the polymerization of olefins because the mechanical and viscoelastic properties depend on the molecular weight. For example, an iso- or syndiotactic polypropylene of high molecular weight is difficult to process in the melt state due to its high viscosity whereas a high molecular weight is a lesser problem for atactic polypropylene. In fact, a high molecular weight is often required to achieve similar high tensile strength and low creep properties.

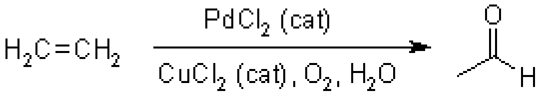
Compounds with a partial ionic character such as metal-alkyls are often very effective in lowering the molecular weight of polyolefins. These compounds transfer negative groups to the catalytic complex, i.e. they act as alkyl transfer agents. Other compouds having a partial ionic character such as alkyl halides are also effective in chain growth stopping and/or molecular weight reduction. The molecular weight can also be reduced by carrying out the polymerization in the presence of hydrogen. In this case, the decrease in MW depends on the hydrogen partial pressure in the reaction vessel. However, in the case of Ziegler-Natta catalysts, hydrogen can also effect the steric purity.[2] The reduction of molecular weight is caused by proton saturation of the growing chain ends (elimination) and by hydride ions replacing alkyl groups attached to the catalyst (Ziegler-Natta catalysts). These hydrid ions react with propylene to form alkyl groups which can reinitiate chain growth.



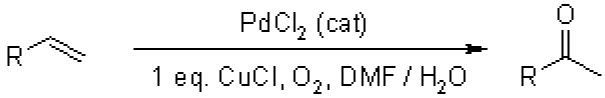
OLEFINS OXIDATION (WACKER PROCESS)

The **Wacker Oxidation** is an industrial process, which allows the synthesis of ethanal from ethene by palladium-catalyzed **oxidation** with oxygen. Copper serves as redox cocatalyst. The lab scale modification - the **Wacker**-Tsuji **Oxidation** - is useful for the synthesis of various ketones.

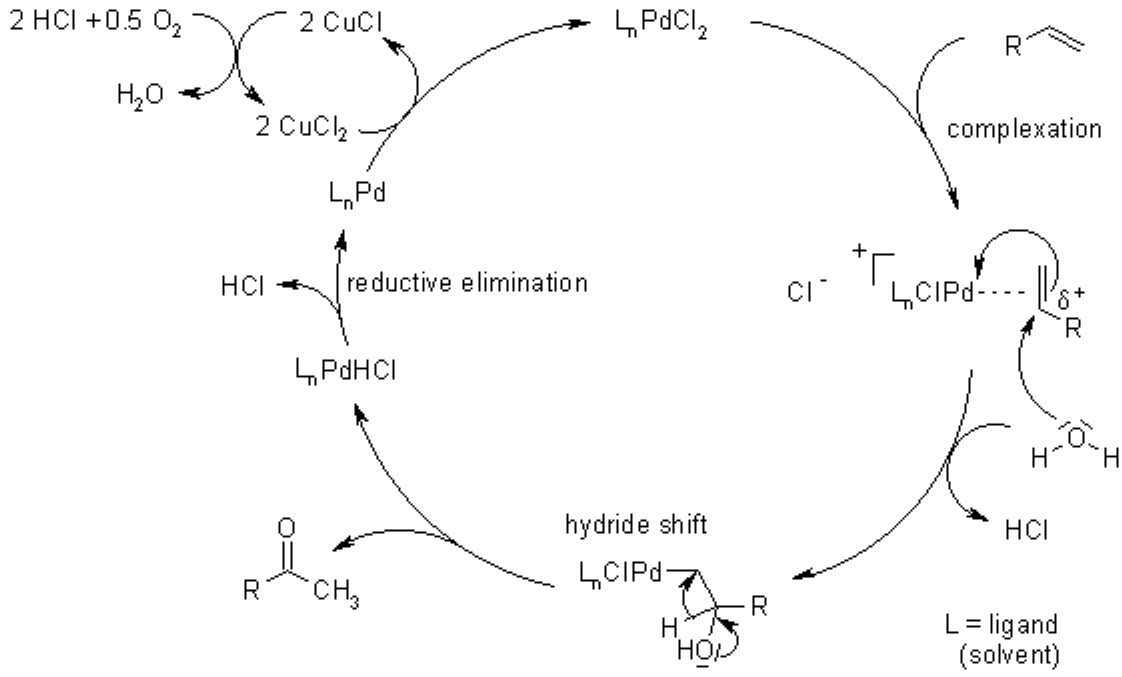
Wacker-Tsuji Oxidation



The Wacker Oxidation is an industrial process, which allows the synthesis of ethanal from ethene by palladium-catalyzed oxidation with oxygen. Copper serves as redox cocatalyst.

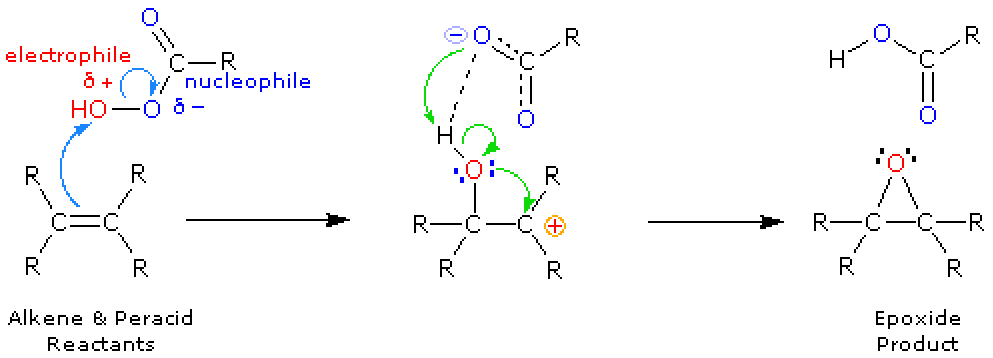


The lab scale modification - the Wacker-Tsuji Oxidation - is useful for the synthesis of various ketones.



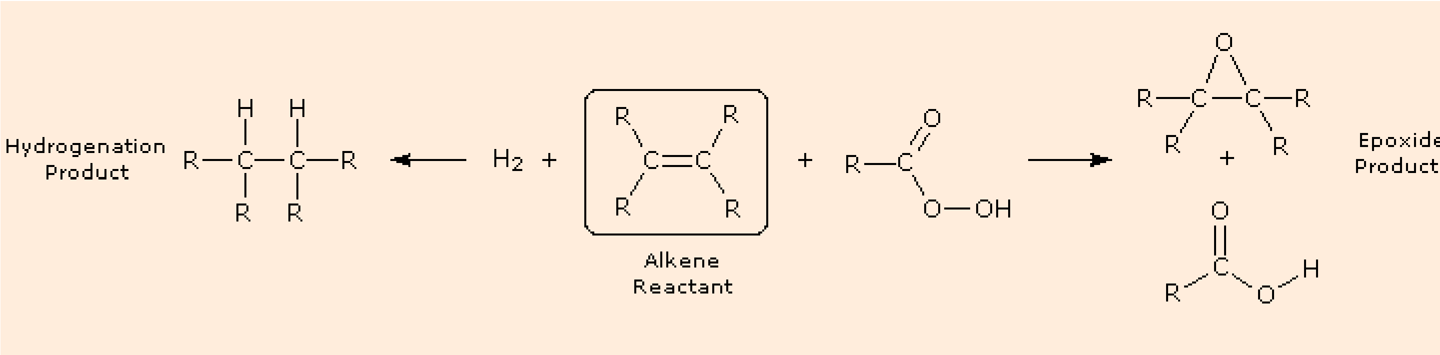
EPOXIDATION

Some oxidation reactions of alkenes give cyclic ethers in which both carbons of a double bond become bonded to the same oxygen atom. These products are called epoxides or **oxiranes**. An important method for preparing epoxides is by reaction with peracids, RCO_3H. The oxygen-oxygen bond of such peroxide derivatives is not only weak (ca. 35 kcal/mole), but in this case is polarized so that the acyloxy group is negative and the hydroxyl group is positive (recall that the acidity of water is about ten powers of ten weaker than that of a carboxylic acid). If we assume electrophilic character for the OH moiety, the following equation may be written.

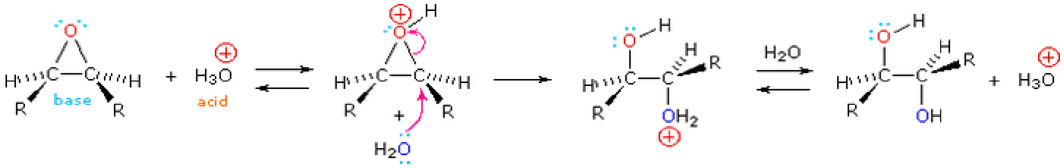


that a dipolar intermediate, as shown above, is actually formed. The epoxidation reaction is believed to occur in a single step with a transition state incorporating all of the bonding events shown in the equation. Consequently, epoxidations by peracids always have syn-stereoselectivity, and seldom give structural rearrangement. You may see the transition state by clicking the Change Equation button. Presumably the electron shifts indicated by the blue arrows induce a charge separation that is immediately neutralized by the green arrow electron shifts.

The previous few reactions have been classified as reductions or oxidations, depending on the change in oxidation state of the functional carbons. It is important to remember that whenever an atom or group is reduced, some other atom or group is oxidized, and a balanced equation must balance the electron gain in the reduced species with the electron loss in the oxidized moiety, as well as numbers and kinds of atoms. Starting from an alkene (drawn in the box), the following diagram shows a hydrogenation reaction on the left (the catalyst is not shown) and an epoxidation reaction on the right. Examine these reactions, and for each identify which atoms are reduced and which are oxidized.

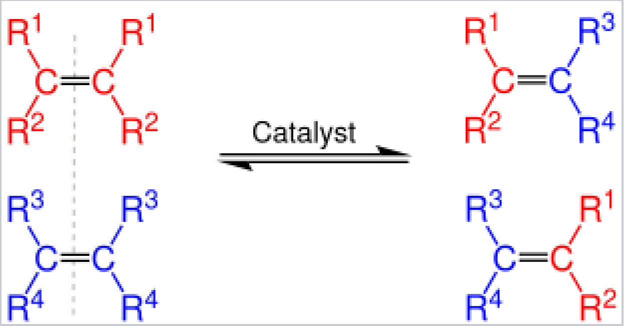


Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups



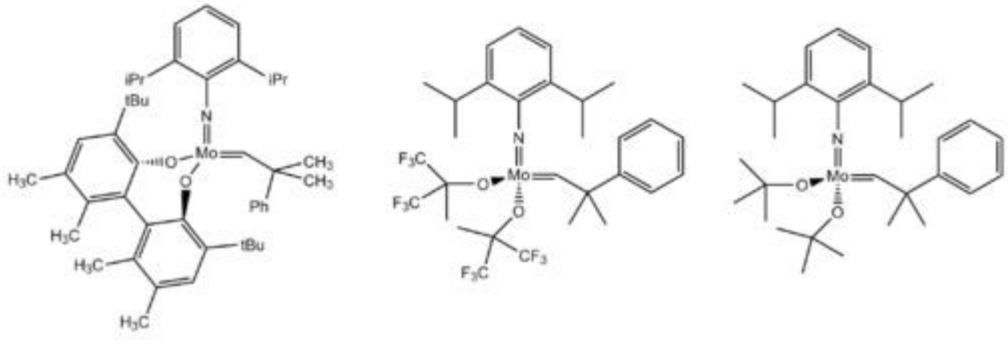
Olefin metathesis

Olefin metathesis is an organic reaction that entails the redistribution of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds. Because of the relative simplicity of olefin metathesis, it often creates fewer undesired by-products and hazardous wastes than alternative organic reactions.



Reaction scheme of the olefin metathesis - changing groups are colored

The reaction requires metal catalysts. Most commercially important processes employ heterogeneous catalysts. The heterogeneous catalysts are often prepared by in-situ activation of a metal halides (MCl_x) using organoaluminium or organotin compounds, e.g. combining MCl_x–$EtAlCl_2$. A typical catalyst support is alumina. Commercial catalysts are often based on molybdenum and ruthenium. Well-defined organometallic compounds have mainly been investigated for small-scale reactions or in academic research. The homogeneous catalysts are often classified as Schrock catalysts and Grubbs catalysts. Schrock catalysts feature molybdenum(VI)- and tungsten(VI)-based centers supported by alkoxide and imido ligands.



Applications

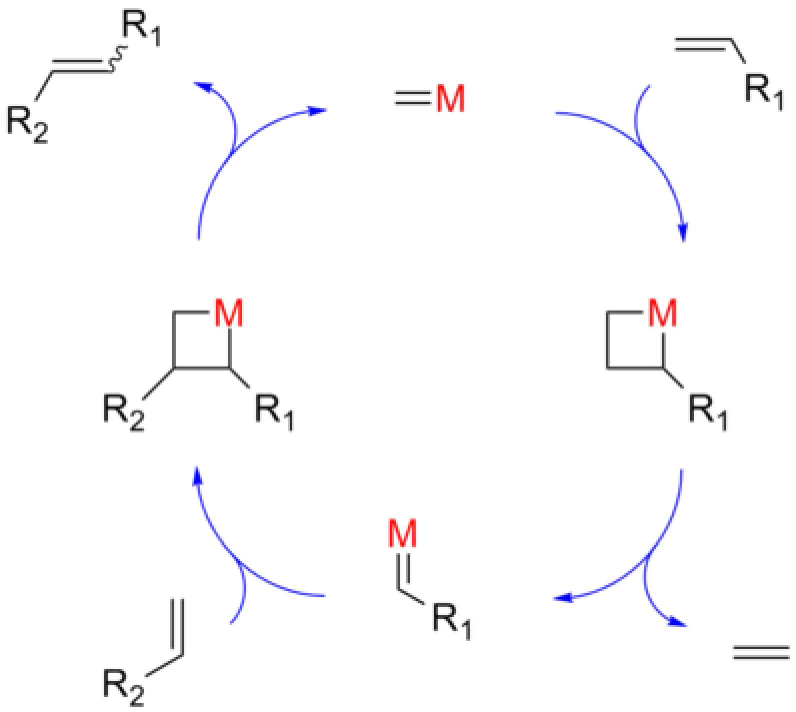
Olefin metathesis has several industrial applications. Almost all commercial applications employ heterogeneous catalysts using catalysts developed well before the Nobel-Prize winning work on homogeneous complexes. Representative processes include:

- The Phillips Triolefin and the Olefin conversion technology. This process interconverts propylene with ethylene and 2-butenes. Rhenium and molybdenum catalysts are used.

Nowadays, only the reverse reaction, i.e., the conversion of ethylene and 2-butene to propylene is industrially practiced, however.

- Shell higher olefin process (SHOP) produces (alpha-olefins) for conversion to detergents. The process recycles certain olefin fractions using metathesis.
- Neohexene production, which involves ethenolysis of isobutene dimers. The catalyst is derived from tungsten trioxide supported on silica and MgO.
- 1,5-Hexadiene and 1,9-decadiene, useful crosslinking agents and synthetic intermediates, are produced commercially by ethenolysis of 1,5-cyclooctadiene and cyclooctene. The catalyst is derived from Re_2O_7 on alumina.
- Synthesis of pharmaceutical drugs,

Reaction mechanism



Olefin metathesis involves little change in enthalpy for unstrained alkenes. Product distributions are determined instead by le Chatelier's Principle, i.e. entropy.