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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – 1 – Organometallic Compounds – SCYA5302

Organometallic Compounds

1. Introduction

The unit deals with the determination of stability of the metal complexes based on EAN rule and determines the hapticity of the chelated ligands for the formation of stable complexes. Structure and bonding in various metal carbonyl complexes have been dealt with on the basis of molecular orbital diagram of the CO ligand.Dinitrogen and dioxygen complexes as ligands give clear insight into the importance of such compounds in biological systems. The unit also deals with the study, interpretation and applications of metals clusters, interstitial atoms and metallocenes.

2. EAN (16 and 18 – electron rule)

Effective atomic number (EAN), number represents the total number of electrons surrounding the nucleus of a metal atom in a metal complex.
It is composed of the metal atom's electrons and the bonding electrons from the surrounding electron-donating atoms and molecules.

Electron counting methods:
There are two popular methods giving same results for the electron count. They are:

Neutral Ligand method (Covalent method)
Donor Pair method (Ionic method)

Neutral Ligand method

In this method, all the ligands are treated as electrically neutral. It takes into account the number of electrons it can donate in its neutral state. The neutral ligands capable of donating two electrons are designated as L. The ligands like Cl^- which can donate one electron in their neutral state are designated as X type ligands. The ligand cyclopentadienyl ($\eta5\text{-}C_5H_5$) which is a five electron donor is designated by a combined symbol L_2X. This method is easy to use when theligands are properly designated. The over emphasis on degree of covalence along with negligence of the charge over the metal ion remain shortcomings of this method. Due to this, it becomes difficult to assign oxidation states to the metal ion resulting in the loss of important information related to the ligands.

The verification of 18-electron rule for a mixed ligand carbonyl complex $(\eta5\text{-}C_5H_5)Fe(CO)_2Cl$ can be carried out as follows:
In this complex, the Fe atom has eight valence electrons.
In addition to this, the ligand $\eta5\text{-}C_5H_5$when considered as a neutral ligand contributes five electrons.
CO is two-electron donor, thus two CO ligands contribute 4 electrons.
Cl, counted as a neutral species is single electron donor, which contributes one electron in total.
Thus the total electron count can be shown as below:
One Fe atom 8 electrons

One ($\eta 5$-C_5H_5) ligand (L2X)	5 electrons
Two CO ligands (L)	4 electrons
One chlorine ligand (X)	1 electron
Total electron count	18 electrons

Donor Pair method

According to this method, some ligands are treated as neutral whereas the others are treated as charged. It is assumed that the ligands donate electrons only as pairs. Neutral ligands like CO are considered as two electron donors. Ligands like halides are considered to take an electron from metal and treated as X-. The ligand ($\eta 5$-C_5H_5) is considered as C_5H_5-, which becomes a six electron donor.

The oxidation state of the metal is calculated as total charge over the complex minus charges over the ligands. The number of electrons contributed by metal is calculated as the group number minus its oxidation number. Finally, the electron count is done as the total of electrons on the metal and the electrons contributed by the ligands.

A sample calculation for ($\eta 5$-C_5H_5)$Fe(CO)_2Cl$ is provided below:

Here oxidation state of Fe, can be calculated as

-1 + X + 0 -1 = 0

X = +2

The group number of Fe is 8.

Therefore, number of electrons contributed by Fe is 8 - 2 = 6.

Number of electrons contributed by one C_5H_5- = 6.

Number of electrons contributed by two CO = 4.

Number of electrons contributed by one Cl- = 2

EAN = 6+6+4+2 = 18 electrons

Thermodynamically stable transition metal organometallic compounds are formed when the sum of the metal d electrons and the electrons conventionally considered as being supplied by the surrounding ligands equals 18.

- By using this rule it is possible to predict the number of ligands in these types of compounds and also the products of their reactions.

Conditions favouring 18 electron rule are:

- Electron rich metal (One which is in Low oxidation state)
- Ligands are good π-acceptors

Thus the effective atomic number of the cobalt atom in the complex $[Co(NH_3)_6]^{3+}$ is 36.

It is obtained from the sum of the number of electrons in the trivalent cobalt ion (24) and the number of bonding electrons from six surrounding ammonia molecules, each of which contributes an electron pair ($2 \times 6 = 12$).

It was first observed by the English chemist **Nevil V. Sidgwick,** since known as the EAN rule, that in a number of metal complexes the metal atom tends to surround itself with sufficient

ligands that the resulting effective atomic number is numerically equal to the atomic number of the noble-gas element found in the same period in which the metal is situated.

This rule seems to hold for most of the metal complexes with carbon monoxide, the metal carbonyls as well as many organometallic compounds.

The EAN rule is often referred to as the "18-electron rule" since, if one counts only valence electrons (6 for Co^{3+} and $2 \times 6 = 12$ for 6 NH_3), the total number is 18.

The 16 and 18 electron rule

Two postulates or rules for organometallic complexes and their reactions are proposed:

1. Diamagnetic organometallic complexes of transition metals may exist in a significant concentration at moderate temperatures only if the metal's valence shell contains 16 or 18 electrons. A significant concentration is one that may be detected spectroscopically or kinetically and may be in the gaseous, liquid, or solid state.

2. Organometallic reactions, including catalytic ones, proceed by elementary steps involving only intermediates with 16 or 18 metal valence electrons.

For example: Association or dissociation of the compound may occur. For example, $Ni[PPh_3]_4$ is substantially dissociated in solution into $Ni[PPh_3]_3$ and PPh_3.

3. Hapticity

The hapto symbol, η, with a numerical superscript, indicate the connectivity between the ligand and the central metal atom.

For example, if all the five carbon atoms of a cyclopentadienyl moiety are equidistant from a metal atom, we term it as η^5-cyclopentadienyl.

Examples: η^1-R, η^1-Ar η^2-C_2R_4 η^1-allyl, η^3-allyl, η^4- Cb, η^5-Cp, η^6-C_6H_6 η^8-C_8H_8 η^2-C_{60}, η^5-R_5C_{60}.

The symbol μ indicates bridging; normally we have μ_2 and rarely μ_3 bridging Examples: μ_2-CO, μ_3-CO, μ_2-CH_3, μ_2-H, μ_2-Cl, , μ_3-Cl, μ_2-OR, μ_2-PR_2, μ_2-NR_2

Example 1: In complex $[Ru(CO)(\eta^3\text{-allyl})(PPH_3)_2]^+$

	Neutral atom method	**Oxidation state method**
Ru	**8**	**6 (Ru +2)**
η^3-allyl	3	4
2 PPH_3	4	4
CO	**2**	**2**

Charge	**-1**	**Not required**
EAN	**16 electrons**	**16 electrons**

Example 2: $[Fe(Cp)_2]$

	Neutral atom method	**Oxidation state method**
Fe	**8**	**6 (Fe +2)**
2 η^5- Cp	10	12
EAN	**18 electrons**	**18 electrons**

Neutral atom method: Metal is taken as in zero oxidation state for counting purpose

Oxidation state method: We first arrive at the oxidation state of the metal by considering the number of anionic ligands present and overall charge of the complex

Exceptions to the 18 electron rule

1. Square planar organometallic complexes of the late transition metals (16e).

2. Some organometallic complexes of the early transition metals (e.g. Cp_2TiCl_2, WMe_6, Me_2NbCl_3, $CpWOCl_3$) [A possible reason for the same is that some of the orbitals of these complexes are too high in energy for effective utilization in bonding or the ligands are mostly σ donors.]

3. Some high valent d^0 complexes have a lower electron count than 18.

4. Sterically demanding bulky ligands force complexes to have less than 18 electrons.

5. The 18 electron rule fails when bonding of organometallic clusters of moderate to big sizes (6 Metal atoms and above) are considered.

6. The rule is not applicable to organometallic compounds of main group metals as well as to those of lanthanide and actinide metals.

4. Metal Carbonyls

Metal carbonyls are coordination complexes with carbon monoxide (CO) as ligands.

Lone pair of electrons are available on both carbon and oxygen atoms of carbon monoxide ligand. However, as the carbon atoms donate electrons to the metal, these complexes are named as carbonyls.

A variety of such complexes such as mono nuclear, poly nuclear, homoleptic and mixed ligand are known.

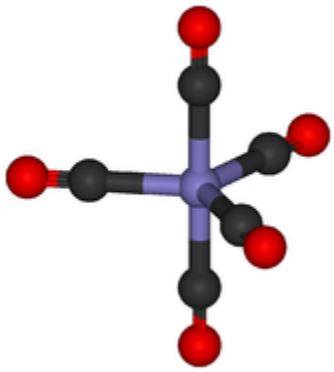
These compounds are widely studied due to industrial importance, catalytic properties and structural interest.

Metal carbonyls are useful in organic synthesis and as catalysts or catalyst precursors in homogeneous catalysis, such as hydroformylation and Reppe chemistry.

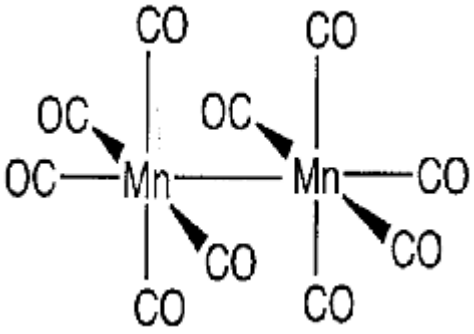
For example, In Mond Process, nickel tetracarbonyl [$Ni(CO)_4$] is used to produce pure nickel.

In organometallic chemistry, metal carbonyls serve as precursors for the preparation of other organometalic complexes.

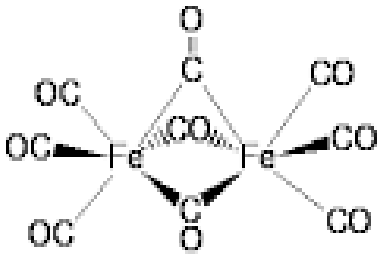
Metal carbonyls are toxic by skin contact, inhalation or ingestion, because of their ability to carbonylate hemoglobin to give carboxyhemoglobin, which prevents the binding of O_2.



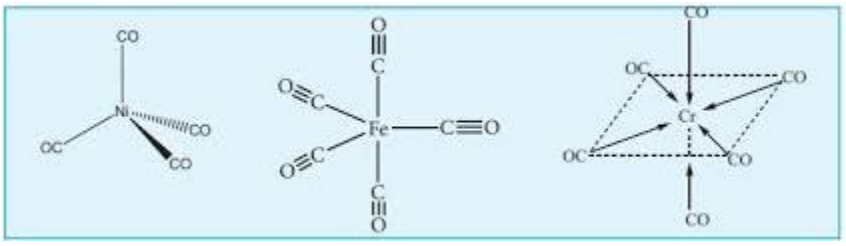
[$Fe(CO)_5$]



[$Mn_2(CO)_{10}$]



[$Fe_2(CO)_9$]



Nomenclature of the metal carbonyls depends on

- the charge of the complex
- the number and type of central atoms
- the number and type of ligands
- their binding modes.

Types of metal carbonyls:

- They occur as neutral complexes
- positively charged metal carbonyl cations
- negatively charged metal carbonylates.

The carbon monoxide ligand may be bound terminally to a single metal atom or bridging to two or more metal atoms.

5. Homoleptic and Heteroleptic complexes

Homoleptic : These complexes contain only one type of ligand such as CO ligand eg. Nickel tetracarbonyl $[Ni(CO)_4]$, $[Co(NH_3)_6]^{3+}$, $[Fe(CN)_6]^{4-}$

- $[Ni(CO)_4]$, $[Fe(CO)_5]$, $[Cr(CO)_6]$

Heteroleptic : Metal carbonyls containing mixture of ligands are heteroleptic complexes. Eg: $[CoCl_2(NH_3)_4]^{+}$**,** $[CoH(CO)_4]$, $[Rh(CO)_2Cl_2]^{-}$, $[Rh(CO)H(PPh_3)_3]$, $[Pt(CO)_2Cl_2]$

Mononuclear metal carbonyls : Mononuclear metal carbonyls contain only one metal atom as the central atom.

Except vanadium hexacarbonyl, only metals with even order number such as chromium, iron, nickel, and their homologs build neutral mononuclear complexes.

Polynuclear metal carbonyls : Polynuclear metal carbonyls are formed from metals with odd order numbers and contain a metal-metal bond.

Isoleptic metal carbonyls : Complexes with different metals, but only one type of ligand are called isoleptic.

Binding modes of Carbon monoxide

Carbon monoxide has distinct binding modes in metal carbonyls.

- They differ in terms of their hapticity, denoted with η,

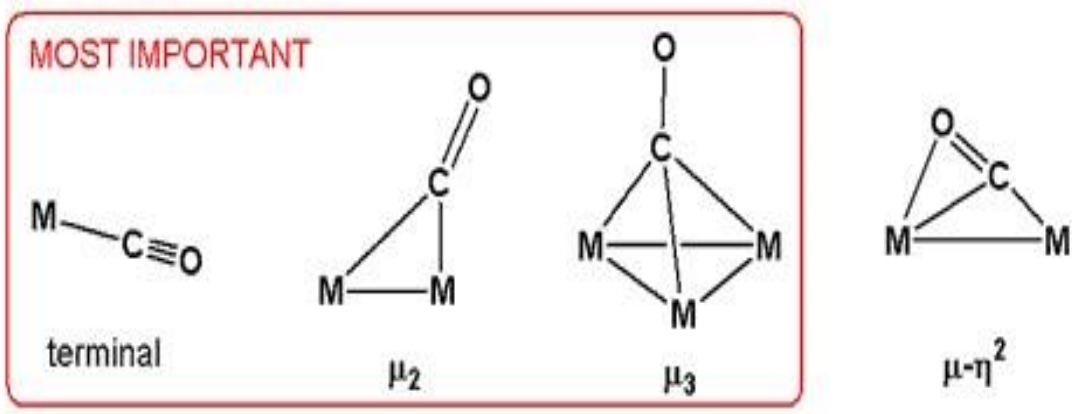
* The bridging mode.

In η^2-CO complexes, both the carbon and oxygen are bonded to the metal. More commonly only carbon is bonded, in which case the hapticity is not mentioned.

The carbonyl ligand engages in a range of bonding modes in metal carbonyl dimers and clusters.

In the most common bridging mode, the CO ligand bridges a pair of metals. This bonding mode is observed in the commonly available metal carbonyls: $Co_2(CO)_8$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, and $Co_4(CO)_{12}$.

In certain higher nuclearity clusters, CO bridges between three or even four metals. These ligands are denoted μ_3-CO and μ_4-CO. Less common are bonding modes in which both C and O bond to the metal, e.g. μ_3-η^2.



$Ni(CO)_4$

$$Ni + 4CO \xrightarrow{60^\circ C} Ni(CO)_4$$

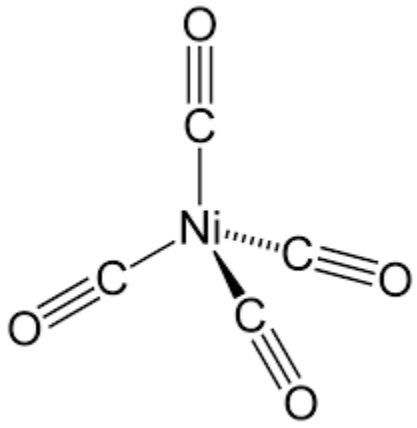
Properties: Colourless liquid, m.pt = -25°C, b.pt = 43°C, decomposition temperature = 180 – 200°C

Insoluble in water and dissolves in organic solvents.

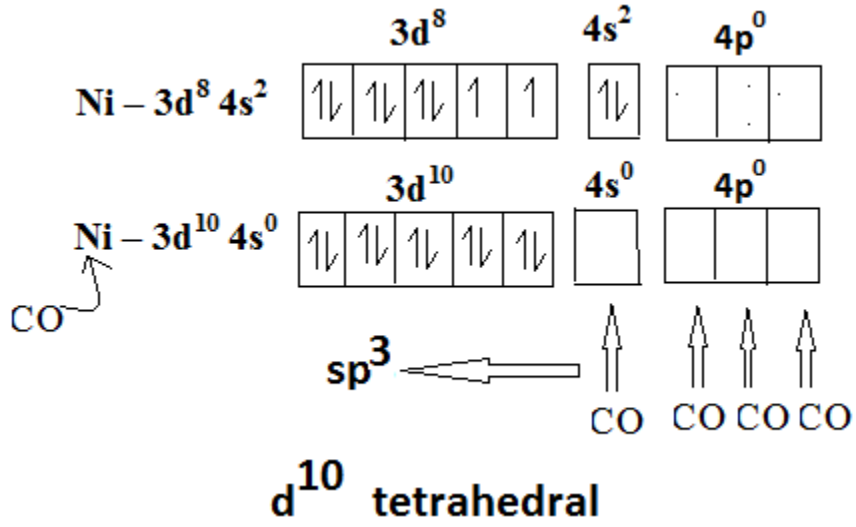
Uses:

- Production of Ni by Mond's process
- Plating of Ni on other metals
- Used as catalyst in the synthesis of acrylic monomers in plastic industries.

Sructure and Geometry



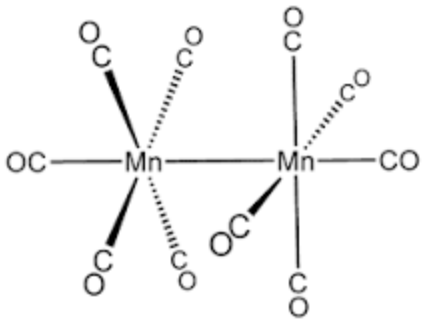
Mononuclear $Ni(CO)_4$



Binuclear $Mn_2(CO)_{10}$

Preparation

$$2MnI_2 + 10CO \xrightarrow[2Mg]{25^0C,\ 210\ atm} Mn_2(CO)_{10} + 2MgI_2$$

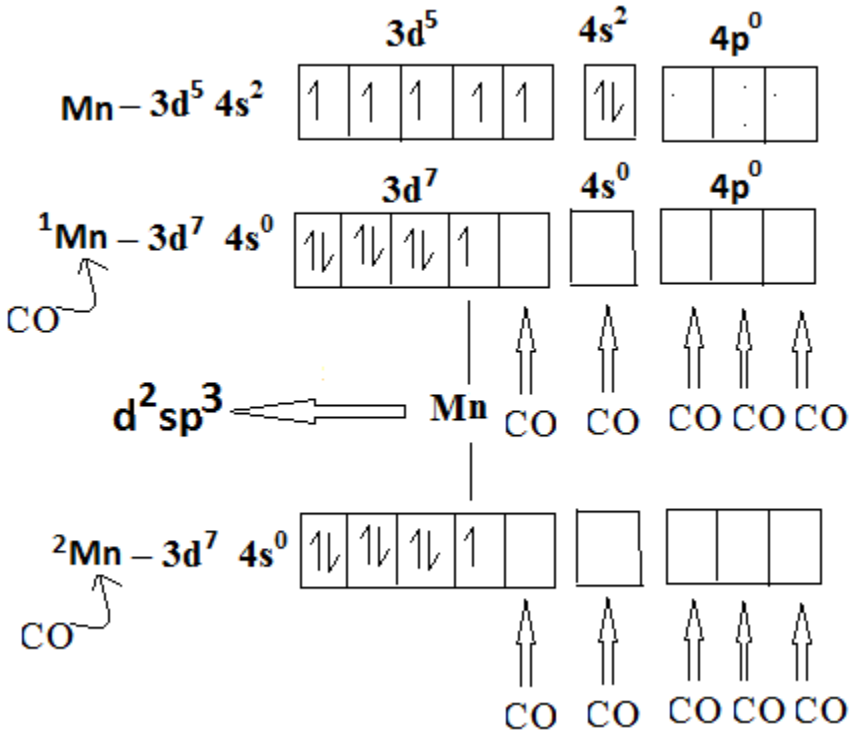


Properties

It is a stable golden yellow crystals with m.pt = 155°C

Structure and Geometry

Mn (Z= 25)



Each Mn atom is octahedrally coordinated to five carbonyl groups and the other manganese atom in such a way that the equatorial carbonyl groups are arranged in a staggered configuration.

Structure and Bonding in Metal Carbonyls

Carbon monoxide bonds to transition metals by "synergistic **π** *back-bonding" which give rise to a partial triple bond between C and O.

A sigma bond (σ) arises from overlap of the nonbonding (or weakly anti-bonding) sp-hybridized electron pair on carbon with a blend of d-, s-, and p-orbitals on the metal. A pair of π bonds

arises from overlap of filled d-orbitals on the metal with a pair of π-antibonding orbitals projecting from the carbon atom of the CO.

The **π bonding** otherwise called the **back bonding** from M → C is possible only when

- metal have d-electrons, and
- metal is in a relatively low oxidation state (<+2) which makes the back donation process favorable.

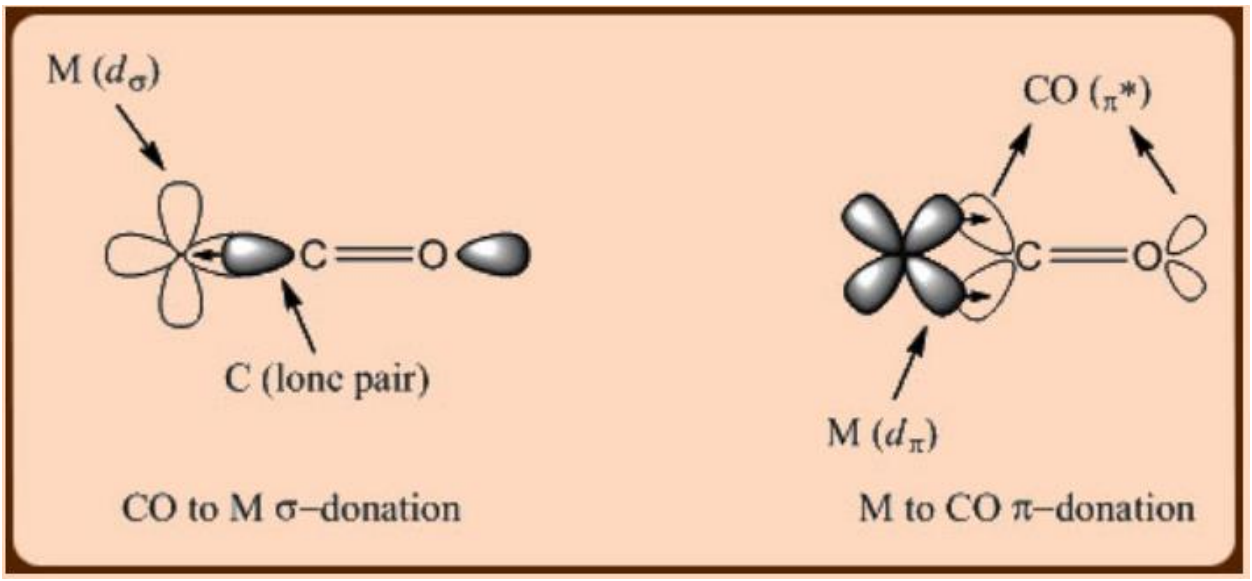
As electrons from the metal fill the π-antibonding orbital of CO, they weaken the carbon-oxygen bond compared with free carbon monoxide, while the metal-carbon bond is strengthened.

Because of the multiple bond character of the M-CO linkage, the distance between the metal and carbon atom is relatively short, often < 1.8 Å, about 0.2 Å shorter than a metal-alkyl bond.

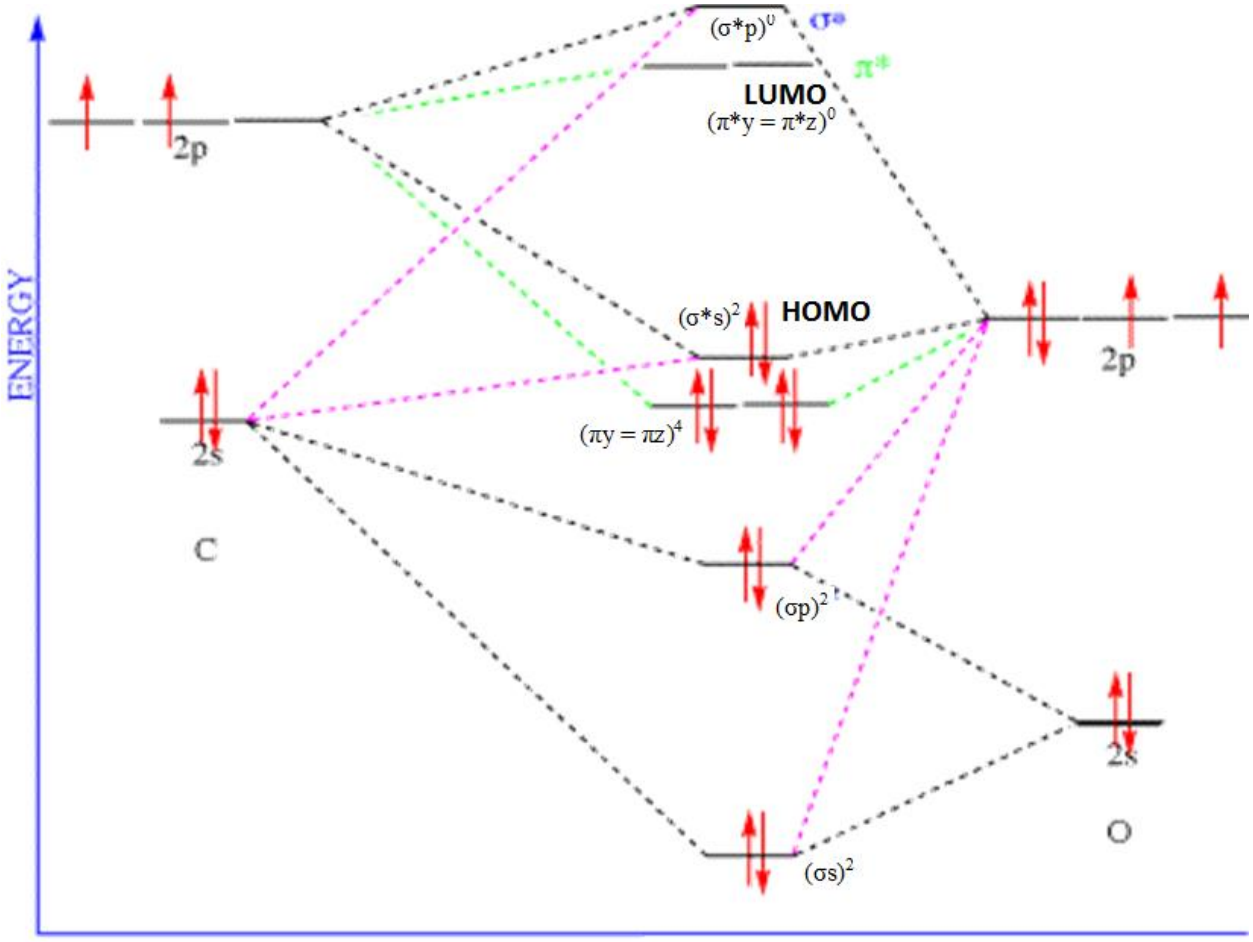
Several canonical forms can be drawn to describe the metal carbonyl bonding modes.

Canonical forms : $M^{-}{-}C{\equiv}O^{+} \leftrightarrow M{=}C{=}O \leftrightarrow M^{+}{\equiv}C{-}O^{-}$

Synergic π back-bonding in Metal Carbonyls



Molecular Orbital Diagram of CO



Electron Distribution : $(\sigma s)^2\,(\sigma p)^2\,(\pi y = \pi z)^4\,(\sigma^* s)^2\;\;(\pi^* y = \pi^* z)^0\,(\sigma^* p)^0$

σ*s is the highest occupied molecular orbital (HOMO) which can donate the lone pair of electrons for the formation of a OC → M σ bond.

π*y = π*z are the lowest unoccupied molecular orbitals (LUMO) which can accept the electron density from an appropriately oriented filled metal orbital resulting in the formation of a M→ CO π bond.

6. IR Spectrum of Metal Carbonyls

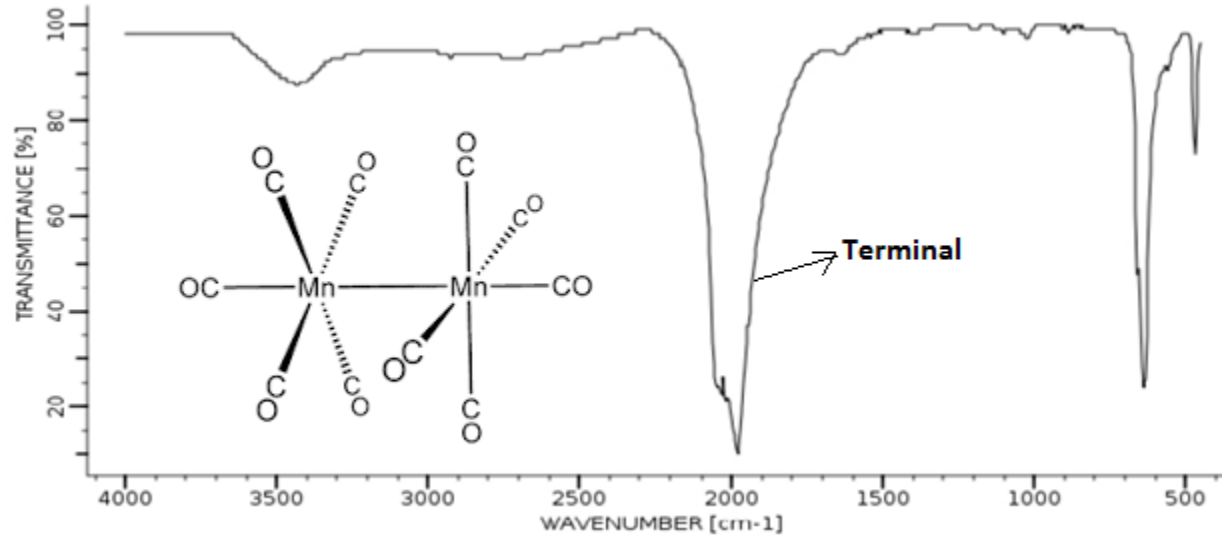
Infrared spectroscopy is an important technique for characterizing metal carbonyls. The C-O vibration is denoted as ν_{CO} and occurs at 2143 cm^{-1} for simple CO gas. The metal carbonyl compounds displays two kinds of bindings in the form of terminal and bridging modes. The infrared spectroscopy can easily distinguish between these two binding modes of the metal carbonyl moiety:

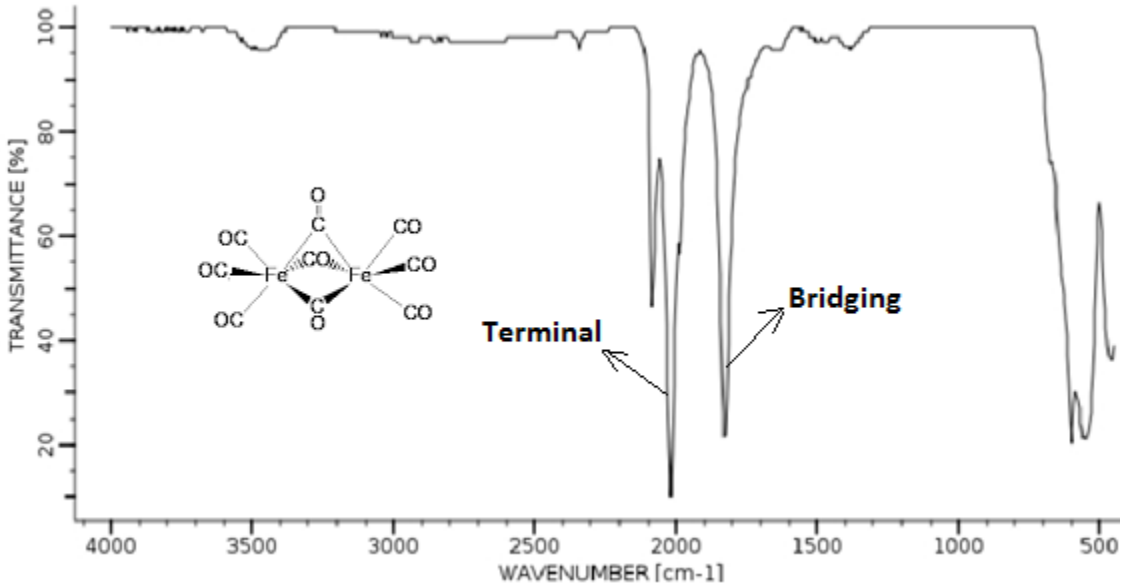
Terminal CO shows ν(CO) stretching band at *ca*. 2100-2000 cm^{-1}

Bridging CO appears in the range 1720−1850 cm^{-1}.

The energies of the ν_{CO} band for the metal carbonyls is determined by the strength of the carbon-oxygen bond, and inversely correlated with the strength of the π-backbonding between the metal and the carbon.
The increased π-bonding due to back-donation from multiple metal centers results in further weakening of the C-O bond. π-Basic ligands increase π-electron density at the metal, and improved backbonding reduces ν_{CO}.

The IR spectrum of the metal carbonyl compound is shown below:





Preparation of metal carbonyl complexes

The common methods of the preparation of the metal carbonyl compounds are,

i. Directly using CO

$$Fe \xrightarrow{CO,200atm,200^\circ C} Fe(CO)_5$$

The main requirement of this method is that the metal center must be in a reduced low oxidation state in order to facilitate CO binding to the metal center through metal to ligand π−back donation.

ii. Using CO and a reducing agent

$NiSO_4+CO+S_2O_4^{2-}\longrightarrow Ni(CO)_4$

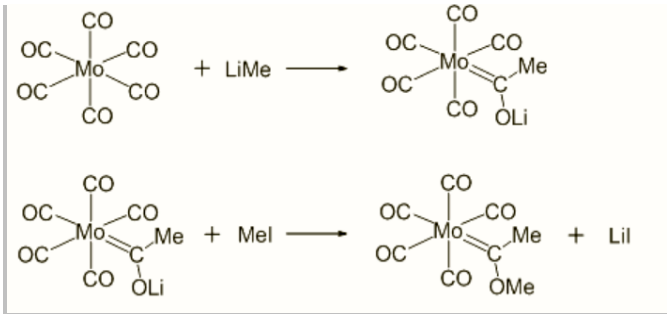
This method is commonly called reductive carbonylation and is mainly used for the compounds having higher oxidation state metal centers. The reducing agent first reduces the metal center to a lower oxidation state prior to the binding of CO to form the metal carbonyl compounds.

iii. From carbonyl compounds

This method involves abstraction of CO from organic compounds like the alcohols, aldehydes and CO_2.

Reactivities of metal carbonyls

i. Nucleophilic attack on carbon : The reaction usually gives rise to carbene moiety.



ii. Electrophilic attack at oxygen

$Cl(PR_3)_4Re{-}CO+AlMe_3\longrightarrow Cl(PR_3)_4Re{-}CO\longrightarrow AlMe_3$

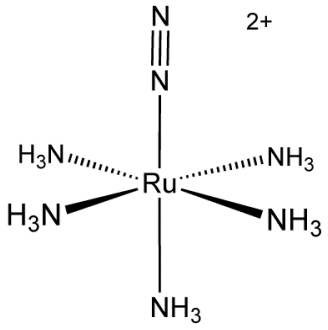
iii. Migratory insertion reaction

$MeMn(CO)_5+PMe_3 \longrightarrow (MeCO)Mn(CO)_4(PMe_3)$

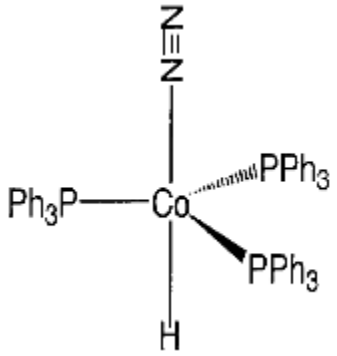
7. Dinitrogen Complexes

Dinitrogen complexes are complexes having coordinated nitrogen molecule to a metal ion. The nitrogen molecule act as a ligand and coordinate through one of the nitrogen atoms. Dinitrogen complexes are known with few transition metal ions such as Mo, Fe, Ru, Os etc.

Since N_2 is isoelectronic with CO, the possible stability of dinitrogen complexes analogous in structure to carbonyl complexes was the subject of speculation for many years. These compounds generated great interest because of the parallels with the interaction and activation of nitrogen molecules on the iron catalyst used in ammonia synthesis and the nitrogen fixing enzyme nitrogenase. However, the first dinitrogen complex, $[Ru(N_2)(NH_3)_5]X_2$, was prepared by A. D. Allen (1965) unexpectedly from the reaction of a ruthenium complex and hydrazine. Subsequently, it was discovered by chance that nitrogen gas coordinates to cobalt, and $[CoH(N_2)(PPh_3)_3]$ was prepared in 1967. Many dinitrogen complexes have been prepared since these early beginnings.



$[Ru(N_2)(NH_3)_5]X_2$



$[CoH(N_2)(PPh_3)_3]$

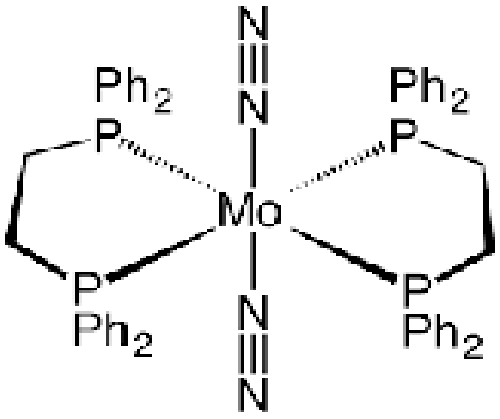
In most dinitrogen complexes, N_2 is coordinated to the metal by one nitrogen atom.

A large number of dinitrogen complexes are known till date. Most of these complexes are applied for artificial dinitrogen fixation. The first example of N_2 Complexes $[Ru(NH_3)_5(N_2)]+2X_2$ (X = Br, I, PF_4, or PF_6) was separated from the reaction of $RuCl_3$ with hydrazine in the aqueous solution in the presence of different anions. While complex $[Co(N_2)(PPh_3)_3]$ prepared directly from gaseous N_2.

Most of the metal ions forming mononuclear dinitrogen complexes also coordinate with carbon monoxide which represents a bonding similarity between the dinitrogen and carbonyl as ligands.

The discovery of dinitrogen complexes was started with the $[Ru(NH_3)_5(N_2)]+2X_2$ (X = Br, I, PF_4, or PF_6) in 1965 after which the preparation was directly by the reaction of nitrogen gas. This has led to chemists understand that biological nitrogen fixation takes place in a similar fashion.

The dinitrogen complexes are of substantial interest and have already shown to be valuable synthetic intermediates.



$[Mo(N_2)_2(Ph_2CH_2CH_2Ph_2)_2]$

In dinitrogen complexes, a large number of other ligands can coexist with nitrogen molecule on a metal atom. Ligands that coexist with nitrogen in a metal complex are phosphines, halides, hydride, ammonia, carbon monoxide, and water.

Preparation

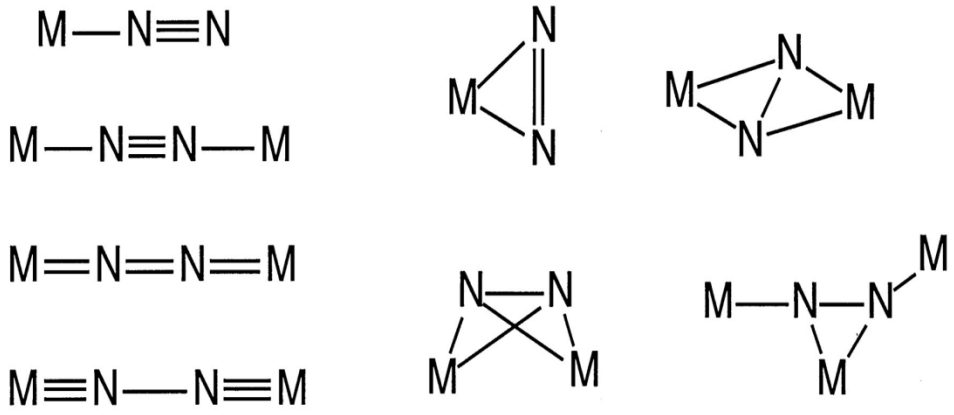
A. The various preparations of N_2 Complexes directly using N_2 gas. 1. $[Co(N_2)(PPh_3)_3]$, $[RuH_2(N_2)(PPh_3)_3]$, $[FeH_2(N_2)(PR_3)_3]$ (R_3 = $EtPh_2$, n-Bu), and $[CoH(N_2)(PR_3)_3]$ have been prepared by following reaction $[MH_n(PR_3)_3] + N_2 \rightarrow [MH_{n-2}(N_2)(PR_3)_3] + H_2$. The reaction is exciting because it may provide a model for the first step in the "fixation" of dinitrogen by nitrogenase. The enzymic reaction is competitively inhibited by dihydrogen, which is consistent with a rapid equilibrium reaction between a polyhydride and N_2 to give a dinitrogen complex.

B. Preparation from Compounds Containing Chains of Nitrogen Atoms 1. A variety of ruthenium(III) and -(lV) and osmium(III) and -(lV) chloro and ammine complexes and even OsO_4 will react with aqueous hydrazine to give complexes of the type $[M(NH_3)_5(N_2)]X_2$. Unfortunately the products are often contaminated with hydrazine or bis dinitrogen complexes.

$[OsCl_3(PBu_2Ph)_3]$ gives a mixture of starting material and $[OsCl_2(N_2)(PBu_2Ph)_3]$ while [Fe(dithiocarbamate)$_3$] with hydrazine gives an unknown product having $\nu(N_2)$ at 2045 cm^{-1} .

C. Preparations in which two nitrogen atoms are combined to give a Dinitrogen Complex

1. Reaction of $[Fe(CN)_5NO]^{2-}$ with hydrazine has been found to give a dinitrogen complex.
$[Fe(CN)_5NO]^{2-} + N_2H_4 \rightarrow [Fe(CN)_5(N_2)]$



8. Dioxygen Complexes

Dioxygen binds with metal ions to form a dioxygen metal complex reversibly or irreversibly. The major functions of molecular oxygen are to act as a ligand as well as a reagent in transition organometallic chemistry. For example, in respiration, dioxygen binds reversibly to the iron atom of the heme group in hemoglobin and myoglobin whereas in corrosion, the formation of metal oxides takes place by the oxidation of pure metal with atmospheric dioxygen. Hence, the isolation/synthesis, characterization and studies of dioxygen metal complexes are of particular interest to biochemists, electrochemists and industrial chemists.

Properties of O_2

The molecular orbital theory which is based on the bonding and antibonding molecular orbitals successfully explained the paramagnetic behavior of dioxygen which the valence bond theory failed to explain.

According to molecular orbital theory, the outer electronic configuration of dioxygen can be written as

$O_2 = (\sigma_{1s})^2 (\sigma^*_{1s})^2 (\sigma_{2s})^2 (\sigma^*_{2s})^2 (\sigma_{2p})^2 (\pi_{2px} = \pi_{2py})^4 (\pi^*_{2px} = \pi^*_{2py})^2$

$(\pi^*_{2px})^1 = (\pi^*_{2py})^1$ demonstrates the paramagnetic behaviour of oxyen molecule.

The half filled antibonding molecular orbitals can accomodate electrons resulting in charged molecules such as the superoxide ion (O_2^-) by the addition of one electron and forming peroxide ion (O_2^{2-}). Hence the strength and the bonding distance of O-O are greatly influenced by the charges on the charged oxygen molecule. The internuclear distance between the atoms is more in the peroxide form due to the presence of more number of electrons in the antibonding molecular orbitals.

Among the several charged forms of the dioxygen molecule, the neutral dioxygen has the ability to coordinate with transition metal ions and form metal complexes. Dioxygen is a strong oxidizing agent and display reactivity in three different ways.

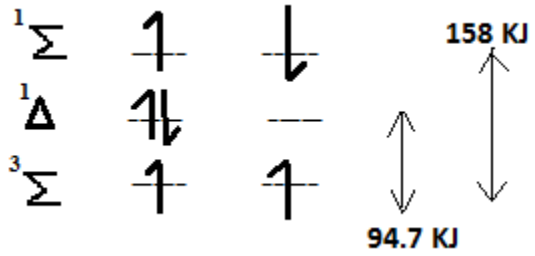
Light energy can excite dioxygen molecule in the triplet ground state to singlet excited state. The formed singlet oxygen is highly reactive and readily reacts with many singlet molecules.

The triplet O_2 binds with transition metal ions such as in biological systems.

The triplet O_2 reacts with certain organic compounds in biological systems.

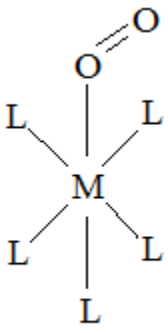
$RH + O_2 \rightarrow R^{\cdot} + OH_2^{\cdot}$

Triplet and Singlet Oxygens

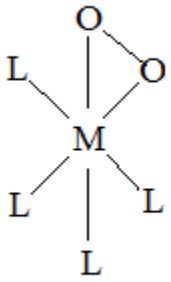


Binding modes of dioxygen

a) Mononuclear metal complexes

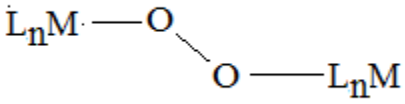


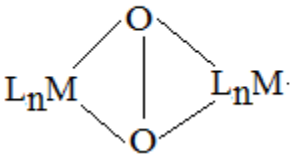
Superoxo

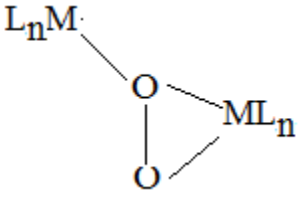


Peroxo

b) Binuclear metal complexes







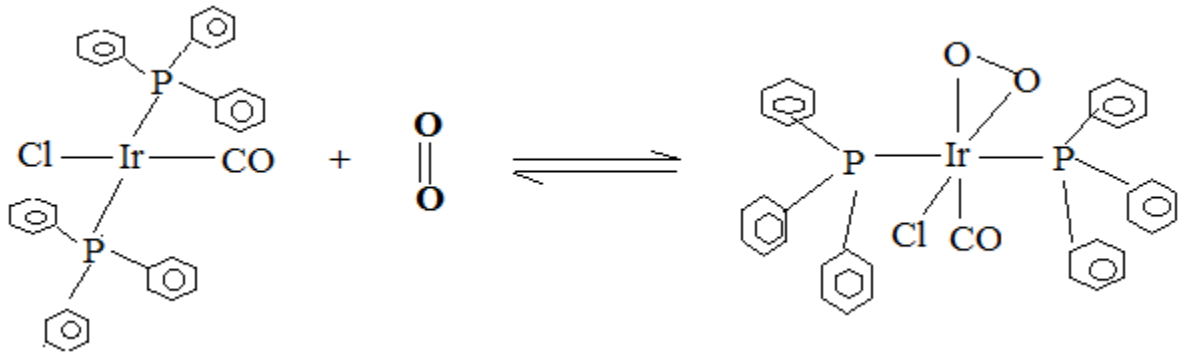
Dioxygen binds with most of the transition metal ions to form dioxygen complexes in which the oxidation states of these metal ion vary from II to VI which are normally greater than usual oxidation states.

The metal complexes are generally diamagnetic and some paramagnetic complexes are also known to exist. The dioxygen metal complexes contain various types of hard (F) and soft ligands (CO, PPh_3). The coordination number varies from 2 to 8.

Few biologically important dioxygen transition metal complexes are:

1. Hemoglobin and myoglobin: They are globular proteins that bind with dioxygen and deliver dioxygen. Both contains a porphyrin subunit with Fe^{2+} ion at the center of the porphyrin rings which is capable of binding with dioxygen.

2. Vaska's Complex: It is a square planar diamagnetic complex with the name transchlorocarbonylbis(triphenylphosphine)Iridium(I). The complex can bind dioxygen with a change in oxidation state of Ir from (I) to (III) and is called oxidative addition.



3. Hemocyanin: Hemocyanins are dioxygen transporting molecules. The deoxy form is a colorless copper-histidine complex which can bind with two units of dioxygen molecule resulting in a dinuclear blue colored complex. The dioxygen molecule binds two Cu ions in a μ_2-η^2,η^2 peroxo (O_2^{2-}) fashion.

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DEPARTMENT OF CHEMISTRY

UNIT – 2 – Synthesis of Organometallic Compounds – SCYA5302

Synthesis of Organometallic Compounds

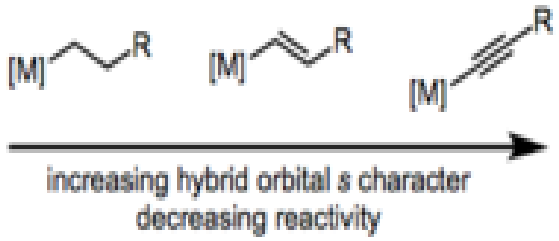
1. Introduction

This unit deals with the structure and bonding in various organometallic compounds in which the ligands are the alkanes, olefins, alkynes, allyl and arenes. The unit also deals with the reactions of metal complexes with the mechanistic steps involved.

2. Alkyl ligands

Alkyl ligands are capable of forming single bond with metal. The alkyl group act as a one electron monohapto ligand where the σ bond can donate one or two electrons to the metal. Such compounds with d-block elements are less common compared to s and p block elements which is due to weak M-C bond. Hence it is difficult to synthesize. The metal alkyls undergo decomposition pathways of low activation barriers.

The metal carbon bond (M-C) bond is composed of a positively charged metal and a negatively charged carbon. As the electronegativity of the metal increases, there is decrease in the reactivity. Based on the hybridization of carbon atom, sp-hybridized ligands are least nucleophilic.

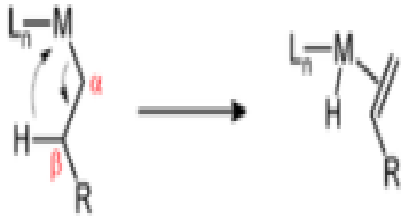


Metal alkyl complexes can be synthesized by the attack of nucleophiles and electrophiles. The complexes can also be prepared by oxidative addition and by miratory insertion methods.

Metal alkyl complexes undergo decomposition mainly through β hydride elimination or by reductive elimination methods.

β hydride elimination

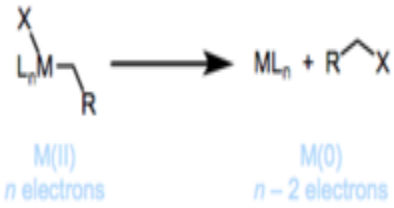
β hydride elimination involves transfer of a hydrogen atom from the β position of the ligand to the metal center of the complex. In order to prevent the decomposition of the metal alkyl complexes, there should not be β-hydrogens in the β carbon of the alkyl group.



β hydride elimination

Reductive Elimination

It is the elimination of groups from the metal alkyl complexes leading to the loss of 2 electrons. Elimination takes place when the groups are cis oriented. This increase the unstability and futher elimination can proceed.

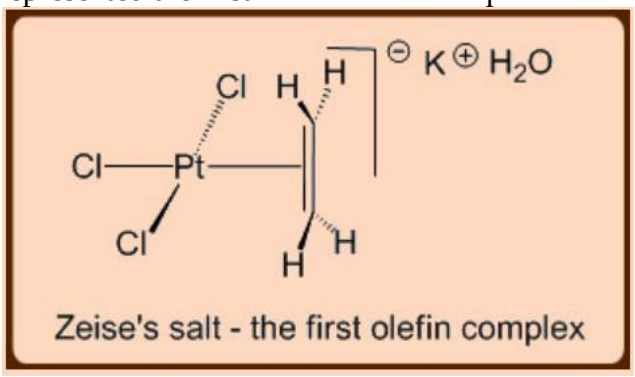


Stability of metal alkyl complexes can be increased by preventing β hydride elimination and reductive elimination.

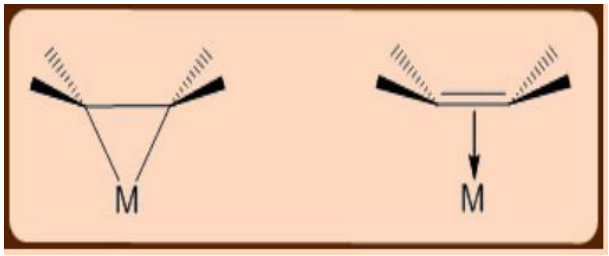
A transition metal-alkyl complex with EAN = 18 electrons shows that the orbitals are completely filled and does not undergo decomposition and remain stable.

3. Metal-Alkene complexes

Though the first metal olefin complex dates back a long time to the beginning of 19th century, its formulation was established only a century later in the 1950s. While reacting K2PtCl4 with EtOH in 1827, the Danish chemist Zeise synthesized the famous **Zeise's salt** K[PtCl3(C2H4)]·H2O containing a Pt bound ethylene moiety and which incidentally represented the first metal−olefin complex.



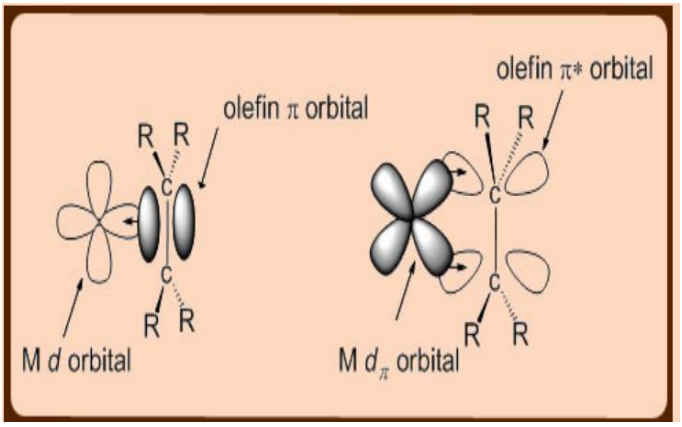
The metal−alkene or metal-olefin bonding interaction is explained by *Dewar−Chatt* model.



It takes into account two mutually opposing electron donation:

1. involving σ−donation of the olefinic C=C π−electrons to an empty d_π metal orbital
2. π−back donation from a filled metal d_π orbital into the unoccupied C=C π* orbital.

Hence for d^0 systems, metal−olefin complexes formation is not observed.
The σ−donation and the π−back donation affect the geometry as well as the hybridizaton of the C=C bond of the metal bound olefinic moiety with a change in the C−C olefin bond distance.



If σ−donation is high from the olefin than the π−back donation, there is C=C bond order is decreased with the lengthening of the C-C bond. If the reverse happens, that is, if π−back donation is high than the σ−donation, there is increase in the bond order of the olefin moiety and there is shortage of the C-C bond in the olefin. Thus for a weak π−basic metal, the C−C bond lengthening would be small while for a strong π−basic metal, the C−C lengthening would be significant.

Ligand to metal π−back donation is found to affect the hybridization of the olefinic C atoms. When there is low or no π−back donation, the hybridization would be sp^2. When there is significant π−back donation from the metal to ligand, the hybridization becomes sp^3 and is accompanied by a slight bending of the olefin away from the metal center. The change is detected by ^1H and ^{13}C – NMR spectroscopy.

An important observation related to π–back donation is that the strained olefins are involved in tighter binding with the metal as observed with cyclopropane and norbornene due to the relief of the strain upon binding with the metal.

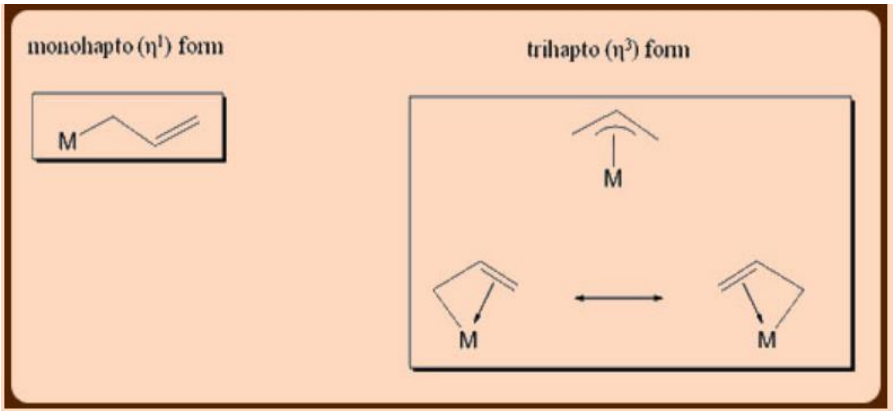
The second observation is that, the free olefins are electron rich due to the presence of the π–electrons and are attacked by electrophiles. In the metal – olefin complexes, the π–electrons are involved in σ–donation and becomes electron deficient. Due to increase in the positive character, the bound olefins are attacked by nucleophiles. This nature of reversal of olefin reactivity is called **umpolung** character.

4. Metal-Allyl complexes

The allyl ligand binds to metals in two ways *i.e.* in a η^1 (monohapto) form and a η^3 (trihapto) form.

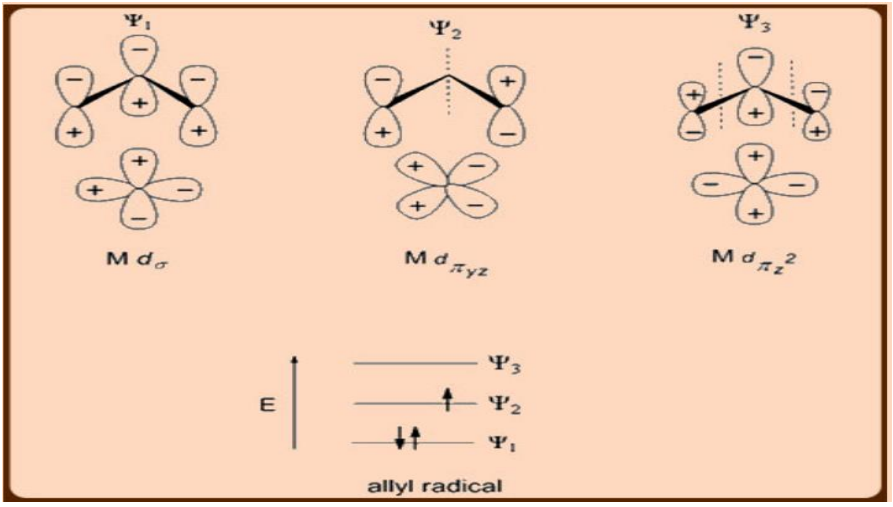
1. In its monohapto (η^1) form, it behaves as an anionic *1e–donor* X type of a ligand analogous to that of a methyl moiety while

2. In trihapto (η^3) form, it acts as an anionic *3e–donor* LX type of a ligand.



Metal-Allyl interaction

The molecular orbitals namely Ψ_1, Ψ_2 and Ψ_3 of the allyl ligand interact with the metal in a metal allyl complex. The energy of these molecular orbitals increase with the increase in the number of nodes. Of the three, the Ψ_1 and Ψ_2 orbitals usually engage in ligand to metal σ–donation, with Ψ_1 involving in a dative L–type bonding and Ψ_2 participating in a covalent X–type bonding with the metal *d* orbitals



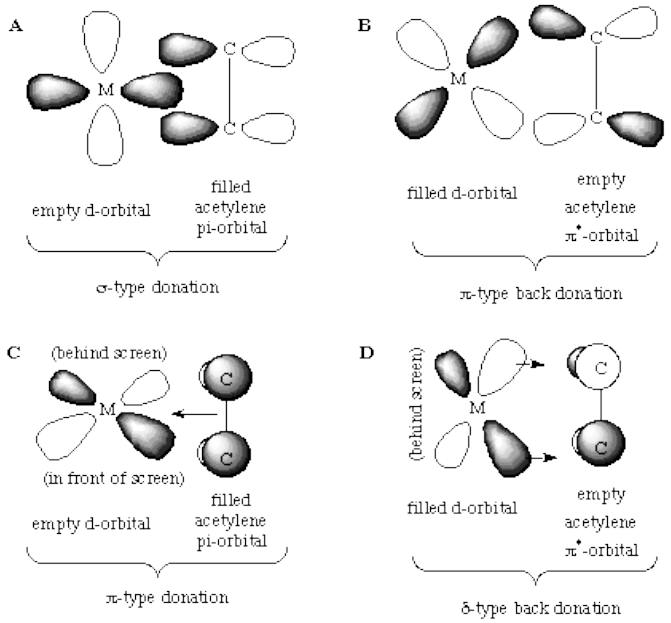
Metal-allyl complexes are synthesized by the attack of nucleophiles, electrophiles and from a diene complex.

Metal-allyl complexes undergo reaction with nucleophiles, electrophiles, insertion reaction and reductive elimination.

5. Metal-alkyne Complexes

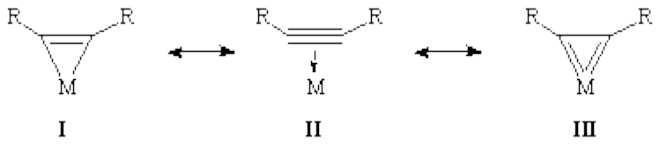
The bonding of an alkyne like acetylene to a transition metal complex is similar to that of an alkene. Alkynes are more electropositive and therefore bind to metal more tightly than alkenes. In fact, alkynes will often displace alkenes.

The primary difference in bonding between alkenes and alkynes is that an alkyne can act as either a 2 or 4 electron donor as the alkynes have **two** sets of mutually orthogonal pi bonds. We can bind one of these to the transition metal in a sigma-type fashion (**A**) as did for alkenes, including a pi-backbond (**B**). The orthogonal set can also bind in a pi-type fashion using an orthogonal metal d-orbital (**C**):



The back-donation to the antibonding orbital (**D**) is a delta-bond (there are two nodes in it), and the degree of overlap is quite small as the two orbitals meet side-to-side rather than engaging in direct overlap. Therefore, the contribution of **D** to the bonding of alkynes is minimal at best.

The net effect of this additional pi-donation is that alkynes are usually non-linear when coordinated to a transition metal complex. We can draw several resonance structures that depict the bonding of an alkyne. **I** is the **metallacyclopropene** resonance form. Support for this versus a simple two electron donor, **II**, can be inferred from the C-C bond distance as well the R-C-C-R angles (see below). **III** generally does not contribute to the bonding of alkyne complexes.

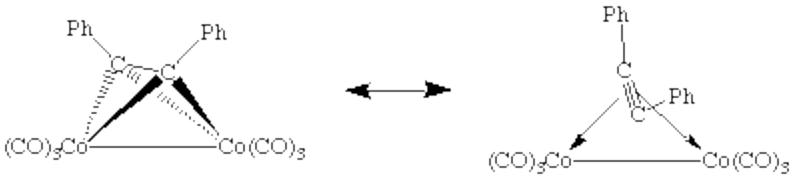


Other than geometry, the other major difference between **I** and **II** is that **I** implies the metal oxidation state is greater by two. In other words, one can sometimes think of alkynes as dianionic ligands instead of as neutral ligands.

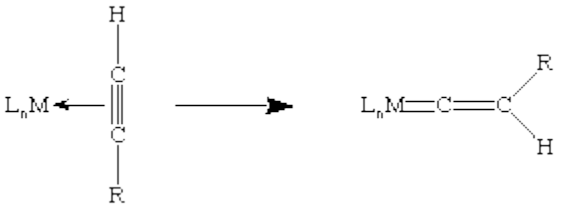
As expected from the reduced C-C bond order, the C-C bond distances for coordinated alkynes are typically larger (125 to 135 pm) than in the uncoordinated ligand (110 to 115 pm).

For 4-electron donors, the R-C-C bond angles are usually in the range of 130 to 146 degrees, with M-C bond distances of 199 to 209 pm.

Finally, it is worth noting that alkynes can also bridge two metal centers. In these cases it is sometimes appropriate to describe the complex as a 1,2-dimetallatetrahedrane. In this case, the alkyne is a 2-electron donor to each metal center:



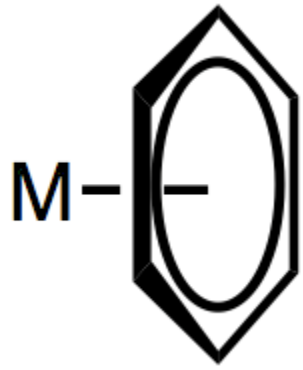
Unlike coordinated polyenes and alkenes, nucleophilic attack on a coordinated alkyne is fairly rare. However, rearrangement of terminal acetylene complexes to the vinylidene tautomer is not uncommon:



A number of transition metal alkyne complexes are intermediates in the cyclotrimerization of alkynes to substituted benzenes. In some cases, nitriles can be co-cyclized with alkynes to give heteroatom-substituted rings.

6. Metal-arene Complexes

Arenes are dative, L-type ligands. Arenes commonly bind to metals through more than two atoms, although η2-arene ligands are known. Structurally, most η6-arenes tend to remain planar after binding to metals. Both "normal" bonding and backbonding are possible for arene ligands; however, arenes are stronger electron donors than CO and backbonding is less important for these ligands. The reactivity of arenes changes dramatically upon metal binding, along lines that we would expect for strongly electron-donating ligands. After coordinating to a transition metal, the arene usually becomes a better electrophile (particularly when the metal is electron poor). Thus, metal coordination can enable otherwise difficult **nucleophilic aromatic substitution** reactions.

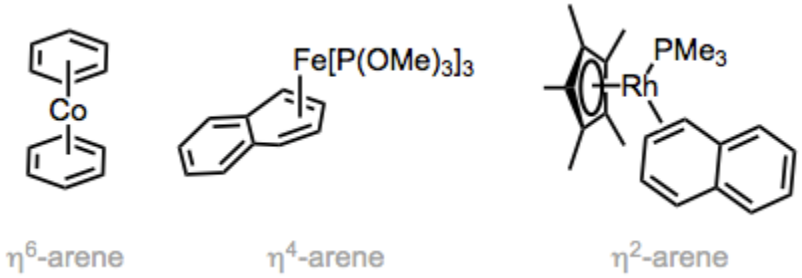


The coordination of an aromatic compound to a metal center through its aromatic π MOs removes electron density from the ring. $\pi \rightarrow d\sigma$ (normal bonding) and $d\pi \rightarrow \pi^*$ (backbonding)

orbital interactions are possible for arene ligands, with the former being much more important, typically.

Multiple coordination modes are possible for arene ligands. When all six atoms of a benzene ring are bound to the metal (η6-mode), the ring is flat and C–C bond lengths are slightly longer than those in the free arene.

The ring is bent and non-aromatic in η4-mode, so that the four atoms bound to the metal are coplanar while the other π bond is out of the plane. η4-Arene ligands show up in both stable complexes (see the figure below) and reactive intermediates that possess an open coordination site. To generate the latter, the corresponding η6-arene ligand undergoes **ring slippage**—one of the π bonds "slips" off of the metal to create an open coordination site.

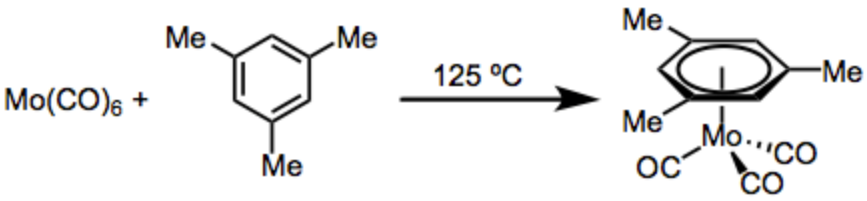


Arene ligands exhibit multiple coordination modes.

Even η2-arene ligands bound through one double bond are known. Coordination of one π bond results in **dearomatization** and makes η2-benzene behave more like butadiene, and furan act more like a vinyl ether. With naphthalene as ligand, there are multiple η2 isomers that could form; the isomer observed is the one that retains aromaticity in the free portion of the ligand. In fact, this result is general for polycyclic aromatic hydrocarbons: binding maximizes aromaticity in the free portion of the ligand. In the linked reference, the authors even observed the coordination of two different rhodium centers to naphthalene—a bridging arene ligand! Other bridging modes include σ, π-binding (the arene is an LX-type ligand, and one C–M bond is covalent, not dative) and L2-type bridging through two distinct π systems (as in biphenyl).

Arene ligands are usually hydrocarbons, not heterocycles. Why? Aromatic heterocycles, such as pyridine, more commonly bind using their basic lone pairs. That said, a few heterocycles form important π complexes.

Syntheses of metal arene carbonyl complexes take advantage of the fact that arenes are strongly binding, "chelating" ligands. Infrared spectroscopic studies have shown that a single benzene ligand is a stronger electron donor than three CO ligands—C–O stretching frequencies are lower in metal arene carbonyls than homoleptic metal carbonyls.



7. Metal Carbonyls as Catalysts

Organometallic compounds and metal carbonyls show catalytic activity. In most of the homogeneous catalysis, the commonly occurring reaction pathways or the steps can be classified as follows:

I. Reactions involving gain or loss of ligands

a. Ligand dissociation and substitution

b. Oxidative addition

c. Reductive elimination

d. Nucleophilic Displacement

II. Reactions involving ligand modification

a. Insertion

b. Carbonyl insertion

c. Hydride elimination

d. Abstraction

I. Reactions invoving Loss and gain of ligands

It is the most important reactions of organometallic compounds which result in a change in the coordination number of the metal by the gain/loss of ligands. If the formal oxidation state of metal is retained, those reactions are considered as addition or dissociation reaction. If the formal oxidation state is changed, those reactions are termed as oxidative addition or reductive elimination.

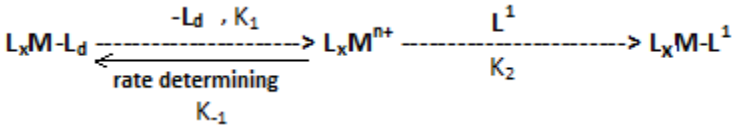
Type of Reaction	Coordination number	Oxidation state
Addition	Increases	None
Dissociation	Decreases	None
Oxidative addition	Increases	Increases
Reductive elimination	Decreases	Decreases

Dissociative reactions upon coupling with addition reactions, are synthetically useful by providing an avenue to replace ligands such as carbon monoxide and phosphines with other ligands.

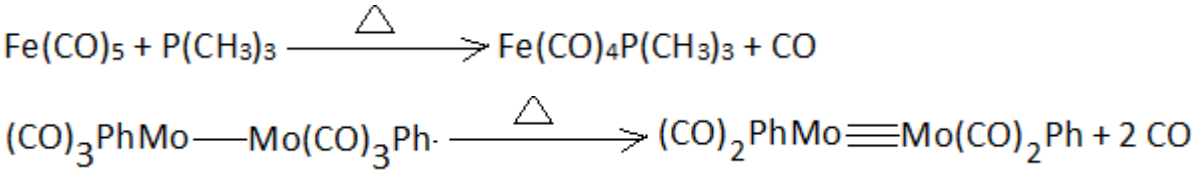
1. Ligand Dissociation and Substitution

An efficient catalytic cycle requires a facile entry and exit of the ligand. Coordination and dissociation of ligands should take place with low activation free energy. It is possible with labile metal complexes and hence they are utilized in catalytic cycles. Unsaturated complexes with a weakly coordinated site are labile. For example square planar 16-electron complexes are employed as catalysts in the reactions involving organic molecules. Examples: ML_4 type complexes with Pd(II), Pt(II), Rh(I) etc.

For 18-electron complexes, dissociative mechanism to form 16-electron intermediate is more likely.



CO dissociation may be attained thermally or photochemically which result in the rearrangement of the remaining molecule or replacement of Co by another ligand.



The first type of reaction, involving ligand replacement is an important way to introduce new ligands into complexes.

Most thermal reactions involving replacement of CO by another ligand L, have rates independant of [L], they are first order with respect to the metal complex. This behaviour is consistent with a dissociative mechanism involving slow loss of CO, followed by rapid reaction with L:

1. $Ni(CO)_4 \rightarrow Ni(CO)_3 + CO$ (slow) Loss of CO from 18e- complex

2. $Ni(CO)_3 + L \rightarrow Ni(CO)_3L$ (fast) addition of L to 16e- intermediate

Step 1 is the rate limiting and has the following rate law

Rate = $k_1[Ni(CO)_4]$

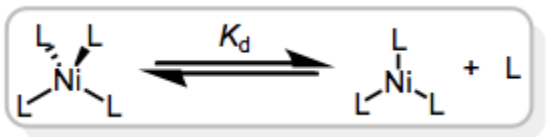
Most of the CO substitution reaction proceed by dissociative mechanism, an associative path occur for complexes of large metals (providing favourable sites for incoming ligands to attack) and for reactions involving highly nucleophilic ligands.

Dissociation of a ligand from an octahedral complex forms ML5 intermediate and the total electron count becomes 16. The geometry of the intermediate changes from octahedral to trigonal bipyramidal geometry and becomes unstable. The unstability is overcome by the distortion to square pyramidal or distorted trigonal bipyramidal geometry.

Based on the geometry of the intermediate, the order of dissociative substitution from fastest to slowest is :

d^8 TBP > d^{10} Tetrahedral > d^6 Octahedral

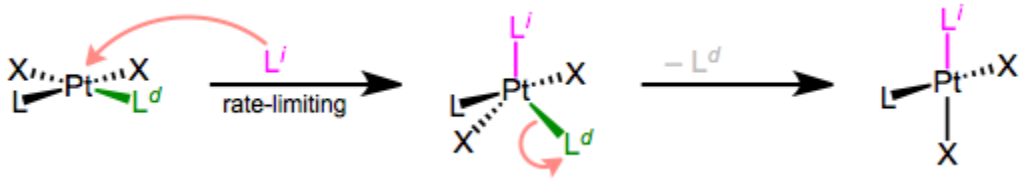
Destabilization of the starting complex is commonly accomplished by introducing bulkiness to the ligands. Dissociation relieves steric congestion in the starting complex. Chelation has the opposite effect and avoids dissociation of the starting complex.



As the bulkiness of the ligand increases dissociation becomes more favourable.

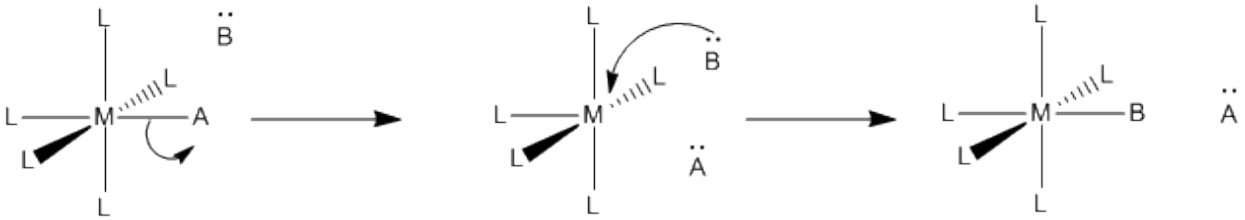
Ligand substitution occurs via association or dissociation. In associative mechanism, a new ligand comes with an electron pair and binds with the metal before the dissociation of the leaving ligand. In dissociative mechanism, the leaving ligand dissociates first with a pair of electrons followed by the binding of the incoming ligand with the central metal atom.

Associative mechanism



The first step is rate determining.

Dissociative mechanism

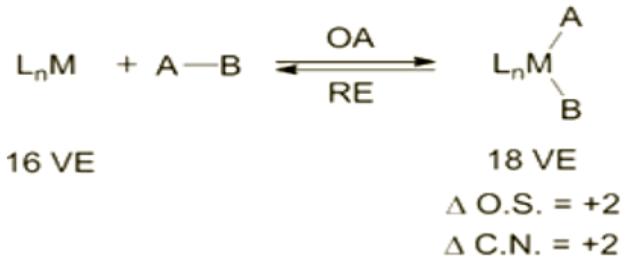


2. Oxidative Addition (OA)

Oxidative addition is a reaction in which there is addition of two anionic ligands which are part of a molecule, like in H_2 or Me−I, on to a metal center. Oxidative addition is important from the perspective of both synthesis and catalysis. As the anionic ligands are added to the metal, oxidative addition is accompanied by an increase in the coordination number, valence electron count as well as there is increase in the formal oxidation state of the metal center by two units. The oxidative addition step may proceed by a variety of pathways. For oxidative addition to takes place, the metal center to be both coordinatively unsaturated and electron deficient.

For example, with Me-I, both Me and I act as anionic ligands and binds with the metal and increases the coordination number by 2 and oxidation number of metal by 2.

As a result of oxidation addition, the number of valence electrons increases from 16 to 18.



Heating $Fe(CO)_5$ in the presence of I_2 leads to formation of cis-$I_2Fe(CO)_4$.

The reaction involves 2 steps:

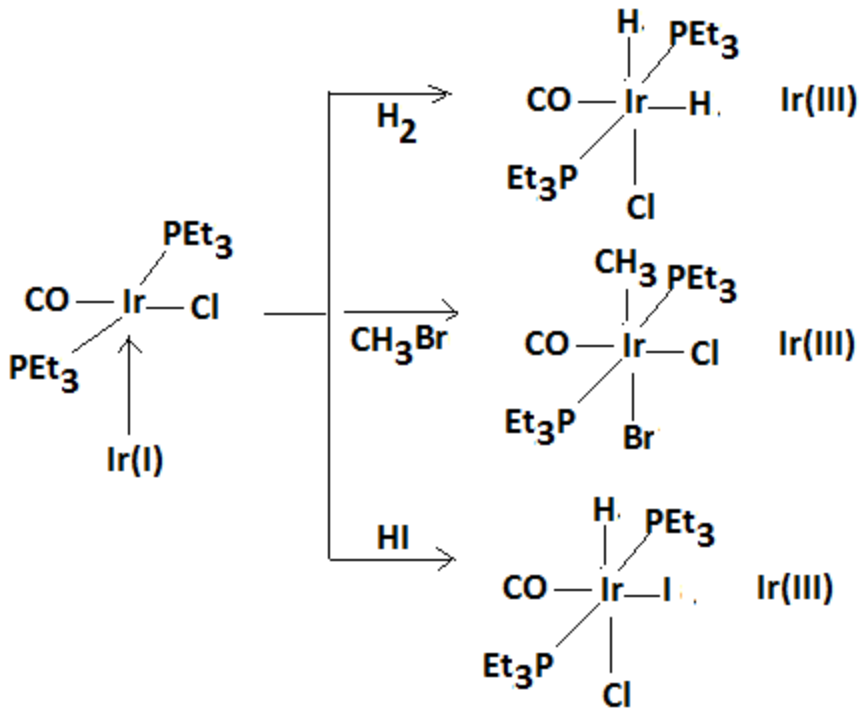
$Fe(CO)_5 \rightarrow Fe(CO)_4 + CO$

$Fe(CO)_4 + I_2 \rightarrow$ cis-$I_2Fe(CO)_4$ (oxidative addition)

$16e^-$ $18e^-$

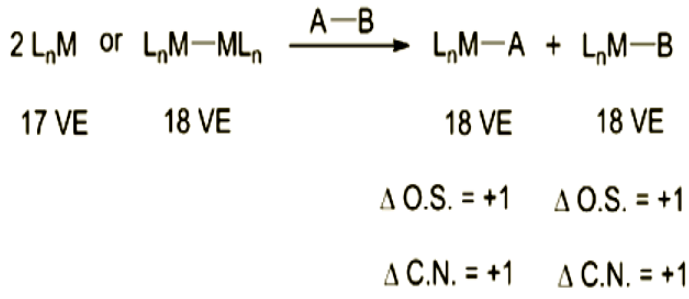
First step involves the dissociation of CO to give a 4-coordinate iron(0) intermediate. In the second step, iron is formally oxidized to iron(II) and the coordination number expanded by the addition of two iodo ligands. The second step is an example of oxidative addition. The oxidative additions, the second step involves an increase by 2 in both the oxidation state and coordination number of the metal.

OA reactions of square-planar d^8 complexes have special significance which is illustrated by the following example:



The formal oxidation state of Iridium increases from (I) to (III) and its coordination number increases from 4 to 6. The new ligands may add in a cis or trans fashion. An important feature of oxidative addition is the expansion of the coordination number of the metal by the newly added ligands which comes in close proximity to the original ligands and may enable chemical reaction to occur between ligands.

Oxidative addition takes place by a change in the valence electron count from 16 to 18 in one step. The second method is that the metal complex loses one of the ligands to reach the 16 electron condition and then proceed with oxidative addition. Both these are found to occur in mononuclear metal complexes. The third method is by the increase in the oxidation number by one with each of the two metals in a binuclear complex. This type of binuclear oxidative addition is observed with 17 valence electron metal complex or for a binuclear 18 valence electron metal complex having a metal-metal bond and, for which the metal has a stable oxidation state at a higher positive oxidative state by one unit.



In oxidative addition, the cleavage of the A-B σ-bond occurs as a result of a net transfer of electrons from the metal center to the σ*- orbital of the A-B bond resulting in two new M-A and M-B bonds. The oxidative addition is facilitated by electron rich metal centers having low oxidation states.

3. Reductive Elimination (RE)

The exact reverse of oxidative addition, in which the ligands, are eliminated from the metal center forming back the molecule, is called reductive elimination (RA). Metal centers with higher oxidation state undergo reductive elimination. Reductive elimination is accompanied by the reduction of the formal oxidation state of the metal and the coordination numbers by two units. Reductive eliminations are commonly observed for d^8 systems, like the Ni(II), Pd(II) and Au(III) ions and the d^6 systems, like the Pt(IV), Pd(IV), Ir(III) and Rh(III) ions. The reaction may proceed by the elimination of several groups.

$L_nMRH \rightarrow L_nM + R\text{-}H$

$L_nMR_2 \rightarrow L_nM + R\text{-}R$

In binuclear metal complexes, there is decrease in the oxidation state by one unit and coordination number also by one unit.

$$\underset{\text{Ta(III)}}{(\eta^5 - C_5H_5)_2TaH} + H_2 \underset{\text{RE}}{\overset{\text{OA}}{\rightleftharpoons}} \underset{\text{Ta(V)}}{(\eta^5 - C_5H_5)_2TaH_3}$$

Reductive elimination is seen in metal centers with higher oxidation state and is accompanied by the decrease in the oxidation state, the valence electron count and the coordination number of the metal by two units.

The forward reaction involves formal oxidation of the metal, accompanied by an increase in the coordination number. The reverse reaction is an example of reductive elimination in which there is a decrease in both oxidation number and coordination number.

Reductive elimination often involve elimination of molecules such as

R-H, R-R', R-X, H-H, (R, R' = alkyl/aryl; X = halogen)

The products eliminated may be useful organic compounds such as R-H, R-R', R-X etc.

The rates of reductive elimination reactions are affected by ligand bulk.

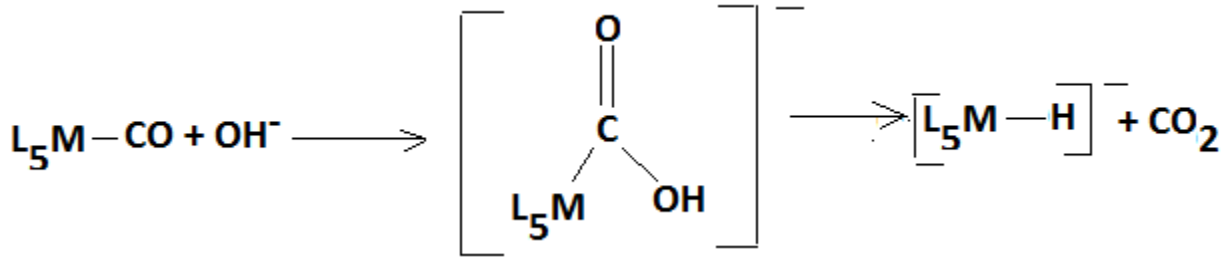
The most crowded complex, $Pd(CH_3)_2(PPH_3)_2$, undergoes reductive elimination the most rapidly.

More interestingly, the oxidative addition and reductive elimination reactions are not restricted to the mononuclear metal complexes but are also observed in binuclear complexes.

4. Nucleophilic Displacement

Ligand displacement reactions may be described as nucleophilic substitutions, involving incoming ligands as nucleophiles.

Coordination of carbonyl group with metal ions in positive oxidation state activates the coordinated C atoms for the attack of nucleophile. A coordinated CO ligand undergoes a nucleophilic attack by an OH- ion at the C atom, forming a –CO(OH) ligand, which loses CO_2 as shown below.

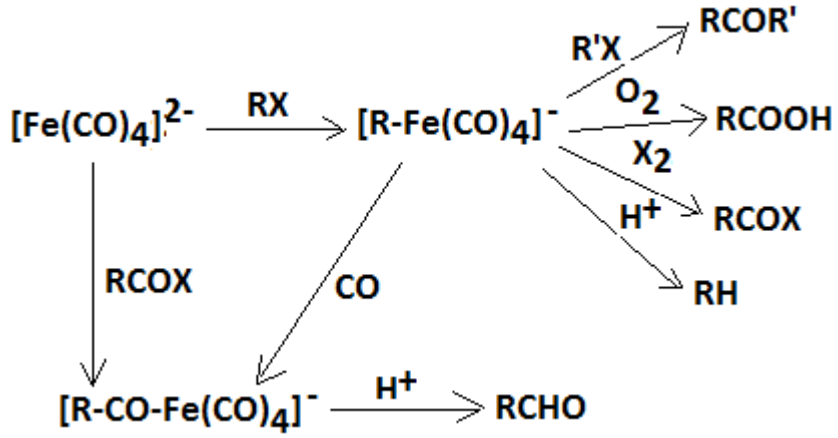


The anion $[\eta^5\text{-}(C_5H_5)Mo(CO)_3]^- + CH_3I \rightarrow [\eta^5\text{-}(C_5H_5)(CH_3)Mo(CO)_3] + I^-$

$[Fe(CO)_4]^{2-}$ is a very important and useful organometallic nucleophile. Cooke and Collman synthesized this nucleophile, $Na_2Fe(CO)_4$ called the Collman's reagent, by the reaction of sodium with $Fe(CO)_5$ in dioxane.

$2\ Na + Fe(CO)_5 \rightarrow Na_2Fe(CO)_4 \cdot 1.5\ \text{dioxane} + CO$

The product of this reaction can be used for the synthesis of variety of organic compounds.



Another useful anionic nucleophile is $[Co(CO)_4]^-$ which is a mild nucleophile. $[Co(CO)_4]^-$ can be synthesized by the reduction of $Co_2(CO)_8$ by sodium; it reacts with organic halides to generate alkyl complexes:

$[Co(CO)_4]^- + RX \rightarrow RCo(CO)_4 + X^-$

The alkyl complex reacts with carbon monoxide to insert CO into the cobalt- alkyl bond to give an acyl complex (containing a -C(=O)R ligand):

$RCo(CO)_4 + CO \rightarrow RCOCo(CO)_4$

The acyl complex can then react with alcohols to generate esters:

$RCOCo(CO)_4 + R'OH \rightarrow RCOOR' + HCo(CO)_4$

Reaction of $HCo(CO)_4$, a strong acid, with base can regenerate the $[Co(CO)_4]^-$ to make the overall process catalytic.

Reactions involving modification of Ligands

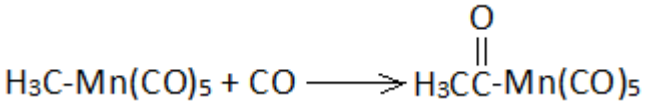
These reactions involve the insertion of a ligand or a molecular fragment in between a metal-ligand bond. Some reactions occur in a single step whereas there are some other types of insertion reactions which takes place in a more complicated fashion and in more than one step. The most studied is the CO insertion.

1. Insertion

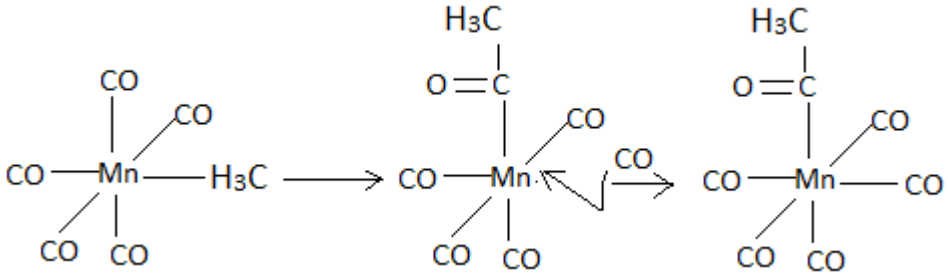
The reactions called 1,1 insertions indicate that both bonds to the inserted molecule are made to the same atom in that molecule. 1,2 insertions give products in which bonds to the sulfur of the inserted molecule are made to the adjacent atoms of the molecule.

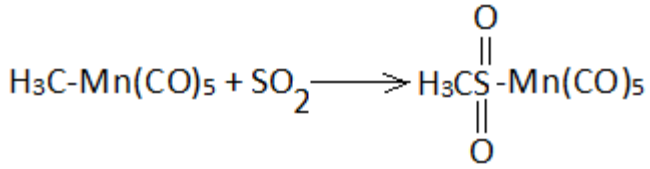
Carbonyl Insertion (Alkyl migration)

In carbonyl insertion, which involves the reaction of CO with an alkyl complex to give an acyl [O=C-R] product. Examples of 1,1-insertions are given below:

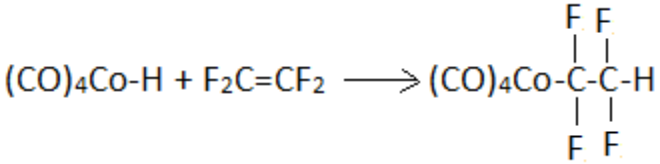


Mechanism: The mechanism of insertion of CO involves the migration of the alkyl group, rather than CO group, and attach itself to a CO cis to the alkyl. This would give rise to a 5-coordinate with a vacant site available for an incoming CO. This mechanism is proved based on isotope labelling technique.



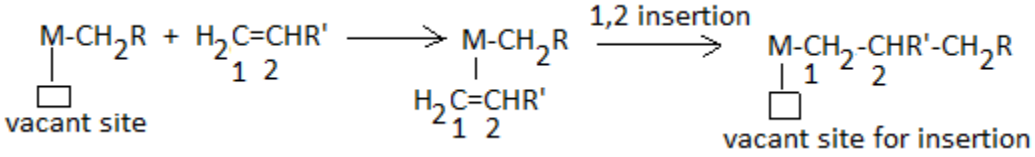


Examples of 1,2- insertion are



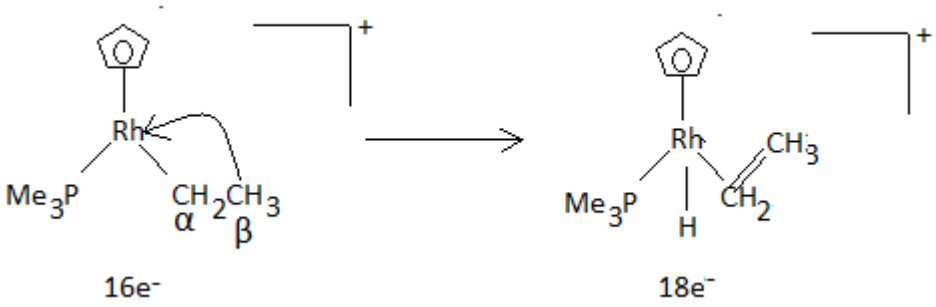
The insertion of CO into a metal-carbon bond in alkyl complexes is of particular interest as it has potential applications in organic synthesis and catalysis.

The importance of 1,2-insertion can be understood from the 1,2-insertion of alkenes into metal-alkyl bonds to yield polymers. Example: Ziegler-Natta polymerization of alkenes. A polymer chain can grow as a consequence of 1,2-insertions into a vacant coordination site.



2. Hydride Elimination

This reaction involves the transfer of a hydrogen atom from a ligand to a metal. This is also a type of oxidative addition reaction where there is increase in the coordination number and oxidation state of the metal. The most common type is β elimination with a proton in a β position on an alkyl ligand being transferred to the metal by way of an intermediate in which the metal, the α and β carbons, and the hydride are coplanar. β -elimination is the reverse of 1,2-insertion.



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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – 3 – Organometallic Catalysts – SCYA5302

Organometallic Catalysts

1. Introduction

The unit deals with the study of organometallic compounds as catalysts in different types of homogeneous and heterogeneous catalysis reactions. The sequence of the reactions are explained based on the mechanistic steps involved.

Terminologies

Turn over frequency (TOF): The turnover frequency quantifies the specific activity of a catalytic centre for a special reaction under defined reaction conditions by the number of molecular reactions or catalytic cycles occurring at the centre per unit time. For heterogeneous catalysts, the number of active centres is derived usually from sorption methods.

$$TOF = \frac{\text{volumetric rate of reaction}}{\text{number of centres/ volume}} = \frac{\text{moles}}{\text{volume} \cdot \text{time}} \quad \frac{\text{volume}}{\text{moles}} = \text{time}^{-1}$$

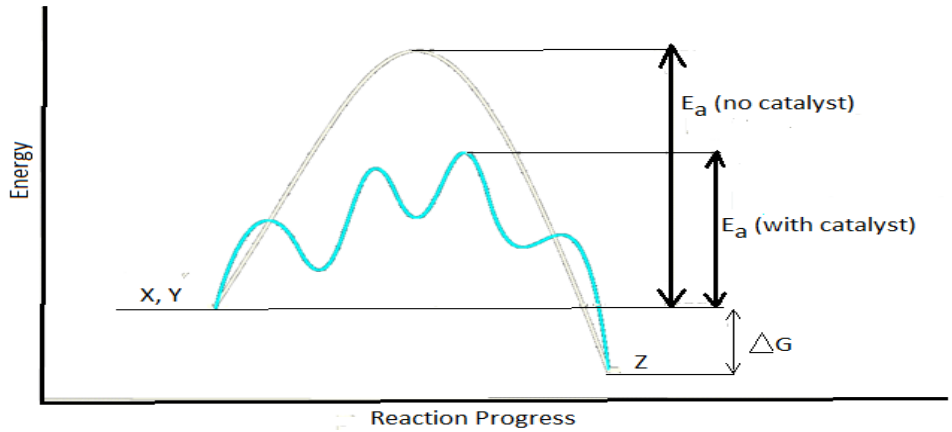
Turn over number (TON): The turnover number specifies the maximum use that can be made of a catalyst for a special reaction under defined conditions by a number of molecular reactions or reaction cycles occurring at the reactive center upto the decay of activity.

Catalysts: Catalysts are compounds that, when added to chemical reactions, reduce the activation energy and increase the reaction rate.

The amount of a catalyst does not change during a reaction, as it is not consumed as part of the reaction process.

Catalysts lower the energy required to reach the transition state of the reaction, allowing more molecular interactions to achieve that state. However, catalysts do not affect the degree to which a reaction progresses. In other words, though catalysts affect reaction kinetics, the equilibrium state remains unaffected.

Catalysts can be classified into two types: **homogeneous and heterogeneous**. Homogeneous catalysts are those which exist in the same phase (gas or liquid) as the reactants, while heterogeneous catalysts are not in the same phase as the reactants. Typically, heterogeneous catalysis involves the use of solid catalysts placed in a liquid reaction mixture.



2. Homogeneous Catalysis

Hydroformylation

The hydroformylation, or oxo, process is commercially useful for converting terminal alkenes into a variety of other organic products, especially those having their carbon chain increased by one.

One of these processes, the conversion of an alkene of formula $R_2C=CH_2$ into an aldehyde, $R_2CH\text{-}CH_2\text{-}CHO$, is shown. The cobalt- containing intermediates in this cycle alternate between 18- and 16-electron species. The 18-electron species react to formally reduce their electron count by 2 (by ligand dissociation, 1,2 insertion of coordinated alkene, alkyl migration, reductive elimination), whereas the 16-electron species can increase their formal electron count (by coordination of alkene or CO or by oxidative addition).

The first step, involving dissociation of CO from $HCo(CO)_4$, is inhibited by high CO pressure, yet the fourth step requires CO; thus, careful control of this pressure is necessary for optimum yields and rates.' The second step is first order in alkene; it is the slow (rate-determining) step. In Step 3, the product is formed preferentially with a CH_2 group rather than a CR_2 group bonded to the metal; this preference for CH_2 bonding to metal is enhanced by bulky R groups. Step 6 involves addition of H_2 (OA); however, high H_2 pressure can lead to addition of H_2 to the 16-electron intermediate from Step 3, which would then eliminate an alkane:

$R_2CH\text{-}CH_2\text{-}CO(CO)_3 + H_2 \rightarrow R_2CH\text{-}CH_2\text{-}CO(H)_2(CO)_3$ oxidative addition

16 e- 18 e-

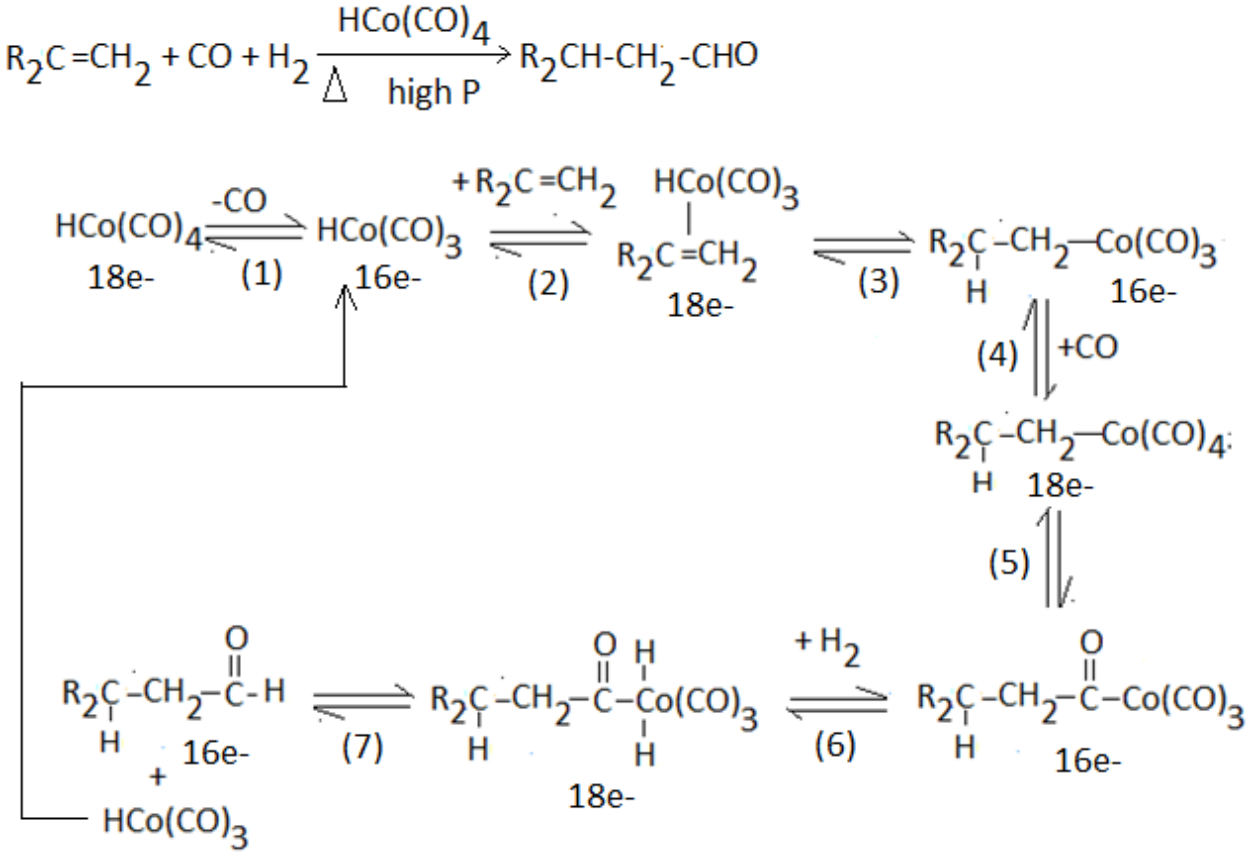
$R_2CH\text{-}CH_2\text{-}CO(H)_2(CO)_3 \rightarrow R_2CH\text{-}CH_3 + HCo(C0)_4$ reductive elimination

18 e- 16 e-

The actual catalytic species in this mechanism is the 16- electron $HCo(CO)_3$.

The main industrial application of hydroformylation is in the production of butanal from propene ($CH_3CH=CH_2 \rightarrow CH_3CH_2CH_2CHO$). Subsequent hydro- genation gives butanol, an important industrial solvent. Other aldehydes are also produced industrially by hydroformylation, using either cobalt catalysts such as the one in Figure. or rhodium-based catalysts.

A shortcoming of the cobalt carbonyl-based hydroformylation process is that it produces only about 80% of the much more valuable linear aldehydes, with the remainder having branched chains. Modifying the catalyst by replacing one of the CO ligands of the starting complex by PBu_3 (Bu = n-butyl) to give $HCO(CO)_3(PBU_3)$ increases the selectivity of the process to give a ratio of linear to branched aldehydes of approximately 9 : 1. Finally, replacing the cobalt with rhodium yields far more active catalysts (much less catalyst needs to be present) that can function with higher linear and branched selectivity at significantly lower temperatures and pressures than cobalt-based catalysts. A proposed mechanism for an example of such a catalytic process using $HRh(CO)_2(PPh_3)_2$ is shown.



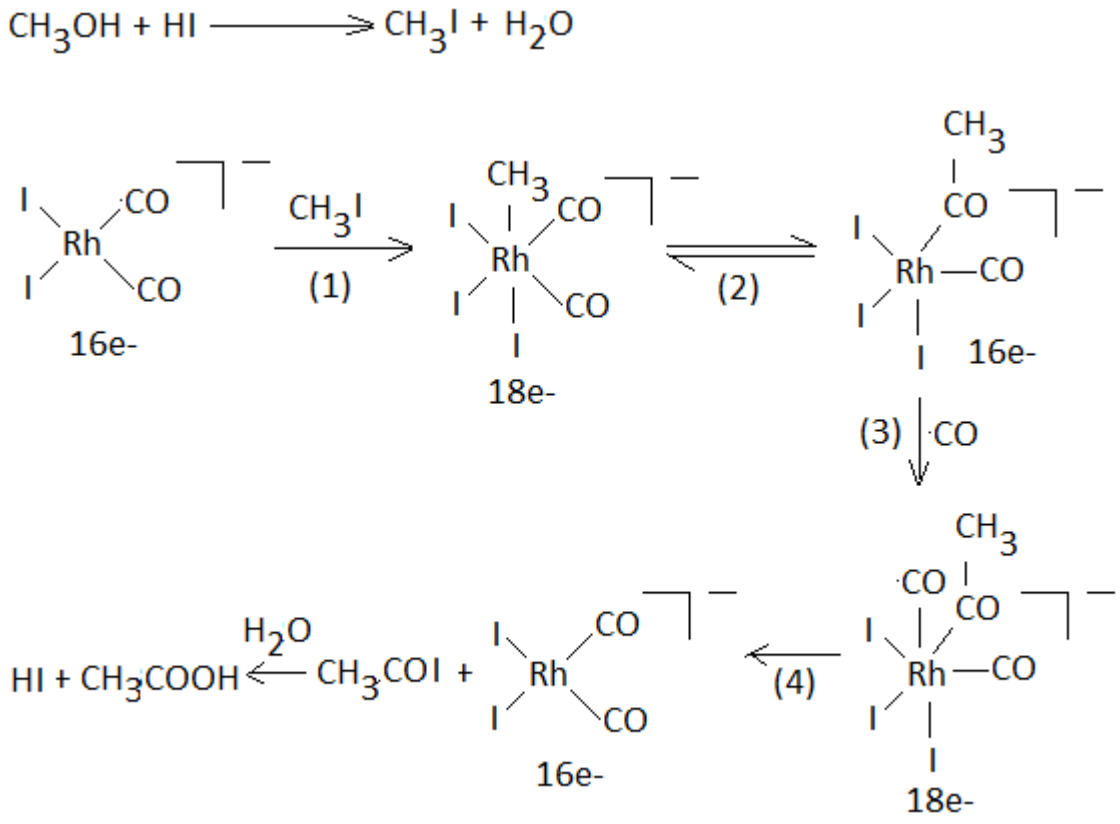
(1) Dissociation of CO; inhibited by excess CO
(2) Coordination of Olefin; first order in olefin
(3) 1,2 insertion (reverse of β elimination)
(4) addition of CO
(5) Alkyl migration
(6) Addition of H_2 (oxidative addition)

(7) Reductive elimination

Monsanto Acetic Acid Process

The synthesis of acetic acid from methanol and CO is a process that has been used with great commercial success by Monsanto since 1971. The mechanism of this process is complex; a proposed outline is shown in Figure. The intermediates are 18- or 16-electron species having the capability to lose or gain, respectively, 2 electrons. (Solvent molecules may occupy empty coordination sites in the 4- and 5-coordinate 16-electron intermediates.) The first step, oxidative addition of CH_3I to $[RhI_2(CO)_2]^-$, is rate determining.

The final step involving rhodium is reductive elimination of $IC(=O)CH_3$. Acetic acid is formed by hydrolysis of this compound. The catalytic species, $[Rh(CO)I_2]^-$ (which may contain solvent in the empty coordination sites) is regenerated. In addition to rhodium-based catalysts, iridium-based catalysts have also been developed in a process known as the Cativa process. The iridium system follows a cycle similar to the rhodium system in Figure, beginning with oxidative addition CH_3I to $[Ir(CO)_2I_2]^-$. The first step in the iridium system is much more rapid than in Monsanto process and the second step is much slower; the second step, involving alkyl migration, is rate determining for the Cativa process.



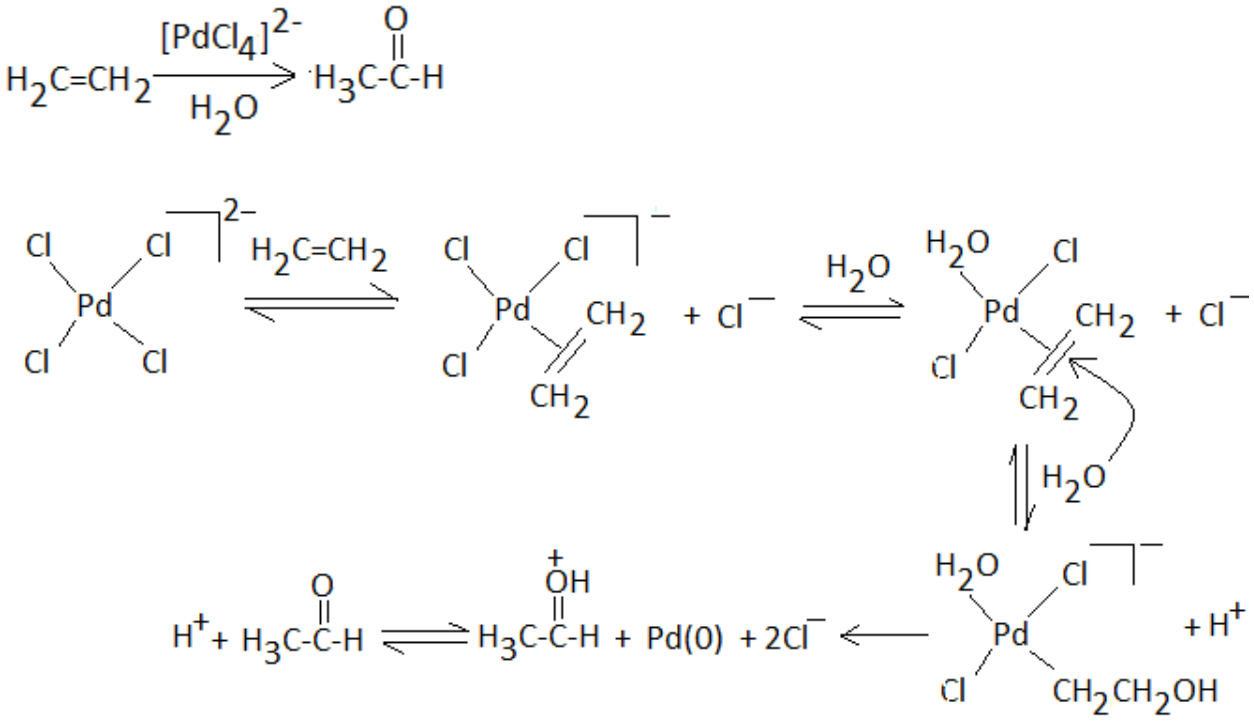
(1) Oxidative Addition, rate – determining step
(2) CO insertion = alkyl migration
(3) Coordination of CO

(4) Reductive elimination

Wacker (Smidt) Process

The Wacker or Smidt process, used to synthesize acetaldehyde from ethylene, involves a catalytic cycle that uses $PdCl_4^{2-}$. The fourth step in this cycle is substantially more complex than that shown.

An important feature of this process is that it uses the ability of palladium to form complexes with the reactant ethylene, with the important chemistry of ethylene occurring while it is attached to the metal. In other words, the palladium modifies the chemical behavior of ethylene to enable reactions to occur that would not be possible for free ethylene. Incidentally, the first ethylene complex with palladium in Figure is isoelectronic with Zeise's complex, $[PtCl_3(\eta^2\text{-}H_2C{=}CH_2)]^-$.

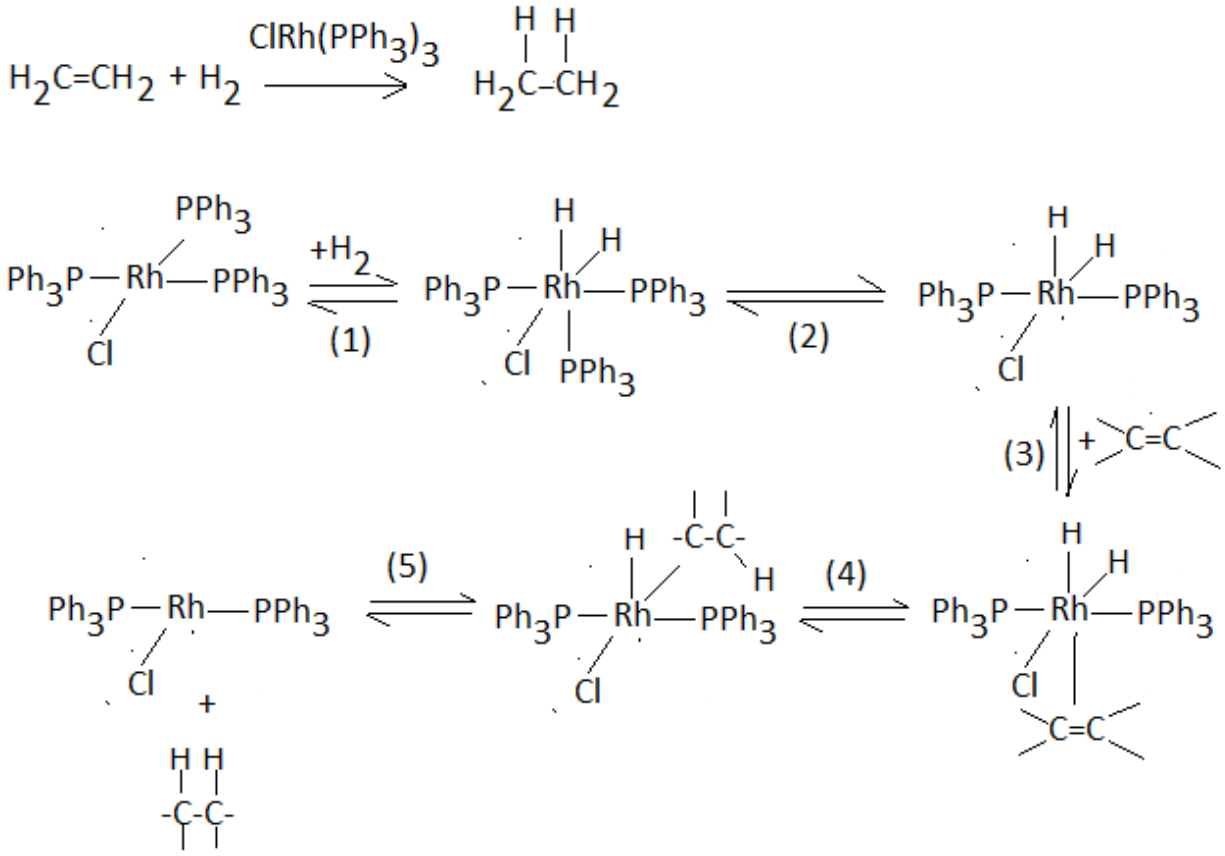


The catalyst $[PdCl_4]^{2-}$ is regenerated using $CuCl_2$.

Hydrogentation by Wilkinson's catalyst

Wilkinson's catalyst, $RhCl(PPh_3)_3$ is not itself an organometallic compound but participates in the same types of reactions as expected for 4-coordinate organometallic compounds; for example, many reactions bear similarities to Vaska's catalyst, trans-$IrCl(CO)(PPh_3)_2$. $RhCl(PPh_3)_3$ participates in a wide variety of catalytic and noncatalytic processes. The bulky phosphine ligands play an important role in making the complex selective-for example, they

limit coordination of Rh to unhindered positions on alkenes. One example, involving catalytic hydrogenation of an alkene is shown.



(1) Oxidative addition
(2) Ligand Dissociation
(3) Coordination of Olefin
(4) 1,2 insertion (rate determining step)
(5) Reductive elimination

Olefin metathesis

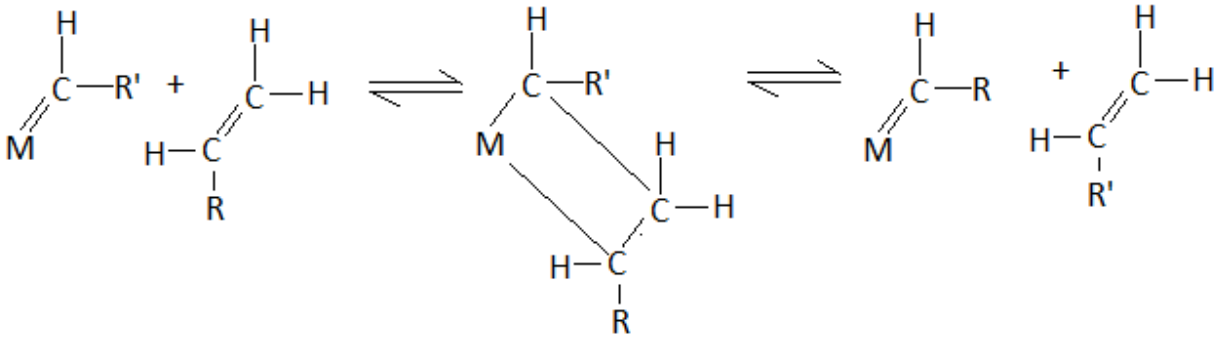
Olefin metathesis involves the formal exchange of **:**CR_2 fragments (R = H or alkyl) between alkenes. For example, metathesis between molecules of formula $H_2C{=}CH_2$ and HRC=CHR would yield two molecules of $H_2C{=}CHR$**:**

$$H_2C{=}CH_2 + RHC{=}CHR \rightleftharpoons 2H_2C{=}CHR$$

New double bonds are formed between the top and bottom two carbons, and the original double bonds are cleaved.

Metathesis, which is reversible and can be catalysed by a variety of organometallic complexes, has been the subject of considerable investigation. In 1970, Herisson and Chauvin proposed that

these reactions are catalyzed by carbene (alkylidene) complexes that react with alkenes via the formation of metallocyclobutane intermediates. This mechanism now known as the “Chauvin mechanism”.



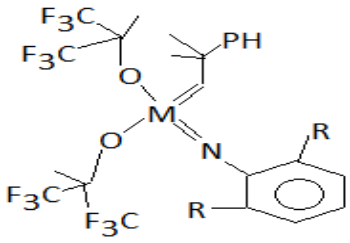
In this mechanism, a metal carbene complex first reacts with an alkene to form a metallacyclobutane intermediate. This intermediate can either revert to reactants or form new products; because all steps in the process are equilibria, an equilibrium mixture of alkenes results.

The most thoroughly studied catalysts that effect alkene metathesis are of two types. Schrock metathesis catalysts are the most effective of all metathesis catalysts but in general are highly sensitive to oxygen and water, These catalysts are now available commercially; the catalyst having M = Mo and R = isopropyl is sometimes called "Schrock's catalyst." An example of a reaction utilizing this catalyst is the final step of the synthesis of the natural product dactylol.

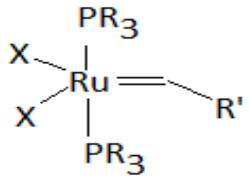
Grubbs metathesis catalysts in general have less catalytic activity than Schrock catalysts, but are less sensitive to oxygen and water. They are also substantially less expensive than the molybdenum and tungsten catalysts. The catalyst having R = cyclohexyl, X = C1, and R' = phenyl has receivcd particular attention and is marketed as Grubbs's catalyst. One requirement of these catalysts is the presence of bulky phosphine ligands. This bulkiness facilitates phosphine dissociation, a key step in the proposed mechanism involving the Grubbs catalyst.

A promising recent development has been the introduction of catalysts that contain ruthenium and N-heterocyclic carbene ligands. These ligands exceed trialkylphosphines in steric requirements and are more strongly electron donating; both features support improved catalytic activity. Such catalysts compare favorably in activity with Schrock's catalyst and typically are thermally stable with low sensitivity toward oxygen and water. The N-heterocyclic catalyst compares favorably with Schrock's catalyst and is far superior to Grubbs's catalyst at least for this reaction.

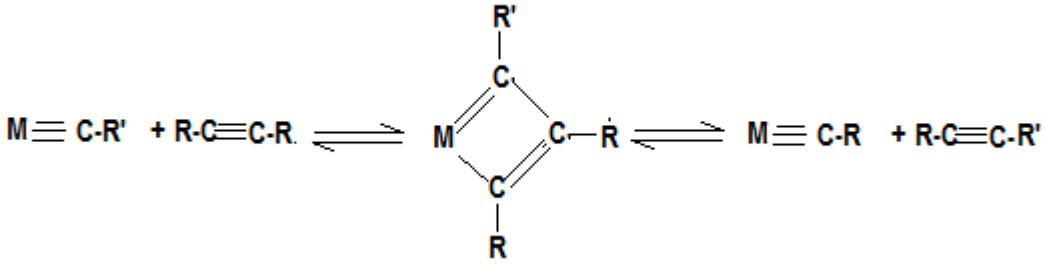
Schrock's catalyst



Grubb's catalyst



Alkynes can also undergo metathesis reactions catalyzed by transition metal carbyne complexes. The intermediates in these reactions are believed to be metallacyclobutadiene species, formed from the addition of an alkyne across a metal-carbon triple bond of the carbyne (Figure 14-26). The structures of a variety of metallacyclobutadiene complexes have been determined, and some have been shown to catalyze alkyne metathesis.



Metallacyclobutadiene (Intermediate)

3. Heterogeneous Catalysts

Heterogeneous processes, involving solid catalytic species, are very important, although the exact nature of the reactions occurring on the surface of the catalyst may be extremely difficult to ascertain.

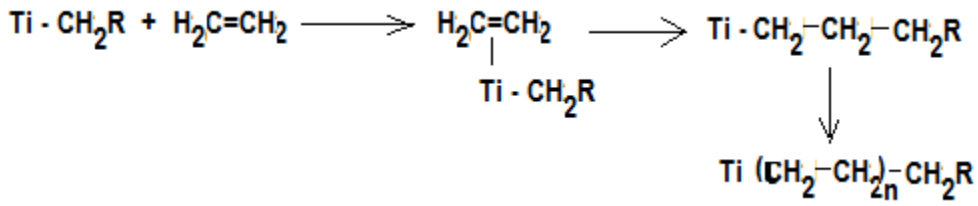
Ziegler-natta polymerizations

In 1955, Ziegler and coworkers reported that solutions of $TiCl_4$ in hydrocarbon solvents in the presence of $Al(C_2H_5)_3$ gave heterogeneous solutions capable of polymerizing ethylene. Subsequently, many other heterogeneous processes were developed for polymerizing alkenes, using aluminium alkyls in combination with transition metal complexes. An outline of a possible

mechanism for the Ziegler-Natta process proposed by Cossee and Arlman. First, reaction of $TiCl_4$ with aluminum alkyl gives $TiCl_3$, which on further reaction with the aluminum alkyl gives a titanium alkyl complex. Ethylene (or propylene) can then insert into the titanium-carbon bond, forming a longer alkyl. This alkyl is further susceptible to insertion of ethylene to lengthen the chain. Although the mechanism of the Ziegler-Natta process has proved difficult to understand, direct insertions of multiple bonded organics into titanium-carbon bonds have been demonstrated, supporting the Cossee-Arlman mechanism.

However, an alternative mechanism, involving a metallacyclobutane intermediate, has also been proposed. This mechanism, involves the initial formation of alkylidene from a metal alkyl complex, followed by addition of ethylene to give the metallacyclobutane, which then yields a product having ethylene inserted into the original metal-carbon bond. Distinguishing between these mechanisms has been a long and difficult process, but experiments by Grubbs and coworkers have strongly supported the Cossee-Arlman mechanism as the likely pathway for polymerization in most cases. In at least one example, however, there is strong evidence for ethene polymerization involving a metallacycle intermediate.

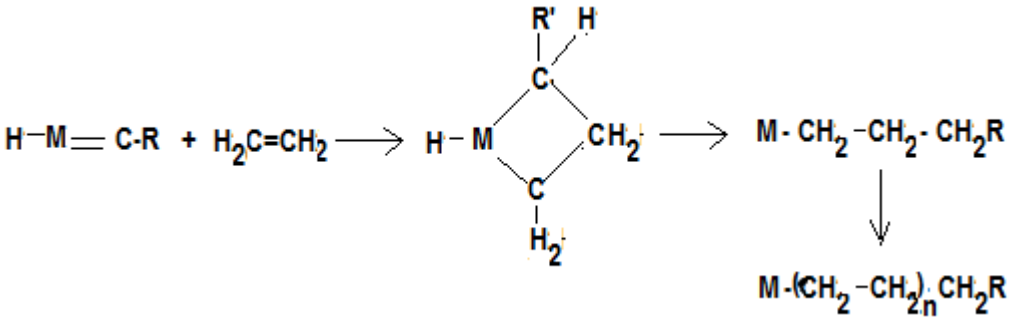
Cossee-Arlman Mechanism



Polymerization via Metallacyclobutane Intermediate

(1) Alkyl-alkylidene equilibrium

(2) Insertion via metallacyclobutane



Water gas reaction

This reaction occurs at elevated temperatures and pressures between water (steam) and natural sources of carbon, such as coal or coke:

$H_2O + C \rightarrow H_2 + CO$

The products of this reaction, an equimolar mixture of H_2 and CO (called "synthesis gas" or "syn gas"; some CO_2 may be produced as a by-product), can be used with metallic heterogeneous catalysts in the synthesis of a variety of useful organic products. For example, the Fischer-Tropsch process, developed by German chemists in the early 1900s, uses transition metal catalysts to prepare hydrocarbons, alcohols, alkenes, and other products from synthesis gas. For example

$H_2 + CO \rightarrow$ Alkanes Co catalyst

$3\ H_2 + CO \rightarrow CH_4 + H_2O$ Ni catalyst

$2\ H_2 + CO \rightarrow CH_3OH$ Co or Zn/Cu catalyst

Various heterogeneous catalysts are used industrially. For example, transition metals on Al_2O_3 and mixed transition metal oxides.

Most of these processes have been conducted under heterogenous conditions. However, there has been considerable interest in developing homogenous systems to catalyze the Fischer-Tropsch conversion. They are, however, uneconomical in most cases, because hydrogen and carbon monoxide in sufficient quantities must be obtained from coal or petroleum sources.

In steam reforming, natural gas (consisting chiefly of methane) is mixed with steam at high temperatures and pressures over a heterogeneous catalyst to generate carbon monoxide and hydrogen:

$CH_4 + H_2O \rightarrow CO + 3H_2$ Ni catalyst, 700°C - 1000°C

(Other alkanes also react with steam to give mixtures of CO and H_2 .) Steam reforming is the principal industrial source of hydrogen gas. Additional hydrogen can be produced by recycling the CO to react further with steam in the water gas shift reaction:

$CO + H_2O \rightarrow CO_2 + H_2,$ Fe-Cr or Zn-Cu catalyst, 400°C

This reaction is favored thermodynamically at 400°C, $\Delta G° = -14.0$ kJ/mol. Removal of CO_2 by chemical means from the product can yield hydrogen of greater than 99% purity. This reaction has been studied extensively with the objective of being able to catalyze formation of H_2 homogeneously. However, these processes have not yet proved efficient enough for commercial use. In general, these processes, when performed using heterogeneous catalysts, require significantly elevated temperatures and pressures. Consequently, as in the case of the water gas

shift rcaction, there has been grcat interest in dcvcloping homogcncous catalysts that can perform the same functions under much milder conditions.

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – 4 – Bioinorganic Chemistry – SCYA5302

BIOINORGANIC CHEMISTRY

1. Introduction

The Unit deals with the structure analysis and functions of heme and non-heme proteins with the study of their structure activity relationship and characterization of their active sites. Bohr Effect in oxygen binding and unloading is discussed. Mechanism of action of various electron transfer proteins gives the importance of enzymes in different biological functions. Therapeutic effects of metal complexes, radioisotopes shows their important applications.

Several transition metals are important to the chemistry of living systems, the most familiar examples being iron, cobalt, copper, and molybdenum. Iron is by far the most widespread and important transition metal that has a function in living systems;

Proteins containing iron participate in two main processes: oxygen transport and electron transfer (i.e., oxidation–reduction) reactions. There are also a number of substances that act to store and transport iron itself.

Though cobalt is understood to be an essential trace element in animal nutrition, the only detailed chemical knowledge of its biochemical action has to do with vitamin B_{12} and related coenzymes. These molecules contain one atom of cobalt bound in a macrocyclic ring (i.e., one consisting of many atoms) called corrin, which is similar to a porphyrin ring.

Copper is found in both plants and animals, and numerous copper-containing proteins have been isolated. The blood of many lower animals, such as mollusks, cephalopods, gastropods, and decapods, contains respiratory proteins called hemocyanins, which contain copper atoms (but no heme) and appear to bind one oxygen molecule per two copper atoms.

Human serum contains a glycoprotein called ceruloplasmin, the molecule of which contains eight copper atoms; its biological function is still uncertain.

Other proteins, called cerebrocuprein, erythrocuprein, and hepatocuprein, that are found in the mammalian brain, erythrocytes, and liver, respectively, contain about 60 percent of the total copper in those tissues; their functions are still unknown.

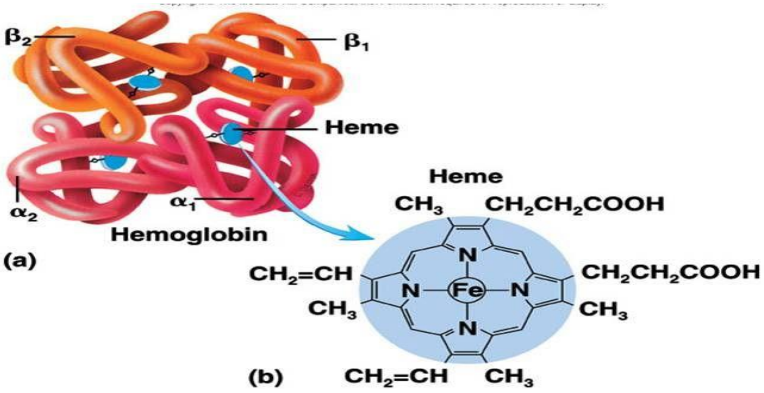
There are a number of copper-containing enzymes; examples are (1) ascorbic acid oxidase (an oxidase is an oxidizing enzyme), which contains eight atoms of copper per molecule; it is widely distributed in plants and microorganisms; (2) cytochrome oxidase, which contains heme and copper in a 1:1 ratio; (3) tyrosinases, which catalyze the formation of melanin (brownish-black pigments occurring in hair, skin, and retina of higher animals) and were the first enzymes in which copper was shown to be essential to function.

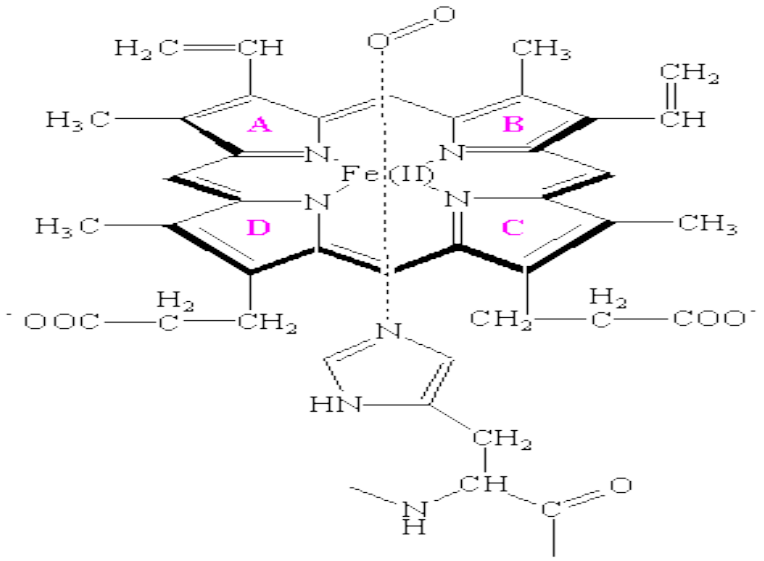
Vanadium occurs widely in petroleum, notably that from Venezuela, and can be isolated as porphyrin complexes, the origin of which is not known. Vanadium is present in high concentrations in blood cells (vanadocytes) of certain ascidians (sea squirts), apparently in a curious, complex, and poorly understood protein-containing substance called hemovanadin, thought to serve in oxygen transport.

Molybdenum is believed to be a necessary trace element in animal diets, but its function and the minimum levels have not been established. Nitrogen-fixing bacteria utilize enzymes that contain both molybdenum and iron. One such enzyme, or at least a part of it that has been isolated in the crystalline state, contains two atoms of molybdenum and 40 atoms of iron. This protein in association with another, which contains only iron, can catalyze the reduction of nitrogen gas to nitrogen compounds.

Efforts to understand the function of transition metals in biological systems have led to the growth of the field of bioinorganic chemistry.

2. Hemoglobin





The site at which oxygen binds to both hemoglobin and myoglobin is the **heme** shown in the figure.

Function

Hemoglobin is an oxygen-transport protein. Hemoglobin is an allosteric protein.

It is a tetramer composed of two types of subunits designated α and β, with stoichiometry α2β2. The four subunits of hemoglobin sit roughly at the corners of a tetrahedron, facing each other across a cavity at the center of the molecule. Each of the subunits contains a heme prosthetic group. The heme molecules give hemoglobin its red color.

Each individual heme molecule contains one Fe^{2+} atom.

In the lungs, where oxygen is abundant, an oxygen molecule binds to the ferrous iron atom of the heme molecule and is later released in tissues needing oxygen. The most well-known disease caused by a mutation in the hemoglobin protein is sickle-cell anemia. It results from a mutation of the sixth residue in the β hemoglobin monomer from glutamic acid to a valine.

For hemoglobin, its function as an oxygen-carrier in the blood is fundamentally linked to the equilibrium between the two main states of its quaternary structure, the unliganded "deoxy" or "T state" versus the liganded "oxy" or "R state". The unliganded (deoxy) form is called the "T" (for "tense") state because it contains extra stabilizing interactions between the subunits.

In the high-affinity R-state conformation the interactions which oppose oxygen binding and stabilize the tetramer are somewhat weaker or "relaxed".

Structural changes that occur during this transition can illuminate how such changes result in important functional properties, such as cooperativity of oxygen binding and allosteric control by pH and anions.

Our blood stream contains about 150 g/L of the protein known as **hemoglobin** (Hb), which is so effective as an oxygen-carrier that the concentration of O_2 in the blood stream reaches 0.01 *M* the same concentration as air. Once the Hb-O_2 complex reaches the tissue that consumes oxygen, the O_2 molecules are transferred to another protein **myoglobin** (Mb) which transports oxygen through the muscle tissue.

At the center of the heme is an Fe(II) atom. Four of the six coordination sites around this atom are occupied by nitrogen atoms from a planar **porphyrin** ring. The fifth coordination site is occupied by a nitrogen atom from a histidine side chain on one of the amino acids in the protein. The last coordination site is available to bind an O_2 molecule. The heme is therefore the oxygen-carrying portion of the hemoglobin and myoglobin molecules.

The structure of myoglobin suggests that the oxygen-carrying heme group is buried inside the protein portion of this molecule, which keeps pairs of hemes group from coming too close together. This is important, because these proteins need to bind O_2 reversibly and the Fe(II) heme, by itself, cannot do this. When there is no globin to protect the heme, it reacts with oxygen to form an oxidized Fe(III) atom instead of an Fe(II)-O_2 complex.

Hemoglobin consists of four protein chains, each about the size of a myoglobin molecule, which fold to give a structure that looks very similar to myoglobin. Thus, hemoglobin has four separate heme groups that can bind a molecule of O_2. Even though the distance between the iron atoms of adjacent hemes in hemoglobin is very large between 250 and 370 nm the act of binding an O_2 molecule at one of the four hemes in hemoglobin leads to a significant increase in the affinity for O_2 binding at the other hemes.

This **cooperative interaction** between different binding sites makes hemoglobin an unusually good oxygen-transport protein because it enables the molecule to pick up as much oxygen as possible once the partial pressure of this gas reaches a particular threshold level, and then give off as much oxygen as possible when the partial pressure of O_2 drops significantly below this threshold level. The hemes are much too far apart to interact directly. But, changes that occur in the structure of the globin that surrounds a heme when it picks up an O_2 molecule are mechanically transmitted to the other globins in this protein. These changes carry the signal that facilitates the gain or loss of an O_2 molecule by the other hemes.

3. Myoglobin: O_2 storage in muscle cells

The respiratory system is an organ system in the body that functions in gas exchange with the environment. Exchange of gases like carbon dioxide (CO_2) and dioxygen (O_2) are essential for sustaining life forms. O_2 is necessary in aerobic metabolism for oxidative phosphorylation (synthesis of ATP) at the electron transport chain (ETC). ATP is the energy source needed for muscular contraction in mammals. ATP synthesis requires oxygen as an electron acceptor in the ETC, therefore oxygen must be readily available for use in metabolically active muscles. Since muscles need large quantities of O_2, it is transported by proteins in the blood and stored in muscle tissue. One of these proteins is myoglobin.

Myoglobin is a hemoprotein found in the skeletal muscle of mammals that functions in oxygen storage and diffusion. A hemoprotein is a protein that contains a heme prosthetic group. The heme in myoglobin can reversibly bind a O_2 molecule to regulate the transportation of O_2 from red blood cells to mitochondria when skeletal muscles are metabolically active.

Structure of Myoglobin

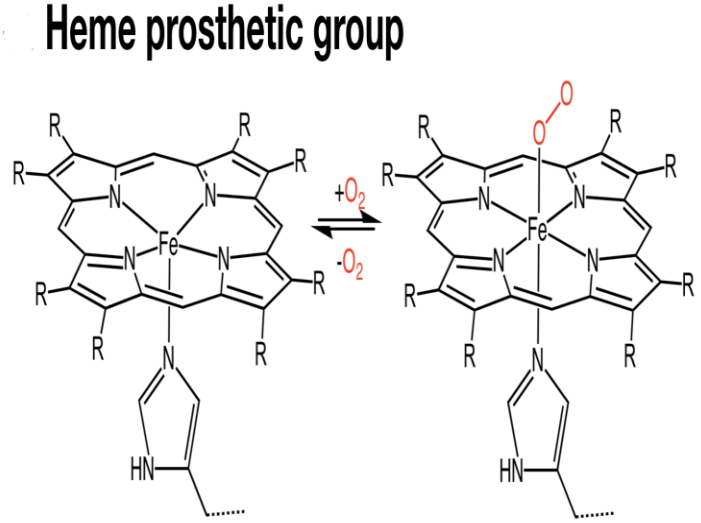
Myoglobin Structure: This is a ribbon depiction of mammalian myoglobin protein. The heme prosthetic group consists of four central nitrogen donor atoms bound to iron (II). The porphyrin ring contains four pyrrole nitrogens bound to a ferrous (Fe(II)) ion center. There are six coordination sites in the Fe(II) ion; four are occupied by the pyrrole nitrogens, one is occupied by a proximal histidine, and the final site has the ability to reversibly bond to an O_2 molecule.

The structure of myoglobin is similar to the structure of one of the β subunits of hemoglobin. Myoglobin and hemoglobin are both part of the globin family; a family of heme-containing globular polypeptides with eight α-helices in their protein fold. Myoglobin contains only one subunit of globin, while hemoglobin has four subunits.

The iron (Fe)-containing heme group allows myoglobin to reversibly bind to O_2.

Heme is a large, aromatic porphyrin ring with four pyrrole nitrogens bound to a ferrous (Fe(II)) ion at the center. The nitrogens from the porphyrin ring and a Histidine imidazole serve as igands for the Fe(II) metal center. The heme Fe is bound to the myoglobin polypeptide through the proximal histidine residue.

The iron ion has six coordination sites: four equitorial sites are occupied by pyrole nitrogens of heme, and one axial site is occupied by a proximal histidine residue. The remaining axial coordination site is available for binding a O_2 molecule.



4. Hemocyanins (Hc)

Hemocyanins are respiratory proteins that use copper binding sites to bind and transport oxygen in a variety of arthropods and mollusks.

Hemocyanins, like hemoglobin, are multi-subunit molecules where each subunit (arthropods) or functional unit of a subunit (mollusks) binds oxygen.

Hemocyanins have a high molecular weight; and pH, temperature and ionic concentration modulate the oxygen affinity. The subunit of hemocyanin has a tendency to aggregate.

The copper in the protein is in the form of Cu(I) and is bound directly to the amino acid side chain, as opposed to the metal being bound to a prosthetic group, as in hemoglobin.

The oxygenated molecule generates the characteristic light absorbance in the near ultraviolet region, around 343 nm, responsible for the blue color of hemocyanins.

Hemocyanins are strong immunogens

Hemocyanin is one of the strongest antigens known.

In mammalians it leads to the formation of very powerful antiserum, moves the T4/T8 ratio in favor of the T4 helper cells and at the site of application leads to local erythema and invasion by macrophages.

Hemocyanin has been in use as an immunological reagent for many years. It is used as a carrier protein for antibody production against antigens.

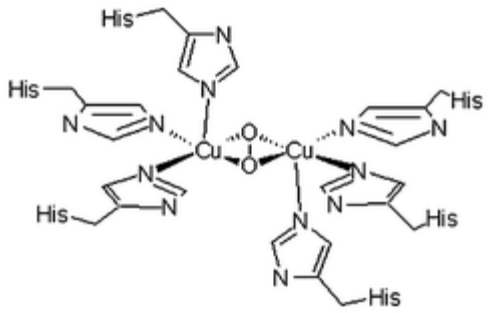
Hemocyanins as carrier proteins

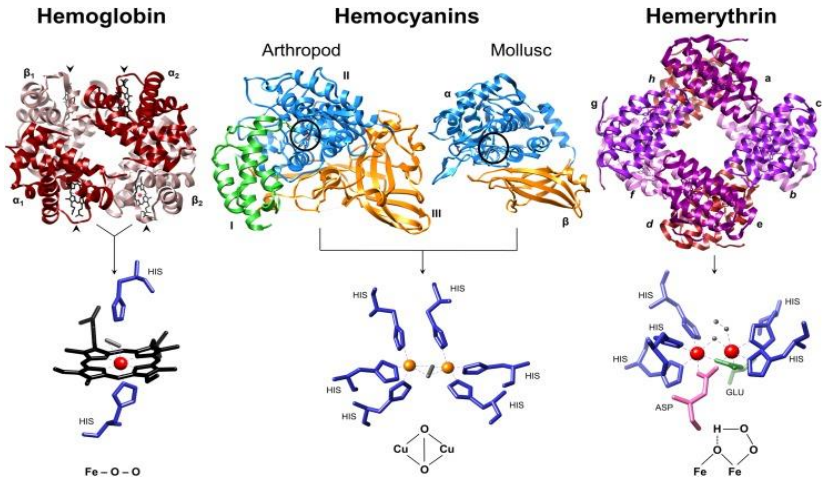
Recent advances in immunology and the role immune system plays in diseases have opened a whole new era of product development activities aimed at developing novel therapeutics which is aimed at teaching the body's immune system to fight diseases like cancer, AIDS, etc.

The approach involves the use of highly immunogenic molecule, like the hemocyanin for non-specific immunostimulation (NSI), or active specific immunostimulation (ASI), using conjugate vaccines, wherein the tumor (disease) specific antigens are covalently bound to carrier protein like KLH and the product used in human clinical studies. Such products are termed 'vaccines'.

The need for such vaccine development is associated with the production and manufacture of large quantities of safe human products. The hemocyanin in such vaccines is an active component and should meet the stringent regulatory requirements, i.e., it must be a safe, characterized product of high quality with batch-to-batch consistency.

The ratio of combined molecular oxygen to copper is O_2:2Cu in all the hemocyanins studied from a variety of different bloods. The deoxygenated protein is colorless, while the oxygenated compound (oxyhemocyanin) has an intense blue color. No evidence has been available as to whether the copper in hemocyanin was in the cupric or cuprous state. The usual oxidizing agents which oxidize the ferrous compounds, hemoglobin and oxyhemoglobin, to the ferric compound, methemoglobin, appear to be without effect on hemocyanin or oxyhemocyanin. We have now found that by the use of the two very powerful oxidizing agents, potassium molybdicyanide or potassium permanganate, it is possible to oxidize the hemocyanin (or oxyhemocyanin) of Limulus polyphemus. In this way two new proteins are formed in which the copper is in the **cupric state**. One of these, prepared from hemocyanin in the absence of oxygen, is colorless and we shall designate it as methemocyanin. The other, oxymethemocyanin, is formed when a solution of methemocyanin is shaken with air or oxygen; the deoxygenation of methemocyanin like that of hemocyanin may be brought about by diminishing the partial pressure of the oxygen above the solution. It is evident that, unlike methemoglobin, methemocyanin combines reversibly with oxygen. The cupric compounds, methemocyanin and oxymethemocyanin, are reduced by the action of a variety of reducing agents





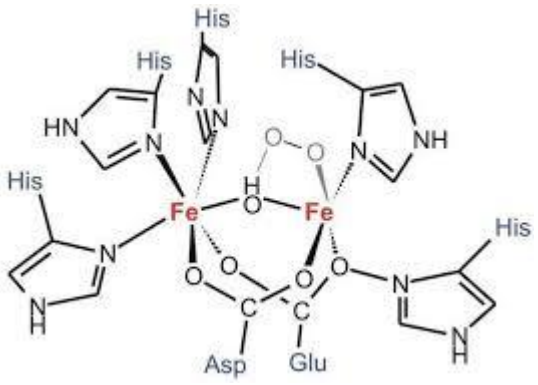
5. Hemerythrin (Hr)

Hemerythrin is a non-heme iron protein used by marine invertebrates for oxygen transfer and/or storage. It differs from the other oxygen-binding proteins (hemoglobin and hemocyanin) both in the polypeptide chain and in the metal complex used to reversibly bind dioxygen.

The two iron atoms in hemerythrin are bound the imidazole rings of five histidine residues and the carboxylates of an aspartic acid and a glutamic acid. In addition, the complex contains an oxygen atom bridging between the two iron atoms. In deoxyhemerythrin, the bridge is a hydroxyl group, while in met- and oxyhemerythrin, the bridge is a μ-oxo atom. In deoxy- and metaquohemerythrin, one of the iron atoms is bound to six liganding atoms while the other is penta-coordinate. This extra site is where small molecules such as dioxygen or azide bind to the protein.

The fundamental polypeptide associated with each metal center is about 115 residues long. The protein is most commonly found as an octamer of molecular weight 108,000. In particular organisms though, dimeric-, trimeric- and tetrameric- forms of the protein are found. The folding topology of the polypeptide is that of a four-helical bundle.

In deoxyhemerythrin, the two iron atoms are in the ferrous oxidation state with a bridging hydroxyl group. As dioxygen is bound to the active site, the hydrogen atom from the hydroxyl bridge moves over onto the bound ligand, stabilizing the peroxo nature of the bound oxygen molecule. In met- derivatives of the protein, with and without small molecules bound to the complex, the iron atoms are both in the ferric oxidation state.



6. Characterization of coordinated O_2 species in oxy forms of heme and non-heme proteins by resonance Raman spectroscopy

Resonance Raman (RR) studies of intermediates generated by cryoreduction of the oxyferrous complex of the D251N mutant of cytochrome $P450_{cam}$ (CYP101) are reported. Owing to the fact that proton delivery to the active site is hindered in this mutant, the unprotonated peroxo-ferric intermediate is observed as the primary species after radiolytic reduction of the oxy-complex in frozen solutions at 77 K. In as much as previous EPR and ENDOR studies have shown that annealing of this species to ∼180 K results in protonation of the distal oxygen atom to form the hydroperoxo intermediate, this system has been exploited to permit direct RR interrogation of the changes in the Fe−O and O−O bonds caused by the reduction and subsequent protonation. Our results show that the ν(O−O) mode decreases from a superoxo-like frequency near ∼1130 cm^{-1} to 792 cm^{-1} upon reduction. The latter frequency, as well as its lack of sensitivity to H/D exchange, is consistent with heme-bound peroxide formulation. This species also exhibits a ν(Fe−O) mode, the 553 cm^{-1} frequency of which is higher than that observed for the nonreduced oxy P450 precursor (537 cm^{-1}), implying a strengthened Fe−O linkage upon reduction. Upon subsequent protonation, the resulting Fe−O−OH fragment exhibits a lowered ν(O−O) mode at 774 cm^{-1}, whereas the ν(Fe−O) increases to 564 cm^{-1}. Both modes exhibit a downshift upon H/D exchange, as expected for a hydroperoxo-ferric formulation. These experimental RR data are compared with those previously acquired for the wild-type protein, and the shifts observed upon reduction and subsequent protonation are discussed with reference to theoretical predictions.

Resonance Raman spectroscopy and heme proteins

The heme groups in heme proteins are examples of molecules called metalloporphyrins. Metalloporphyrins are one of the most studied classes of molecules in the area of Raman spectroscopy. The first reason is about the aromatic macrocyclic structure of the heme group. The extended aromatic system of the porphyrin ring gives rise to two low-lying π-π* electronic transitions. It is convenient to excite metalloporphyrins with a visible laser. For instance, the vibrational frequencies changes in the Raman spectra are responsive to porphyrin geometry and electronic structure change; these effects can be examined selectively by changing the excitation wavelength. Moreover, the vibrational modes of the active site heme chromophore of heme proteins and their associated ligands can be selectively enhanced by exciting within the absorption spectral region of the heme chromophore. The vibrational modes of the non-absorbing polypeptide retain the much weaker scattering of the non-resonant event and are not

detected above the spectral background. However, if one uses deep UV laser it is possible to selectively enhance aromatic amino acid groups, such as tyrosine, tryptophan and phenylalanine. For example, in human hemoglobin, when the excitation line is in the UV laser near 220-280 nm, the Raman spectrum shows the information about the amino acid and protein structure. If the excitation line is just at Soret band which is the most intensive π-π^* transition, or close to Q band, the signals from the heme group are stronger than when other excitation line is applied. So resonance Raman spectroscopy (RR) is characterized by enhanced detection and selection capabilities.

7. Bohr Effect

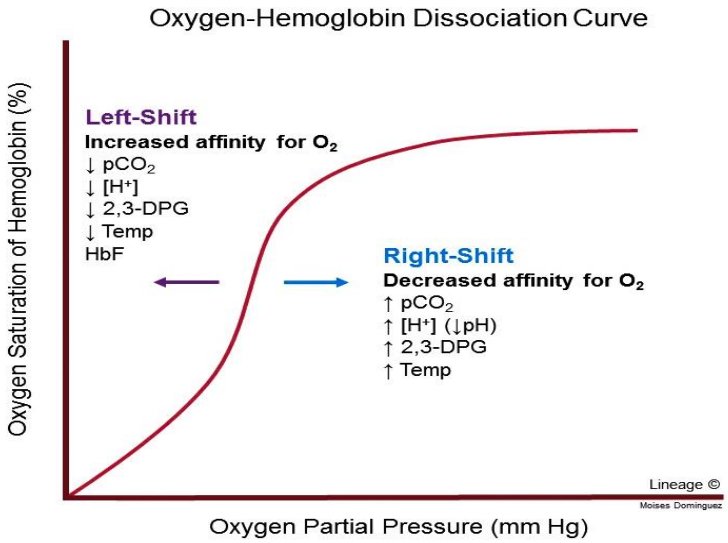
The Bohr Effect refers to the observation that increases in the carbon dioxide partial pressure of blood or decreases in blood pH result in a lower affinity of hemoglobin for oxygen. This manifests as a right-ward shift in the Oxygen-Hemoglobin Dissociation Curve described in oxygen transport and yields enhanced unloading of oxygen by hemoglobin.

Mechanism

Decreases in blood pH, meaning increased H^+ concentration, are likely the direct cause of lower hemoglobin affinity for oxygen. Specifically, the association of H^+ ions with the amino acids of hemoglobin appear to reduce hemoglobin's affinity for oxygen. Because changes in the carbon dioxide partial pressure can modify blood pH, increased partial pressures of carbon dioxide can also result in right-ward shifts of the oxygen-hemoglobin dissociation curve. The relationship between carbon dioxide partial pressure and blood pH is mediated by carbonic anhydrase which converts gaseous carbon dioxide to carbonic acid that in turn releases a free hydrogen ion, thus reducing the local pH of blood.

Significance

The Bohr Effect allows for enhanced unloading of oxygen in metabolically active peripheral tissues such as exercising skeletal muscle. Increased skeletal muscle activity results in localized increases in the partial pressure of carbon dioxide which in turn reduces the local blood pH. Because of the Bohr Effect, this results in enhanced unloading of bound oxygen by hemoglobin passing through the metabolically active tissue and thus improves oxygen delivery. Importantly, the Bohr Effect enhances oxygen delivery proportionally to the metabolic activity of the tissue. As more metabolism takes place, the carbon dioxide partial pressure increases thus causing larger reductions in local pH and in turn allowing for greater oxygen unloading. This is especially true in exercising skeletal muscles which may also release lactic acid that further reduces local blood pH and thus enhances the Bohr Effect.



Modulation of the Oxygen-Hemoglobin Dissociation Curve

A variety of environmental factors can shift the Oxygen-Hemoglobin Dissociation Curve. Effects which are associated with increased peripheral tissue metabolism, such as reduced pH, increased CO_2, increased temperature, shift the curve to the right, reducing hemoglobin's affinity for oxygen and thus improving oxygen unloading. Chronic hypoxia increases the blood's concentration of 2,3-DPG which also shifts the curve to the right. The presence of HbF and carbon monoxide (CO) shift the curve to the left, increasing the oxygen affinity of hemoglobin.

8. Cytochromes – Electron Transfer Proteins

Cyto – cell; Chrome – color

Cytochrome is a protein that can transfer electrons with a chemical group called a heme group. The heme group of cytochrome are similar to those of hemoglobin as they both have the same basic structure of porphyrin ring structure. Function of heme groups of cytochrome are different from that of the heme groups of the blood. The cytochrome transfer electron through heme.

Introduction and definitions

Hemeproteins that transfer electrons belong to the family of the cytochromes. The name 'cytochrome' was introduced by Keilin in 1925 to describe a group of intracellular hemeproteins that undergo oxidation-reduction and, upon reduction, exhibit intense absorption bands between 510 and 615 nm. As currently used, the name appears to include all intracellular hemeproteins with the exception of hemoglobin, myoglobin, the peroxidases, catalase, tryptophan 2,3-dioxygenase, heme-thiolate proteins (*P*-450) and the nitrite and sulfite reductases.

Thus a number of enzymes are also referred to as cytochromes. These include cytochrome-*c* oxidase, L-lactate dehydrogenase (cytochrome) (yeast cytochrome) and cytochrome *P*-450.

A cytochrome is a hemeprotein whose characteristic mode of action involves transfer of reducing equivalents associated with a reversible change in oxidation state of the prosthetic group. Formally, this redox change involves a single-electron, reversible equilibrium between the Fe(II) and Fe(III) states of the central iron atom.

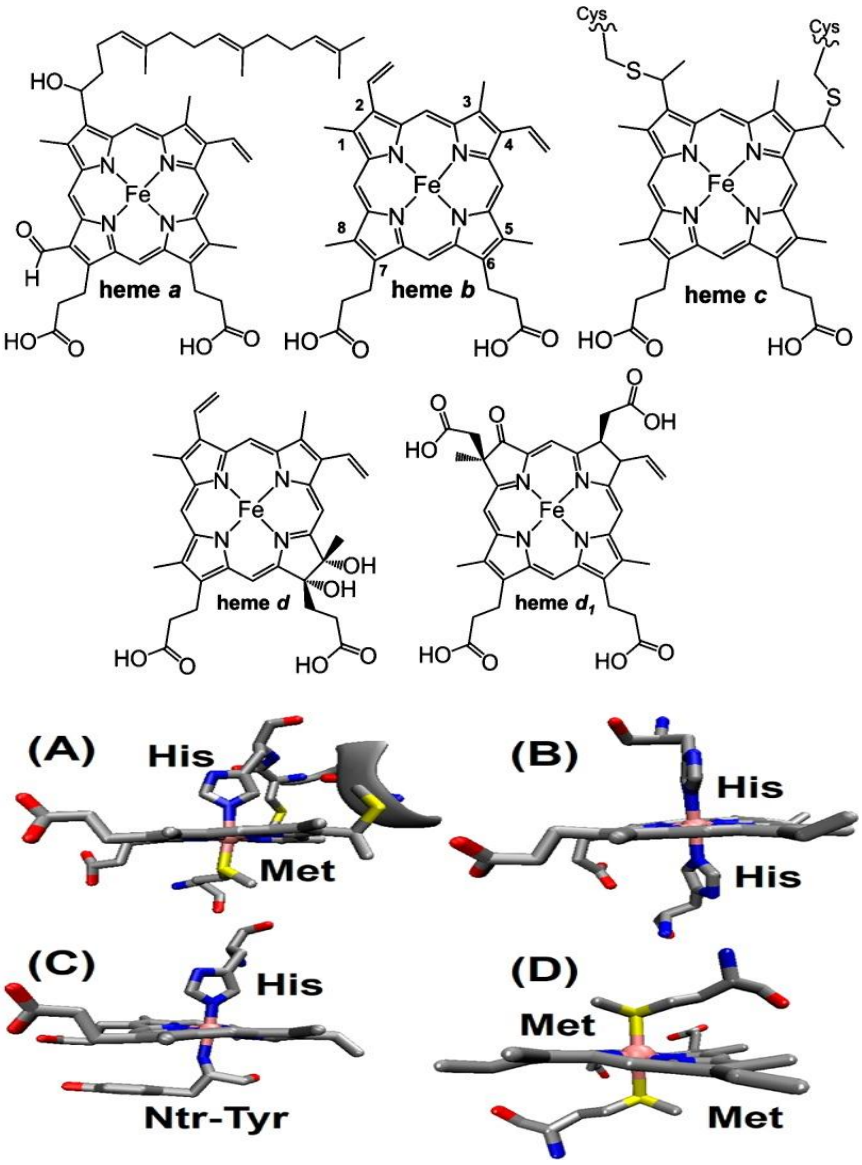
The intense red color combined with relatively high thermodynamic stability makes cytochromes easy to observe and to purify. As of today, more than 70 000 cytochromes have been discovered. In addition, due to their small size, high solubility, and well-folded helical structure and the presence of the heme chromophore, cytochromes are one of the most extensively studied classes of proteins spanning several decades.

Cytochromes are present mostly in the inner mitochondrial membrane of eukaryotic organisms and are also found in a wide variety of both Gram-positive and Gram-negative bacteria. Cytochromes play crucial roles in a number of biological ET processes associated with many different energy metabolisms. Additionally, cytochromes are involved in apoptosis in mammalian cells.

Cytochromes are electron-transporting protein pigments concerned with **cell respiration** that contain an iron-containing molecule called heme, allied to that of hemoglobin. When the iron of heme accepts an elctron, it changes from the oxidized ferric (Fe III) state to the reduced ferrous (Fe II) state. The oxidation of cytochromes to molecular oxygen and their subsequent reduction by oxidizable substances in the cell is the main way in which atmospheric oxygen enters into the metabolism of the cell. About 90% of all oxygen consumed is mediated by the cytochromes.

Cytochromes make up two of the three large enzyme complexes that together comprise the electron transport or respiratory chain. This chain represents the end of oxidative phosphorylation, the process by which many organisms synthesize the energy-rich molecules of adenosine triphosphate (ATP) needed for life processes.

Cytochromes are classified on the basis of the electronic absorption maxima of the heme macrocycle, such as *a*, *b*, *c*, *d*, *f*, and *o* types of heme. More specifically, these letter names represent characteristic absorbance maxima in the UV–vis electronic absorption spectrum when the heme iron is coordinated with pyridine in its reduced (ferrous) state, designated as the "pyridine hemochrome" spectrum.



Commonly found heme axial ligands in various cytochromes.

Cytochrome Groups

Four major groups of cytochromes are currently recognized:

Cytochromes *a*. Cytochromes in which the heme prosthetic group is heme *a*, *i.e.* the iron chelate of cytoporphyrin IX.

Cytochromes *b*. Cytochromes with protoheme [the iron chelate of protoporphyrin IX] as prosthetic group but which lack a covalent bond between the porphyrin and the protein.

Cytochromes *c*. Cytochromes with covalent thioether linkages between either or both of the vinyl side chains of protoheme side chains and the protein.

Cytochromes *d*. Cytochromes with a tetrapyrrolic chelate of iron as prosthetic group in which the degree of conjugation of double bonds is less than in porphyrin, *e.g.* dihydroporphyrin [chlorin; heme *d* , tetrahydroporphyrin [isobacteriochlorins; heme d_1, siroheme]. Heme *d* has also been known as heme a_2.

The *b*-type cytochromes have four methyl substitutions at positions 1, 3, 5, and 8, two vinyl groups in positions 2 and 4, and two propionate groups at positions 6 and 7, resulting in a 22-π-electron porphyrin. Hemes *a* and *c* are biosynthesized as derivatives of heme *b*. In heme *a*, the vinyl group at position 2 of the porphyrin ring of heme *b* is replaced by a hydroxyethylfarnesyl side chain while the methyl group at position 8 is oxidized to a formyl group. These substituents make heme *a* more hydrophobic as well as more electron-withdrawing than heme *b* due to the presence of farnesyl and formyl groups, respectively. Covalent cross-linking of the vinyl groups at β-pyrrole positions 2 and 4 of heme *b* with Cys residues from the protein yields heme *c*, where the vinyl groups of heme *b* are replaced by thioether bonds.

The exchange of electrons begins at the NADH dehydrogenase complex, which passes electrons to ubiquinone (coenzyme Q). Ubiquinone, in turn, passes electrons to the cytochrome b-c_1 complex, which is composed of cytochromes and iron-sulfur proteins. The last cytochrome in this complex (cytochrome c) passes electrons to the cytochrome oxidase complex, composed of both cytochromes and **copper atoms**. Finally, the cytochrome oxidase complex passes electrons to oxygen.

9. Iron Sulphur Proteins

Iron-sulfur proteins are proteins characterized by the presence of iron-sulfur clusters containing sulfide-linked di-, tri-, and tetra iron centers in variable oxidation states.

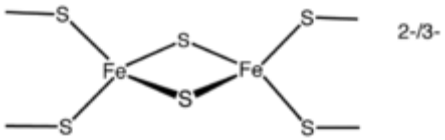
Iron–sulfur clusters are found in a variety of metalloproteins, such as ferredoxins, NADH dehydrogenase, hydrogenases, coenzyme Q – cytochrome c reductase, succinate – coenzyme Q reductase and nitrogenase.

Iron–sulfur clusters are best known for their role in the oxidation-reduction reactions of electron transport in mitochondria and chloroplasts. Both Complex I and Complex II of oxidative phosphorylation have multiple Fe–S clusters. They have many other functions including catalysis as illustrated by aconitase, generation of radicals as illustrated by SAM-dependent enzymes, and as sulfur donors in the biosynthesis of lipoic acid and biotin.

The prevalence of these proteins on the metabolic pathways of most organisms leads some scientists to theorize that iron–sulfur compounds had a significant role in the origin of life in the iron-sulfur world theory.

In almost all Fe–S proteins, the Fe centers are tetrahedral and the terminal ligands are thiolato sulfur centers from cysteinyl residues. The sulfide groups are either two- or three-coordinated. Three distinct kinds of Fe–S clusters with these features are most common.

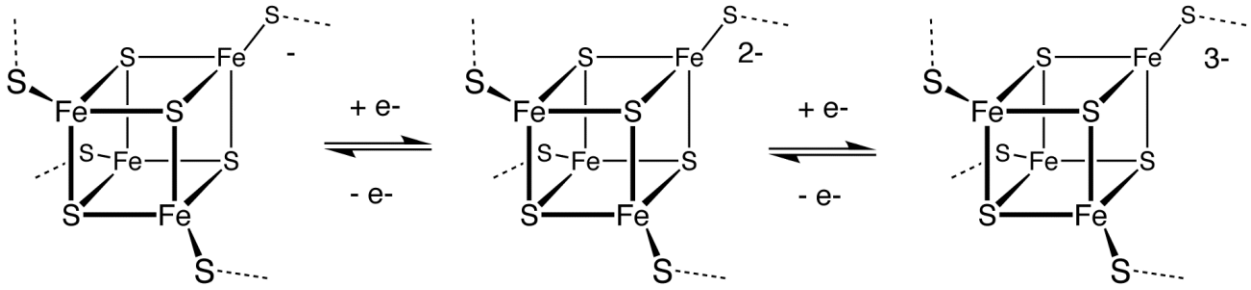
2Fe–2S clusters



The simplest polymetallic system, the $[Fe_2S_2]$ cluster, is constituted by two iron ions bridged by two sulfide ions and coordinated by four cysteinyl ligands (in Fe_2S_2 ferredoxins) or by two cysteines and two histidines (in Rieske proteins). The oxidized proteins contain two Fe^{3+} ions, whereas the reduced proteins contain one Fe^{3+} and one Fe^{2+} ion. These species exist in two oxidation states, $(Fe^{III})_2$ and $Fe^{III}Fe^{II}$.

4Fe–4S clusters

A common motif features a four iron ions and four sulfide ions placed at the vertices of a cubane-type cluster. The Fe centers are typically further coordinated by cysteinyl ligands. The $[Fe_4S_4]$ electron-transfer proteins ($[Fe_4S_4]$ 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:



4Fe-4S Clusters

The two families of 4Fe–4S clusters share the $Fe_4S_4^{2+}$ oxidation state. The difference in the redox couples is attributed to the degree of hydrogen bonding, which strongly modifies the basicity of the cysteinyl thiolate ligands. A further redox couple, which is still more reducing than the bacterial ferredoxins is implicated in the nitrogenase.

Some 4Fe–4S clusters bind substrates and are thus classified as enzyme cofactors. In aconitase, the Fe–S cluster binds aconitate at the one Fe centre that lacks a thiolate ligand. The cluster does not undergo redox, but serves as a Lewis acid catalyst to convert citrate to isocitrate.

3Fe–4S clusters

Proteins are also known to contain $[Fe_3S_4]$ centres, which feature one iron less than the more common $[Fe_4S_4]$ cores. Three sulfide ions bridge two iron ions each, while the fourth sulfide bridges three iron ions. Their formal oxidation states may vary from $[Fe_3S_4]^+$ (all-Fe^{3+} form) to $[Fe_3S_4]^{2-}$ (all-Fe^{2+} form). In a number of iron–sulfur proteins, the $[Fe_4S_4]$ cluster can be reversibly converted by oxidation and loss of one iron ion to a $[Fe_3S_4]$ cluster.

Other Fe–S clusters

More complex polymetallic systems are common. Examples include both the 8Fe and the 7Fe clusters in nitrogenase. Carbon monoxide dehydrogenase and the [FeFe]-hydrogenase also feature unusual Fe–S clusters. A special 6 cysteine-coordinated $[Fe_4S_3]$ cluster was found in oxygen-tolerant membrane-bound [NiFe] hydrogenases.

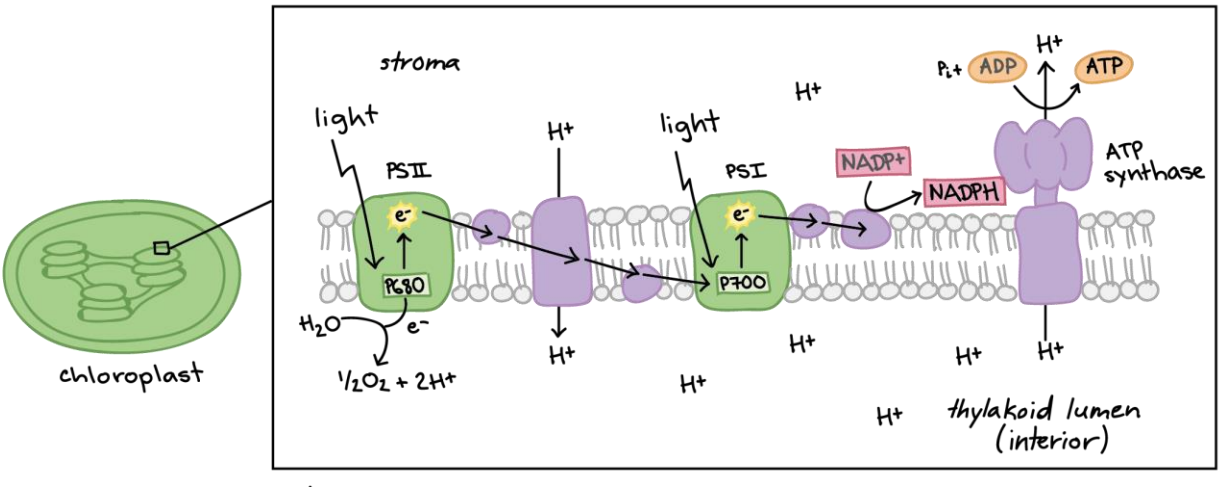
10. Chloroplasts and Photosynthesis

Light energy is converted to chemical energy during the first stage of photosynthesis, which involves a series of chemical reactions known as the light-dependent reactions.

The **light-dependent reactions** use light energy to make two molecules needed for the next stage of photosynthesis: the energy storage molecule ATP and the reduced electron carrier NADPH. In plants, the light reactions take place in the thylakoid membranes of organelles called chloroplasts.

Photosystems, large complexes of proteins and pigments (light-absorbing molecules) that are optimized to harvest light, play a key role in the light reactions. There are two types of photosystems: photosystem I (PSI) and photosystem II (PSII).

Both photosystems contain many pigments that help collect light energy, as well as a special pair of chlorophyll molecules found at the core (reaction center) of the photosystem. The special pair of **photosystem I** is called **P700**, while the special pair of **photosystem II** is called **P680**.



In a process called **non-cyclic photophosphorylation** (the "standard" form of the light-dependent reactions), electrons are removed from water and passed through PSII and PSI before ending up in NADPH. This process requires light to be absorbed twice, once in each photosystem, and it makes ATP . In fact, it's called photophosphorylation because it involves using light energy (*photo*) to make ATP from ADP (*phosphorylation*). Here are the basic steps:

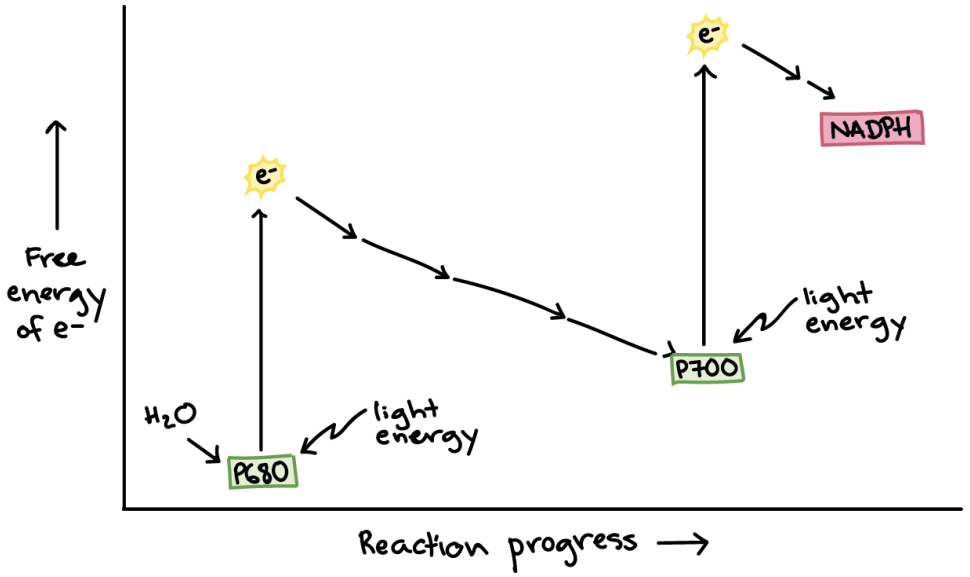
- **Light absorption in PSII.** When light is absorbed by one of the many pigments in photosystem II, energy is passed inward from pigment to pigment until it reaches the reaction center. There,

energy is transferred to P680, boosting an electron to a high energy level. The high-energy electron is passed to an acceptor molecule and replaced with an electron from water. This splitting of water releases the oxygen we breathe.

- **ATP synthesis.** The high-energy electron travels down an electron transport chain, losing energy as it goes. Some of the released energy drives pumping of H^+ ions from the stroma into the thylakoid interior, building a gradient. (H^+ions from the splitting of water also add to the gradient.) As H^+ ions flow down their gradient and into the stroma, they pass through ATP synthase, driving ATP production in a process known as **chemiosmosis**.
- **Light absorption in PSI.** The electron arrives at photosystem I and joins the P700 special pair of chlorophylls in the reaction center. When light energy is absorbed by pigments and passed inward to the reaction center, the electron in P700 is boosted to a very high energy level and transferred to an acceptor molecule. The special pair's missing electron is replaced by a new electron from PSII (arriving via the electron transport chain).
- **NADPH formation.** The high-energy electron travels down a short second leg of the electron transport chain. At the end of the chain, the electron is passed to $NADP^+$ to make NADPH.

The net effect of these steps is to convert light energy into chemical energy in the form of ATP and NADPH. The ATP and NADPH from the light-dependent reactions are used to make sugars in the next stage of photosynthesis, the Calvin cycle. In another form of the light reactions, called **cyclic photophosphorylation**, electrons follow a different, circular path and only ATP (no NADPH) is produced.

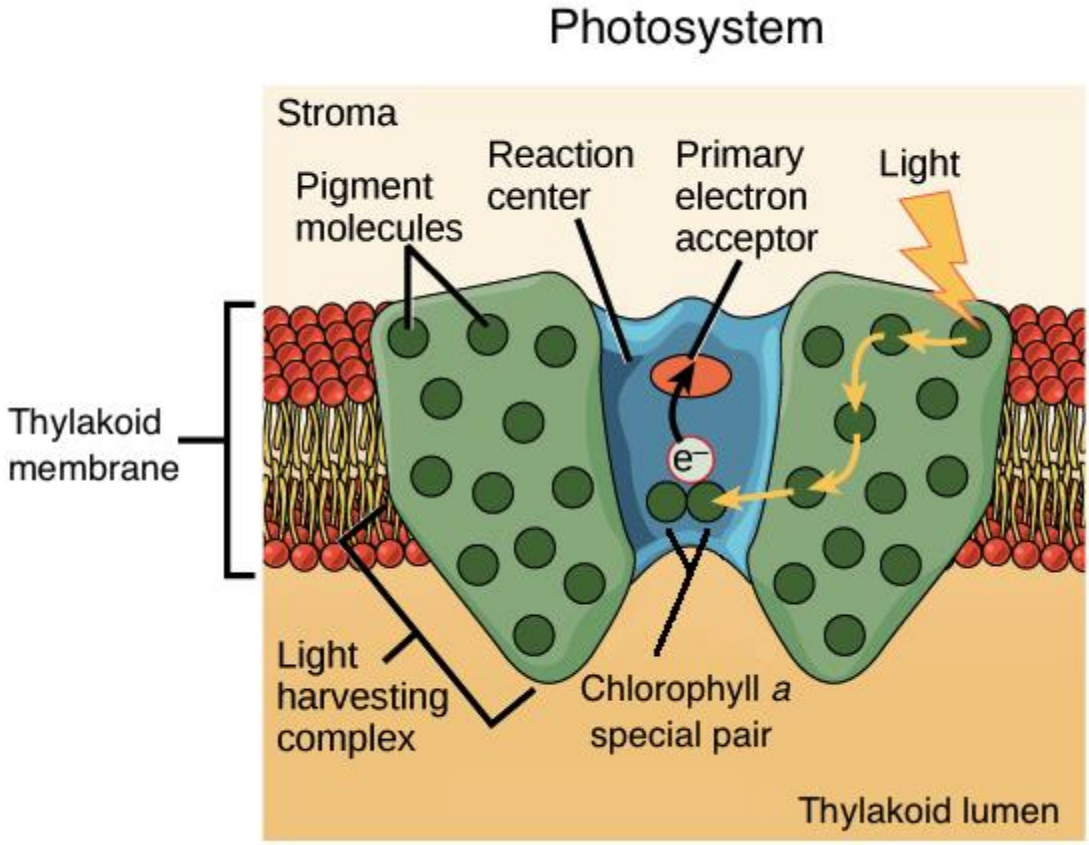
It's important to realize that the electron transfers of the light-dependent reactions are driven by, and indeed made possible by, the absorption of energy from light. In other words, the transfers of electrons from PSII to PSI, and from PSI to NADPH, are only energetically "downhill" (energy-releasing, and thus spontaneous) because electrons in P680 and P700 are boosted to very high energy levels by absorption of energy from light.



Photosynthetic pigments, such as chlorophyll *a*, chlorophyll *b*, and carotenoids, are light-harvesting molecules found in the thylakoid membranes of chloroplasts. As mentioned above, pigments are organized along with proteins into complexes called **photosystems**. Each photosystem has **light-harvesting complexes** that contain proteins, 300-400 chlorophylls, and other pigments. When a pigment absorbs a photon, it is raised to an excited state, meaning that one of its electrons is boosted to a higher-energy orbital.

Most of the pigments in a photosystem act as an energy funnel, passing energy inward to a main reaction center. When one of these pigments is excited by light, it transfers energy to a neighboring pigment through direct electromagnetic interactions in a process called **resonance energy transfer**. The neighbor pigment, in turn, can transfer energy to one of its own neighbors, with the process repeating multiple times. In these transfers, the receiving molecule cannot require more energy for excitation than the donor, but may require less energy (i.e., may absorb light of a longer wavelength.

Collectively, the pigment molecules collect energy and transfer it towards a central part of the photosystem called the **reaction center**.



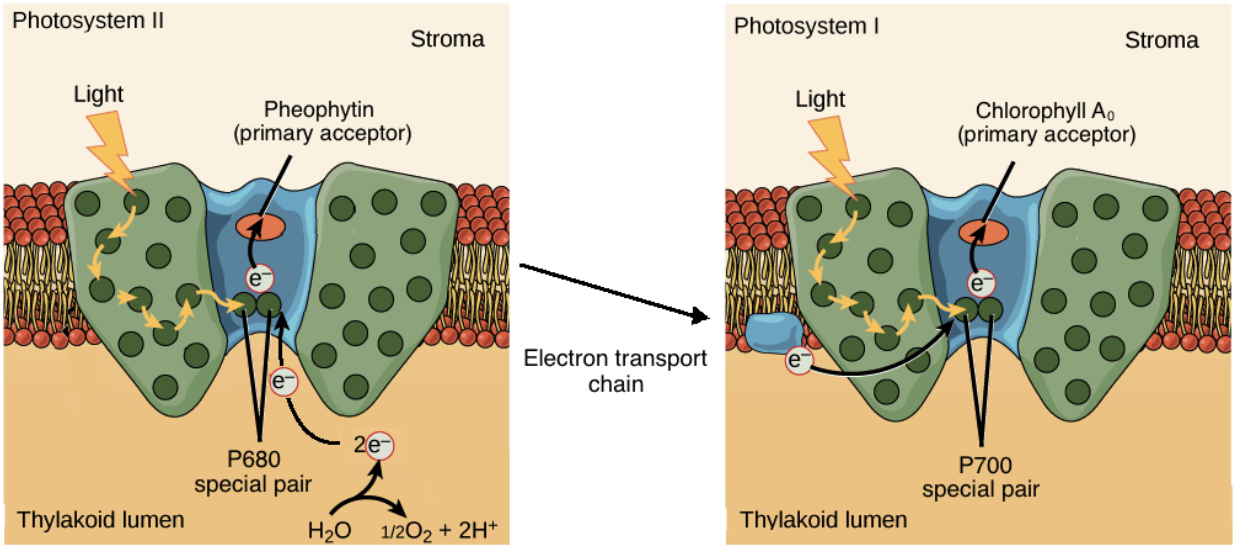
The reaction center of a photosystem contains a unique pair of chlorophyll *a* molecules, often called **special pair**. Once energy reaches the special pair, it will no longer be passed on to other pigments through resonance energy transfer. Instead, the special pair can actually lose an

electron when excited, passing it to another molecule in the complex called the **primary electron acceptor**. With this transfer, the electron will begin its journey through an electron transport chain.

Photosystem I vs. photosystem II

There are two types of photosystems in the light-dependent reactions, **photosystem II (PSII)** and **photosystem I (PSI)**. PSII comes first in the path of electron flow, but it is named as second because it was discovered after PSI. Here are some of the key differences between the photosystems:

- **Special pairs.** The chlorophyll *a* special pairs of the two photosystems absorb different wavelengths of light. The PSII special pair absorbs best at 680 nm, while the PSI special absorbs best at 700 nm. Because of this, the special pairs are called **P680** and **P700**, respectively.
- **Primary acceptor**. The special pair of each photosystem passes electrons to a different primary acceptor. The primary electron acceptor of PSII is pheophytin, an organic molecule that resembles chlorophyll, while the primary electron acceptor of PSI is a chlorophyll called A_0.
- **Source of electrons**. Once an electron is lost, each photosystem is replenished by electrons from a different source. The PSII reaction center gets electrons from water, while the PSI reaction center is replenished by electrons that flow down an electron transport chain from PSII.



During the light-dependent reactions, an electron that's excited in PSII is passed down an electron transport chain to PSI (losing energy along the way). In PSI, the electron is excited again and passed down the second leg of the electron transport chain to a final electron acceptor.

Photosystem II

When the P680 special pair of photosystem II absorbs energy, it enters an excited (high-energy) state. Excited P680 is a good electron donor and can transfer its excited electron to the primary electron acceptor, pheophytin. The electron will be passed on through the first leg of the photosynthetic **electron transport chain** in a series of redox, or electron transfer, reactions.

After the special pair gives up its electron, it has a positive charge and needs a new electron. This electron is provided through the splitting of water molecules, a process carried out by a portion of PSII called the manganese center. The positively charged P680 can pull electrons off of water (which doesn't give them up easily) because it's extremely "electron-hungry."

When the manganese center splits water molecules, it binds two at once, extracting four electrons, releasing four H^+ ions and producing a molecule of O_2. About 10 percent of the oxygen is used by mitochondria in the leaf to support oxidative phosphorylation. The remainder escapes to the atmosphere where it is used by aerobic organisms to support respiration.

Electron transport chains and photosystem I

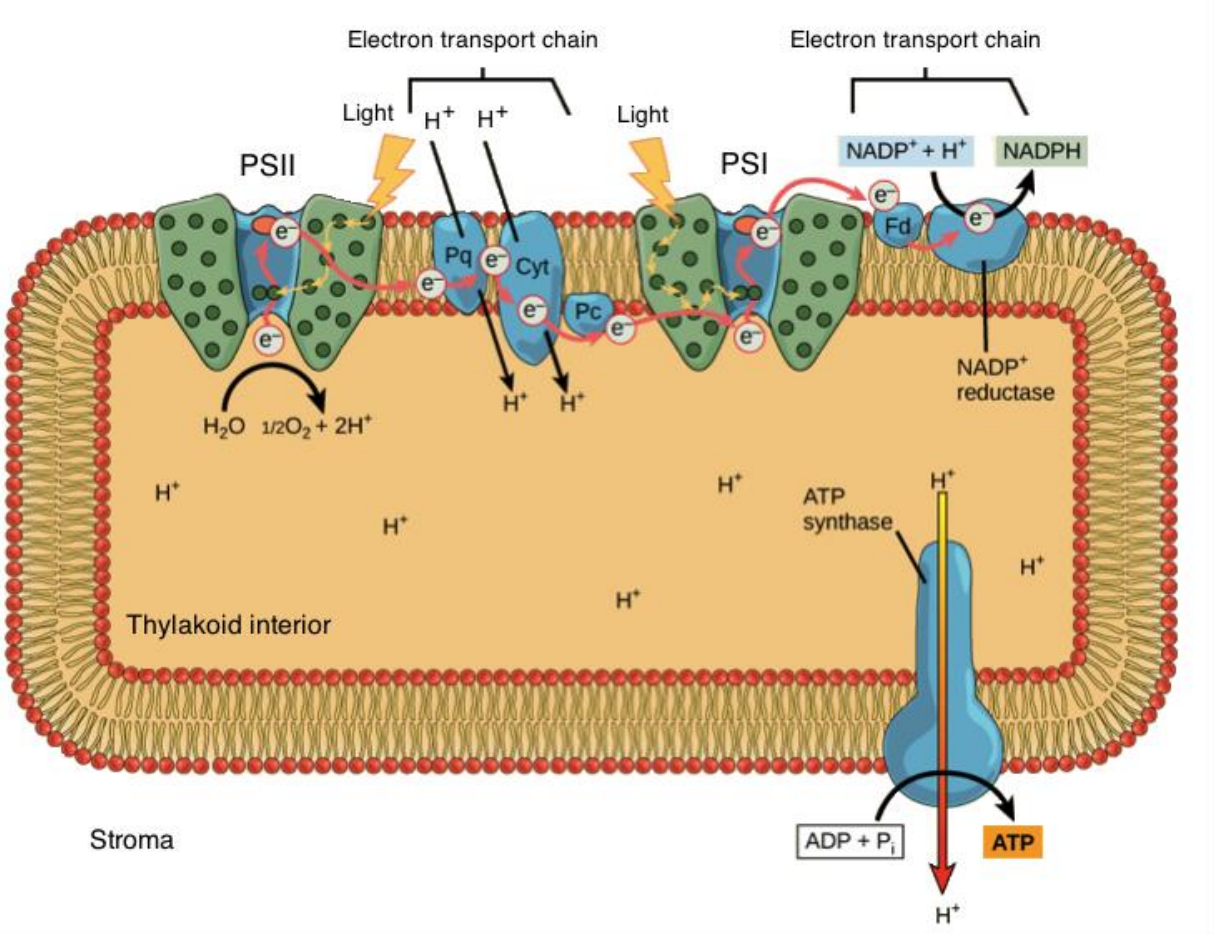
When an electron leaves PSII, it is transferred first to a small organic molecule (plastoquinone, Pq), then to a cytochrome complex (Cyt), and finally to a copper-containing protein called plastocyanin (Pc). As the electron moves through this electron transport chain, it goes from a higher to a lower energy level, releasing energy. Some of the energy is used to pump protons H^+ from the stroma (outside of the thylakoid) into the thylakoid interior.

This transfer of H^+, along with the release of H^+ from the splitting of water, forms a proton gradient that will be used to make ATP.

Once an electron has gone down the first leg of the electron transport chain, it arrives at PSI, where it joins the chlorophyll *a* special pair called P700. Because electrons have lost energy prior to their arrival at PSI, they must be re-energized through absorption of another photon.

Excited P700 is a very good electron donor, and it sends its electron down a short electron transport chain. In this series of reactions, the electron is first passed to a protein called ferredoxin (Fd), then transferred to an enzyme called **$NADP^+$**. $NADP^+$ reductase transfers electrons to the electron carrier $NADP^+$ to make NADPH. NADPH will travel to the Calvin cycle, where its electrons are used to build sugars from carbon dioxide.

The other ingredient needed by the Calvin cycle is ATP, and this too is provided by the light reactions. As we saw above, H^+ ions build inside the thylakoid interior and make a concentration gradient. Protons "want" to diffuse back down the gradient and into the stroma, and their only route of passage is through the enzyme **ATP synthase**. ATP synthase harnesses the flow of protons to make ATP from ADP and phosphate P*i*. This process of making ATP using energy stored in a chemical gradient is called **chemiosmosis**.

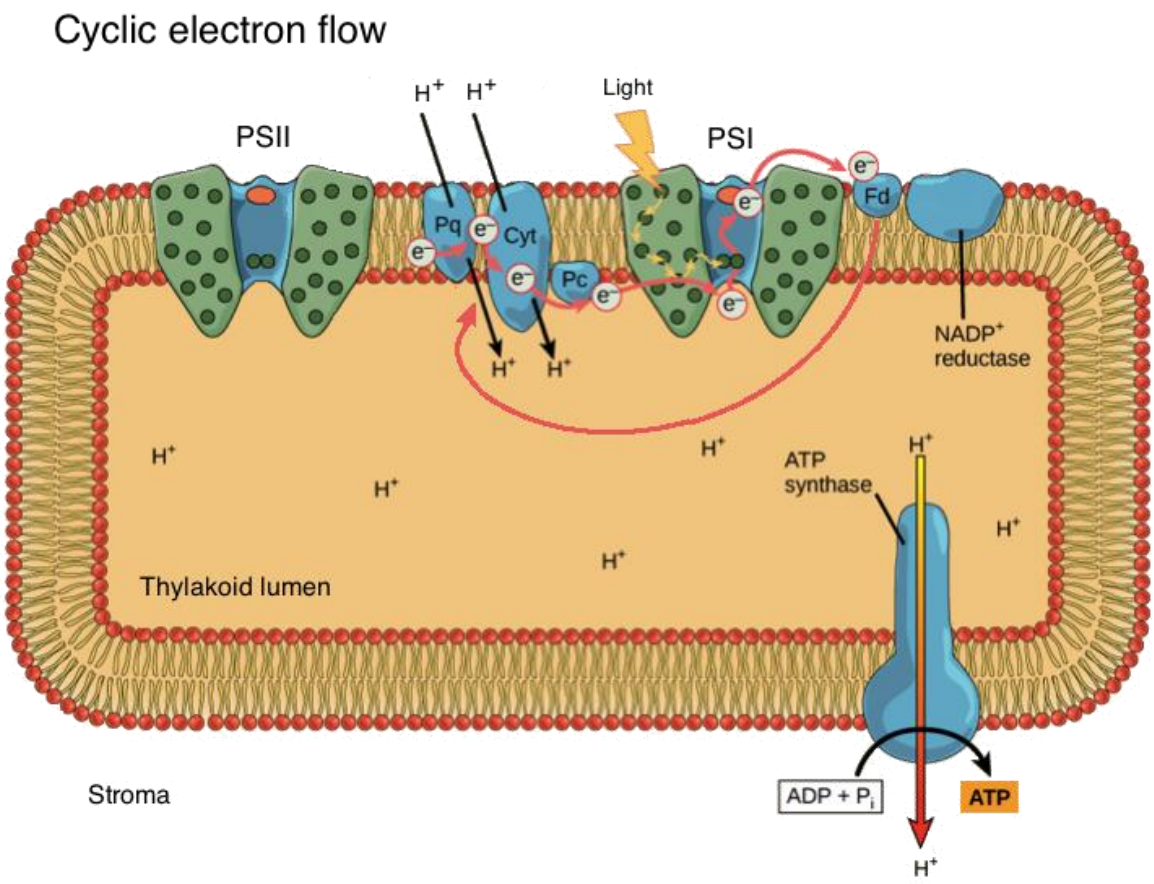


Some electrons flow cyclically

The pathway above is sometimes called **linear photophosphorylation**. That's because electrons travel in a line from water through PSII and PSI to NADPH. (*Photophosphorylation* = light-driven synthesis of ATP.)

In some cases, electrons break this pattern and instead loop back to the first part of the electron transport chain, repeatedly cycling through PSI instead of ending up in NADPH. This is called **cyclic photophosphorylation**.

After leaving PSI, cyclically flowing electrons travel back to the cytochrome complex (Cyt) or plastoquinone (Pq) in the first leg of the electron transport chain. The electrons then flow down the chain to PSI as usual, driving proton pumping and the production of ATP. The cyclic pathway does not make NADPH, since electrons are routed away from $NADP^+$ start superscript, plus, end superscript reductase.



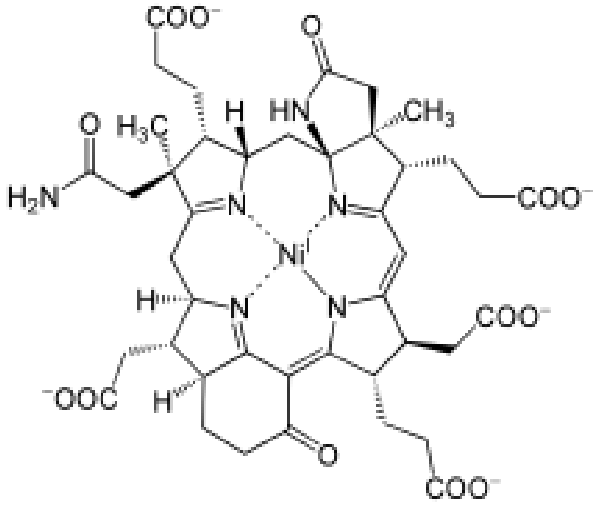
At least in some cases, chloroplasts seem to switch from linear to cyclic electron flow when the ratio of NADPH to $NADP^+$ is too high (when too little $NADP^+$ is available to accept electrons). In addition, cyclic electron flow may be common in photosynthetic cell types with especially high ATP needs (such as the sugar-synthesizing bundle-sheath cells of plants that carry out C4 photosynthesis. Finally, cyclic electron flow may play a photoprotective role, preventing excess light from damaging photosystem proteins and promoting repair of light-induced damage.

11. Coenzyme F430

F_{430} is the cofactor (sometimes called the coenzyme) of the enzyme methyl coenzyme M reductase (MCR). MCR catalyzes the reaction that releases methane in the final step of methanogenesis. The trivial name cofactor F_{430} was assigned in 1978 based on the properties of a yellow sample extracted from Methanobacterium *thermoautotrophicum*, which had a spectroscopic maximum at 430 nm. It was identified as the MCR cofactor in 1982 and the complete structure was deduced by X-ray crystallography and NMR spectroscopy.

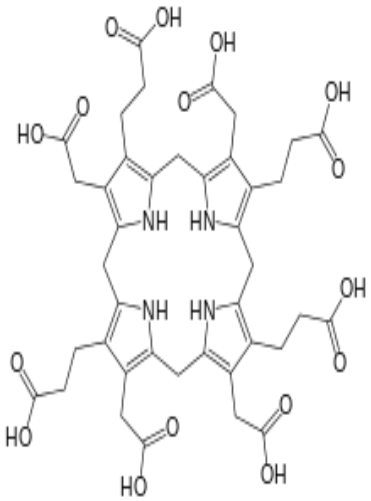
Coenzyme F_{430} features a reduced porphyrin in a macrocyclic ring system called a corphin. In addition, it possesses two additional rings in comparison to the standard tetrapyrrole (rings A-D), having a √-Lactam ring E and a keto-containing carboxylic ring F.

It is the only natural tetrapyrrole containing nickel, an element rarely found in biological systems.

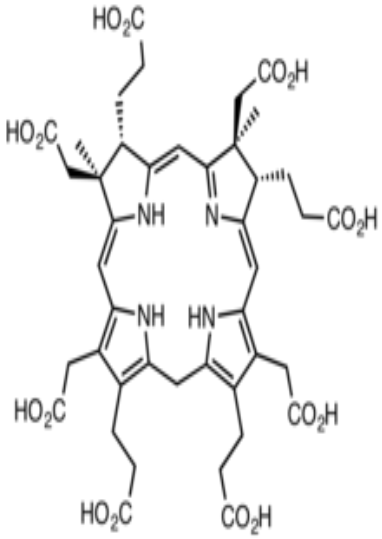


The biosynthesis of Cofactor 430 builds from uroporphyrinogen III, the progenitor of all natural tetrapyrroles, including chlorophyll, vitamin B_{12}, phycobilins, siroheme, heme, and heme d_1. It is converted to sirohydrochlorin via dihydrosirohydrochlorin.

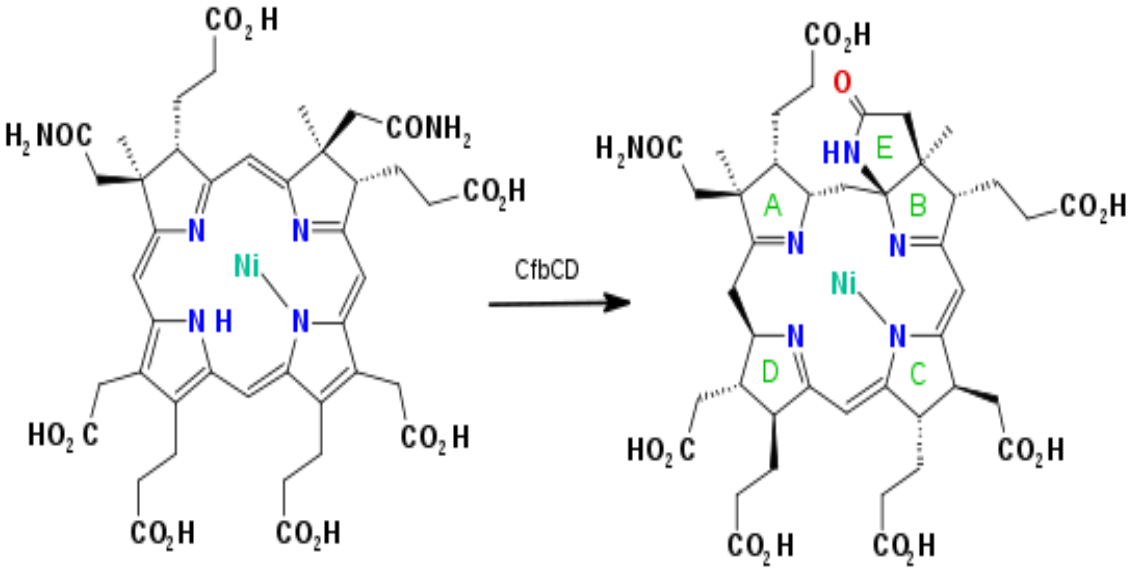
Insertion of nickel into this tetrapyrrole is catalysed in reaction by the same chelatase, CbiX, which inserts cobalt in the biosynthesis of cobalamin, here giving nickel(II)-sirohydrochlorin.



Uroporphyrinogen III



sirohydrochlorin



Nickel(II)-sirohydrochlorin a,c-diamide is converted to seco-F430

The ATP-dependent Ni-sirohydrochlorin a,c-diamide synthase (CfbE) then converts the *a* and *c* acetate side chains to acetamide, generating nickel(II)-sirohydrochlorin *a*,*c*-diamide. The sequence of the two amidations is random. A two-component complex Ni-sirohydrochlorin a,c-diamide reductive cyclase (CfbCD) carries out a 6-electron and 7-proton reduction of the ring system generating the 15,17^3-*seco*-F_{430}-17^3-acid (*seco*-F_{430}) intermediate. Reduction involves ATP hydrolysis and electrons are relayed through two 4Fe-4S centres. In the final step, the keto-containing carbocylic ring F is formed by an ATP-dependent enzyme Coenzyme F(430) synthetase (CfbB), generating coenzyme F_{430}.

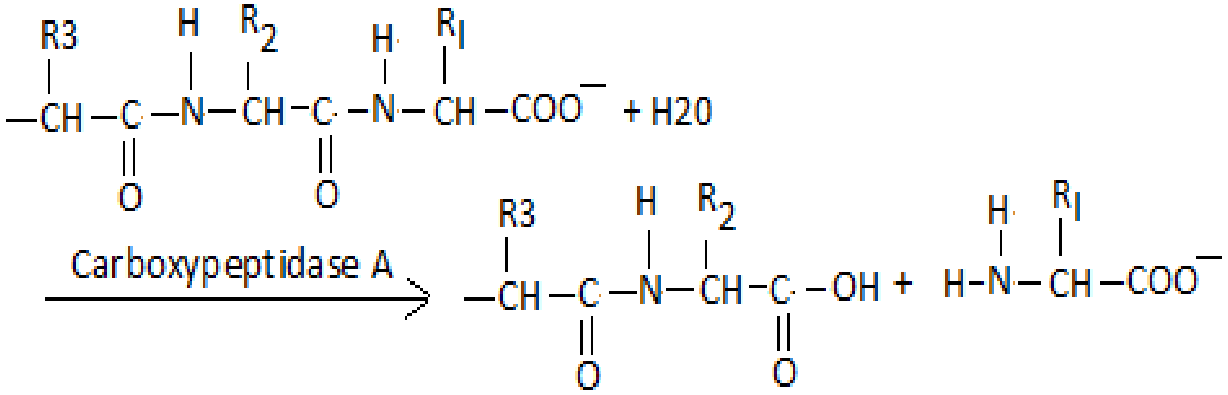
12. Carboxypeptidase

In the human body, proteins are essential molecules in organisms and have a multitude of functions ranging from providing tensile strength to bones and tendons to providing storage and transportation of necessary substances such as O_2 and iron throughout the body. Hence, within the body's cells, proteins from foods must first be separated into their constituent amino acids. Then these amino acids are used to construct the proteins needed by our body. To break down a protein into its constituent amino acids, the cell uses a hydrolysis reaction. The protein reacts with a water molecule to produce an amino acid and a new smaller protein. The enzyme carboxypeptidase A is secreted by the pancreas and is used to speed up this hydrolysis reaction. CPDA was the first metalloprotease and second zinc enzyme to be identified. This enzyme consists of a single chain of 307 amino acids. It assumes a compact, globular shape containing regions of both α helices and β pleated sheets. This globular shape contains a region resembling a pocket, where a substrate can fit. This region is the active site of the enzyme.

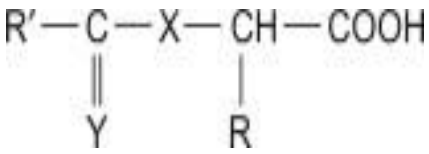
Carboxypeptidase A is an exopeptidase that hydrolyzes peptide bonds in peptides and proteins in biological systems, and also esters under experimental conditions, at the carboxy terminal end. It cleaves only L-amino acids with free carboxyl groups adjacent to the peptide or ester bond and is specific for amino acids that have aromatic or hydrophobic side chains, such as phenylalanine, tryptophan, or leucine.

Naturally occurring enzyme contains one atom of zinc per protein molecule.

The zinc atom plays an integral role in the cleavage of the substrate; it polarizes the carbonyl group of the-substrate, in order to render the carbon atom of this carbonyl group more susceptible to nucleophilic attack.



Carboxypeptidase A cleaves the C-terminal peptide or ester bond of peptides or depsipeptides that have a free C-terminal carboxyl group. Acylated-amino and -hydroxy carboxylic acids are also substrates. Carboxypeptidase A (CPDA) is a pancreatic metalloexopeptidase that hydrolyzes the peptide bond adjacent to the C-terminal end of a polypeptide chain. Carboxypeptidase A is a good illustration of the induced-fit theory, because the active site changes appreciably when the substrate binds. As the protein substrate binds to carboxypeptidase, the active site closes in around it. Hydrolysis of the peptide bond is most likely to occur if the terminal residue has an aromatic or bulky hydrocarbon side chain. A zinc ion (Zn^{2+}) is tightly bound near the active site and assists in catalysis. Three hydrogen bonding and electrostatic interactions are critical for the enzyme to recognize the terminal amino acid in the peptide chain. The intermediate is stabilized by interactions with Zn^{2+} and the carboxypeptidase molecule. The last step is a proton transfer and cleavage of the peptide bond. This entire process requires considerable mobility of the carboxypeptidase A protein itself.



X is O, NH or S and Y is O or S. The rate of peptide substrate hydrolysis is enhanced if the side chain R is aromatic or branched aliphatic, *e.g.* ↓Phe, ↓Tyr, ↓Trp, ↓Leu or ↓Ile.

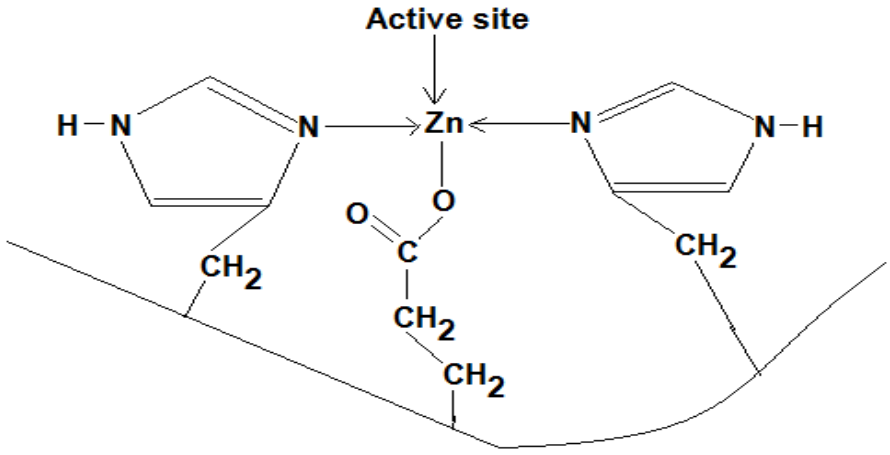
C-terminal L-amino acids with aromatic or branched sidechains are preferentially cleaved, and ester bonds of peptides with a free C-terminal carboxyl group can also cleaved by CPDA. Acylated -amino and -hydroxy carboxylic acids are also substrates.

CPDA is secreted as a proenzyme, with a 94 amino acid segment that is cleaved by trypsin during activation. The active enzyme is composed of 309 amino acid residues. Only one form of CPDA has been found in cattle, while two forms have been found to exist in humans and rats. The monomeric form of the proenzyme is found in most species; however, it also can be found as a binary or ternary complex. When it occurs as a binary complex, it is complexed with either chymotrypsinogen C or proproteinase E, and when it occurs as a ternary complex it is complexed with both. The activation segment lies at the center of the three subunits.

The enzyme consists of a protein chain of 307 aminoacid residues plus one Zn^{2+} ion for a molecular weight of about 34,600 Dalton. The molecule is roughly egg-shaped, with a maximum dimension of approximately 5000 pm and a minimum dimension of about 3800 pm. There is a cleft on one side that contains the zinc ion, the active site. The metal is coordinated tetrehedrally to two nitrogen atoms and an oxygen atom from three amino acids in the protein chain. The fourth coordination site is free to accept a pair of electron from a donor atom in the substrate to be cleaved.

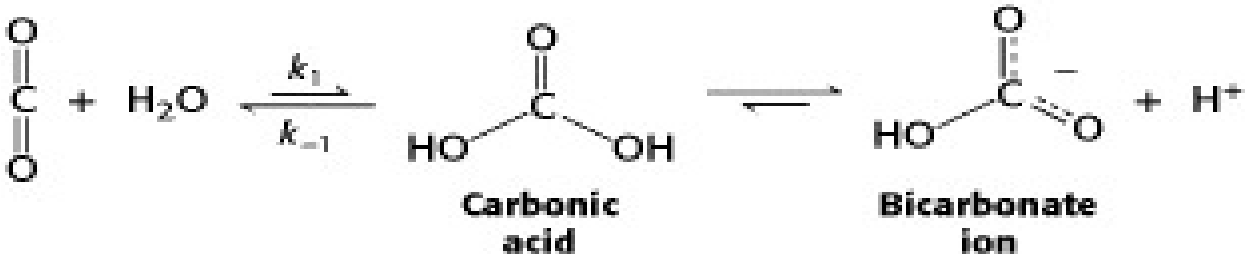
The enzyme is thought to act through coordination of the zinc atom to the carbonyl group of the amide linkage. In addition, a nearby hydrophobic pocket envelops the organic group of the amino acid to be cleaved and those amino acids with aromatic side groups react most readily. Accompanying these will be the movement of arginine side chain in the enzyme to about 200 pm closer to the carboxylate group of the substrate, and the phenolic group of the tyrosine comes within hydrogen bonding distance of the imido group of the C-terminal amino acid, a shift of 1200pm. The hydrogen bonding to the free carboxyl group (by arginine) and the amide linkage (by tyrosine) not only holds the substrate to the enzyme but helps break the N-C bond.

Nucleophilic displacement of the amide group by an attaching carboxylate group from glutamate group could form an anhydride link to the reminder of the peptide chain. Hydrolysis of this anhydride could then complete the cycle and generate the original enzyme.



13. Carbonic Anhydrase

Carbon dioxide is a major end product of aerobic metabolism. In complex organisms, this carbon dioxide is released into the blood and transported to the lungs for exhalation. While in the blood, carbon dioxide reacts with water. The product of this reaction is a moderately strong acid, carbonic acid ($pK_a = 3.5$), which becomes bicarbonate ion on the loss of a proton.



Despite the fact that CO_2 hydration and HCO_3^- dehydration occur spontaneously at reasonable rates in the absence of catalysts, almost all organisms contain enzymes, referred to as *carbonic anhydrases,* that catalyze these processes. Such enzymes are required because CO_2 hydration and HCO_3^- dehydration are often coupled to rapid processes, particularly transport processes.

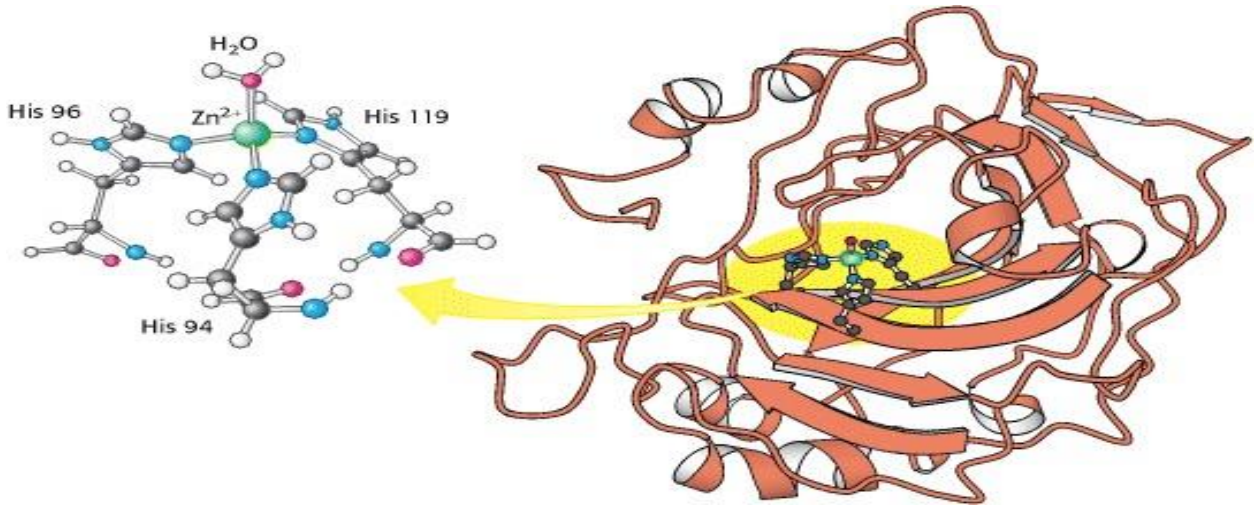
For example, HCO_3^- in the blood must be dehydrated to form CO_2 for exhalation as the blood passes through the lungs. Conversely, CO_2 must be converted into HCO_3^- for the generation of the aqueous humor of the eye and other secretions. Furthermore, both CO_2 and HCO_3^- are substrates and products for a variety of enzymes, and the rapid interconversion of these species may be necessary to ensure appropriate substrate levels.

So important are these enzymes in human beings that mutations in some carbonic anhydrases have been found to cause osteopetrosis (excessive formation of dense bones accompanied by anemia) and mental retardation.

Carbonic anhydrases accelerate CO_2 hydration dramatically. The most active enzymes, typified by human carbonic anhydrase II, hydrate CO_2 at rates as high as $k_{cat} = 10^6\ s^{-1}$, or a million times a second. Fundamental physical processes such as diffusion and proton transfer ordinarily limit the rate of hydration, and so special strategies are required to attain such prodigious rates.

After the discovery of carbonic anhydrase in 1932, this enzyme was found to contain bound zinc, associated with catalytic activity. This discovery, remarkable at the time, made carbonic anhydrase the first known zinc-containing enzyme.

The results of x-ray crystallographic studies have supplied the most detailed and direct information about the zinc site in carbonic anhydrase. At least seven carbonic anhydrases, each with its own gene, are present in human beings. They are all clearly homologous, as revealed by substantial levels of sequence identity. Carbonic anhydrase II, present in relatively high concentrations in red blood cells, has been the most extensively studied.



The zinc is bound to the imidazole rings of three histidine residues as well as to a water molecule.

Zinc is found only in the +2 state in biological systems.

A zinc atom is essentially always bound to four or more ligands; in carbonic anhydrase, three coordination sites are occupied by the imidazole rings of three histidine residues and an additional coordination site is occupied by a water molecule (or hydroxide ion, depending on pH). Because all of the molecules occupying the coordination sites are neutral, the overall charge on the $Zn(His)_3$ unit remains +2.

A major clue comes from the pH profile of enzymatically catalyzed carbon dioxide hydration. At pH 8, the reaction proceeds near its maximal rate. As the pH decreases, the rate of the reaction drops. The midpoint of this transition is near pH 7, suggesting that a group with $pK_a = 7$ plays an important role in the activity of carbonic anhydrase and that the deprotonated (high pH) form of this group participates more effectively in catalysis.

Histidine, have pK_a values near 7, a variety of evidence suggests that the group responsible for this transition is not an amino acid but is the zinc-bound water molecule. Thus, the binding of a water molecule to the positively charged zinc center reduces the pK_a of the water molecule from 15.7 to 7. With the lowered pK_a, a substantial concentration of hydroxide ion (bound to zinc) is generated at neutral pH. A zinc-bound hydroxide ion is sufficiently nucleophilic to attack carbon dioxide much more readily than water does. The importance of the zinc-bound hydroxide ion suggests a simple mechanism for carbon dioxide hydration.

Mechanism of Carbonic Anhydrase

The zinc-bound hydroxide mechanism for the hydration of carbon dioxide catalyzed by carbonic anhydrase.

1. Zinc facilitates the release of a proton from a water molecule, which generates a hydroxide ion.

2. The carbon dioxide substrate binds to the enzyme's active site and is positioned to react with the hydroxide ion.

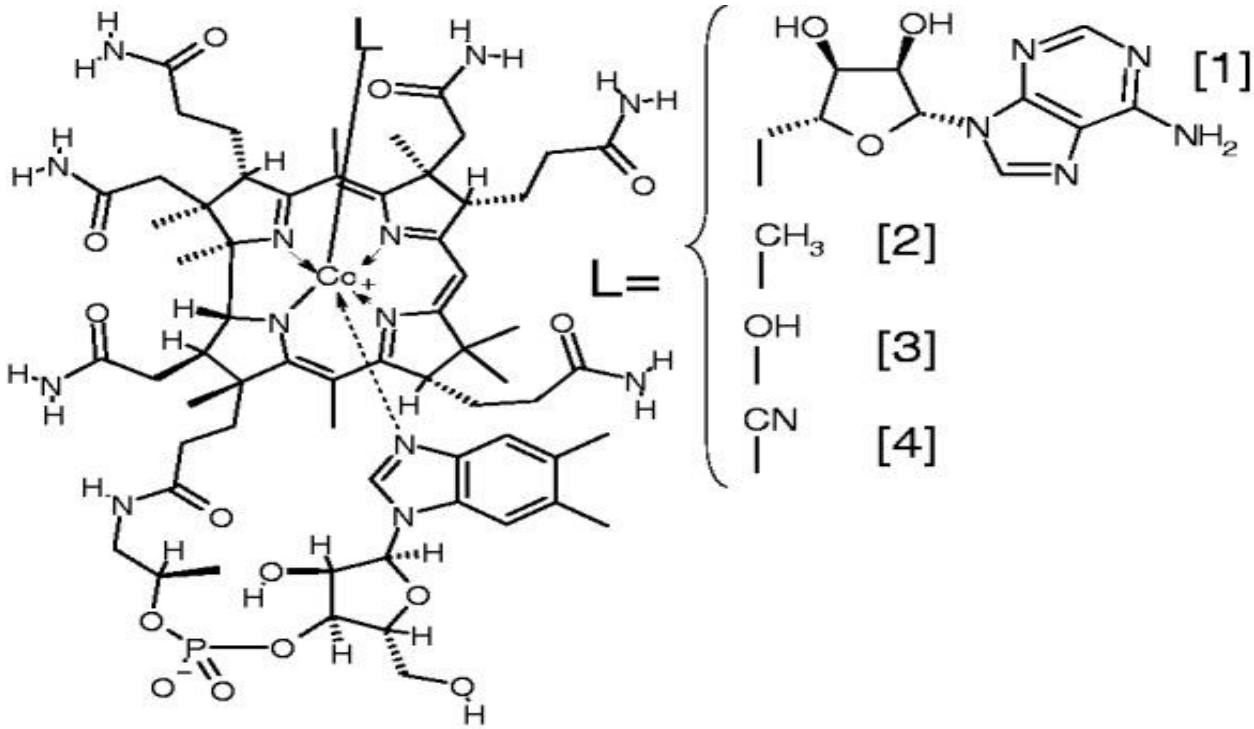
3. The hydroxide ion attacks the carbon dioxide, converting it into bicarbonate ion.

4. The catalytic site is regenerated with the release of the bicarbonate ion and the binding of another molecule of water.

14. Vitamin B12 (Cyanocobalamine)

Vitamin B_{12} is well known as a corrinoid compound containing a corrin macrocycle in their structure.

Vitamin B_{12} is usually presented as cyanocobalamin (CN-B_{12}). This unnatural form of cobalamin is more chemically stable than naturally occurring cobalamins. The term vitamin B_{12} refers to cobalamin compounds having B_{12} activity. CN-B_{12} is usually used for human dietary supplements and the CN-B_{12} taken up by living cells is synthesized into the coenzyme forms of cobalamin, methylcobalamin (CH_3-B_{12}), and 5′-deoxyadenosylcobalamin ($AdoB_{12}$). Methionine synthase (MTR) contains CH_3-B_{12} as a prosthetic group and functions in methionine biosynthesis. $AdoB_{12}$ functions as a coenzyme for methylmalonyl-CoA mutase (MCM) catalyzing the isomerization of *R*-methylmalonyl-CoA to succinyl-CoA in the catabolism of amino acid and odd-chain fatty acid in mammalian cells.

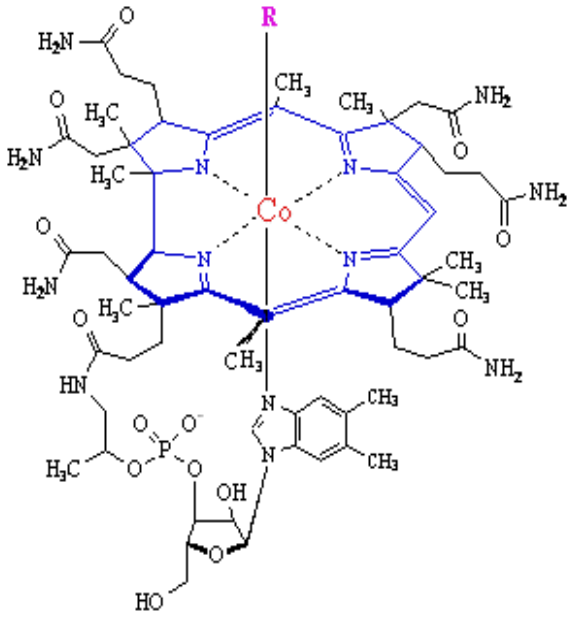


Vitamin B_{12} is the only known essential biomolecule with a stable metal-carbon bond, that is, it is an organometallic compound. The cobalt can link to

- a methyl group - as in methylcobalamin
- a 5'-deoxyadenosine at the the 5' position - as in adenosylcobalamin (coenzyme B_{12})
- a cyanide group - as in Vitamin B_{12}

The particular link in the cobalamin has a profound effect upon the mechanism of the enyme reaction.

A methyl-nickel intermediate on acetyl-CoA synthase is also known, but only as an intermediate rather than a stable, isolable compound as the three cobalamins. Other organometals such as the methylmercury ion are highly toxic, it is interesting that there is an unfortunate connection between CH_3Hg^+ and methylcobalamin.



The core of the molecule is a corrin ring with various attached side groups. The ring consists of 4 pyrrole subunits, joined on opposite sides by a C-CH_3 methylene link, on one side by a C-H methylene link, and with the two of the pyrroles joined directly. It is thus like a porphyrin, but with one of the bridging methylene groups removed. The nitrogen of each pyrrole is coordinated to the central cobalt atom.

The sixth ligand below the ring is a nitrogen of a 5,6-dimethylbenzimidazole. The other nitrogen of the 5,6-dimethylbenzimidazole is linked to a five-carbon sugar, which in turn connects to a phosphate group, and thence back onto the corrin ring via one of the seven amide groups attached to the periphery of the corrin ring. The base ligand thus forms a 'strap' back onto the corrin ring.

An important aspect of the corrin ring, when compared to the porphyrin, is the relative flexibility of the corrin system, the corrin ring is also less flat when viewed from the side than is a porphyrin ring. This adds up to some considerable differences between the chemistry of a

cobalt porphyrin and a cobalt corrin. In addition, the corrin only has a conjugated chain around part of the ring system, whereas a porphyrin is delocalised around the whole four pyrrole rings.

The center-piece in the structure is the cobalt(III), the octahedral coordination to five nitrogens and a carbon is common to all three cobalamins, and can be found in a number of simple coordination complexes. The simple complexes have attracted wide interest as models for cobalamins.

15. Ferritin

Ferritin is a universal intracellular hollow globular protein that stores iron and releases it in a controlled fashion. It consist of 24 protein subunits forming a nanocage with multiple metal–protein interactions. It is the primary *intracellular iron-storage protein* in both prokaryotes and eukaryotes, keeping iron in a soluble and non-toxic form.

Ferritin that is not combined with iron is called **apoferritin.** The protein is produced by almost all living organisms, including archaea, bacteria, algae, higher plants, and animals.

In humans, it acts as a buffer against iron deficiency and iron overload. Ferritin is found in most tissues as a cytosolic protein, but small amounts are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body; hence, serum ferritin is used as a diagnostic test for iron-deficiency anaemia.

Ferritin is a hollow of mass 474 kDa and comprising 24 subunits. It is present in every cell type. Typically it has internal and external diameters of about 8 and 12 nm, respectively.

Ferritin complexes in vertebrates are hetero-oligomers of two highly related gene products with slightly different physiological properties. The ratio of the two homologous proteins in the complex depends on the relative expression levels of the two genes.

A human mitochondrial ferritin, MtF, was found to express as a pro-protein. When a mitochondrion takes it up, it processes it into a mature protein similar to the ferritins found in the cytoplasm, which it assembles to form functional ferritin shells. The mitochondrial ferritin's Ramachandran’s plot shows its structure to be mainly alpha helical with a low prevalence of beta sheets.

Iron storage

Ferritin serves to store iron in a non-toxic form, to deposit it in a safe form, and to transport it to areas where it is required.

The function and structure of the expressed ferritin protein varies in different cell types.

Free iron is toxic to cells as it acts as a catalyst in the formation of free radicals from reactive oxygen species via the Fenton reaction. Hence vertebrates have an elaborate set of protective mechanisms to bind iron in various tissue compartments.

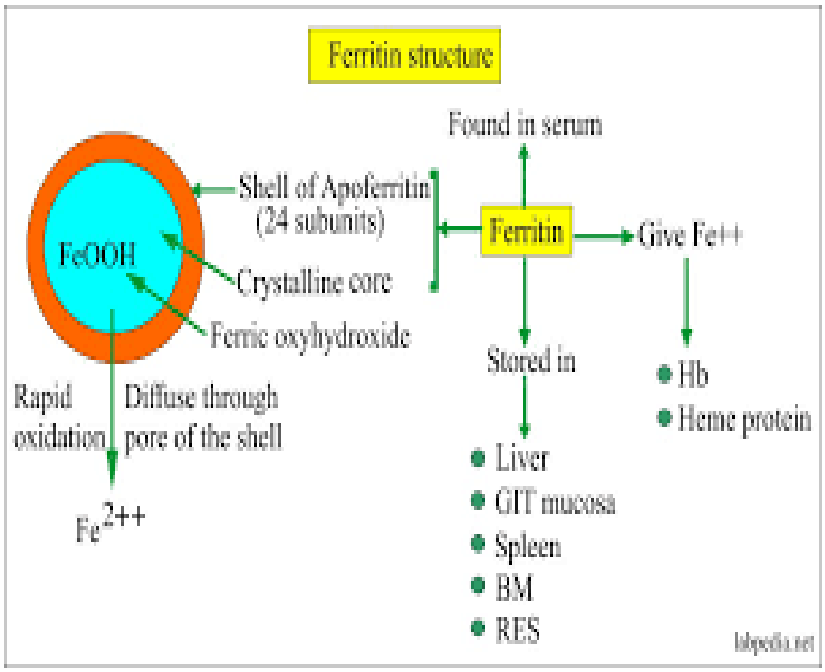
Within cells, iron is stored in a protein complex as ferritin or the related complex hemosiderin.

Apoferritin binds to free ferrous iron and stores it in the ferric state. As ferritin accumulates within cells of the reticuloendothelial system, protein aggregates are formed as hemosiderin. Iron in ferritin or hemosiderin can be extracted for release by the RE cells, although hemosiderin is less readily available.

Ferroxidase activity

Vertebrate ferritin consists of two or three subunits which are named based on their molecular weight: L "light", H "heavy", and M "middle" subunits. H and M subunits of eukaryotic ferritin and all subunits of bacterial and archaeal ferritin are H-type and have ferroxidase activity, which is the conversion of iron from the ferrous (Fe^{2+}) to ferric (Fe^{3+}) forms. This limits the deleterious reaction which occurs between ferrous iron and hydrogen peroxide known as the Fenton reaction which produces the highly damaging hydroxyl radical.

The ferroxidase activity occurs at a diiron binding site in the middle of each H-type subunits. After oxidation of Fe(II), the Fe(III) product stays metastably in the ferroxidase center and is displaced by Fe(II). The light chain of ferritin has no ferroxidase activity but may be responsible for the electron transfer across the protein cage.



16. Transferrin

Transferrins are glycoproteins found in vertebrates which bind to and consequently mediate the transport of Iron (Fe) through blood plasma.

It is produced in the liver and contains binding sites for two Fe^{3+} atoms.

Transferrin glycoproteins bind iron tightly, but reversibly.

Transferrin has a molecular weight of around 80 kDa and contains two specific high-affinity Fe(III) binding sites. The affinity of transferrin for Fe(III) is extremely high but decreases progressively with decreasing pH below neutrality.

Transferrins are not limited to only binding to iron but also to different metal ions. These glycoproteins are located in various bodily fluids of vertebrates.

When not bound to iron, transferrin is known as "apotransferrin".

Transferrins are glycoproteins that are often found in biological fluids of vertebrates. When a transferrin protein loaded with iron encounters a transferrin receptor on the surface of a cell, e.g., erythroid precursors in the bone marrow, it binds to it and is transported into the cell in a vesicle by receptor-mediated endocytosis. The pH of the vesicle is reduced by hydrogen ion pumps to about 5.5, causing transferrin to release its iron ions.

Iron release rate is dependent on several factors including pH levels, interactions between lobes, temperature, salt, and chelator.

The liver is the main site of transferrin synthesis but other tissues and organs, including the brain, also produce transferrin. The main role of transferrin is to deliver iron from absorption centers in the duodenum and white blood cell macrophages to all tissues. The receptor helps maintain iron homeostasis in the cells by controlling iron concentrations.

Transferrin

1. Transport form of iron.

2. Structure – 678 amino acid glycoprotein

3. One or two molecules of ferric iron bind to one molecule of transferrin ->mono/diferric forms

4. Synthesized as apoferritin in liver+ iron -> transferrin

5. Rate of synthesis – inversely proportional to iron stores.

Structure

In humans, transferrin consists of a polypeptide chain containing 679 amino acids and two carbohydrate chains. The protein is composed of alpha helices and beta sheets that form two domains. The N- and C- terminal sequences are represented by globular lobes and between the two lobes is an iron-binding site.

The amino acids which bind the iron ion to the transferrin are identical for both lobes; two tyrosines, one histidine, and one aspartic acid. For the iron ion to bind, an anion is required, preferably carbonate (CO^{2-}_3).

Transferrin also has a transferrin iron-bound receptor; it is a disulfide-linked homodimer. In humans, each monomer consists of 760 amino acids. It enables ligand bonding to the transferrin, as each monomer can bind to one or two atoms of iron. Each monomer consists of three domains: the protease, the helical, and the apical domains. The shape of a transferrin receptor

resembles a butterfly based on the intersection of three clearly shaped domains. Two main transferrin receptors found in humans denoted as transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2).

17. Cytochrome P450

Cytochrome P450 (CYP) is a hemeprotein that plays a key role in the metabolism of drugs and other xenobiotics.

Drug metabolism occurs in many sites in the body, including the liver, intestinal wall, lungs, kidneys, and plasma. As the primary site of drug metabolism, the liver functions to detoxify and facilitate excretion of xenobiotics (foreign drugs or chemicals) by enzymatically converting lipid-soluble compounds to more water-soluble compounds. Drug metabolism is achieved through phase I reactions, phase II reactions, or both.

The most common phase I reaction is oxidation, which is catalyzed by the CYP system.

Klingenberg first discovered CYP in 1954. In 1963, Estabrook, Cooper, and Rosenthal described the role of CYP as a catalyst in steroid hormone synthesis and drug metabolism. Cooper and colleagues later confirmed CYP to be a key enzyme involved in drug and steroid hydroxylation reactions.

Numerous CYP proteins have since been discovered and found to be widespread throughout the body, demonstrating significant involvement in chemical activation, deactivation, and carcinogenesis.

Classification

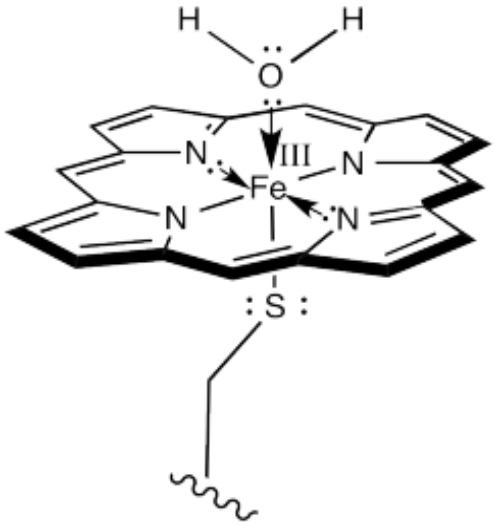
Cytochrome P450 pathways are classified by similar gene sequences; they are assigned a family number (e.g., CYP1, CYP2) and a subfamily letter (e.g., CYP1A, CYP2D) and are then differentiated by a number for the isoform or individual enzyme (e.g., CYP1A1, CYP2D6).

Cytochromes P450 form an important class of enzymes involved in the oxidation of substrates, chiefly in the liver. One atom of oxygen from an O_2 molecule is incorporated into the substrate molecule; the remaining oxygen atom is converted to water. This type of enzyme is called a "monooxygenase" because of the addition of one oxygen atom from O_2 into the substrate.

The addition of oxygen atoms to molecules, typically in the form of hydroxyl groups, is vitally important. The reaction may have evolved for a number of reasons. A key reason is to increase the water-solubility of small organic molecules. Hydroxylation lets us get rid of foreign substances. Otherwise, these hydrophobic molecules would build up in the tissues.

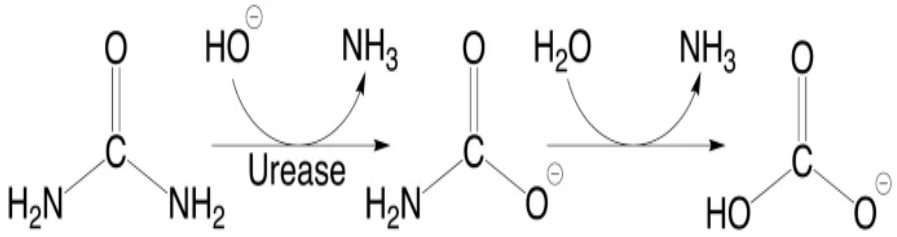
The cytochrome P450 pathway is a major avenue for the breakdown of pharmaceuticals, for instance. We can get rid of these substances after they have done their job. In other cases, pharmaceuticals are not active until they are hydroxylated; the reaction acts as an "on" switch. In still other cases, hydroxylation is a dangerous complication, converting a helpful pharmaceutical into a toxin.

The first step is just the binding of dioxygen to a metal. In cytochrome P450, that iron atom looks very much like the one in hemoglobin. In its resting state, it is formally an Fe(III) ion in a porphyrin ring, but with an axial cysteine donor instead of a histidine. In addition, a water molecule is coordinated to form an octahedral complex. That leaves no place for the dioxygen to bind. However, once the substrate enters the enzyme, a conformational change results in loss of the water molecule. After that, an electron is delivered from a cofactor, leading to an Fe(II) complex.



18. Urease

Urease (urea amidohydrolase) is a nickel-containing enzyme produced by plants, fungi, and bacteria that catalyzes the hydrolysis of urea into ammonia and carbamate. Urease is of historical importance in Biochemistry as it was the first enzyme ever to be crystallized (1926). Finding nickel in urease's active site (1975) was the first indication of a biological role for this metal.



This alkalization effect is utilized by numerous human pathogenic microorganisms that exploit urease as a virulence factor to infect and colonize the host. *Mycobacterium tuberculosis*, is an intracellular bacterium that infects macrophages, living inside their phagosomes. In this environment, its survival depends on the activity of nickel-dependent urease. In particular, urea hydrolysis is essential for bacterial survival, since it contributes to nitrogen availability and environmental pH modulation. Moreover, ammonia derived from this reaction can block the phagosome–lysosome fusion, being an important defensive mechanism against the immune system of the host.

The alkalizing effect of the urease activity within the mycobacterium-containing vacuole in resting macrophages, and the role for the urease activity in *M. tuberculosis* nitrogen metabolism that could be crucial for the pathogen's survival in nutrient-limited microenvironments where urea is the sole nitrogen source, have been demonstrated.

The widespread presence of urease in soils, both inside living cells of plants and microbes as well as extracellular enzyme adsorbed onto organic and inorganic soil components, poses significant environmental and economic problems: it causes the release of large amounts of ammonia in the atmosphere, thus negatively affecting the efficiency of urea-based soil fertilization, inducing plant damage by ammonia toxicity and soil pH increase with the consequent formation of airborne particulate matter (PM) that contributes to atmospheric pollution. It has been found that the presence of ultrafine PM has been significantly associated with an increase of the mortality rate in the SARS (severe acute respiratory syndrome) epidemics in the early 2000s, suggesting that containment of air pollution through well-managed agricultural activities is absolutely necessary not only for the environment but also for human health.

In the resting state of the enzyme, one of the two active site nickel ions [Ni(1) and Ni(2)] would coordinate a water molecule [W(1)] and the other a hydroxide ion [W(2)]. The initial step of this mechanism entailed the replacement of W(1) by a urea molecule, bound to Ni(1) in a monodentate mode using its carbonyl oxygen. Urea would be additionally stabilized through the interaction of one of its NH_2 groups with a nearby negatively charged carboxylate group from aspartate or glutamate residues. The subsequent nucleophilic attack on the urea carbonyl C atom would be carried out by the Ni(2)-coordinated hydroxide, to form a tetrahedral intermediate that would readily collapse to form carbamate, which would remain, at this stage, coordinated to Ni(1) through one of its O atoms. Carbamate was indeed known to be the product of the urease-catalyzed hydrolysis of urea. The concomitant production of an ammonium cation would be facilitated by an active-site thiol group from a nearby cysteine residue acting as a general acid catalyst. In the last step, the resting state of the enzyme would be regenerated by the entrance of water molecules and release of carbamate.

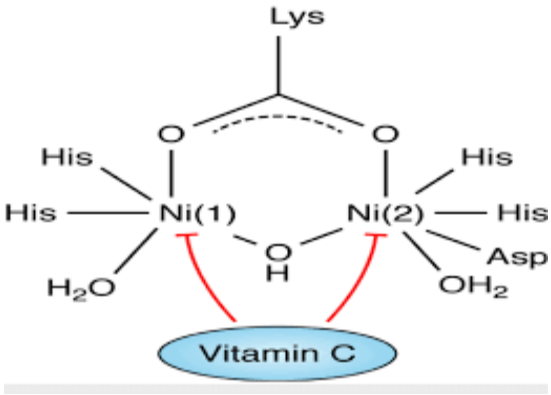
The active site of the enzyme was investigated using spectroscopic studies. UV–visible absorption spectra were interpreted as indicating the presence of Ni(II) ions in a six-coordinated pseudo-octahedral geometry in the active site, while the presence of four- and five-coordinated Ni(II) ions was considered unlikely.

X-ray absorption spectroscopic (XAS) studies were also interpreted as suggesting the presence of pseudo-octahedral Ni(II) ions coordinated, on average, to three histidine N atoms at 2.04 Å, two O atoms at 2.07 Å, and one O atom at 2.25 Å.

Magnetic susceptibility studies interpreted the presence of a metal cluster containing two high-spin ($S = 1$) octahedrally coordinated Ni(II) ions, with a weak anti-ferromagnetic coupling.

This result confirmed the early assumptions of the presence of two closely-spaced Ni(II) ions, and was further supported by the diamagnetism, resulting in a strong anti-ferromagnetically

coupled Ni(II)-Ni(II) dimer bridged by a thiolate *S* atom, and by the evidence that this binding involved a ligand exchange in the coordination sphere of nickel.



19. Cisplatin

Cisplatin is in the platinum-based antineoplastic family of medications. It works in part by binding to DNA and inhibiting its replication.

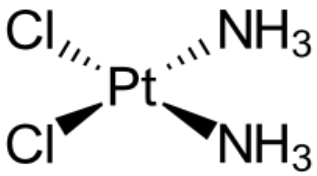
Cisplatin interferes with DNA replication, which kills the fastest proliferating cells, which in theory are cancerous. Upon administration, one chloride ion is slowly displaced by water to give the aquo complex *cis*-$[PtCl(NH_3)_2(H_2O)]^+$, in a process termed aquation. Dissociation of the chloride is favored inside the cell because the intracellular chloride concentration is only 3–20% of the approximately 100 mM chloride concentration in the extracellular fluid.

The water molecule in *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ is itself easily displaced by the *N*-heterocyclic bases on DNA. Guanine preferentially binds. Subsequent to formation of $[PtCl(guanine\text{-}DNA)(NH_3)_2]^+$, crosslinking can occur via displacement of the other chloride, typically by another guanine. Cisplatin crosslinks DNA in several different ways, interfering with cell division by mitosis. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible.

Cisplatin resistance

Cisplatin combination chemotherapy is the cornerstone of treatment of many cancers. Initial platinum responsiveness is high but the majority of cancer patients will eventually relapse with cisplatin-resistant disease.

Transplatin, the *trans* stereoisomer of cisplatin, has formula *trans*-$[PtCl_2(NH_3)_2]$ and does not exhibit a comparably useful pharmacological effect.



20. Therapeutic effects of Tc, Co, Cu as radioisotopes

Radioisotopes are an essential part of medical diagnostic procedures. In combination with imaging devices which register the gamma rays emitted from within, they can study the dynamic processes taking place in various parts of the body.

In using radiopharmaceuticals for diagnosis, a radioactive dose is given to the patient and the activity in the organ can then be studied either as a two dimensional picture or, using tomography, as a three dimensional picture.

Diagnostic techniques in nuclear medicine use radioactive tracers which emit gamma rays from within the body. These tracers are generally short-lived isotopes linked to chemical compounds which permit specific physiological processes to be scrutinised.

A more recent development is positron emission tomography (PET) which is a more precise and sophisticated technique using isotopes produced in a cyclotron. A positron-emitting radionuclide is introduced, usually by injection, and accumulates in the target tissue. As it decays it emits a positron, which promptly combines with a nearby electron resulting in the simultaneous emission of two identifiable gamma rays in opposite directions. These are detected by a PET camera and give very precise indications of their origin. PET's most important clinical role is in oncology.

Diagnostic radiopharmaceuticals can be used to examine :

- blood flow to the brain
- functioning of the liver, lungs, heart, or kidneys,
- assess bone growth
- to confirm other diagnostic procedures.

Another important use is to predict the effects of surgery and assess changes since treatment.

The radioisotope most widely used in medicine is Tc-99, employed in some 80% of all nuclear medicine procedures. It is an isotope of the artificially-produced element technetium and it has almost ideal characteristics for a nuclear medicine scan, such as with SPECT- Single photon emission computerised tomography.

It has a half-life of six hours which is long enough to examine metabolic processes yet short enough to minimize the radiation dose to the patient.

It decays by an 'isomeric' process, which involves the emitting of gamma rays and low energy electrons. Since there is no high-energy beta emission the radiation dose to the patient is low.

The low-energy gamma rays it emits easily escape the human body and are accurately detected by a gamma camera.

The chemistry of technetium is so versatile it can form tracers by being incorporated into a range of biologically-active substances that ensure it concentrates in the tissue or organ of interest.

Sterilisation / Co-60

Many medical products today are sterilised by gamma rays from a Co-60 source, a technique which generally is much cheaper and more effective than steam heat sterilisation.

The disposable syringe is an example of a product sterilised by gamma rays. Because it is a 'cold' process radiation can be used to sterilise a range of heat-sensitive items such as powders, ointments, and solutions, as well as biological preparations such as bone, nerve, and skin to be used in tissue grafts.

Sterilisation by radiation has several benefits. It is safer and cheaper because it can be done after the item is packaged. The sterile shelf-life of the item is then practically indefinite provided the seal is not broken. Apart from syringes, medical products sterilised by radiation include cotton wool, burn dressings, surgical gloves, heart valves, bandages, plastic, and rubber sheets and surgical instruments.

Most of this Co-60 is used for sterilization, with high-specific-activity Co-60 for cancer treatment.

All types of radiations are not recommended for food irradiation; only three types of radiation are recommended they are ^{60}Co or ^{137}Cs, X-rays, or electron beams from particle accelerators.

The food products are exposed to γ-radiations from the intense controlled sources to kills pests, bacteria, insects, and parasites and extends shelf-life but also reduces the food's nutritional value somewhat by destroying vitamins A, B_1 (thiamin), C, and E. No radiation remains in the food after treatment.

Copper-64

Copper-64(13h):
Used to study genetic diseases affecting copper metabolism, such as Wilson's and Menke's diseases, for PET imaging of tumours, and also cancer therapy.

Copper-67(2.6d):
Beta emitter, used in therapy.

21. Magnetic Resonance Imaging (MRI) – Basic Principles

Magnetic resonance imaging (MRI) is the most sophisticated imaging method used in clinical medicine. In recent years, MRI scans have become increasingly common, as costs decrease.

MRI scans work as an imaging method due to the unique make-up of the human body. We are comprised entirely of cells which all contain water – principally made of **hydrogen ions** (H_2O).

The magnet embedded within the MRI scanner can act on these positively charged hydrogen ions (H^+ ions) and cause them to **'spin'** in an identical manner. By varying the strength and direction of this magnetic field, we can change the direction of 'spin' of the protons, enabling us to build layers of detail.

When the magnet is switched off, the protons will gradually return to their original state in a process known as **precession**. Fundamentally, the different tissue types within the body return at different rates and it is this that allows us to visualise and differentiate between the different tissues of the body.

MRI scanning is based on the excitation and relaxation of protons.

Uses of MRI Scanning

Magnetic resonance imaging can produce highly sophisticated and highly detailed images of the human body. Generally speaking, MRI scanning is excellent for visualising **soft tissue** – and so it is often used in the detection of tumours, strokes and bleeds. It also can be used to visualise the functionality of suspected masses and tumours through IV, gadolinium-based agents.

MRI scans have many advantages. As stated previously, they provide excellent detail of the soft tissues of the body, and they do not cause any radiation exposure to the patient. However, they are **time consuming** – averaging approximately 35-45 minutes to complete.

At present, there are no known long lasting adverse effects from MRI scans. However, MRI safety has recently become a major focus in hospital and outpatient environments due to the potential attraction to **ferromagnetic objects** and devices. Some medical and implantable devices are considered contraindications for MRI evaluation – such as cardiac pacemakers, heart monitors, defibrillators and other battery-operated devices.

22. Mn-Fe as contrast agents

Magnetic nanoferrites has become the important research area in the past two decades mainly because of their magnetic behaviour, a magneto-optical and magneto-resistive property which made its way in various fields from technology to medical applications. Ferrites are usually metal oxides where iron is considered as the main metallic constituent. These ferrites exhibit a superparamagnetic property which makes this particle highly useable in the field of biomedical applications. However, most of them are susceptible to weak chemical stability, which discloses the necessity of surface modification or doping of other elements. Therefore, researchers ended up in doping elements like Co, Mg, Mn, Zn, Ni, etc, to make it chemically stable in the biological system and also for tuning the magnetic behaviour of the ferrites.

Among other ferrites, manganese (Mn) ferrite is a well-known soft magnetic material with high coercivity, moderate magnetization, excellent physiochemical stability and high cubic magneto-crystalline anisotropy, finding its various biological applications.

Mn-doped ferrite is an efficient magnetic resonance imaging (MRI) contrast agent as compared to magnetite since it has same saturation magnetization as of iron oxide, but possess a higher order of crystalline anisotropy thus causing slower magnetic moment relaxation in comparison.

23. Toxicity of Cd, Hg and Pb

Lead (Pb) is a toxic xenobiotic which causes different critical health conditions at the fatal stage. Though it is toxic, it has been found or incorporated in different products including paints, water

tape, cosmetics, fuel etc. for its different properties like low melting point, resistance to corrosion.

As a result, gastrointestinal, hematological, reproductive, immunomodulogical disorder have been recorded. Kidney is one of targeted site of Pb-toxicity and facilitates kidney damage via oxidative stress and lipid peroxidation.

Lead (Pb) can readily be absorbed by intestine, lung, less commonly through the skin and almost 90% of it binds to erythrocyte proteins (albumin). Through endocytosis and/or Erythrophagocytosis, it locates into different tissues and organs including liver, kidney where it exhibits oxidative damage on cells and tissue, and cellular organelles.

Hypothetically Pb^{2+} competes with Ca^{2+} and dysregulate the calcium homeostasis. As a result, Ca^{2+} release from mitochondria is stimulated; initiate the opening of the mitochondrial transitional pore; in turn total mitochondrial damages, reactive species generation and oxidative stress including altered lipid metabolism. Among the cells, proximal tubules are more susceptible to Pb-induced cellular damage followed by apoptosis.

Besides, it also displaces essential metal ion like Zn^{2+} and Ca^{2+} in proteins and inhibits Cys2His2 zinc finger transcription factors.

From the different point of view, Pb also hinders the integrity of cell–cell junctions (tight junction) and modify cellular structure.

Human lead exposure occurs as the result of gastrointestinal absorption or pulmonary absorption.

Ingestion is the most significant route of exposure. The bioavailability of the lead is dependent on the form of lead (ie, inorganic, organic, or metallic), quantity ingested, age of the individual, and current dietary status.

A diet high in calcium inhibits the binding of lead absorption through the intestinal binding sites. A calcium deficiency activates vitamin D and calbindin-D, a calcium-binding protein in the intestines enhancing the absorption of calcium. However, if calcium is not available in a sufficient quantity, lead and other trace metals will be absorbed in place of the calcium.

After absorption, 99% of the lead is bound to the hemoglobin portion of erythrocytes and is circulated via the vascular system to soft tissues (liver and kidney), bone, and hair. Lead has a half-life in the blood of approximately 30 days, consistent with the half-life of a RBC. During systemic circulation, lead interrupts the heme biosynthesis pathway primarily through inhibition of ∂-amino levulinic acid. Elevated levels of zinc protoporphyrin (ZPP) often accompany elevated lead.

Approximately 96% of the lead entering the body throughout a person's life is stored in the bones with a half-life in bone of approximately 32 years. Lead mobilization from bone is dependent on the rate of biological activity. Trabecular bones are a significant source of endogenous lead, due to greater level of biological activity, surface area, and volume of blood flow in comparison to cortical bones. Evidence supports that teeth and bone share similar qualities, such as a high affinity for metals and similar accumulation rates. The appearance of a

“lead line” also known as a “Burtonian blue” line, at the gum line, is indicative of chronic lead poisoning. The blue line is a common manifestation occurring in individuals with poor dental hygiene and is best described as the deposition of lead between collagen fibers, around blood vessels, and within cells.

Acute exposures often manifest as central nervous system (CNS) and gastrointestinal symptoms. Central nervous system symptoms include encephalopathy, convulsion, and stupor. Colic, a gastrointestinal symptom, is a consistent symptom of lead poisoning characterized by abdominal pain, cramps, and nausea. Chronic exposure differs from acute exposure in that chronic symptoms manifest as general malaise, anorexia, constipation, wrist drop, hematuria, and anemia.

Treatment strategy against Pb

Chelation therapy with dimercaprol or succimer, meso-2,3-dimercaptosuccinic acid (DMSA) and $CaNa_2EDTA$ could be considered. Conversely, if Pb-level ranges in between 45 and 69 mg/dL, oral chelation therapy with DMSA is suggested.

Cadmium (Cd)

Cd pollution was first recognized by its complication named “Itai-itai", following the second world war in Japan. A few decades later, the experimental study revealed the harmful consequences of Cd depicting severe damages and histological changes in kidney along with renal dysfunction.

Following exposure, Cd is transported either from GI or lungs to blood plasma where it binds to albumin and a little of it secretes into the bile from liver. In addition to albumin, large amount of Cd make a complex with metallothionein (MT).

Upon absorption in the blood, cadmium binds to albumin and is transported to the liver. Cadmium-induced liver damage increases hepatic enzymes. Metallothionein (MT), a low molecular weight metal-binding protein, binds cadmium where it is either stored in this conjugated form in the liver or transported to the kidney. Renal tubule damage is a hallmark of cadmium toxicity and is reflected in increased concentrations of biomarkers such as β2-microglobulin. Glomerular damage may follow with corresponding increased levels of albumin and transferrin. Elimination of cadmium is very slow, as the elimination half-life of cadmium is up to 20 years.

A disease unique to cadmium exposure, *Ouch Ouch* disease, is characterized with severe osteomalacia and osteoporosis from the long-term consumption of cadmium-contaminated rice but has implications for aging patients in general who are diagnosed with osteoporosis.

Treatment strategy against Cd

Acute high dose toxicity of Cd:

- fluid replacement
- mechanical ventilation

- and oxygen supply are recommended.

Mercury (Hg)

Mercury is ubiquitous in nature and available in three forms: elemental mercury, organic mercury like methyl mercury and ethyl mercury, and finally inorganic mercury i.e. mercuric mercury.

All form have notorious effects on organs including kidney. Human being can be exposed to Hg through many ways like contaminated food, battery industry or dental amalgam and mercury-containing product handling including mining. **"**Minamata disease" in Japan and disaster happened in Iraq from 1955 to 1972 pointed out the detrimental effect on human.

Most human exposure to mercury comes from the diet, and, in particular, through consumption of contaminated fish. Mercury accumulates in fish due to contamination of their marine environment and diet. As such, fish living in contaminated waters, or predatory fish living a long time, are more likely to be contaminated with mercury.

The risk of mercury toxicity depends very much on the form of mercury and route of exposure. Metallic mercury exposure can occur by inhalation of mercury vapor. Mercury vapor in the atmosphere is typically low and not considered a major route of exposure. However, mercury vapor is a potential occupational exposure in gold mining where mercury is used to form an amalgam with gold during its extraction, in dentistry for tooth restoration, and in the manufacture of scientific instruments and electrical control devices.

Mercury vapor can demonstrate substantial toxicity in this form as it easily penetrates the blood-brain and placental barriers to cause neurotoxicity, developmental toxicity, and at higher levels, mortality. Acute mercury poisoning occurs in 3 phases. In the first 1–3 days, flu-like symptoms appear, followed by severe pulmonary toxicity and then gingivostomatitis, tremor, memory loss, emotional lability, depression, insomnia, and shyness.

Mercuric chloride ($HgCl_2$) is a potent nephrotoxin, altering renal glutathione levels, increasing urinary albumin and β_2-microglobulin. Mercuric chloride exposure may also cause systemic autoimmune disease, setting the stage for nephrotic syndrome. Fortunately, $HgCl_2$ is poorly absorbed through the gastrointestinal tract, thereby limiting its exposure via ingestion.

For most, fish consumption is the major route of exposure of MeHg. Unlike some other contaminants, such as poly-chlorinated diphenyls, cooking does not alter the levels found in this food. Neurodevelopmental abnormalities occurred in children after a range of gestational exposures from maternal consumption of highly contaminated fish at the following levels.

Methylmercury poisoning is insidious as there is a latency period before symptoms appear, and a very small exposure can be deadly. Specific neuronal cell loss occurred, leading to paresthesia, with progression to cerebellar ataxia, constriction of the visual fields, and loss of hearing.

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – 5 – Nuclear Chemistry – SCYA5302

Nuclear Chemistry

1. Introduction

The first part of the unit deals with the terminologies and concepts related to nuclear energy, the nuclear reactions and the chemical effects of nuclear transformations. The second part deals with the nuclear fusion and fission reactions and their energy release. The last part of the unit deals with different counting techniques and the applications of radioisotopes.

Terminologies

Alpha particle: A positively-charged particle emitted from the nucleus of an atom during radioactive decay. Alpha particles are helium nuclei, with 2 protons and 2 neutrons.

Beta particle: A particle emitted from an atom during radioactive decay. Beta particles are generally electrons (with negative charge) but may be positrons.

Decay: Disintegration of atomic nuclei resulting in the emission of alpha or beta particles (usually with gamma radiation). Also the exponential decrease in radioactivity of a material as nuclear disintegrations take place and more stable nuclei are formed.

Gamma rays: High energy electro-magnetic radiation from the atomic nucleus, virtually identical to X-rays.

Half-life: The period required for half of the atoms of a particular radioactive isotope to decay and become an isotope of another element.

Ionising radiation: Radiation (including alpha particles) capable of breaking chemical bonds, thus causing ionisation of the matter through which it passes and damage to living tissue.

Nuclear reactor: A device in which a nuclear fission chain reaction occurs under controlled conditions so that the heat yield can be harnessed or the neutron beams utilised. All commercial reactors are thermal reactors, using a moderator to slow down the neutrons.

Synchrocyclotron: An ion accelerator, the chief components and configurations of which are similar to those of a cyclotron and in which the phase of the accelerating potential is synchronized with the frequency of the accelerated particles by frequency modulation to compensate for relativistic increases in mass at high speeds.

Radioactivity: It is the property exhibited by certain types of matter of emitting energy and subatomic particles spontaneously.

In natural radioactive decay, three common emissions occur. When these emissions were originally observed, scientists were unable to identify them as some already known particles and so named them

- alpha particles (α),

- beta particles, (β), and
- gamma rays (γ)

using the first three letters of the Greek alphabet. Some later time, alpha particles were identified as helium-4 nuclei, beta particles were identified as electrons, and gamma rays as a form of electromagnetic radiation like x-rays except much higher in energy and even more dangerous to living systems.

The ability of radiation to damage molecules is analyzed in terms of what is called **ionizing power**.

The ability of each type of radiation to pass through matter is expressed in terms of **penetration power.**

Alpha particles have the greatest mass. Alpha particles have approximately four times the mass of a proton or neutron and approximately 8,000 times the mass of a beta particle. Because of the large mass of the alpha particle, it has the highest ionizing power and the greatest ability to damage tissue. That same large size of alpha particles, however, makes them less able to penetrate matter. They collide with molecules very quickly when striking matter, add two electrons, and become a harmless helium atom. Alpha particles have the least penetration power.

Beta particles are much smaller than alpha particles and therefore, have much less ionizing power (less ability to damage tissue), but their small size gives them much greater penetration power.

Gamma rays are not particles but a high energy form of electromagnetic radiation (like x-rays except more powerful). Gamma rays are energy that has no mass or charge. Gamma rays have tremendous penetration power and require several inches of dense material (like lead) to shield them. Gamma rays may pass all the way through a human body without striking anything. They are considered to have the least ionizing power and the greatest penetration power.

2. Alpha Decay

The nuclear disintegration process that emits alpha particles is called alpha decay. An example of a nucleus that undergoes alpha decay is uranium-238. The alpha decay of U-238 is

$^{238}_{92}U \rightarrow {}^{4}_{2}He + {}^{234}_{90}Th$

In this nuclear change, the uranium atom ($^{238}_{92}U$) transmuted into an atom of thorium ($^{234}_{90}Th$) and, in the process, gave off an alpha particle. Look at the symbol for the alpha particle: $^{4}_{2}He$. The bottom number in a nuclear symbol is the number of protons. That means that the alpha particle has two protons in it which were lost by the uranium atom. The two protons also have a charge of +2. The top number, 4, is the mass number or the total of the protons and neutrons in the particle. Because it has 2 protons, and a total of 4 protons and neutrons, alpha particles must also have two neutrons. Alpha particles always have this same composition: two protons and two neutrons.

These types of equations are called nuclear equations.

3. Beta Decay

Another common decay process is beta particle emission, or beta decay. A beta particle is simply a high energy electron that is emitted from the nucleus. Nuclei do not contain electrons and yet during beta decay, an electron is emitted from a nucleus. At the same time that the electron is being ejected from the nucleus, a neutron is becoming a proton. We treat beta decay as a neutron splitting into a proton and an electron. The proton stays in the nucleus, increasing the atomic number of the atom by one. The electron is ejected from the nucleus and is the particle of radiation called beta.

To insert an electron into a nuclear equation and have the numbers add up properly, an atomic number and a mass number had to be assigned to an electron. The mass number assigned to an electron is zero (0) which is reasonable since the mass number is the number of protons plus neutrons and an electron contains no protons and no neutrons. The atomic number assigned to an electron is negative one (-1), because that allows a nuclear equation containing an electron to balance atomic numbers. Therefore, the nuclear symbol representing an electron (beta particle) is

$^{0}_{-1}e$ or $^{0}_{-1}\beta$

Thorium-234 is a nucleus that undergoes beta decay. Here is the nuclear equation for this beta decay.

$^{234}_{90}Th \rightarrow ^{0}_{-1}e + Pa$

4. Gamma Radiation

Frequently, gamma ray production accompanies nuclear reactions of all types. In the alpha decay

of U-238, two gamma rays of different energies are emitted in addition to the alpha particle.

$^{238}_{92}U \rightarrow ^{4}_{2}He + ^{234}_{90}Th + 2^{0}_{0}\gamma$

Nuclear reactions produce a great deal more energy than chemical reactions. Chemical reactions

release the difference between the chemical bond energy of the reactants and products, and the energies released have an order of magnitude of 1×10^{3}kJ/mol. Nuclear reactions release some of the binding energy and may convert tiny amounts of matter into energy. The energy released in a

nuclear reaction has an order of magnitude of 1×10^{18}kJ/mol. That means that nuclear changes involve almost **a million times more energy** per atom than chemical changes.

5. Radioactive decay constant

Decay constant determines the rate of decay. Decay constant is denoted by λ, "lambda".

The radioactive decay law states that the probability per unit time that a nucleus will decay is a constant, independent of time. This constant is called the decay constant and is denoted by λ, "lambda". This constant probability may vary greatly between different types of nuclei, leading to the many different observed decay rates. The radioactive decay of certain number of atoms (mass) is exponential in time.

Radioactive decay law: $N = N.e^{-\lambda t}$

The rate of nuclear decay is also measured in terms of half-lives.
The half-life is the amount of time it takes for a given isotope to lose half of its radioactivity. If a radioisotope has a half-life of 14 days, half of its atoms will have decayed within 14 days. In 14 more days, half of that remaining half will decay, and so on. Half lives range from millionths of a second for highly radioactive fission products to billions of years for long-lived materials (such as naturally occurring uranium). Notice that short half lives go with large decay constants. Radioactive material with a short half life is much more radioactive (at the time of production) but will obviously lose its radioactivity rapidly. No matter how long or short the half life is, after seven half lives have passed, there is less than 1 percent of the initial activity remaining.
The radioactive decay law can be derived also for activity calculations or mass of radioactive material calculations:

(Number of nuclei) $\mathbf{N = N.e^{-\lambda t}}$ **(Activity)** $\mathbf{A = A.e^{-\lambda t}}$ **(Mass)** $\mathbf{m = m.e^{-\lambda t}}$

where N (number of particles) is the total number of particles in the sample, A (total activity) is the number of decays per unit time of a radioactive sample, m is the mass of remaining radioactive material.

6. Decay Constant and Half-Life

In calculations of radioactivity one of two parameters (**decay constant** or **half-life**), which characterize the rate of decay, must be known. There is a relation between the half-life ($t_{1/2}$) and the decay constant λ. The relationship can be derived from decay law by setting $N = ½ N_o$. This gives:

$$\lambda(s^{-1}) = \frac{ln\,2}{t_{1/2}}$$

where *ln 2* (the natural log of 2) equals 0.693. If the decay constant (λ) is given, it is easy to calculate the half-life, and vice-versa.

7. Decay Constant and Radioactivity

The relationship between **half-life** and the amount of a radionuclide required to give an activity of one curie. This amount of material can be calculated using **λ**, which is the **decay constant** of certain nuclide:

$$N(atoms)\ x\ \lambda(s^{-1}) = 1\ Ci = 3.7\ x\ 10^{10}\ Bq$$

8. Equilibrium

A **radioactive equilibrium** exists when a radioactive nuclide is decaying at the same rate at which it is being produced. The disintegrating nucleus is usually referred to as the **parent nucleus** and the nucleus remaining after the event as the **daughter nucleus**. The daughter nucleus can either be stable or radioactive. If it is radioactive, then it decays into a daughter nucleus and so on. Thus, each radioactive parent nucleus can initiate a series of decays, with each decay-product having its own characteristic decay constant.

Concentration of daughter nuclei in the radioactive equilibrium depends primarily on proportions of half-lives (or decay constants) of parent and daughter nuclei. Since the production rate and decay rate are equal, the number of atoms present remains constant over time. In any case, a radioactive equilibrium is not established immediately, but it only takes place after a **transition period**. This period is of the order of few half-lifes of the longest-lived nucleus in the decay chain. In case of radioactive decay chains, a radioactive equilibrium may be established between each member of the decay chain.

As was written, proportionality of half-lives is a key parameter, which determines **type of radioactive equilibrium**:

- Radioactive equilibrium is not established when a half-life of the parent nucleus is shorter than a half-life of the daughter nucleus. In this case the production rate and decay rate of certain member of decay chain cannot be equal.
- **Secular radioactive equilibrium** exists when the parent nucleus has an extremely long half-life. This type of equilibrium is particularly important in nature. Over the 4.5 billion years of the Earth's history, especially uranium 238, uranium 235 and thorium 232 and members of their decay chains have reached radioactive equilibria between the parent nucleus and the various descendants.
- **Transient radioactive equilibrium** exists when a half-life of the parent nucleus is longer than a half-life of the daughter nucleus. In this case, the parent nuclide and the daughter nuclide decay at essentially the same rate.

9. Nuclear Reactions

Nuclear reaction, change in the identity or characteristics of an atomic nucleus, induced by bombarding it with an energetic particle. The bombarding particle may be an alpha particle, a gamma-ray photon, a neutron, a proton, or a heavy ion. In any case, the bombarding particle must have enough energy to approach the positively charged nucleus to within range of the strong nuclear force.

A typical nuclear reaction involves two reacting particles—a heavy target nucleus and a light bombarding particle—and produces two new particles—a heavier product nucleus and a lighter ejected particle. In the first observed nuclear reaction (1919), Ernest Rutherford bombarded nitrogen with alpha particles and identified the ejected lighter particles as hydrogen nuclei or protons ($^1_1$H or p) and the product nuclei as a rare oxygen isotope. In the first nuclear reaction produced by artificially accelerated particles (1932), the English physicists J.D. Cockcroft and E.T.S. Walton bombarded lithium with accelerated protons and thereby produced two helium nuclei, or alpha particles. As it has become possible to accelerate charged particles to increasingly greater energy, many high-energy nuclear reactions have been observed that produce a variety of subatomic particles called mesons, baryons, and resonance particles.

10. Q value

In nuclear and particle physics the energitics of nuclear reactions is determined by the Q-value of that reaction. The Q-value of the reaction is defined as the difference between the sum of the masses of the initial reactants and the sum of the masses of the final products, in energy units (usually in MeV).

Consider a typical reaction, in which the projectile a and the target A gives place to two products, B and b. This can also be expressed in the notation that we used so far,

$\mathbf{a + A \rightarrow B + b}$, or even in a more compact notation, **A(a,b)B**.

The **Q-value** of this reaction is given by:

$$\mathbf{Q = [m_a + m_A - (m_b + m_B)]c^2}$$

which is the same as the excess kinetic energy of the final products:

$$\mathbf{Q = T_{final} - T_{initial}}$$
$$\mathbf{= T_b + T_B - (T_a + T_A)}$$

For reactions in which there is an increase in the kinetic energy of the products **Q is positive**. The positive Q reactions are said to be **exothermic** (or **exergic**). There is a net release of energy, since the kinetic energy of the final state is greater than the kinetic energy of the initial state.

For reactions in which there is a decrease in the kinetic energy of the products **Q is negative**. The negative Q reactions are said to be **endothermic** (or **endoergic**) and they require a net energy input.

11. Nuclear Transformations

Nuclear transmutation is the conversion of one nuclide into another. It can occur by the radioactive decay of a nucleus, or the reaction of a nucleus with another particle. The first manmade nucleus was produced in Ernest Rutherford's laboratory in 1919 by a transmutation reaction, the bombardment of one type of nuclei with other nuclei or with neutrons. Rutherford bombarded nitrogen atoms with high-speed α particles from a natural radioactive isotope of radium and observed protons resulting from the reaction:

$^{14}_{7}N + ^{4}_{2}He \longrightarrow ^{17}_{8}O + ^{1}_{1}H$

The $^{17}_{8}O$ and $^{1}_{1}H$ nuclei that are produced are stable, so no further (nuclear) changes occur.

To reach the kinetic energies necessary to produce transmutation reactions, devices called particle accelerators are used. These devices use magnetic and electric fields to increase the speeds of nuclear particles. In all accelerators, the particles move in a vacuum to avoid collisions with gas molecules. When neutrons are required for transmutation reactions, they are usually obtained from radioactive decay reactions or from various nuclear reactions occurring in nuclear reactors.

12. Fission and Fusion

Fission and fusion are two physical processes that produce massive amounts of energy from atoms.

They yield millions of times more energy than other sources through nuclear reactions.

Fission

Fission occurs when a neutron slams into a larger atom, forcing it to excite and spilt into two smaller atoms—also known as fission products. Additional neutrons are also released that can initiate a chain reaction.

When each atom splits, a tremendous amount of energy is released.

Uranium and plutonium are most commonly used for fission reactions in nuclear power reactors because they are easy to initiate and control.

The energy released by fission in these reactors heats water into steam. The steam is used to spin a turbine to produce carbon-free electricity.

$$^{235}_{92}\mathbf{U}+^{1}_{0}\mathbf{n}\rightarrow^{141}_{56}\mathbf{Ba}+^{92}_{36}\mathbf{Kr}+3^{1}_{0}\mathbf{n}$$

In a typical nuclear fission reaction, more than one neutron is released by each dividing nucleus. When these neutrons collide with and induce fission in other neighboring nuclei, a self-sustaining series of nuclear fission reactions known as a nuclear chain reaction can result. For example, the fission of ^{235}U releases two to three neutrons per fission event. If absorbed by other ^{235}U nuclei, those neutrons induce additional fission events, and the rate of the fission reaction increases geometrically. Each series of events is called a generation. Experimentally, it is found that some minimum mass of a fissile isotope is required to sustain a nuclear chain reaction; if the mass is too low, too many neutrons are able to escape without being captured and inducing a fission reaction. The minimum mass capable of supporting sustained fission is called the critical mass. This amount depends on the purity of the material and the shape of the mass, which corresponds to the amount of surface area available from which neutrons can escape, and on the identity of the isotope. If the mass of the fissile isotope is greater than the critical mass, then under the right conditions, the resulting supercritical mass can release energy explosively. The enormous energy released from nuclear chain reactions is responsible for the massive destruction caused by the detonation of nuclear weapons such as fission bombs, but it also forms the basis of the nuclear power industry.

Fusion

Fusion occurs when two atoms slam together to form a heavier atom, like when two hydrogen atoms fuse to form one helium atom.

This is the same process that powers the sun and creates huge amounts of energy—several times greater than fission. It also doesn't produce highly radioactive fission products.

Fusion reactions are being studied by scientists, but are difficult to sustain for long periods of time because of the tremendous amount of pressure and temperature needed to join the nuclei together.

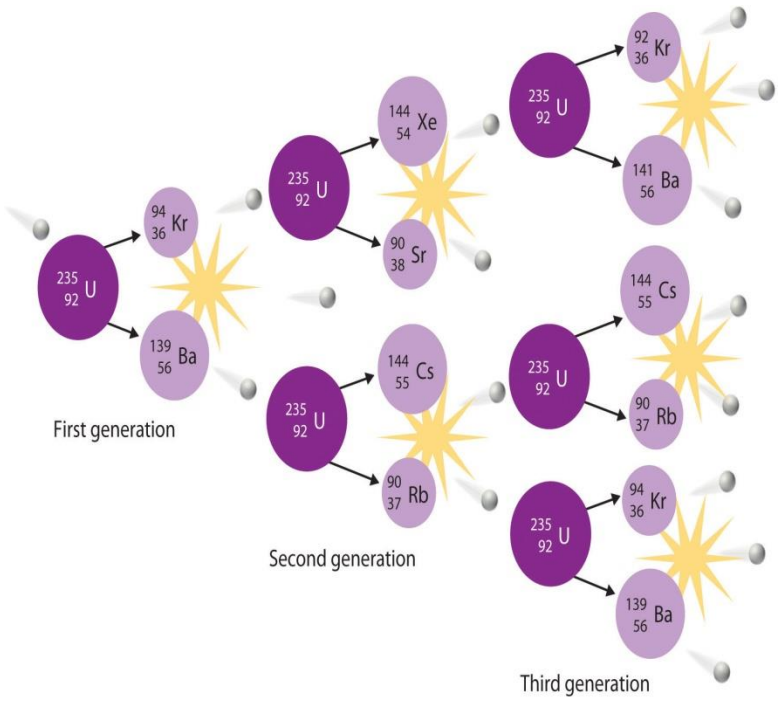
Nuclear fusion, in which two light nuclei combine to produce a heavier, more stable nucleus, is the opposite of nuclear fission. The positive charge on both nuclei results in a large electrostatic energy barrier to fusion. This barrier can be overcome if one or both particles have sufficient kinetic energy to overcome the electrostatic repulsions, allowing the two nuclei to approach close enough for a fusion reaction to occur. The principle is similar to adding heat to increase the rate of a chemical reaction. Fusion reactions are most exothermic for the lightest element. For example, in a typical fusion reaction, two deuterium atoms combine to produce helium-3, a process known as deuterium–deuterium fusion (D–D fusion):

$$2^{2}_{1}\mathrm{H}\rightarrow^{3}_{2}\mathrm{He}+^{1}_{0}\mathrm{n}$$

In another reaction, a deuterium atom and a tritium atom fuse to produce helium-4, a process

known as deuterium–tritium fusion (D–T fusion):

$$^{2}_{1}\mathrm{H}+^{3}_{1}\mathrm{H}\rightarrow^{4}_{2}\mathrm{He}+^{1}_{0}\mathrm{n}$$



13. Nuclear Stability

A nucleus is stable if it cannot be transformed into another configuration without adding energy from the outside. Of the thousands of nuclides that exist, about 250 are stable. A plot of the number of neutrons versus the number of protons for stable nuclei reveals that the stable isotopes fall into a narrow band. This region is known as the **band of stability** (also called the belt, zone, or valley of stability). The straight line in represents nuclei that have a 1:1 ratio of protons to neutrons (n:p ratio). Note that the lighter stable nuclei, in general, have equal numbers of protons and neutrons. For example, nitrogen-14 has seven protons and seven neutrons. Heavier stable nuclei, however, have increasingly more neutrons than protons. For example: iron-56 has 30 neutrons and 26 protons, an n:p ratio of 1.15, whereas the stable nuclide lead-207 has 125 neutrons and 82 protons, an n:p ratio equal to 1.52. This is because larger nuclei have more proton-proton repulsions, and require larger numbers of neutrons to provide compensating strong forces to overcome these electrostatic repulsions and hold the nucleus together.

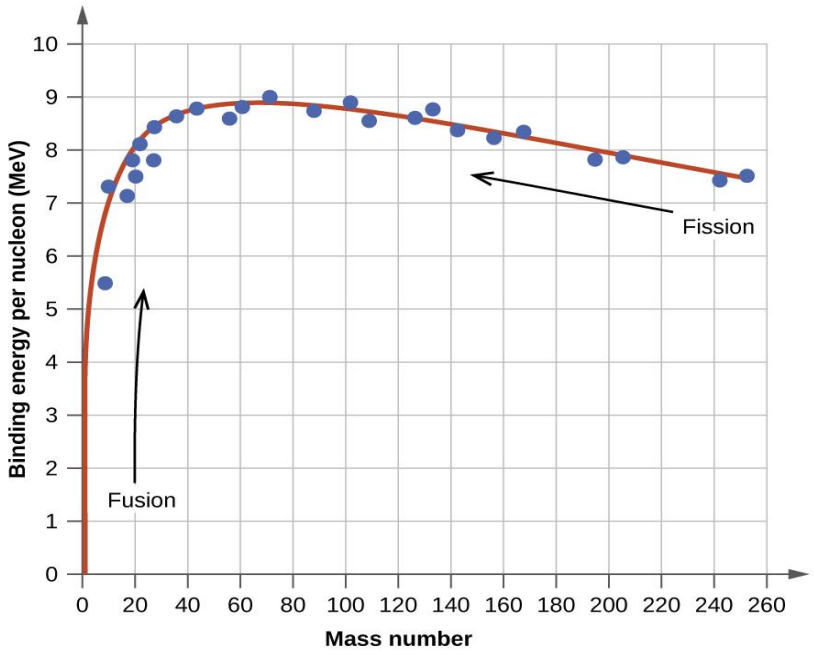
The nuclei that are to the left or to the right of the band of stability are unstable and exhibit **radioactivity**. They change spontaneously (decay) into other nuclei that are either in, or closer to, the band of stability. These nuclear decay reactions convert one unstable isotope (or **radioisotope**) into another, more stable, isotope.

Several observations may be made regarding the relationship between the stability of a nucleus and its structure. Nuclei with even numbers of protons, neutrons, or both are more likely to be stable. Nuclei with certain numbers of nucleons, known as **magic numbers**, are stable against nuclear decay. These numbers of protons or neutrons (2, 8, 20, 28, 50, 82, and 126) make complete shells in the nucleus. These are similar in concept to the stable electron shells observed

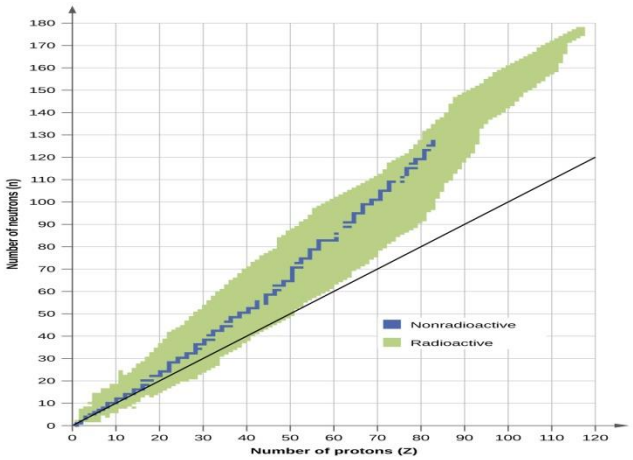
for the noble gases. Nuclei that have magic numbers of both protons and neutrons, such as $^{4}_{2}He$, $^{16}_{8}O$, $^{40}_{20}Ca$, and $^{208}_{82}Pb$, are called "double magic" and are particularly stable. These trends in nuclear stability may be rationalized by considering a quantum mechanical model of nuclear energy states.

Number of Stable Isotopes	Proton Number	Neutron Number
157	even	even
53	even	odd
50	odd	even
5	odd	odd

The relative stability of a nucleus is correlated with its **binding energy per nucleon**, the total binding energy for the nucleus divided by the number or nucleons in the nucleus.



The binding energy per nucleon is largest for nuclides with mass number of approximately 56.



This plot shows the nuclides that are known to exist and those that are stable. The stable nuclides are indicated in blue, and the unstable nuclides are indicated in green. Note that all isotopes of elements with atomic numbers greater than 83 are unstable. The solid line is the line where n = Z.

14. Radioactive Tracers

A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope. Monitoring its radioactive decay, a radiotracer can be used to explore the mechanism of chemical reactions . They are also used for flow visualisation through different technologies, such as Single Photon Emission Computed Tomography (SPECT), Positon Emission Tomography (PET) and Computed Radioactive Particle Tracking (CARPT).

Radiotracer technology is playing a more and more important role in industry. It is used to diagnose specific causes of inefficiency in a plant or process operation and to generally investigate processes in industries and those related environments where a great cost-benefit ratio can be gleaned from process optimization and troubleshooting, such as in the transport of sediments. It is expected that this important role will continue to expand, especially if students and engineers are exposed in their academic training to the many possibilities of this tool for research, development and application.

The labelled compound can be prepared by use of two types of isotopes.

Radioactive isotopes.

Stable isotopes.

Radioactive isotopes: - [e.g. ^{1}H, ^{14}C, ^{24}Na, ^{42}K, ^{35}S, ^{35}P, ^{131}I decay with emission of radiation]

For biological investigation - carbon & hydrogen

For metabolic studies - S, P, and alkali and alkaline earth metals are used.

For studies on protein, alkaloids, and amino acid- labelled nitrogen atom give more specific information.

Stable isotopes: - [e.g. ^{2}H, ^{13}C, ^{15}N, ^{18}O] – Used for labelling compounds as possible intermediates in biosynthetic pathways. – Usual method of detection are: – MASS spectroscopy [^{15}N, ^{18}O] – NMR spectroscopy [^{2}H, ^{13}C]

Significance of tracer technique

Tracing of Biosynthetic Pathway:

By incorporation of radioactive isotope of ^{14}C into phenylalanine, the biosynthetic cyanogenetic glycoside prunasin, can be detected.

Location & Quantity of compound containing tracer: - ^{14}C labelled glucose is used for determination of glucose in biological system

Different tracers for different studies: - For studies on nitrogen and amino acid. (Labelled nitrogen give specific information than carbon)

Convenient and suitable technique

ADVANTAGES - High sensitivity, Applicable to all living organism, Wide ranges of isotopes are available, More reliable, easily administration & isolation procedure, Gives accurate result, if proper metabolic time & technique applied.

LIMITATION - Kinetic effect, Chemical effect, Radiation effect, Radiochemical purity, High concentration distorting the result.

APPLICATION OF TRACER TECHNIQUE

1. Study of squalene cyclization by use of ^{14}C, ^{3}H labelled mevalonic acid.
2. Interrelationship among 4 – methyl sterols & 4, 4 dimethyl sterols, by use of ^{14}C acetate.
3. Terpenoid biosynthesis by chloroplast isolated in organic solvent, by use of 2-^{14}C mevalonate.
4. Study the formation of cinnamic acid in pathway of coumarin from labelled coumarin.
5. Origin of carbon & nitrogen atoms of purine ring system by use of ^{14}C or ^{15}N labelled precursor.
6. Study of formation of scopoletin by use of labelled phenylalanine.
7. By use of ^{45}Ca as tracer, - found that the uptake of calcium by plants from the soil. (CaO & $CaCO_2$).
8. By adding ammonium phosphate labelled with ^{32}P of known specific activity the uptake of phosphorus is followed by measuring the radioactivity as label reaches first in lower part of plant, than the upper part i.e. branches, leaves etc.

15. Neutron Activation Analysis

Neutron activation analysis is a method for the qualitative and quantitative determination of elements based on the measurement of characteristic radiation from radionuclides formed by irradiating materials by neutrons.

The technique of neutron activation analysis is based on the measurement of radiation released by the decay of radioactive nuclei formed by neutron irradiation of the material. The most suitable source of neutrons for such an application is usually a research reactor. The samples that can be analysed with this method stem from a number of different fields, including medicine, nutrition, biology, chemistry, forensics, the environment and mining.

Neutron activation analysis can be performed in a variety of ways. This depends on the element and the corresponding radiation levels to be measured, as well as on the nature and the extent of interference from other elements present in the sample. Most of the methods used are non-destructive, based on the detection of gamma radiation emitted by the irradiated material after or during the irradiation.

Neutron activation analysis (NAA) is a nuclear process used for determining the concentrations of elements in a vast amount of materials. NAA relies on excitation by neutrons so that the treated sample emits gamma-rays. It allows the precise identification and quantification of the elements, above all of the trace elements in the sample. NAA has applications in chemistry but also in other research fields, such as geology, archeology, medicine, environmental monitoring and even in the forensic science.
The method is based on neutron activation and therefore requires a source of neutrons. The sample is bombarded with neutrons, causing the elements to form radioactive isotopes. The radioactive emissions and radioactive decay paths for each element are well known. Using this information, it is possible to study spectra of the emissions of the radioactive sample, and determine the concentrations of the elements within it. A particular advantage of this technique is that it does not destroy the sample, and thus has been used for analysis of works of art and historical artifacts.

NAA was used to learn how to go from ash to eco-friendly solution for hazardous metals removal. Neutron Activation Analysis is very sensitive and is therefore used to analyse for minor elements, which are present in very low concentrations. The method is especially useful for trace element analysis, e.g. in high-purity substances, and is therefore important in semiconductor techniques. It can also be used to detect trace element in water, biological material and minerals.

In archaeology, NAA can give useful information about the origin of the findings according to the so-called “fingerprint” of the individual element composition in their raw materials. It is usually used as an important reference for other analysis methods.

NAA can detect up to 74 elements depending on the experimental procedure, with minimum detection limits ranging from 10-7 to 10-15g/g, depending on the elements and matrix materials. Some nuclei can capture a number of neutrons and remain relatively stable, not undergoing transmutation or decay for many months or even years. Different nuclei have different cross sections and half lives, and the intensities of the emitted gamma-rays can also vary – therefore the detection limits are quite variable. Rare earth elements (REE) have very high thermal neutron cross sections and NAA is usually the first choice for the determination of REEs in a trace elements analysis.

Next to education and training, neutron activation analysis is the most widely used application of research reactors. Almost any reactor operating at 10-30 kilowatt of thermal power is capable of providing a sufficient neutron flux to irradiate samples for selective applications of this analysis technique.

The costs of setting up a facility for neutron activation analysis, is relatively low compared with the costs of neutron scattering instruments. Since many of the uses of trace element determination (identifying elements in low concentration, for instance used in food and water analysis, medicine etc.) can be directly linked to potential economic benefits, neutron activation analysis is regarded as a key component of most strategic plans for research reactors.

16. Geiger Muller Counter

Geiger Muller Counter is named after its developers: Geiger and Muller. It is a metal cylinder filled with low-pressure gas sealed with a plastic or ceramic window at one end. This counter works in Geiger region with two specialities.

- The gas multiplication factor is so large that an avalanche dies in at one point but spreads all over the entire length of the central wire.
- Large output pulses are obtained as the output pulse is independent both of the energy and nature of the particles detected.

The Principle of Working of GM Counter

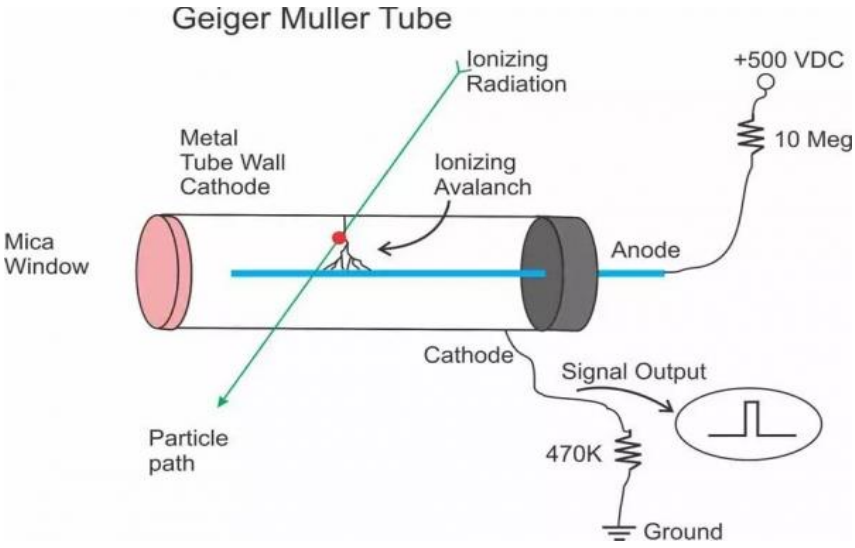
The ionizing particle passing through the tube ionizes the gas and electrons so produced move towards Anode. The velocity is quite high and they later produce secondary electrons after repeated collisions with the particles of the gas. These secondary electrons further produce more electrons in Geometric progression.

Due to this large multiplication action, a large ionization current is produced.

Advantages of GM Counter

- It can count alpha, beta, gamma particles as well as cosmic rays.

- It has high sensitivity.
- Power supply need not be precisely regulated as the pulse height is constant over a large range.
- Because of the fact that output pulse is very high, so the Amplification needed is also very subtle.



Disadvantages of GM Counter

- Energies cannot be measured by it as it has a lack of differentiating abilities.
- It cannot detect uncharged particles like Neutrons.
- It is less efficient due to the large paralysis time limits and large dead time.
- Quenching agent used in this counter often decomposes, leading to less lifetime of the GM Counter.

Thus, GM Counter is the one which is primarily used due to its advantages. Although it is not free from disadvantages, still its uses make it preferable over other counters.

17. Proportional Counter

A **proportional counter**, also known as the **proportional detector**, is an electrical device that detects various types of ionizing radiation. The voltage of detector is adjusted so that the conditions correspond to the proportional region. In this region, the voltage is high enough to provide the primary electrons with sufficient acceleration and energy so that they can ionize additional atoms of the medium. These secondary ions (**gas amplification**) formed are also accelerated causing an effect known as **Townsend avalanches**, which creates a single large electrical pulse. Gaseous proportional counters usually operate in high electric fields of the order of 10 kV/cm and achieve typical **amplification factors of about 10^5**. Since the amplification

factor is strongly dependent on the applied voltage, the charge collected (output signal) is also dependent on the applied voltage and proportional counters require constant voltage.

Proportional counters amplify each of the individual bursts of ionisation so that each ionising event is detected separately. They therefore measure the number of ionising events (which is why they are called counters).
The process of charge amplification greatly improves the signal-to-noise ratio of the detector and reduces the subsequent electronic amplification required. When instruments are operated in the proportional region, the **voltage must be kept constant**. If a voltage remains constant the gas amplification factor also does not change. Proportional counter detection instruments are very sensitive to low levels of radiation. By proper functional arrangements, modifications, and biasing, the proportional counter can be used to detect alpha, beta, gamma, or neutron radiation in mixed radiation fields. Moreover, proportional counters are capable of **particle identification** and energy measurement (spectroscopy). The pulse height reflects the energy deposited by the incident radiation in the detector gas. As such, it is possible to distinguish the larger pulses produced by alpha particles from the smaller pulses produced by beta particles or gamma rays.

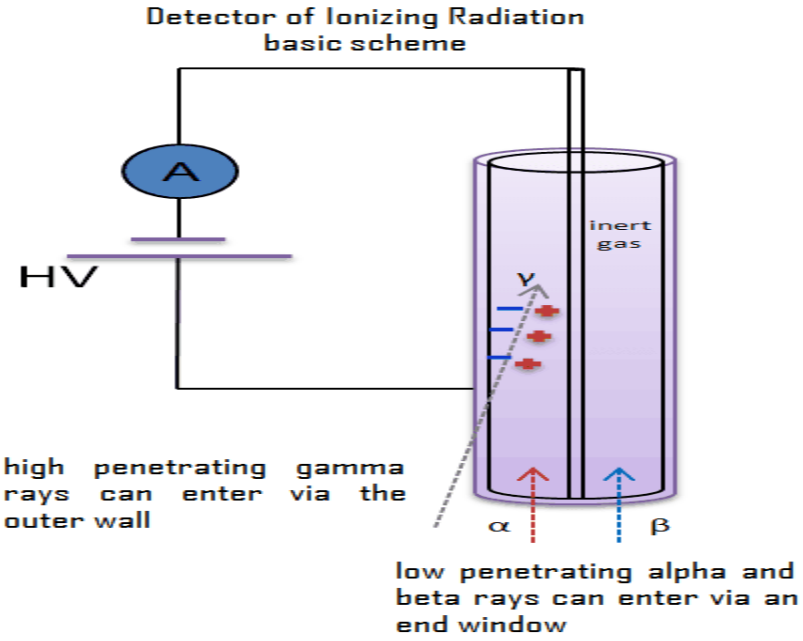
Proportional counters or Geiger counters are almost always used in pulse mode.

Basic Principle of Proportional Counters

The proportional counter has a cathode and an anode that are held at some voltage (above 1000 V), and the device is characterized by a capacitance that is determined by the geometry of the electrodes. In a proportional counter the fill gas of the chamber is an inert gas which is ionized by incident radiation, and a quench gas to ensure each pulse discharge terminates; a common mixture is 90% argon, 10% methane, known as P-10.

As ionizing radiation enters the gas between the electrodes, a finite number of ion-pairs are formed. In air, the average energy needed to produce an ion is about 34 eV, therefore a 1 MeV radiation completely absorbed in the detector produces about 3×10^4 pair of ions. The behavior of the resultant ion-pairs is affected by the potential gradient of the electric field within the gas and the type and pressure of the fill gas. Under the influence of the electric field, the positive ions will move toward the negatively charged electrode (outer cylinder), and the negative ions (electrons) will migrate toward the positive electrode (central wire). The electric field in this region keeps the ions from recombining with the electrons. In the immediate vicinity of the anode wire, the field strength becomes large enough to produce Townsend avalanches. This avalanche region occurs only fractions of a millimeter from the anode wire, which itself is of a very small diameter. The purpose of this is to use the multiplication effect of the avalanche produced by each ion pair. This is the "avalanche" region. A key design goal is that each original ionizing event due to incident radiation produces only one avalanche. Gas amplification factors can range from unity in the ionization region to **10^3 or 10^4 in the proportional region**. The high amplification factor of the proportional counter is the major advantage over the ionization chamber.

The collection of all these electrons will produce a charge on the electrodes and an electrical pulse across the detection circuit. Each pulse corresponds to one gamma ray or particle interaction. The pulse height is proportional to the number of original electrons produced. But in this case the pulse height is significantly amplified by the detector. The proportionality factor in this case is the gas amplification factor. The number of electrons produced is proportional to the energy of the incident particle. Therefore, proportional counters are capable of particle identification and energy measurement (spectroscopy). Different energies of radiation and different types of radiation can be distinguished by analyzing the pulse height, since they significantly differ in the primary ionization (low-LET vs high-LET). Since the process of charge amplification greatly improves the signal-to-noise ratio of the detector, the subsequent electronic amplification is usually not required.



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