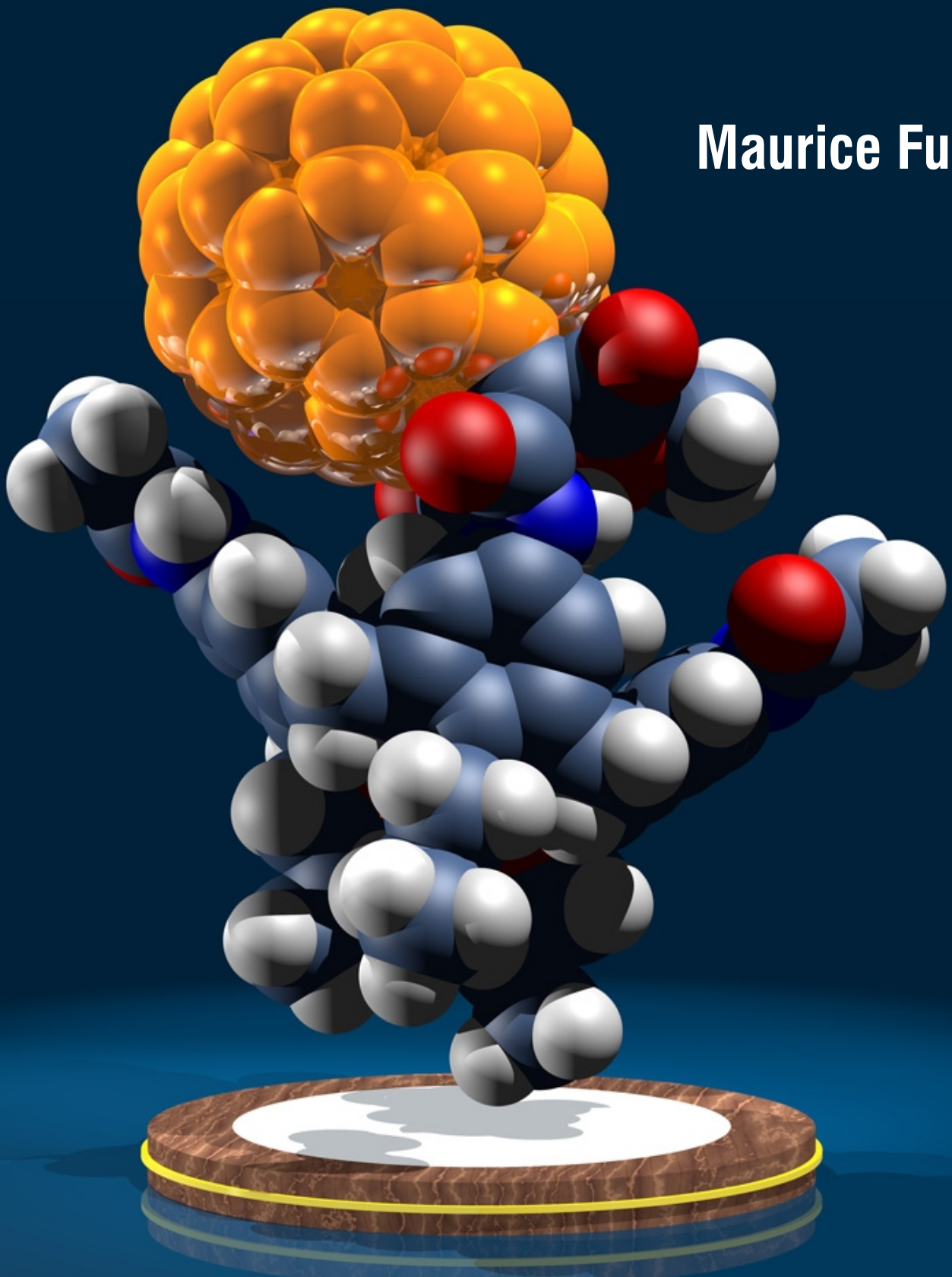
Coordination Chemistry and its Application

Maurice Fuller



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Chapter 1

Coordination Complex

A **coordination complex** consists of a central atom or ion, which is usually metallic and is called the *coordination centre*, and a surrounding array of boundmolecules or ions, that are in turn known as *ligands* or complexing agents. Many metal-containing compounds, especially those of transition metals (d block elements), are coordination complexes.

Nomenclature and terminology

Coordination complexes are so pervasive that their structures and reactions are described in many ways, sometimes confusingly. The atom within a ligand that is bonded to the central metal atom or ion is called the **donor atom**. In a typical complex, a metal ion is bonded to several donor atoms, which can be the same or different. A polydentate (multiple bonded) ligand is a molecule or ion that bonds to the central atom through several of the ligand's atoms; ligands with 2, 3, 4 or even 6 bonds to the central atom are common. These complexes are called chelate complexes; the formation of such complexes is called chelation, complexation, and coordination.

The central atom or ion, together with all ligands, comprise the coordination sphere. The central atoms or ion and the donor atoms comprise the first coordination sphere.

Coordination refers to the "coordinate covalent bonds" (dipolar bonds) between the ligands and the central atom. Originally, a complex implied a reversible association of molecules, atoms,

or ions through such weak chemical bonds. As applied to coordination chemistry, this meaning has evolved. Some metal complexes are formed virtually irreversibly and many are bound together by bonds that are quite strong.

The number of donor atoms attached to the central atom or ion is called the coordination number. The most common coordination numbers are 2, 4, and especially 6. A hydrated ion is one kind of a complex ion (or simply a complex), a species formed between a central metal ion and one or more surrounding ligands, molecules or ions that contain at least one lone pair of electrons.

If all the ligands are monodentate, then the number of donor atoms equals the number of ligands. For example, the cobalt(II) hexahydrate ion or the hexaaquacobalt(II) ion $[Co(H_2O)_6]$ is a hydrated-complex ion that consists of six water molecules attached to a metal ion Co. The oxidation state and the coordination number reflect the number of bonds formed between the metal ion and the ligands in the complex ion. However, the coordination number of $Pt(en)_2$ is 4 (rather than 2) since it has two bidentate ligands, which contain four donor atoms in total.

Any donor atom will give a pair of electrons. There are some donor atoms or groups which can offer more than one pair of electrons. Such are called bidentate (offers two pairs of electrons) or polydentate (offers more than two pairs of electrons). In some cases an atom or a group offers a pair of electrons to two similar or different central metal atoms or acceptors—by division of the electron pair—into a three-center two-electron bond. These are called bridging ligands.

History

Coordination complexes have been known since the beginning of modern chemistry. Early well-known coordination complexes include dyes such as Prussian blue. Their properties were first well understood in the late 1800s, following the 1869 work of Christian Wilhelm Blomstrand. Blomstrand developed what has come to be known as the *complex ion chain theory.* In considering metal amine complexes, he theorized that the ammonia molecules compensated for the charge of the ion by forming chains of the type $[(NH_3)_X]$, where X is the coordination number of the metal ion. He compared his theoretical ammonia chains to hydrocarbons of the form $(CH_2)_X$.

Following this theory, Danish scientist Sophus Mads Jørgensen made improvements to it. In his version of the theory, Jørgensen claimed that when a molecule dissociates in a solution there were two possible outcomes: the ions would bind via the ammonia chains Blomstrand had described or the ions would bind directly to the metal.

It was not until 1893 that the most widely accepted version of the theory today was published by Alfred Werner. Werner's work included two important changes to the Blomstrand theory. The first was that Werner described the two possibilities in terms of location in the coordination sphere. He claimed that if the ions were to form a chain, this would occur outside of the coordination sphere while the ions that bound directly to the metal would do so within the coordination sphere. In one of his most important discoveries however Werner disproved the majority of the chain theory. Werner discovered the spatial arrangements of the ligands that were

involved in the formation of the complex hexacoordinate cobalt. His theory allows one to understand the difference between a coordinated ligand and a charge balancing ion in a compound, for example the chloride ion in the cobaltammine chlorides and to explain many of the previously inexplicable isomers.

In 1911, Werner first resolved the coordination complex hexol into optical isomers, overthrowing the theory that only carbon compounds could possess chirality.

Structures

The ions or molecules surrounding the central atom are called ligands. Ligands are classified as L or X (or a combination thereof), depending on how many electrons they provide for the bond between ligand and central atom. L ligands provide two electrons from a lone electron pair, resulting in a coordinate covalent bond. X ligands provide one electron, with the central atom providing the other electron, thus forming a regular covalent bond. The ligands are said to be **coordinated** to the atom. For alkenes, the pi bonds can coordinate to metal atoms. An example is ethylene in the complex $[PtCl_3(C_2H_4)]$.

Geometry

In coordination chemistry, a structure is first described by its coordination number, the number of ligands attached to the metal (more specifically, the number of donor atoms). Usually one can count the ligands attached, but sometimes even the counting can become ambiguous. Coordination numbers are normally between two and nine, but large numbers of ligands are not uncommon for the lanthanides and actinides. The

number of bonds depends on the size, charge, and electron configuration of the metal ion and the ligands. Metal ions may have more than one coordination number.

Typically the chemistry of transition metal complexes is dominated by interactions between s and p molecular orbitals of the donor-atoms in the ligands and the d orbitals of the metal ions. The s, p, and d orbitals of the metal can accommodate 18 electrons (see 18-Electron rule). The maximum coordination number for a certain metal is thus related to the electronic configuration of the metal ion (to be more specific, the number of empty orbitals) and to the ratio of the size of the ligands and the metal ion. Large metals and small ligands lead to high coordination numbers, e.g. $[Mo(CN)_8]$. Small metals with large ligands lead to low coordination numbers, e.g. $Pt[P(CMe_3)]_2$. Due to their large size, lanthanides, actinides, and early transition metals tend to have high coordination numbers.

Most structures follow the points-on-a-sphere pattern (or, as if the central atom were in the middle of a polyhedron where the corners of that shape are the locations of the ligands), where orbital overlap (between ligand and metal orbitals) and ligand-ligand repulsions tend to lead to certain regular geometries. The most observed geometries are listed below, but there are many cases that deviate from a regular geometry, e.g. due to the use of ligands of diverse types (which results in irregular bond lengths; the coordination atoms do not follow a points-on-a-sphere pattern), due to the size of ligands, or due to electronic effects (see, e.g., Jahn–Teller distortion):

- Linear for two-coordination

- Trigonal planar for three-coordination
- Tetrahedral or square planar for four-coordination
- Trigonal bipyramidal for five-coordination
- Octahedral for six-coordination
- Pentagonal bipyramidal for seven-coordination
- Square antiprismatic for eight-coordination
- Tricapped trigonal prismatic for nine-coordination

The idealized descriptions of 5-, 7-, 8-, and 9- coordination are often indistinct geometrically from alternative structures with slightly differing L-M-L (ligand-metal-ligand) angles, e.g. the difference between square pyramidal and trigonal bipyramidal structures.

- Square pyramidal for five-coordination
- Capped octahedral or capped trigonal prismatic for seven-coordination
- Dodecahedral or bicapped trigonal prismatic for eight-coordination
- Capped square antiprismatic for nine-coordination

In systems with low d electron count, due to special electronic effects such as (second-order) Jahn–Teller stabilization, certain geometries (in which the coordination atoms do not follow a points-on-a-sphere pattern) are stabilized relative to the other possibilities, e.g. for some compounds the trigonal prismatic geometry is stabilized relative to octahedral structures for six-coordination.

- Bent for two-coordination
- Trigonal pyramidal for three-coordination
- Trigonal prismatic for six-coordination

Isomerism

The arrangement of the ligands is fixed for a given complex, but in some cases it is mutable by a reaction that forms another stable isomer.

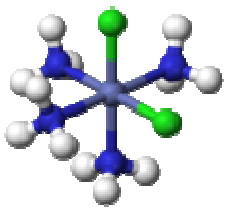
There exist many kinds of isomerism in coordination complexes, just as in many other compounds.

Stereoisomerism

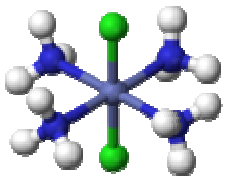
Stereoisomerism occurs with the same bonds in distinct orientations. Stereoisomerism can be further classified into:

Cis–trans isomerism and facial–meridional isomerism

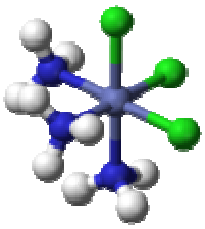
Cis–trans isomerism occurs in octahedral and square planar complexes (but not tetrahedral). When two ligands are adjacent they are said to be **cis**, when opposite each other, **trans**. When three identical ligands occupy one face of an octahedron, the isomer is said to be facial, or **fac**. In a *fac* isomer, any two identical ligands are adjacent or *cis* to each other. If these three ligands and the metal ion are in one plane, the isomer is said to be meridional, or **mer**. A *mer* isomer can be considered as a combination of a *trans* and a *cis*, since it contains both trans and cis pairs of identical ligands.

- 

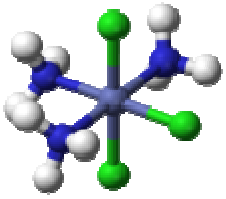
cis-$[CoCl_2(NH_3)_4]$

- 

trans-$[CoCl_2(NH_3)_4]$

- 

fac-$[CoCl_3(NH_3)_3]$

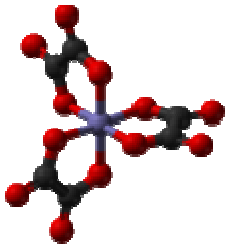
- 

mer-$[CoCl_3(NH_3)_3]$

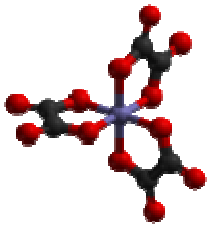
Optical isomerism

Optical isomerism occurs when a complex is not superimposable with its mirror image. It is so called because the two isomers are each optically active, that is, they rotate the plane of polarized light in opposite directions. In the first molecule shown, the symbol Λ (*lambda*) is used as a prefix to describe the left-handed propeller twist formed by three bidentate ligands. The second molecule is the mirror image of the first, with the symbol Δ (*delta*) as a prefix for the right-handed propeller twist. The third and fourth molecules are a

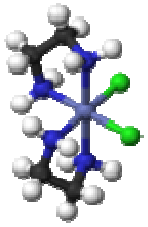
similar pair of Λ and Δ isomers, in this case with two bidentate ligands and two identical monodentate ligands.

- 

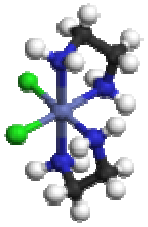
Λ-[Fe(ox)$_3$]

- 

Δ-[Fe(ox)$_3$]

- 

Λ-*cis*-[CoCl$_2$(en)$_2$]

- 

Δ-*cis*-[CoCl$_2$(en)$_2$]

Structural isomerism

Structural isomerism occurs when the bonds are themselves different. Four types of structural isomerism are recognized: ionisation isomerism, solvate or hydrate isomerism, linkage isomerism and coordination isomerism.

- **Ionisation isomerism** – the isomers give different ions in solution although they have the same composition. This type of isomerism occurs when the counter ion of the complex is also a potential ligand. For example, pentaamminebromocobalt(III) sulphate $[Co(NH_3)_5Br]SO_4$ is red violet and in solution gives a precipitate with barium chloride, confirming the presence of sulphate ion, while pentaamminesulphatecobalt(III) bromide $[Co(NH_3)_5SO_4]Br$ is red and tests negative for sulphate ion in solution, but instead gives a precipitate of AgBr with silver nitrate.
- **Solvate or hydrate isomerism** – the isomers have the same composition but differ with respect to the number of molecules of solvent that serve as ligand vs simply occupying sites in the crystal. Examples: $[Cr(H_2O)_6]Cl_3$ is violet colored, $[CrCl(H_2O)_5]Cl_2 \cdot H_2O$ is blue-green, and $[CrCl_2(H_2O)_4]Cl \cdot 2H_2O$ is dark green. See water of crystallization.
- **Linkage isomerism** occurs with ligands with more than one type of donor atom, known as ambidentate ligands. For example, nitrite can coordinate through O or N. One pair of nitrite linkage isomers have structures $(NH_3)_5CoNO_2$ (nitro isomer) and $(NH_3)_5CoONO$ (nitrito isomer).

- **Coordination isomerism** – this occurs when both positive and negative ions of a salt are complex ions and the two isomers differ in the distribution of ligands between the cation and the anion. For example, $[Co(NH_3)_6][Cr(CN)_6]$ and $[Cr(NH_3)_6][Co(CN)_6]$.

Electronic properties

Many of the properties of transition metal complexes are dictated by their electronic structures. The electronic structure can be described by a relatively ionic model that ascribes formal charges to the metals and ligands. This approach is the essence of crystal field theory (CFT). Crystal field theory, introduced by Hans Bethe in 1929, gives a quantum mechanically based attempt at understanding complexes. But crystal field theory treats all interactions in a complex as ionic and assumes that the ligands can be approximated by negative point charges.

More sophisticated models embrace covalency, and this approach is described by ligand field theory (LFT) and Molecular orbital theory (MO). Ligand field theory, introduced in 1935 and built from molecular orbital theory, can handle a broader range of complexes and can explain complexes in which the interactions are covalent. The chemical applications of group theory can aid in the understanding of crystal or ligand field theory, by allowing simple, symmetry based solutions to the formal equations.

Chemists tend to employ the simplest model required to predict the properties of interest; for this reason, CFT has been a

favorite for the discussions when possible. MO and LF theories are more complicated, but provide a more realistic perspective.

The electronic configuration of the complexes gives them some important properties:

Color of transition metal complexes

- Transition metal complexes often have spectacular colors caused by electronic transitions by the absorption of light. For this reason they are often applied as pigments. Most transitions that are related to colored metal complexes are either d–d transitions or charge transfer bands. In a d–d transition, an electron in a d orbital on the metal is excited by a photon to another d orbital of higher energy, therefore d–d transitions occur only for partially-filled d-orbital complexes (d). For complexes having d or d configuration, charge transfer is still possible even though d–d transitions are not. A charge transfer band entails promotion of an electron from a metal-based orbital into an empty ligand-based orbital (metal-to-ligand charge transfer or MLCT). The converse also occurs: excitation of an electron in a ligand-based orbital into an empty metal-based orbital (ligand-to-metal charge transfer or LMCT). These phenomena can be observed with the aid of electronic spectroscopy; also known as UV-Vis. For simple compounds with high symmetry, the d–d transitions can be assigned using Tanabe–Sugano diagrams. These assignments are gaining increased support with computational chemistry.

Colors of lanthanide complexes

Superficially lanthanide complexes are similar to those of the transition metals in that some are colored. However, for the common Ln ions (Ln = lanthanide) the colors are all pale, and hardly influenced by the nature of the ligand. The colors are due to 4f electron transitions. As the 4f orbitals in lanthanides are "buried" in the xenon core and shielded from the ligand by the 5s and 5p orbitals they are therefore not influenced by the ligands to any great extent leading to a much smaller crystal field splitting than in the transition metals. The absorption spectra of an Ln ion approximates to that of the free ion where the electronic states are described by spin-orbit coupling. This contrasts to the transition metals where the ground state is split by the crystal field. Absorptions for Ln are weak as electric dipole transitions are parity forbidden (Laporte forbidden) but can gain intensity due to the effect of a low-symmetry ligand field or mixing with higher electronic states (*e.g.* d orbitals). f-f absorption bands are extremely sharp which contrasts with those observed for transition metals which generally have broad bands. This can lead to extremely unusual effects, such as significant color changes under different forms of lighting.

Magnetism

Metal complexes that have unpaired electrons are magnetic. Considering only monometallic complexes, unpaired electrons arise because the complex has an odd number of electrons or because electron pairing is destabilized. Thus, monomeric Ti(III) species have one "d-electron" and must be (para)magnetic, regardless of the geometry or the nature of the

ligands. Ti(II), with two d-electrons, forms some complexes that have two unpaired electrons and others with none. This effect is illustrated by the compounds $TiX_2[(CH_3)_2PCH_2CH_2P(CH_3)_2]_2$: when X = Cl, the complex is paramagnetic (high-spin configuration), whereas when X = CH_3, it is diamagnetic (low-spin configuration). It is important to realize that ligands provide an important means of adjusting the ground state properties.

In bi- and polymetallic complexes, in which the individual centres have an odd number of electrons or that are high-spin, the situation is more complicated. If there is interaction (either direct or through ligand) between the two (or more) metal centres, the electrons may couple (antiferromagnetic coupling, resulting in a diamagnetic compound), or they may enhance each other (ferromagnetic coupling). When there is no interaction, the two (or more) individual metal centers behave as if in two separate molecules.

Reactivity

Complexes show a variety of possible reactivities:

- Electron transfers
- Electron transfer (ET) between metal ions can occur via two distinct mechanisms, inner and outer sphere electron transfers. In an inner sphere reaction, a bridging ligand serves as a conduit for ET.
- (Degenerate) ligand exchange
- One important indicator of reactivity is the rate of degenerate exchange of ligands. For example, the rate of interchange of coordinate water in $[M(H_2O)_6]$

complexes varies over 20 orders of magnitude. Complexes where the ligands are released and rebound rapidly are classified as labile. Such labile complexes can be quite stable thermodynamically. Typical labile metal complexes either have low-charge (Na), electrons in d-orbitals that are antibonding with respect to the ligands (Zn), or lack covalency (Ln, where Ln is any lanthanide). The lability of a metal complex also depends on the high-spin vs. low-spin configurations when such is possible. Thus, high-spin Fe(II) and Co(III) form labile complexes, whereas low-spin analogues are inert. Cr(III) can exist only in the low-spin state (quartet), which is inert because of its high formal oxidation state, absence of electrons in orbitals that are M–L antibonding, plus some "ligand field stabilization" associated with the d configuration.

- Associative processes
- Complexes that have unfilled or half-filled orbitals often show the capability to react with substrates. Most substrates have a singlet ground-state; that is, they have lone electron pairs (e.g., water, amines, ethers), so these substrates need an empty orbital to be able to react with a metal centre. Some substrates (e.g., molecular oxygen) have a triplet ground state, which results that metals with half-filled orbitals have a tendency to react with such substrates (it must be said that the dioxygen molecule also has lone pairs, so it is also capable to react as a 'normal' Lewis base).

If the ligands around the metal are carefully chosen, the metal can aid in (stoichiometric or catalytic) transformations of molecules or be used as a sensor.

Classification

Metal complexes, also known as coordination compounds, include virtually all metal compounds. The study of "coordination chemistry" is the study of "inorganic chemistry" of all alkali and alkaline earth metals, transition metals, lanthanides, actinides, and metalloids. Thus, coordination chemistry is the chemistry of the majority of the periodic table. Metals and metal ions exist, in the condensed phases at least, only surrounded by ligands.

The areas of coordination chemistry can be classified according to the nature of the ligands, in broad terms:

- Classical (or "Werner Complexes"): Ligands in classical coordination chemistry bind to metals, almost exclusively, via their lone pairs of electrons residing on the main-group atoms of the ligand. Typical ligands are H_2O, NH_3, Cl, CN, en. Some of the simplest members of such complexes are described in metal aquo complexes, metal ammine complexes,
- Examples: [Co(EDTA)], $[Co(NH_3)_6]$, $[Fe(C_2O_4)_3]$
- Organometallic Chemistry: Ligands are organic (alkenes, alkynes, alkyls) as well as "organic-like" ligands such as phosphines, hydride, and CO.
- Example: $(C_5H_5)Fe(CO)_2CH_3$
- Bioinorganic Chemistry: Ligands are those provided by nature, especially including the side chains of

amino acids, and many cofactors such as porphyrins.

- Example: hemoglobin contains heme, a porphyrin complex of iron
- Example: chlorophyll contains a porphyrin complex of magnesium
- Many natural ligands are "classical" especially including water.
- Cluster Chemistry: Ligands include all of the above as well as other metal ions or atoms as well.
- Example $Ru_3(CO)_{12}$
- In some cases there are combinations of different fields:
- Example: $[Fe_4S_4(Scysteinyl)_4]$, in which a cluster is embedded in a biologically active species.

Mineralogy, materials science, and solid state chemistry – as they apply to metal ions – are subsets of coordination chemistry in the sense that the metals are surrounded by ligands. In many cases these ligands are oxides or sulfides, but the metals are coordinated nonetheless, and the principles and guidelines discussed below apply. In hydrates, at least some of the ligands are water molecules. It is true that the focus of mineralogy, materials science, and solid state chemistry differs from the usual focus of coordination or inorganic chemistry. The former are concerned primarily with polymeric structures, properties arising from a collective effects of many highly interconnected metals. In contrast, coordination chemistry focuses on reactivity and properties of complexes containing individual metal atoms or small ensembles of metal atoms.

Nomenclature of coordination complexes

The basic procedure for naming a complex is:

- When naming a complex ion, the ligands are named before the metal ion.
- The ligands' names are given in alphabetical order. Numerical prefixes do not affect the order.
- Multiple occurring monodentate ligands receive a prefix according to the number of occurrences: *di-*, *tri-*, *tetra-*, *penta-*, or *hexa-*.
- Multiple occurring polydentate ligands (e.g., ethylenediamine, oxalate) receive *bis-*, *tris-*, *tetrakis-*, etc.
- Anions end in *o*. This replaces the final 'e' when the anion ends with '-ide', '-ate' or '-ite', e.g. *chloride* becomes *chlorido* and *sulfate* becomes *sulfato*. Formerly, '-ide' was changed to '-o' (e.g. *chloro* and *cyano*), but this rule has been modified in the 2005 IUPAC recommendations and the correct forms for these ligands are now *chlorido* and *cyanido*.
- Neutral ligands are given their usual name, with some exceptions: NH_3 becomes *ammine*; H_2O becomes *aqua* or *aquo*; CO becomes *carbonyl*; NO becomes *nitrosyl*.
- Write the name of the central atom/ion. If the complex is an anion, the central atom's name will end in *-ate*, and its Latin name will be used if available (except for mercury).

- The oxidation state of the central atom is to be specified (when it is one of several possible, or zero), and should be written as a Roman numeral (or 0) enclosed in parentheses.
- Name of the cation should be preceded by the name of anion. (if applicable, as in last example)

Application of coordination compounds

Metals only exist in solution as coordination complexes, it follows then that this class of compounds is useful in a wide variety of ways.

Bioinorganic chemistry

In bioinorganic chemistry and bioorganometallic chemistry, coordination complexes serve either structural or catalytic functions.

An estimated 30% of proteins contain metal ions. Examples include the intensely colored vitamin B_{12}, the heme group in hemoglobin, the cytochromes, the chlorin group in chlorophyll, and carboxypeptidase, a hydrolytic enzyme important in digestion.

Another complex ion enzyme is catalase, which decomposes the cell's waste hydrogen peroxide. Synthetic coordination compounds are also used to bind to proteins and especially nucleic acids (e.g. anticancer drug cisplatin).

Industry

Homogeneous catalysis is a major application of coordination compounds for the production of organic substances. Processes include hydrogenation, hydroformylation, oxidation. In one example, a combination of titanium trichloride and triethylaluminium gives rise to Ziegler–Natta catalysts, used for the polymerization of ethylene and propylene to give polymers of great commercial importance as fibers, films, and plastics.

Nickel, cobalt, and copper can be extracted using hydrometallurgical processes involving complex ions. They are extracted from their ores as ammine complexes. Metals can also be separated using the selective precipitation and solubility of complex ions. Cyanide is used chiefly for extraction of gold and silver from their ores.

Phthalocyanine complexes are an important class of pigments.

Analysis

At one time, coordination compounds were used to identify the presence of metals in a sample. Qualitative inorganic analysis has largely been superseded by instrumental methods of analysis such as atomic absorption spectroscopy (AAS), inductively coupled plasma atomic emission spectroscopy (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS).

Chapter 2

Characteristics of Coordination Chemistry

Coordination cage

Coordination cages are three-dimensional ordered structures in solution that act as hosts in host–guest chemistry. They are self-assembled in solution from organometallic precursors, and often rely solely on noncovalent interactions rather than covalent bonds. Coordinate bonds are useful in such supramolecular self-assembly because of their versatile geometries. However, there is controversy over calling coordinate bonds noncovalent, as they are typically strong bonds and have covalent character. The combination of a coordination cage and a guest is a type of inclusion compound. Coordination complexes can be used as "nano-laboratories" for synthesis, and to isolate interesting intermediates. The inclusion complexes of a guest inside a coordination cage show intriguing chemistry as well; often, the properties of the cage will change depending on the guest. Coordination complexes are molecular moieties, so they are distinct from clathrates and metal-organic frameworks.

History

Chemists have long been interested in mimicking chemical processes in nature. Coordination cages quickly became a hot

topic as they can be made by self-assembly, a tool of chemistry in nature. The conceptualization of a closed-surface molecule capable of incorporating a guest was described by Donald Cram in 1985. Early cages were synthesized from bottom-up. Makoto Fujita introduced self-assembling cages, which are less tedious to prepare. These cages arise from the condensation of square planar complexes using polypodal ligands.

Approaches to assembly

- There are five main methodologies to create coordination cages. In directional bonding, also called edge-directed self-assembly, polyhedra are designed using a stoichiometric ratio of ligand to metal precursor. The symmetry interaction method involves combining naked metal ions with multibranched chelating ligands. This results in highly symmetric cages. The molecular paneling method, also called the face-directed method, was the method developed by Fujita. Here, rigid ligands act as 'panels' and coordination complexes join them together to create the shape. In the figure at left, the yellow triangles represent panel ligands, and the blue dots are metal complexes. The ligands of the complex itself helps enforce the final geometry.

In the weak link method, a hemilabile ligand is used: a weak metal-heteroatom bond is the 'weak link.' The formation of the complexes is driven by favorable π-π interactions between the spacers and the ligands, as well as the chelation of the metal. The metals used in the assembly must be available to perform further in the final structure, without compromising the cage

structure. The initial structure is referred to as 'condensed.' In the condensed structure, the weak M-X bond can be selectively replaced by introducing an ancillary ligand with a higher binding affinity, leading to an open cage structure. In the figure to the right, the M is the metal, the orange ellipses are ligands, and the A is the ancillary ligand. For the dimetallic building block method, two pieces are needed: the metal dimer and its nonlinking ligands, and linking ligands. The nonlinking ligands need to be relatively nonlabile, and not too bulky; amidinates, for instance, work well. The linking ligands are either equatorial or axial: equatorial ligands are small polycarboxylato anions, and axial linkers are usually rigid aromatic structures. Axial and equatorial ligands may be used separately or in combination, depending on the desired cage structure.

Classification

- Many varieties of coordination cages exist.

In general, coordination cages are either homoleptic or heteroleptic. That is, they assembled either from a single type of ligand or multiple types. Generic coordination cages are often classified just as coordination complexes, with a MxLy formula. Heteroleptic complexes typically form more complex geometries, as illustrated with the following cages: $[M_{16}(L)_{24}]$ and $[M_{12}(\mu\text{-}L)_{12}(\mu\text{-}L)_4](BF_4)_{24}$. The former cage is assembled from a 2:3 ratio of metal (M) and ligand (L), where the metal can be copper, zinc, or cadmium. This cage is homoleptic and assembles into a hexadecanuclear framework. The second cage is assembled from a 4:1:4 ratio of MBF_4, the ligand L and the ligand L. This cage is heteroleptic and assembles into a

dodecanuclear cuboctohedral framework. Four of the triangular faces of this shape are occupied by L, which acts as a triply bridging ligand. The twelve remaining edges are spanned with the edge ligands, L. Ligands are the building blocks of coordination cages, and the choice and ratio of ligands determine the final structure. Due to their highly symmetrical nature, coordination cages are also often referred to by their geometry. The geometry of high-symmetry cages is often that of Platonic or Archimedean solids; sometimes cages are casually referred to by their geometries.

Of the named categories of coordination cages, cavitand cages and metalloprisms are some of the more common.

Cavitand cages

Cavitand cages are formed by linking bowl-shaped organic molecules called cavitands. The two "bowls" are linked with organometallic complexes.

In order for a cavitand cage to efficiently self-assemble, the following requirements must be met: The cavitand scaffold must be rigid, the incoming metal complex must impose cis geometry, and there must be enough preorganization in the structure such that the entropic barrier to create the cage can be overcome. The complexes used to assemble cavitand cages are square planar with one η2 ligand; this helps enforce the final geometry. Without cis geometry, only small oligomers will form. Self-assembly also requires a ligand exchange; weakly bound ions such as BF_4- and PF_6- promote assembly because they leave the complex so it can bind with the nitriles on the rest of the structure.

Metalloprisms

Metalloprisms are another common type of coordination cage. They can be assembled from planar modules linked with column-like ligands.

One illustrative synthesis starts with $[(\eta\text{-p-cymene})_6Ru_6(\mu_3\text{-tpt-}\kappa N)_2(\mu\text{-}C_6HRO_4\text{-}\kappa O)_3]$ using the linker of 2,4,6-tri(pyridine-4-yl)-1,3,5-triazine (tpt). Various guest molecules have been encapsulated in the hydrophobic cavity of metallaprisms. A few examples of guests are bioconjugatederivatives, metal complexes, and nitroaromatics.

Keplerates

Keplerates are cages that are similar to edge-transistive $\{Cu_2\}$ MOFs with A_4X_3 stoichiometry. In fact, they can be thought of as metal-organic polyhedra. These cages are quite different than the types previously discussed as they are much larger, and contain many cavities. Complexes with large diameters can be desirable as target guest molecules are becoming more large and complex. These cages have multiple shells, like an onion. Secondary building units such as dinuclear $\{Cu_2\}$ acetate species are used as building blocks.

In the cage above, the outer shell is a cuboctohedron; its structure comes from two adjacent benzoate moieties from the m-BTEB ligand. The third benzoate is attached to the inner shell. The $\{Cu_2\}$ units in the inner sphere adapt several different orientations. The labile complexes in the inner sphere allow binding of large target guests on the nanometer scale.

Building a complex of this size that is still soluble is a challenge.

Interactions

Coordination cages are used to study guest-guest and host–guest interactions and reactions.

In some instance, planar aromatic molecules stack inside of metalloprisms, as can be observed by UV-visible spectroscopy. Metal-metal interactions can also be observed. Mixed valence species have also been trapped inside of coordination cages.

Coordination geometry

The term **coordination geometry** is used in a number of related fields of chemistry and solid state chemistry/physics.

Molecules

The coordination geometry of an atom is the geometrical pattern formed by atoms around the central atom.

Inorganic coordination complexes

In the field of inorganic coordination complexes it is the geometrical pattern formed by the atoms in the ligands that are bonded to the central atom in a molecule or a coordination complex. The geometrical arrangement will vary according to the number and type of ligands bonded to the metal centre,

and to the coordination preference of the central atom, typically a metal in a coordination complex. The number of atoms bonded, (i.e. the number of σ-bonds between central atom and ligands) is termed the coordination number. The geometrical pattern can be described as a polyhedron where the vertices of the polyhedron are the centres of the coordinating atoms in the ligands.

The coordination preference of a metal often varies with its oxidation state. The number of coordination bonds (coordination number) can vary from two as high as 20 in Th(η-$C_5H_5)_4$.

One of the most common coordination geometries is octahedral, where six ligands are coordinated to the metal in a symmetrical distribution, leading to the formation of an octahedron if lines were drawn between the ligands. Other common coordination geometries are tetrahedral and square planar.

Crystal field theory may be used to explain the relative stabilities of transition metal compounds of different coordination geometry, as well as the presence or absence of paramagnetism, whereas VSEPR may be used for complexes of main group element to predict geometry.

Crystallography usage

- In a crystal structure the coordination geometry of an atom is the geometrical pattern of coordinating atoms where the definition of coordinating atoms depends on the bonding model used. For example, in

the rock salt ionic structure each sodium atom has six near neighbour chloride ions in an octahedral geometry and each chloride has similarly six near neighbour sodium ions in an octahedral geometry. In metals with the body centred cubic (bcc) structure each atom has eight nearest neighbours in a cubic geometry. In metals with the face centred cubic (fcc) structure each atom has twelve nearest neighbours in a cuboctahedral geometry.

Naming of inorganic compounds

IUPAC have introduced the polyhedral symbol as part of their IUPAC nomenclature of inorganic chemistry 2005 recommendations to describe the geometry around an atom in a compound.IUCr have proposed a symbol which is shown as a superscript in square brackets in the chemical formula. For example, CaF_2 would be CaF_2, where [8cb] means cubic coordination and [4t] means tetrahedral. The equivalent symbols in IUPAC are *CU*–8 and *T*–4 respectively. The IUPAC symbol is applicable to complexes and molecules whereas the IUCr proposal applies to crystalline solids.

Coordination isomerism

Coordination isomerism is a form of structural isomerism in which the composition of the coordination complex ion varies. In a coordination isomer the total ratio of ligand to metal remains the same, but the ligands attached to a specific metal ion change. Examples of a complete series of coordination isomers require at least two metal ions and sometimes more.

For example, a solution containing ([$Co(NH_3)_6$] and [$Cr(CN)_6$]) is a coordination isomer with a solution containing [$Cr(NH_3)_6$] and [$Co(CN)_6$].

Coordination number

In chemistry, crystallography, and materials science, the **coordination number**, also called **ligancy,** of a central atom in a molecule or crystal is the number of atoms, molecules or ions bonded to it. The ion/molecule/atom surrounding the central ion/molecule/atom is called a ligand. This number is determined somewhat differently for molecules than for crystals.

For molecules and polyatomic ions the coordination number of an atom is determined by simply counting the other atoms to which it is bonded (by either single or multiple bonds). For example, [$Cr(NH_3)_2Cl_2Br_2$] has Cr as its central cation, which has a coordination number of 6 and is described as *hexacoordinate*. The common coordination numbers are **4**, **6** and **8.**

Molecules, polyatomic ions and coordination complexes

In chemistry, **coordination number** (C.N.), defined originally in 1893 by Alfred Werner, is the total number of neighbors of a central atom in a molecule or ion. The concept is most commonly applied to coordination complexes.

Simple and commonplace cases

The most common coordination number for *d*-block transition metal complexes is 6. The CN does not distinguish the geometry of such complexes, i.e. octahedral vs trigonal prismatic.

For transition metal complexes, coordination numbers range from 2 (e.g., Au in Ph_3PAuCl) to 9 (e.g., Re in $[ReH_9]$). Metals in the *f*-block (the lanthanoids and actinoids) can accommodate higher coordination number due to their greater ionic radii and availability of more orbitals for bonding. Coordination numbers of 8 to 12 are commonly observed for *f*-block elements. For example, with bidentatenitrate ions as ligands, Ce and Th form the 12-coordinate ions $[Ce(NO_3)_6]$ (ceric ammonium nitrate) and $[Th(NO_3)_6]$. When the surrounding ligands are much smaller than the central atom, even higher coordination numbers may be possible. One computational chemistry study predicted a particularly stable $PbHe_{15}$ ion composed of a central lead ion coordinated with no fewer than 15 helium atoms.

Among the Frank–Kasper phases, the packing of metallic atoms can give coordination numbers of up to 16. At the opposite extreme, steric shielding can give rise to unusually low coordination numbers. An extremely rare instance of a metal adopting a coordination number of 1 occurs in the terphenyl-based arylthallium(I) complex 2,6-$Tipp_2C_6H_3Tl$, where Tipp is the 2,4,6-triisopropylphenyl group.

Polyhapto ligands

Coordination numbers become ambiguous when dealing with polyhapto ligands. For π-electron ligands such as the cyclopentadienide ion [C_5H_5], alkenes and the cyclooctatetraenide ion [C_8H_8], the number of adjacent atoms in the π-electron system that bind to the central atom is termed the hapticity. In ferrocene the hapticity, η, of each cyclopentadienide anion is five, $Fe(\eta\text{-}C_5H_5)_2$. Various ways exist for assigning the contribution made to the coordination number of the central iron atom by each cyclopentadienide ligand. The contribution could be assigned as one since there is one ligand, or as five since there are five neighbouring atoms, or as three since there are three electron pairs involved. Normally the count of electron pairs is taken.

Surfaces and reconstruction

The coordination numbers are well defined for atoms in the interior of a crystal lattice: one counts the nearest neighbors in all directions. The number of neighbors of an interior atom is termed the **bulk coordination number**. For surfaces, the number of neighbors is more limited, so the **surface coordination number** is smaller than the bulk coordination number. Often the surface coordination number is unknown or variable. The surface coordination number is also dependent on the Miller indices of the surface. In a body-centered cubic (BCC) crystal, the bulk coordination number is 8, whereas, for the (100) surface, the surface coordination number is 4.

Case studies

A common way to determine the coordination number of an atom is by X-ray crystallography. Related techniques include neutron or electron diffraction. The coordination number of an atom can be determined straightforwardly by counting nearest neighbors.

α-Aluminium has a regular cubic close packed structure, fcc, where each aluminium atom has 12 nearest neighbors, 6 in the same plane and 3 above and below and the coordination polyhedron is a cuboctahedron. α-Iron has a body centered cubic structure where each iron atom has 8 nearest neighbors situated at the corners of a cube.

- The two most common allotropes of carbon have different coordination numbers. In diamond, each carbon atom is at the centre of a regular tetrahedron formed by four other carbon atoms, the coordination number is four, as for methane. Graphite is made of two-dimensional layers in which each carbon is covalently bonded to three other carbons; atoms in other layers are further away and are not nearest neighbours, giving a coordination number of 3.

For chemical compounds with regular lattices such as sodium chloride and caesium chloride, a count of the nearest neighbors gives a good picture of the environment of the ions. In sodium chloride each sodium ion has 6 chloride ions as nearest neighbours (at 276 pm) at the corners of an octahedron and each chloride ion has 6 sodium atoms (also at 276 pm) at the corners of an octahedron. In caesium chloride each

caesium has 8 chloride ions (at 356 pm) situated at the corners of a cube and each chloride has eight caesium ions (also at 356 pm) at the corners of a cube.

Complications

In some compounds the metal-ligand bonds may not all be at the same distance. For example in $PbCl_2$, the coordination number of Pb could be said to be seven or nine, depending on which chlorides are assigned as ligands. Seven chloride ligands have Pb-Cl distances of 280–309 pm. Two chloride ligands are more distant, with a Pb-Cl distances of 370 pm.

In some cases a different definition of coordination number is used that includes atoms at a greater distance than the nearest neighbours. The very broad definition adopted by the International Union of Crystallography, IUCR, states that the coordination number of an atom in a crystalline solid depends on the chemical bonding model and the way in which the coordination number is calculated.

Some metals have irregular structures. For example, zinc has a distorted hexagonal close packed structure. Regular hexagonal close packing of spheres would predict that each atom has 12 nearest neighbours and a triangular orthobicupola (also called an anticuboctahedron or twinned cuboctahedron) coordination polyhedron. In zinc there are only 6 nearest neighbours at 266 pm in the same close packed plane with six other, next-nearest neighbours, equidistant, three in each of the close packed planes above and below at 291 pm. It is considered to be reasonable to describe the coordination number as 12 rather than 6. Similar considerations can be applied to the

regular body centred cube structure where in addition to the 8 nearest neighbors there 6 more, approximately 15% more distant, and in this case the coordination number is often considered to be 14.

- Many chemical compounds have distorted structures. Nickel arsenide, NiAs has a structure where nickel and arsenic atoms are 6-coordinate. Unlike sodium chloride where the chloride ions are cubic close packed, the arsenic anions are hexagonal close packed. The nickel ions are 6-coordinate with a distorted octahedral coordination polyhedron where columns of octahedra share opposite faces. The arsenic ions are not octahedrally coordinated but have a trigonal prismatic coordination polyhedron. A consequence of this arrangement is that the nickel atoms are rather close to each other. Other compounds that share this structure, or a closely related one are some transition metal sulfides such as FeS and CoS, as well as some intermetallics. In cobalt(II) telluride, CoTe, the six tellurium and two cobalt atoms are all equidistant from the central Co atom.Two other examples of commonly-encountered chemicals are Fe_2O_3 and TiO_2. Fe_2O_3 has a crystal structure that can be described as having a near close packed array of oxygen atoms with iron atoms filling two thirds of the octahedral holes. However each iron atom has 3 nearest neighbors and 3 others a little further away. The structure is quite complex, the oxygen atoms are coordinated to four iron atoms and the iron atoms in turn share vertices, edges and faces of the distorted octahedra. TiO_2 has the rutile

structure. The titanium atoms 6-coordinate, 2 atoms at 198.3 pm and 4 at 194.6 pm, in a slightly distorted octahedron. The octahedra around the titanium atoms share edges and vertices to form a 3-D network. The oxide ions are 3-coordinate in a trigonal planar configuration.

Coordination sphere

In coordination chemistry, the **first coordination sphere** refers to the array of molecules and ions (the ligands) directly attached to the central metal atom. The **second coordination sphere** consists of molecules and ions that attached in various ways to the first coordination sphere.

First coordination sphere

- The first coordination sphere refers to the molecules that are attached directly to the metal. The interactions between the first and second coordination spheres usually involve hydrogen-bonding. For charged complexes, ion pairing is important.

n hexamminecobalt(III) chloride ($[Co(NH_3)_6]Cl_3$), the cobalt cation plus the 6 ammonia ligands comprise the first coordination sphere. The coordination sphere of this ion thus consists of a central MN_6 core "decorated" by 18 N–H bonds that radiate outwards.

Second coordination sphere

Metal ions can be described as consisting of series of two concentric coordination spheres, the first and second. More distant from the second coordination sphere, the solvent molecules behave more like "bulk solvent." Simulation of the second coordination sphere is of interest in computational chemistry. The second coordination sphere can consist of ions (especially in charged complexes), molecules (especially those that hydrogen bond to ligands in the first coordination sphere) and portions of a ligand backbone. Compared to the first coordination sphere, the second coordination sphere has a less direct influence on the reactivity and chemical properties of the metal complex. Nonetheless the second coordination sphere is relevant to understanding reactions of the metal complex, including the mechanisms of ligand exchange and catalysis.

Role in catalysis

Mechanisms of metalloproteins often invoke modulation of the second coordination sphere by the protein.

Role in mechanistic inorganic chemistry

The rates at which ligands exchange between the first and the second coordination sphere is the first step in ligand substitution reactions. In associative ligand substitution, the entering nucleophile resides in the second coordination sphere. These effects are relevant to practical applications such as contrast agents used in MRI.

The energetics of inner sphere electron transfer reactions are discussed in terms of second coordination sphere. Some proton coupled electron transfer reactions involve atom transfer between the second coordination spheres of the reactants:

- $[Fe^*(H_2O)_6]$ + $[Fe(H_2O)_5(OH)]$ → $[Fe(H_2O)_6]$ + $[Fe^*(H_2O)_5(OH)]$

Role in spectroscopy

Solvent effects on colors and stability are often attributable to changes in the second coordination sphere. Such effects can be pronounced in complexes where the ligands in the first coordination sphere are strong hydrogen-bond donors and acceptors, e.g. respectively $[Co(NH_3)_6]$ and $[Fe(CN)_6]$. Crown-ethers bind to polyamine complexes through their second coordination sphere. Polyammonium cations bind to the nitrogen centres of cyanometallates.

Role in supramolecular chemistry

Macrocyclic molecules such as cyclodextrins act often as the second coordination sphere for metal complexes.

Coordinate covalent bond

A **coordinate covalent bond**, also known as a **dative bond**, **dipolar bond**, or **coordinate bond** is a kind of two-center, two-electron covalent bond in which the two electrons derive from the same atom. The bonding of metalions to ligands involves this kind of interaction. This type of interaction is central to Lewis theory.

Examples

Coordinate covalent bonding is ubiquitous. In all metal aquo-complexes $[M(H_2O)_n]$, the bonding between water and the metal cation is described as a coordinate covalent bond. Metal-ligand interactions in most organometalliccompounds and most coordination compounds are described similarly.

The term *dipolar bond* is used in organic chemistry for compounds such as amine oxides for which the electronic structure can be described in terms of the basic amine donating two electrons to an oxygen atom.

- $R_3N \rightarrow O$

The arrow → indicates that both electrons in the bond originate from the amine moiety. In a standard covalent bond each atom contributes one electron. Therefore, an alternative description is that the amine gives away one electron to the oxygen atom, which is then used, with the remaining unpaired electron on the nitrogen atom, to form a standard covalent bond. The process of transferring the electron from nitrogen to oxygen creates formal charges, so the electronic structure may also be depicted as

- R_3NO

This electronic structure has an electric dipole, hence the name polar bond. In reality, the atoms carry partial charges; the more electronegative atom of the two involved in the bond will usually carry a partial negative charge. One exception to this is carbon monoxide. In this case, the carbon atom carries

the partial negative charge although it is less electronegative than oxygen.

An example of a dative covalent bond is provided by the interaction between a molecule of ammonia, a Lewis base with a lone pair of electrons on the nitrogen atom, and boron trifluoride, a Lewis acid by virtue of the boron atom having an incomplete octet of electrons. In forming the adduct, the boron atom attains an octet configuration.

The electronic structure of a coordination complex can be described in terms of the set of ligands each donating a pair of electrons to a metal centre. For example, in hexamminecobalt(III) chloride, each ammonia ligand donates its lone pair of electrons to the cobalt(III) ion. In this case, the bonds formed are described as coordinate bonds.

Comparison with other electron-sharing modes

In all cases, the bond, whether dative or "normal" electron-sharing, is a covalent bond. In common usage, the prefix dipolar, dative or coordinate merely serves to indicate the origin of the electrons used in creating the bond. For example, $F_3B \leftarrow O(C_2H_5)_2$ ("boron trifluoride (diethyl) etherate") is prepared from BF_3 and $:O(C_2H_5)_2$, as opposed to the radical species $[\bullet BF_3]$ and $[\bullet O(C_2H_5)_2]$. The dative bond is also a convenience in terms of notation, as formal charges are avoided: we can write D**:** + ()A ⇌ D → A rather than D–A (here **:** and () represent the lone-pair and empty orbital on the electron-pair donor D and acceptor A, respectively). The

notation is sometimes used even when the Lewis acid-base reaction involved is only notional (e.g., the sulfoxide $R_2S \rightarrow O$ is rarely if ever made by reacting the sulfide R_2S with atomic oxygen O). Thus, most chemists *do not* make any claim with respect to the properties of the bond when choosing one notation over the other (formal charges vs. arrow bond).

It is generally true, however, that bonds depicted this way are polar covalent, sometimes strongly so, and some authors claim that there are genuine differences in the properties of a dative bond and electron-sharing bond and suggest that showing a dative bond is more appropriate in particular situations. As far back as 1989, Haaland characterized dative bonds as bonds that are (i) weak and long; (ii) with only a small degree of charge-transfer taking place during bond formation; and (iii) whose preferred mode of dissociation in the gas phase (or low ε inert solvent) is heterolytic rather than homolytic. The ammonia-borane adduct ($H_3N \rightarrow BH_3$) is given as a classic example: the bond is weak, with a dissociation energy of 31 kcal/mol (cf. 90 kcal/mol for ethane), and long, at 166 pm (cf. 153 pm for ethane), and the molecule possesses a dipole moment of 5.2 D that implies a transfer of only 0.2 *e* from nitrogen to boron. The heterolytic dissociation of $H_3N \rightarrow BH_3$ is estimated to require 27 kcal/mol, confirming that heterolysis into ammonia and borane is more favorable than homolysis into radical cation and radical anion. However, aside from clear-cut examples, there is considerable dispute as to when a particular compound qualifies and, thus, the overall prevalence of dative bonding (with respect to an author's preferred definition). Computational chemists have suggested quantitative criteria to distinguish between the two "types" of bonding.

Some non-obvious examples where dative bonding is claimed to be important include carbon suboxide (O≡C → C ← C≡O), tetraaminoallenes (described using dative bond language as "carbodicarbenes"; $(R_2N)_2C$ → C ← $C(NR_2)_2$), the Ramirez carbodiphosphorane (Ph_3P → C ← PPh_3), and bis(triphenylphosphine)iminium cation (Ph_3P → N ← PPh_3), all of which exhibit considerably bent equilibrium geometries, though with a shallow barrier to bending. Simple application of the normal rules for drawing Lewis structures by maximizing bonding (using electron-sharing bonds) and minimizing formal charges would predict heterocumulene structures, and therefore linear geometries, for each of these compounds. Thus, these molecules are claimed to be better modeled as coordination complexes of **:C:** (carbon(0) or "carbone") or **:N:** (mononitrogen cation) with CO, PPh_3, or *N*-heterocycliccarbenes as ligands, the lone-pairs on the central atom accounting for the bent geometry. However, the usefulness of this view is disputed.

Chapter 3

Non-coordinating Anion

Anions that interact weakly with cations are termed **non-coordinating anions**, although a more accurate term is **weakly coordinating anion**. Non-coordinating anions are useful in studying the reactivity of electrophilic cations. They are commonly found as counterions for cationic metal complexes with an unsaturated coordination sphere. These special anions are essential components of homogeneousalkene polymerisation catalysts, where the active catalyst is a coordinatively unsaturated, cationic transition metal complex. For example, they are employed as counterions for the 14 valence electron cations $[(C_5H_5)_2ZrR]$ (R = methyl or a growing polyethylene chain). Complexes derived from non-coordinating anions have been used to catalyzehydrogenation, hydrosilylation, oligomerization, and the living polymerization of alkenes. The popularization of non-coordinating anions has contributed to increased understanding of agostic complexes wherein hydrocarbons and hydrogen serve as ligands. Non-coordinating anions are important components of many superacids, which result from the combination of Brønsted acids and Lewis acids.

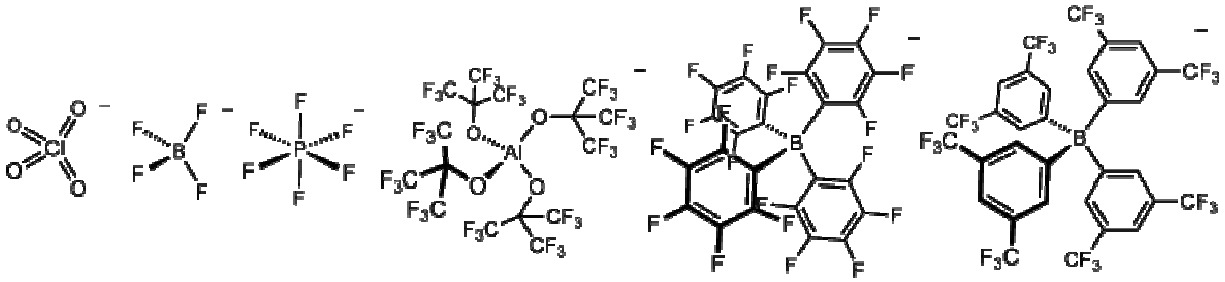
Pre-"BARF" era

Before 1990s, tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), and perchlorate (ClO_4) were considered weakly coordinating anions. These species are now known to bind to strongly electrophilic metal centers. Tetrafluoroborate and

hexafluorophosphate anions are coordinating toward highly electrophilic metal ions, such as cations containing Zr(IV) centers, which can abstract fluoride from these anions. Other anions, such as triflates are considered to be low-coordinating with some cations.

Era of BARF

A revolution in this area occurred in the 1990s with the introduction of the tetrakis[3,5-bis (trifluoromethyl)phenyl]borate ion, $B[3,5\text{-}(CF_3)_2C_6H_3]_4$, commonly abbreviated as BAr_4 and colloquially called "BARF". This anion is far less coordinating than tetrafluoroborate, hexafluorophosphate, and perchlorate, and consequently has enabled the study of still more electrophilic cations. Related tetrahedral anions include tetrakis (pentafluorophenyl)borate$B(C_6F_5)_4$, and $Al[OC(CF_3)_3]_4$.



In the bulky borates and aluminates, the negative charge is symmetrically distributed over many electronegative atoms. Related anions are derived from tris(pentafluorophenyl)boron $B(C_6F_5)_3$. Another advantage of these anions is that their salts are more soluble in non-polar organic solvents such as dichloromethane, toluene, and, in some cases, even alkanes. Polar solvents, such as acetonitrile, THF, and water, tend to

bind to electrophilic centers, in which cases, the use of a non-coordinating anion is pointless.

Salts of the anion $B[3,5\text{-}(CF_3)_2C_6H_3]_4$ were first reported by Kobayashi and co-workers. For that reason, it is sometimes referred to as *Kobayashi's anion*. Kobayashi's method of preparation has been superseded by a safer route.

The neutral molecules that represent the parents to the non-coordinating anions are strong Lewis acids, e.g. boron trifluoride, BF_3 and phosphorus pentafluoride, PF_5. A notable Lewis acid of this genre is tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, which abstracts alkyl ligands:

- $(C_5H_5)_2Zr(CH_3)_2 + B(C_6F_5)_3 \rightarrow [(C_5H_5)_2Zr(CH_3)][(CH_3)B(C_6F_5)_3]$

Other types of non-coordinating anions

Another large class of non-coordinating anions are derived from carborane anion $CB_{11}H_{12}$. Using this anion, the first example of a three-coordinate silicon compound, the salt $[(mesityl)_3Si][HCB_{11}Me_5Br_6]$ contains a non-coordinating anion derived from a carborane.

Bistriflimide

Bistriflimide, systematically known as **bis(trifluoromethane)sulfonimide** (or 'imidate', *see below*) and

colloquially as TFSI, is a non-coordinating anion with the chemical formula $[(CF_3SO_2)_2N]$. Its salts are typically referred to as being metal triflimidates.

Applications

The anion is widely used in ionic liquids (such as trioctylmethylammonium bis(trifluoromethylsulfonyl)imide), since it is less toxic and more stable than more "traditional" counterions such as tetrafluoroborate. This anion is also of importance in lithium-ion and lithium metal batteries (LiTFSI) because of its high dissociation and conductivity. It has the added advantage of suppressing crystallinity in poly(ethylene oxide), which increases the conductivity of that polymer below its melting point at 50 °C.

Bistriflimidic acid

The conjugate acid of bistriflimide, which is frequently referred to by the trivial name **bistriflimidic acid** (CAS: 82113-65-3), is a commercially available superacid. It is a crystalline compound, but is hygroscopic to the point of being deliquescent. Owing to its very high acidity and good compatibility with organic solvents it has been employed as a catalyst in a wide range of chemical reactions.

Its pK_a value in water cannot be accurately determined but in acetonitrile it has been estimated as −0.10 and in 1,2-dichloroethane−12.3 (relative to the pK_a value of 2,4,6-trinitrophenol (picric acid), anchored to zero to crudely approximate the aqueous pK_a scale), making it more acidic

than triflic acid (pK_a = 0.70, pK_a(relative to picric acid) = −11.4).

Naming

Developing an IUPAC name for bistriflimide that indicates the structure and reactivity is challenging, and changes to current names have been proposed. The main difficulty arises from the ambiguous use of the word ***amide*** to mean an acylated (including sulfonylated) amine *or* the anionic form of an amine. Likewise, ***imide*** can refer to a bisacylated amine *or* a twice deprotonated amine. Thus, depending on the system used, there is ambiguity as to whether amide or imide is being used to refer to the parent acid or the anion. (The anion has been referred to as an ***amidate*** or ***imidate*** in an attempt to distinguish it from the acid.) The complications in naming these compounds was highlighted in an article by the IUPAC. Since then, the IUPAC has recommended (2013) that derivatives of anionic nitrogen can be named as azanides, so bis[(trifluoromethane)sulfonyl]azanide would be an acceptable and unambiguous name for bistriflimide anion. The parent acid, whose trivial name is triflimidic acid, would then be called bis[(trifluoromethane)sulfonyl]azane.

Brookhart's acid

Brookhart's acid is the salt of the diethyl etheroxonium ion and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr'_4). It is a colorless solid, used as a strong acid. The compound was first reported by Volpe, Grant, and Brookhart in 1992.

Preparation

This compound is prepared by treatment of $NaBAr'_4$ in diethyl ether (Et_2O) with hydrogen chloride:

- $NaBAr'_4 + HCl + 2\ Et_2O \rightarrow [H(OEt_2)_2]BAr'_4 + NaCl$

$NaBAr'_4$ is soluble in diethyl ether, whereas sodium chloride is not. Precipitation of sodium chloride thus drives the formation of the oxonium acid compound, which is isolable as a solid.

Structure and properties

The acid crystallizes as a white, hygroscopic crystalline solid. NMR and elemental analysis showed that the crystal contains two equivalents of diethyl ether. In solution, the compound slowly degrades to *m*-$C_6H_3(CF_3)_2$ and BAr'_3.

$[H(OEt_2)_2][B(C_6F_5)_4]$ is a related compound with a slightly different weakly coordinating anion; it was first reported in 2000. An X-ray crystal structure of that compound was obtained, showing the acidic proton coordinated by both ethereal oxygen centers, although the crystal was not good enough to determine whether the proton is located symmetrically or unsymmetrically between the two.

Uses

Traditional weakly coordinating anions, such as perchlorate, tetrafluoroborate, and hexafluorophosphate will coordinate to very electrophilic cations, making these counterions unsuitable

for some complexes. The highly reactive species $[Cp_2Zr(CH_3)]$, for example, has been reported to abstract F from PF_6. Starting in the 1980s, new types weakly coordinating anions began to be developed. BAr'_4 anions are used as counterions for highly electrophilic, cationic transition metal species, as they are very weakly coordinating and unreactive towards electrophilic attack. One common method of generating these cationic species is via protonolysis of a dialkyl complexes or an olefin complex. For example, an electrophilic palladium catalyst, $[(2,2'\text{-bipyridine})Pd(CH_3)(CH_3CN)][BAr'_4]$, is prepared by protonating the dimethyl complex with Brookhart's acid. This electrophilic, cationic palladium species is used for the polymerization of olefins with carbon monoxide to polyketones in aprotic solvents.

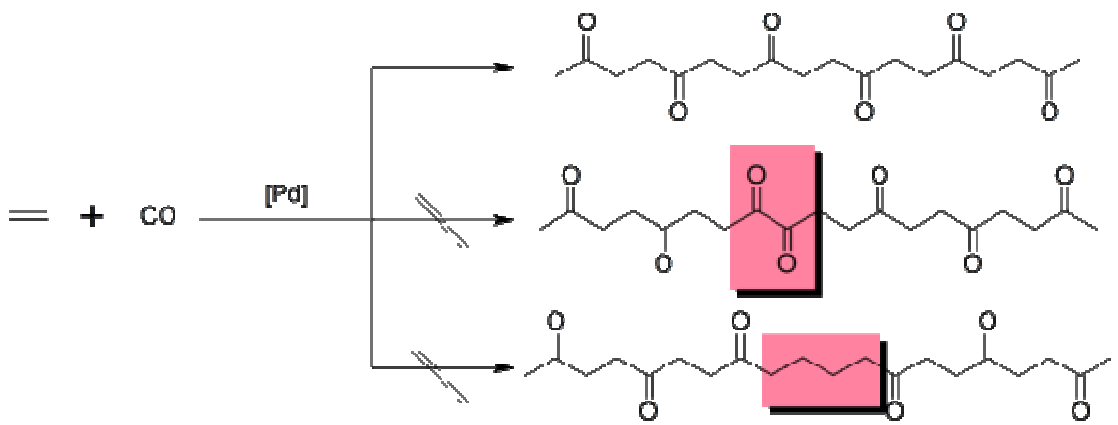
Potential application

Polyketones, thermoplasticpolymers, are formed by the copolymerisation of carbon monoxide and one or more alkenes (typically ethylene with propylene). The process utilises a palladium(II) catalyst with a bidentate ligand like 2,2′-bipyridine or 1,10-phenanthroline (phen) with a non-coordinating BARF counterion, such as $[(phen)Pd(CH_3)(CO)]BAr_4$. The preparation of the catalyst involves the reaction of a dimethyl palladium complex with Brookhart's acid in acetonitrile with loss of methane and the catalytic species is formed by uptake of carbon monoxide to displace acetonitrile.

- $[(Et_2O)_2H]BAr_4 + [(phen)Pd(CH_3)_2] + MeCN \rightarrow [(phen)Pd(CH_3)(MeCN)]BAr_4 + 2\ Et_2O + CH_4$

- $[(phen)Pd(CH_3)(MeCN)]BAr_4 + CO \rightarrow [(phen)Pd(CH_3)(CO)]BAr_4 + MeCN$

The mechanism involves migratory insertion whereby the polymer chain is bound to the catalytic centre and grows by the sequential insertion of carbon monoxide and the alkene between the palladium atom and the existing chain. Defects occur when insertions do not alternate – that is, a carbon monoxide insertion follows a carbon monoxide insertion or an alkene insertion follows an alkene insertion – these are highlighted in red in the figure below. This catalyst produces a very low rate of defects due to the difference in Gibbs energy of activation of each insertion – the energy barrier to inserting an alkene immediately following an alkene insertion is ~12 kJ mol higher than barrier to carbon monoxide insertion. Use of monodentate phosphine ligands also leads to undesirable side-products but bidentate phosphine ligands like 1,3-bis(diphenylphosphino)propane have been used industrially.



- Copolymerisation of ethylene and carbon monoxide to a polyketone. Examples of defects from double insertions are highlighted in red.

Hexafluorophosphate

Hexafluorophosphate is an anion with chemical formula of PF_6. It is an octahedral species that imparts no color to its salts. PF_6 is isoelectronic with sulfur hexafluoride, SF_6, and the hexafluorosilicate dianion, SiF_6, and fluoroantimonateSbF_6. Being poorly nucleophilic, hexafluorophosphate is classified as a non-coordinating anion.

Synthesis

Hexafluorophosphate salts can be prepared by the reaction of phosphorus pentachloride and alkali or ammonium halide in a solution of hydrofluoric acid:

- $PCl_5 + MCl + 6\ HF \rightarrow MPF_6 + 6\ HCl$

Hexafluorophosphoric acid can be prepared by direct reaction of hydrogen fluoride with phosphorus pentafluoride. It is a strong Brønsted acid that is typically generated *in situ* immediately before its use.

- $PF_5 + HF \rightarrow HPF_6$

These reactions require specialized equipment to safely handle the hazards associated with hydrofluoric acid and hydrogen fluoride.

Quantitative analysis

Several methods of quantitative analysis for the hexafluorophosphate ion have been developed. Tetraphenylarsonium chloride, $[(C_6H_5)_4As]Cl$, has been used both for titrimetric and gravimetric quantifications of hexafluorophosphate. Both of these determinations depend on the formation of tetraphenylarsonium hexafluorophosphate:

- $[(C_6H_5)_4As] + PF_6 \rightarrow [(C_6H_5)_4As]PF_6$

Hexafluorophosphate can also be determined spectrophotometrically with ferroin.

Reactions

Hydrolysis is extremely slower under basic conditions. Acid-catalyzed hydrolysis to the phosphate ion is also slow. Nonetheless, hexafluorophosphate is prone to decomposition with the release of hydrogen fluoride in ionic liquids.

Organometallic and inorganic synthesis

Hexafluorophosphate is a common counteranion for cationicmetal complexes. It is one of three widely used non-coordinating anions: hexafluorophosphate, tetrafluoroborateBF_4, and perchlorateClO_4. Of these, the hexafluorophosphate ion has the least coordinating tendency.

Hexafluorophosphate salts can be prepared by reactions of silver hexafluorophosphate with halide salts. Precipitation of

insoluble silver halide helps drive this reaction to completion. Since hexafluorophosphate salts are often insoluble in water but soluble in polar organic solvents, even the addition of ammonium hexafluorophosphate (NH_4PF_6) to aqueous solutions of many organic and inorganic salts gives solid precipitates of hexafluorophosphate salts. One example is the synthesis of rhodocenium salts: The overall conversion equation is

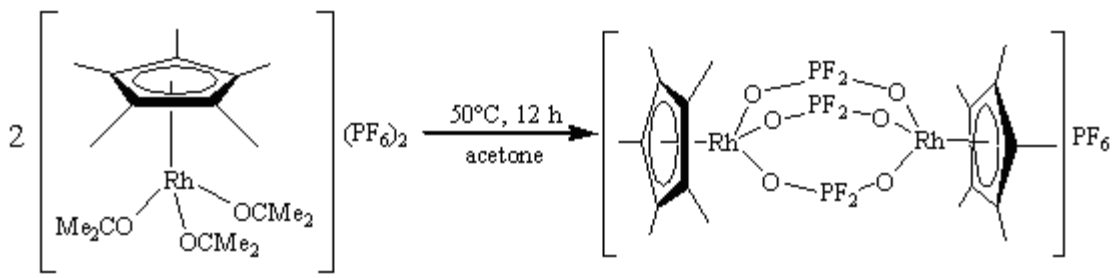
- $RhCl_3 \cdot xH_2O + 2\ C_5H_6 + NH_4PF_6 \rightarrow [(\eta\text{-}C_5H_5)_2Rh]PF_6 + 2\ HCl + NH_4Cl + x\ H_2O$

Tetrakis(acetonitrile)copper(I) hexafluorophosphate is produced by the addition of hexafluorophosphoric acid to a suspension of copper(I) oxide in acetonitrile:

- $Cu_2O + 2\ HPF_6 + 8\ CH_3CN \rightarrow 2\ [Cu(CH_3CN)_4]PF_6 + H_2O$

Hydrolysis of hexafluorophosphate complexes

While the hexafluorophosphate ion is generally inert and hence a suitable counterion, its solvolysis can be induced by highly electrophilic metal centers. For example, the tris(solvento) rhodium complex $[(\eta\text{-}C_5Me_5)Rh(Me_2CO)_3](PF_6)_2$ undergoes solvolysis when heated in acetone, forming a difluorophosphate-bridged complex $[(\eta\text{-}C_5Me_5)Rh(\mu\text{-}OPF_2O)_3Rh(\eta\text{-}C_5Me_5)]PF_6$.



Applications

Practical uses of the hexafluorophosphate ion typically exploit one or more of the following properties: that it is a non-coordinating anion; that hexafluorophosphate compounds are typically soluble in organic solvents, particularly polar ones, but have low solubility in aqueous solution; or, that it has a high degree of stability, including resistance to both acidic and basic hydrolysis.

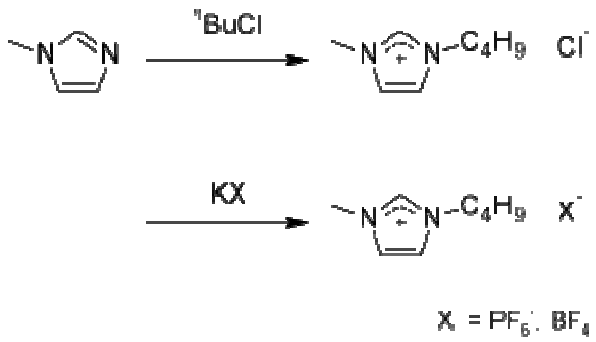
Secondary batteries

The main commercial use of hexafluorophosphate is as its lithium salt, lithium hexafluorophosphate. This salt, in combination with dimethyl carbonate, is a common electrolyte in commercial secondary batteries such as lithium-ion cells. This application exploits the high solubility of hexafluorophosphate salts in organic solvents and the resistance of these salts to reduction by the alkali metal cathode. Since the lithium ions in these batteries are generally present as coordination complexes within the electrolyte, the non-coordinating nature of the hexafluorophosphate ion is also a useful property for these applications.

Ionic liquids

Room temperature ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate (typically abbreviated as $bmimPF_6$) have been prepared. The advantage of the anion exchange in favour of a non-coordinating anion is that the resulting ionic liquid has much greater thermal stability. 1-

Butyl-3-methylimidazolium chloride decomposes to *N*-methylimidazole and 1-chlorobutane or to *N*-butylimidazole and chloromethane. Such decompositions are not possible for $bmimPF_6$. However, thermal decompositions of hexafluorophosphate ionic liquids to generate hydrogen fluoride gas are known.



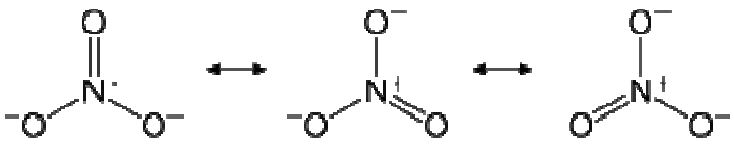
Nitrate

Nitrate is a polyatomic ion with the chemical formulaNO_3. Salts containing this ion are called **nitrates**. Nitrates are common components of fertilizers and explosives. Almost all inorganic nitrates are soluble in water. An example of an insoluble nitrate is bismuth oxynitrate.

Structure

The ion is the conjugate base of nitric acid, consisting of one central nitrogenatom surrounded by three identically bonded oxygen atoms in a trigonal planar arrangement. The nitrate ion carries a formal charge of −1. This charge results from a combination formal charge in which each of the three oxygens carries a −2/3 charge, whereas the nitrogen carries a +1

charge, all these adding up to formal charge of the polyatomic nitrate ion. This arrangement is commonly used as an example of resonance. Like the isoelectroniccarbonate ion, the nitrate ion can be represented by resonance structures:



Dietary nitrates

A rich source of inorganic nitrate in the human diets come from leafy green foods, such as spinach and arugula. NO_3 (inorganic nitrate) is the viable active component within beetroot juice and other vegetables. Drinking water is also a dietary source.

Dietary nitrate supplementation delivers positive results when testing endurance exercise performance.

Ingestion of large doses of nitrate either in the form of pure sodium nitrate or beetroot juice in young healthy individuals rapidly increases plasma nitrate concentration by a factor of 2 to 3, and this elevated nitrate concentration can be maintained for at least 2 weeks. Increased plasma nitrate stimulates the production of nitric oxide. Nitric oxide is important physiological signalling molecule that is used in, among other things, regulation of muscle blood flow and mitochondrial respiration.

Cured meats

Nitrite consumption is primarily determined by the amount of processed meats eaten, and the concentration of nitrates in these meats. Although nitrites are the nitrogen compound chiefly used in meat curing, nitrates are used as well. Nitrates lead to the formation of nitrosamines. The production of carcinogenic nitrosamines may be inhibited by the use of the antioxidants vitamin C and the alpha-tocopherol form of vitamin E during curing.

Anti-hypertensive diets, such as the DASH diet, typically contain high levels of nitrates, which are first reduced to nitrite in the saliva, as detected in saliva testing, prior to forming nitric oxide.

Occurrence and production

Nitrate salts are found naturally on earth as large deposits, particularly of nitratine, a major source of sodium nitrate.

Nitrates are produced by a number of species of nitrifying bacteria in the natural environment using ammonia or urea as a source of nitrogen. Nitrate compounds for gunpowder were historically produced, in the absence of mineral nitrate sources, by means of various fermentation processes using urine and dung.

Lightning strikes in earth's nitrogen-oxygen rich atmosphere produce a mixture of oxides of nitrogen which form nitrous ions and nitrate ions which are washed from the atmosphere by rain or in occult deposition.

Nitrates are produced industrially from nitric acid.

Uses

Nitrates are mainly produced for use as fertilizers in agriculture because of their high solubility and biodegradability. The main nitrate fertilizers are ammonium, sodium, potassium, calcium, and magnesium salts. Several million kilograms are produced annually for this purpose.

The second major application of nitrates is as oxidizing agents, most notably in explosives where the rapid oxidation of carbon compounds liberates large volumes of gases (see gunpowder for an example). Sodium nitrate is used to remove air bubbles from molten glass and some ceramics. Mixtures of the molten salt are used to harden some metals.

Nitrate was also used as a film stock through nitrocellulose. Due to its high combustibility, the studios swapped to acetate safety film in 1950.

Detection

Almost all methods for detection of nitrate rely on its conversion to nitrite followed by nitrite-specific tests. The reduction of nitrate to nitrite is effected by copper-cadmium material. The sample is introduced with a flow injection analyzer, and the resulting nitrite-containing effluent is then combined with a reagent for colorimetric or electrochemical detection. The most popular of these assays is the Griess test, whereby nitrite is converted to a deeply colored azo dye, suited

for UV-vis spectroscopic analysis. The method exploits the reactivity of nitrous acid derived from acidification of nitrite. Nitrous acid selectively reacts with aromatic amines to give diazonium salts, which in turn couple with a second reagent to give the azo dye. The detection limit is 0.02 to 2 μM. Methods have been highly adapted to biological samples.

Safety

The acute toxicity of nitrate is low. "Substantial disagreement" exists about the long-term risks of nitrate exposure. The two areas of possible concern are that (i) nitrate could be a precursor to nitrite in the lower gut, and nitrite is a precursor to nitrosamines, which are implicated in carcinogenesis, and (ii) nitrate is implicated in methemoglobinemia, a disorder of red blood cells hemoglobin.

Methemoglobinemia

Nitrates do not affect infants and pregnant women. Blue baby syndrome is caused by a number of other factors such as gastric upset, such as diarrheal infection, protein intolerance, heavy metal toxicity etc., with nitrates playing a minor role.

Drinking water standards

Through the Safe Drinking Water Act, the United States Environmental Protection Agency has set a maximum contaminant level of 10 mg/L or 10 ppm of nitrates in drinking water.

An acceptable daily intake (ADI) for nitrate ions was established in the range of 0–3.7 mg (kg body weight) day by the Joint FAO/WHO Expert Committee on Food additives (JEFCA).

Aquatic toxicity

In freshwater or estuarine systems close to land, nitrate can reach concentrations that are lethal to fish. While nitrate is much less toxic than ammonia, levels over 30 ppm of nitrate can inhibit growth, impair the immune system and cause stress in some aquatic species. Nitrate toxicity remains the subject of debate.

In most cases of excess nitrate concentrations in aquatic systems, the primary sources are wastewater discharges, as well as surface runoff from agricultural or landscaped areas that have received excess nitrate fertilizer. The resulting eutrophication and algae blooms result in anoxia and dead zones. As a consequence, as nitrate forms a component of total dissolved solids, they are widely used as an indicator of water quality.

Domestic animal feed

- Symptoms of nitrate poisoning in domestic animals include increased heart rate and respiration; in advanced cases blood and tissue may turn a blue or brown color. Feed can be tested for nitrate; treatment consists of supplementing or substituting existing supplies with lower nitrate material.

Perchlorate

A **perchlorate** is a chemical compound containing the perchlorate ion, ClO_4. The majority of perchlorates are commercially produced salts. They are mainly used as oxidizers for pyrotechnic devices and to control static electricity in food packaging. Perchlorate contamination in food, water, and other parts of the environment has been studied in the U.S. because of harmful effects on human health. Perchlorate ions are somewhat toxic to the thyroid gland.

Most perchlorates are colorless solids that are soluble in water. Four perchlorates are of primary commercial interest: ammonium perchlorate (NH_4ClO_4), perchloric acid ($HClO_4$), potassium perchlorate ($KClO_4$), and sodium perchlorate ($NaClO_4$). Perchlorate is the anion resulting from the dissociation of perchloric acid and its salts upon their dissolution in water. Many perchlorate salts are soluble in non-aqueous solutions.

Production

Perchlorate salts are produced industrially by the oxidation of aqueous solutions of sodium chlorate by electrolysis. This method is used to prepare sodium perchlorate. The main application is for rocket fuel. The reaction of perchloric acid with bases, such as ammonium hydroxide, give salts. The highly valued ammonium perchlorate can be produced electrochemically.

Curiously, perchlorate can be produced by lightning discharges in the presence of chloride. Perchlorate has been detected in rain and snow samples from Florida and Lubbock, Texas. It is also present in Martian soil.

Uses

- The dominant use of perchlorates is as oxidizers in propellants for rockets, fireworks and highway flares. Of particular value is ammonium perchlorate composite propellant as a component of solid rocket fuel. In a related but smaller application, perchlorates are used extensively within the pyrotechnics industry and in certain munitions and for the manufacture of matches.
- Perchlorate is used to control static electricity in food packaging. Sprayed onto containers it stops statically charged food from clinging to plastic or paper/cardboard surface.
- Niche uses include lithium perchlorate, which decomposes exothermically to produce oxygen, useful in oxygen "candles" on spacecraft, submarines, and in other situations where a reliable backup oxygen supply is needed.
- Potassium perchlorate has, in the past, been used therapeutically to help manage Graves' disease. It impedes production of the thyroid hormones that contain iodine.

Gas phase measurements of heats of reaction (which allow computation of $\Delta H_f°$) of various chlorine oxides do follow the

expected trend wherein Cl_2O_7 exhibits the largest endothermic value of $\Delta H_f°$ (238.1 kJ/mol) while Cl_2O exhibits the lowest endothermic value of $\Delta H_f°$ (80.3 kJ/mol).

The chlorine in the perchlorate anion is a closed shell atom and is well protected by the four oxygens. Most perchlorate compounds, especially salts of electropositive metals such as sodium perchlorate or potassium perchlorate, do not oxidize organic compounds until the mixture is heated. This property is useful in many applications, such as flares, where ignition is required to initiate a reaction. Ammonium perchlorate is stable when pure but can form potentially explosive mixtures with reactive metals or organic compounds. The PEPCON disaster destroyed a production plant for ammonium perchlorate when a fire caused the ammonium perchlorate stored on site to react with the aluminum that the storage tanks were constructed with and explode.

Potassium perchlorate has the lowest solubility of any alkali metal perchlorate (1.5 g in 100 ml of water at 25 °C).

Biology

Over 40 phylogenetically and metabolically diverse microorganisms capable of growth via perchlorate reduction have been isolated since 1996. Most originate from the Proteobacteria but others include the Firmicutes, *Moorella perchloratireducens* and *Sporomusa* sp., and the archaeon*Archaeoglobus fulgidus*. With the exception of *A. fulgidus*, all known microbes that grow via perchlorate reduction utilize the enzymes perchlorate reductase and chlorite dismutase, which collectively take perchlorate to

innocuous chloride. In the process, free oxygen (O_2) is generated.

Natural abundance

Terrestrial abundance

Naturally occurring perchlorate at its most abundant can be found comingled with deposits of sodium nitrate in the Atacama Desert of northern Chile. These deposits have been heavily mined as sources for nitrate-based fertilizers. Chilean nitrate is in fact estimated to be the source of around 81,000 tonnes (89,000 tons) of perchlorate imported to the U.S. (1909–1997). Results from surveys of ground water, ice, and relatively unperturbed deserts have been used to estimate a 100,000 to 3,000,000 tonnes (110,000 to 3,310,000 tons) "global inventory" of natural perchlorate presently on Earth.

On Mars

Perchlorate was detected in martian soil at the level of ~0.6% by weight. It is conjectured to exist as a mixture of 48% $Ca(ClO_4)_2$ 32% $Mg(ClO_4)_2$ and 20% ammonium (NH_4ClO_4). These salts, formed from perchlorates, act as antifreeze and substantially lower the freezing point of water. Based on the temperature and pressure conditions on present-day Mars at the *Phoenix* lander site, conditions would allow a perchlorate salt solution to be stable in liquid form for a few hours each day during the summer.

The possibility that the perchlorate was a contaminant brought from Earth has been eliminated by several lines of evidence.

The *Phoenix* retro-rockets used ultra pure hydrazine and launch propellants consisting of ammonium perchlorate or ammonium nitrate. Sensors on board *Phoenix* found no traces of ammonium nitrate, and thus the nitrate in the quantities present in all three soil samples is indigenous to the Martian soil. Instead, the *Viking* found traces of ammonium perchlorate on the planet's surface in 1977. Perchlorate is widespread in Martian soils at concentrations between 0.5 and 1%. At such concentrations, perchlorate could be an important source of oxygen, but it could also become a critical chemical hazard to astronauts.

In 2006, a mechanism was proposed for the formation of perchlorates that is particularly relevant to the discovery of perchlorate at the *Phoenix* lander site. It was shown that soils with high concentrations of chloride converted to perchlorate in the presence of titanium dioxide and sunlight/ultraviolet light. The conversion was reproduced in the lab using chloride-rich soils from Death Valley. Other experiments have demonstrated that the formation of perchlorate is associated with wide band gap semiconducting oxides. In 2014, it was shown that perchlorate and chlorate can be produced from chloride minerals under Martian conditions via UV using only NaCl and silicate.

Further findings of perchlorate and chlorate in the Martian meteorite EETA79001 and by the Mars *Curiosity* rover in 2012-2013 support the notion that perchlorates are globally distributed throughout the Martian surface. With concentrations approaching 0.5% and exceeding toxic levels on Martian soil, Martian perchlorates would present a serious challenge to human settlement, as well as microorganisms. On

the other hand, the perchlorate would provide a convenient source of oxygen for the settlements.

On September 28, 2015, NASA announced that analyses of spectral data from the Compact Reconnaissance Imaging Spectrometer for Mars instrument (CRISM) on board the Mars Reconnaissance Orbiter from four different locations where recurring slope lineae (RSL) are present found evidence for hydrated salts. The hydrated salts most consistent with the spectral absorption features are magnesium perchlorate, magnesium chlorate and sodium perchlorate. The findings strongly support the hypothesis that RSL form as a result of contemporary water activity on Mars.

Contamination in environment

Perchlorate is of concern because of uncertainties about toxicity and health effects at low levels in drinking water, impact on ecosystems, and indirect exposure pathways for humans due to accumulation in vegetables. Perchlorate is water-soluble, exceedingly mobile in aqueous systems, and can persist for many decades under typical groundwater and surface water conditions.

Detected perchlorate originates from disinfectants, bleaching agents, herbicides, and mostly from rocket propellants. Perchlorate is a byproduct of the production of a rocket fuel and fireworks. The removal and recovery of the perchlorate compounds in explosives and rocket propellants include high-pressure water washout, which generate aqueous ammonium perchlorate.

In U.S. drinking water

Low levels of perchlorate have been detected in both drinking water and groundwater in 26 states in the U.S., according to the Environmental Protection Agency (EPA). The chemical has been detected at levels as high as 5 μg/L at Joint Base Cape Cod (formerly Massachusetts Military Reservation), well over the Massachusetts state regulation of 2 μg/L. Fireworks are also a source of perchlorate in lakes.

At the Olin Flare Facility, Morgan Hill, California perchlorate contamination beneath the former flare manufacturing plant was first discovered in 2000, several years after the plant had closed. The plant had used potassium perchlorate as one of the ingredients during its 40 years of operation. By late 2003, the State of California and the Santa Clara Valley Water District had confirmed a groundwater plume currently extending over nine miles through residential and agricultural communities. The California Regional Water Quality Control Board and the Santa Clara Valley Water District have engagedin a major outreach effort, a water well testing program has been underway for about 1,200 residential, municipal, and agricultural wells. Large ion exchange treatment units are operating in three public water supply systems which include seven municipal wells with perchlorate detection. The potentially responsible parties, Olin Corporation and Standard Fuse Incorporated, have been supplying bottled water to nearly 800 households with private wells, and the Regional Water Quality Control Board has been overseeing cleanup efforts.

The source of perchlorate in California was mainly attributed to two manufacturers in the southeast portion of the Las Vegas

Valley in Nevada, where perchlorate has been produced for industrial use. This led to perchlorate release into Lake Mead in Nevada and the Colorado River which affected regions of Nevada, California and Arizona, where water from this reservoir is used for consumption, irrigation and recreation for approximately half the population of these states. Lake Mead has been attributed as the source of 90% of the perchlorate in Southern Nevada's drinking water. Based on sampling, perchlorate has been affecting 20 million people, with highest detection in Texas, southern California, New Jersey, and Massachusetts, but intensive sampling of the Great Plains and other middle state regions may lead to revised estimates with additional affected regions. An action level of 18 μg/L has been adopted by several affected states.

In food

In 2004, the chemical was found in cow's milk in California at an average level of 1.3 parts per billion (ppb, or μg/L), which may have entered the cows through feeding on crops exposed to water containing perchlorates. A 2005 study suggested human breast milk had an average of 10.5 μg/L of perchlorate.

In minerals and other natural occurrences

In some places, there is no clear source of perchlorate, and it may be naturally occurring. Natural perchlorate on earth was first identified in terrestrial nitrate deposits of the Atacama Desert in Chile as early as the 1880s and for a long time considered a unique perchlorate source. The perchlorate released from historic use of Chilean nitrate based fertilizer which the U.S.imported by the hundreds of tons in the early

19th century can still be found in some groundwater sources of the United States. Recent improvements in analytical sensitivity using ion chromatography based techniques have revealed a more widespread presence of natural perchlorate, particularly in subsoils of Southwest USA, salt evaporites in California and Nevada, Pleistocene groundwater in New Mexico, and even present in extremely remote places such as Antarctica. The data from these studies and others indicate that natural perchlorate is globally deposited on Earth with the subsequent accumulation and transport governed by the local hydrologic conditions.

Despite its importance to environmental contamination, the specific source and processes involved in natural perchlorate production remain poorly understood. Laboratory experiments in conjunction with isotopic studies have implied that perchlorate may be produced on earth by oxidation of chlorine species through pathways involving ozone or its photochemical products. Other studies have suggested that perchlorate can also be created by lightning activated oxidation of chloride aerosols (e.g., chloride in sea salt sprays), and ultraviolet or thermal oxidation of chlorine (e.g., bleach solutions used in swimming pools) in water.

From fertilizers

Although perchlorate as an environmental contaminant is usually associated with the storage, manufacture, and testing of solid rocket motors, contamination of perchlorate has been focused in the use of fertilizer and its perchlorate release into ground water. Fertilizer leaves perchlorate anions to leak into the ground water and threaten the water supplies of many

regions in the US. One of the main sources of perchlorate contamination from fertilizer use was found to come from the fertilizer derived from Chilean caliche (calcium carbonate), because Chile has rich source of naturally occurring perchlorate anion. Perchlorate in the solid fertilizer ranged from 0.7 to 2.0 mg g, variation of less than a factor of 3 and it is estimated that sodium nitrate fertilizers derived from Chilean caliche contain approximately 0.5–2 mg g of perchlorate anion. The direct ecological effect of perchlorate is not well known; its impact can be influenced by factors including rainfall and irrigation, dilution, natural attenuation, soil adsorption, and bioavailability. Quantification of perchlorate concentrations in fertilizer components via ion chromatography revealed that in horticultural fertilizer components contained perchlorate ranging between 0.1 and 0.46%. Perchlorate concentration was the highest in Chilean nitrate, ranging from 3.3 to 3.98%.

Cleanup

There have been many attempts to eliminate perchlorate contamination. Current remediation technologies for perchlorate have downsides of high costs and difficulty in operation. Thus, there have been interests in developing systems that would offer economic and green alternatives.

Treatment ex situ and in situ

Several technologies can remove perchlorate, via treatments ex situ and in situ.

Ex situ treatments include ion exchange using perchlorate-selective or nitrite-specific resins, bioremediation using packed-bed or fluidized-bed bioreactors, and membrane technologies via electrodialysis and reverse osmosis. In ex situ treatment via ion exchange, contaminants are attracted and adhere to the ion exchange resin because such resins and ions of contaminants have opposite charge. As the ion of the contaminant adheres to the resin, another charged ion is expelled into the water being treated, in which then ion is exchanged for the contaminant. Ion exchange technology has advantages of being well-suitable for perchlorate treatment and high volume throughput but has a downside that it does not treat chlorinated solvents. In addition, ex situ technology of liquid phase carbon adsorption is employed, where granular activated carbon (GAC) is used to eliminate low levels of perchlorate and pretreatment may be required in arranging GAC for perchlorate elimination.

In situ treatments, such as bioremediation via perchlorate-selective microbes and permeable reactive barrier, are also being used to treat perchlorate. In situ bioremediation has advantages of minimal above-ground infrastructure and its ability to treat chlorinated solvents, perchlorate, nitrate, and RDX simultaneously. However, it has a downside that it may negatively affect secondary water quality. In situ technology of phytoremediation could also be utilized, even though perchlorate phytoremediation mechanism is not fully founded yet.

Bioremediation using perchlorate-reducing bacteria, which reduce perchlorate ions to harmless chloride, has also been proposed.

Health effects

Thyroid inhibition

Perchlorate is a potent competitive inhibitor of the thyroid sodium-iodide symporter. Thus, it has been used to treat hyperthyroidism since the 1950s. At very high doses (70,000–300,000 ppb) the administration of potassium perchlorate was considered the standard of care in the United States, and remains the approved pharmacologic intervention for many countries.

In large amounts perchlorate interferes with iodine uptake into the thyroid gland. In adults, the thyroid gland helps regulate the metabolism by releasing hormones, while in children, the thyroid helps in proper development. The NAS, in its 2005 report, *Health Implications of Perchlorate Ingestion*, emphasized that this effect, also known as Iodide Uptake Inhibition (IUI) is not an adverse health effect. However, in January 2008, California's Department of Toxic Substances Control stated that perchlorate is becoming a serious threat to human health and water resources. In 2010, the EPA's Office of the Inspector General determined that the agency's own perchlorate reference dose of 24.5 parts per billion protects against all human biological effects from exposure. This finding was due to a significant shift in policy at the EPA in basing its risk assessment on non-adverse effects such as IUI instead of adverse effects. The Office of the Inspector General also found that because the EPA's perchlorate reference dose is conservative and protective of human health further reducing perchlorate exposure below the reference dose does not

effectively lower risk. Perchlorate affects only thyroid hormone. Because it is neither stored nor metabolized, effects of perchlorate on the thyroid gland are reversible, though effects on brain development from lack of thyroid hormone in fetuses, newborns, and children are not.

Toxic effects of perchlorate have been studied in a survey of industrial plant workers who had been exposed to perchlorate, compared to a control group of other industrial plant workers who had no known exposure to perchlorate. After undergoing multiple tests, workers exposed to perchlorate were found to have a significant systolic blood pressure rise compared to the workers who were not exposed to perchlorate, as well as a significant decreased thyroid function compared to the control workers.

A study involving healthy adult volunteers determined that at levels above 0.007 milligrams per kilogram per day (mg/(kg·d)), perchlorate can temporarily inhibit the thyroid gland's ability to absorb iodine from the bloodstream ("iodide uptake inhibition", thus perchlorate is a known goitrogen). The EPA converted this dose into a reference dose of 0.0007 mg/(kg·d) by dividing this level by the standard intraspecies uncertainty factor of 10. The agency then calculated a "drinking water equivalent level" of 24.5 ppb by assuming a person weighs 70 kg (150 lb) and consumes 2 L (0.44 imp gal; 0.53 US gal) of drinking water per day over a lifetime.

In 2006, a study reported a statistical association between environmental levels of perchlorate and changes in thyroid hormones of women with low iodine. The study authors were careful to point out that hormone levels in all the study

subjects remained within normal ranges. The authors also indicated that they did not originally normalize their findings for creatinine, which would have essentially accounted for fluctuations in the concentrations of one-time urine samples like those used in this study. When the Blount research was re-analyzed with the creatinine adjustment made, the study population limited to women of reproductive age, and results not shown in the original analysis, any remaining association between the results and perchlorate intake disappeared. Soon after the revised Blount Study was released, Robert Utiger, a doctor with the Harvard Institute of Medicine, testified before the US Congress and stated: "I continue to believe that that reference dose, 0.007 milligrams per kilo (24.5 ppb), which includes a factor of 10 to protect those who might be more vulnerable, is quite adequate."

At a 2013 presentation of a previously unpublished study, it was suggested that environmental exposure to perchlorate in pregnant women with hypothyroidism may be associated with significant risk of low IQ in their children.

Lung toxicity

Some studies suggest that perchlorate has pulmonary toxic effects as well. Studies have been performed on rabbits where perchlorate has been injected into the trachea. The lung tissue was removed and analyzed, and it was found that perchlorate injected lung tissue showed several adverse effects when compared to the control group that had been intratracheally injected with saline. Adverse effects included inflammatory infiltrates, alveolar collapse, subpleural thickening, and lymphocyte proliferation.

Aplastic anemia

In the early 1960s, potassium perchlorate used to treat Graves disease was implicated in the development of aplastic anemia—a condition where the bone marrow fails to produce new blood cells in sufficient quantity—in thirteen patients, seven of whom died. Subsequent investigations have indicated the connection between administration of potassium perchlorate and development of aplastic anemia to be "equivocable at best", which means that the benefit of treatment, if it is the only known treatment, outweighs the risk, and it appeared a contaminant poisoned the 13.

Regulation in the U.S.

Water

In 1998, perchlorate was included in the EPA Contaminant Candidate List, primarily due to its detection in California drinking water.

In 2003, a federal district court in California found that the Comprehensive Environmental Response, Compensation and Liability Act applied, because perchlorate is ignitable, and therefore was a "characteristic" hazardous waste.

In 2003, California's legislature enacted AB 826, the Perchlorate Contamination Prevention Act of 2003, requiring California's Department of Toxic Substances Control (DTSC) to adopt regulations specifying best management practices for perchlorate and perchlorate-containing substances. On

December 31, 2005, the "Perchlorate Best Management Practices" were adopted and became operative on July 1, 2006.

In early 2006, EPA issued a "Cleanup Guidance" and recommended a Drinking Water Equivalent Level (DWEL) for perchlorate of 24.5 μg/L. Both DWEL and Cleanup Guidance were based on a 2005 review of the existing research by the National Academy of Sciences (NAS).

Lacking a federal drinking water standard, several states subsequently published their own standards for perchlorate including Massachusetts in 2006and California in 2007. Other states, including Arizona, Maryland, Nevada, New Mexico, New York, and Texas have established non-enforceable, advisory levels for perchlorate.

In 2008 EPA issued an interim drinking water health advisory for perchlorate and with it a guidance and analysis concerning the impacts on the environment and drinking water. California also issued guidanceregarding perchlorate use. Both the Department of Defense and some environmental groups voiced questions about the NAS report, but no credible science has emerged to challenge the NAS findings.

In February 2008, the U.S. Food and Drug Administration (FDA) reported that U.S. toddlers on average are being exposed to more than half of EPA's safe dose from food alone. In March 2009, a Centers for Disease Control study found 15 brands of infant formula contaminated with perchlorate. Combined with existing perchlorate drinking water contamination, infants could be at risk for perchlorate exposure above the levels considered safe by EPA.

On February 11, 2011, EPA determined that perchlorate meets the Safe Drinking Water Act criteria for regulation as a contaminant. The agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public water systems with a frequency and at levels that it presents a public health concern. Since then EPA has continued to determine what level of contamination is appropriate. EPA prepared extensive responses to submitted public comments.

In 2016 the Natural Resources Defense Council (NRDC) filed a lawsuit to accelerate EPA's regulation of perchlorate. In 2019 EPA proposed a Maximum Contaminant Level of 0.056 mg/L for public water systems.

On June 18, 2020 EPA announced that it was withdrawing its 2019 proposal and its 2011 regulatory determination, stating that it had taken "proactive steps" with state and local governments to address perchlorate contamination. In September 2020 NRDC filed suit against EPA for its failure to regulate perchlorate, and stated that 26 million people may be affected by perchlorate in their drinking water.

Other

FDA approved perchlorate use in food packaging in 2005.

Tetrachloroaluminate

Tetrachloroaluminate [$AlCl_4$] is an anion formed from aluminium and chlorine. The anion has a tetrahedral shape, similar to carbon tetrachloride where carbon is replaced with

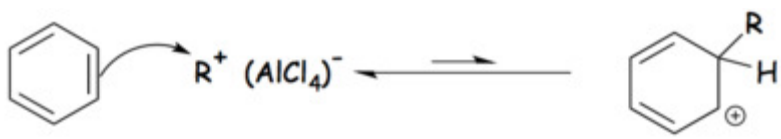
aluminium. Some tetrachloroaluminates are soluble in organic solvents, creating an ionic non-aqueous solution, making them suitable as component of electrolytes for batteries. For example, lithium tetrachloroaluminate is used in some lithium batteries.

Formation

Tetrachloroaluminate ions are formed as intermediates in the Friedel–Crafts reactions when aluminium chloride is used as the catalyst. In the case of the Friedel–Crafts alkylation, the reaction can be broken into three steps as follows:

Step 1: The alkyl halide reacts with the strong Lewis acid to form an activated electrophile composed of the tetrachloroaluminate ion and the alkyl group.

Step 2: The aromatic ring (benzene in this case) reacts with the activated electrophile forming an alkylbenzenium carbocation.



Step 3: The alkylbenzenium carbocation reacts with a tetrachloroaluminate anion, regenerating the aromatic ring and the Lewis acid and forming hydrochloric acid (HCl).

A similar mechanism occurs in the Friedel–Crafts acylation.

Tetrafluoroborate

Tetrafluoroborate is the anionBF_4. This tetrahedral species is isoelectronic with tetrafluoroberyllate (BeF_4), tetrafluoromethane (CF_4), and tetrafluoroammonium (NF_4) and is valence isoelectronic with many stable and important species including the perchlorate anion, ClO_4, which is used in similar ways in the laboratory. It arises by the reaction of fluoride salts with the Lewis acidBF_3, treatment of tetrafluoroboric acid with base, or by treatment of boric acid with hydrofluoric acid.

As an anion in inorganic and organic chemistry

The popularization of BF_4 has led to decreased use of ClO_4 in the laboratory as a weakly coordinating anion. With organic compounds, especially amine derivatives, ClO_4 forms potentially explosive derivatives. Disadvantages to BF_4 include its slight sensitivity to hydrolysis and decomposition via loss of a fluoride ligand, whereas ClO_4 does not suffer from these problems. Safety considerations, however, overshadow this inconvenience. With a formula weight of 86.8, BF_4 is also conveniently the smallest weakly coordinating anion from the

point of view of equivalent weight, often making it the anion of choice for preparing cationic reagents or catalysts for use in synthesis, in the absence of other substantial differences in chemical or physical factors.

The BF_4 anion is less nucleophilic and basic (and therefore more weakly coordinating) than nitrates, halides or even triflates. Thus, when using salts of BF_4, one can usually assume that the cation is the reactive agent and this tetrahedral anion is inert. BF_4 owes its inertness to two factors: (i) it is symmetrical so that the negative charge is distributed equally over four atoms, and (ii) it is composed of highly electronegative fluorine atoms, which diminish the basicity of the anion. In addition to the weakly coordinating nature of the anion, BF_4 salts are often more soluble in organic solvents (lipophilic) than the related nitrate or halide salts. Related to BF_4 are hexafluorophosphate, PF_6, and hexafluoroantimonate, SbF_6, both of which are even more stable toward hydrolysis and other chemical reactions and whose salts tend to be more lipophilic.

Illustrative of a fluoroborate salt is $[Ni(CH_3CH_2OH)_6](BF_4)_2$, a kinetically labile octahedral complex, which is used as a source of Ni.

Extremely reactive cations such as those derived from Ti, Zr, Hf, and Si do in fact abstract fluoride from BF_4, so in such cases BF_4 is not an "innocent" anion and less coordinating anions (e.g., SbF_6, BARF, or $[Al((CF_3)_3CO)_4]$) must be employed. Moreover, in other cases of ostensibly "cationic" complexes, the fluorine atom in fact acts as a bridging ligand between boron and the cationic center. For instance, the gold complex [μ-

(DTBM-SEGPHOS)(Au–BF_4)$_2$] was found crystallographically to contain two Au–F–B bridges.

Despite the low reactivity of the tetrafluoroborate anion in general, BF_4 serves as a fluorine source to deliver an equivalent of fluoride to highly electrophilic carbocationic species to generate carbon–fluorine bonds. The Balz–Schiemann reaction for the synthesis of aryl fluorides is the best known example of such a reaction. Ether and halopyridine adducts of HBF_4 have been reported to be effective reagents for the hydrofluorination of alkynes.

Transition and heavy metal fluoroborates are produced in the same manner as other fluoroborate salts; the respective metal salts are added to reacted boric and hydrofluoric acids. Tin, lead, copper, and nickel fluoroborates are prepared through electrolysis of these metals in a solution containing HBF_4.

Examples of salts

Potassium fluoroborate is obtained by treating potassium carbonate with boric acid and hydrofluoric acid.

- $B(OH)_3 + 4\ HF \rightarrow HBF_4 + 3\ H_2O$
- $2\ HBF_4 + K_2CO_3 \rightarrow 2\ KBF_4 + H_2CO_3$

Fluoroborates of alkali metals and ammonium ions crystallize as water-soluble hydrates with the exception of potassium, rubidium, and cesium.

Fluoroborate is often used to isolate highly electrophilic cations. Some examples include:

- Solvated proton (H (solv.), fluoroboric acid), including $H\cdot(H_2O)_n$ ("hydronium"), $H\cdot(Et_2O)_n$
- Diazonium compounds (ArN_2).
- Meerwein reagents such as OEt_3, the strongest commercial alkylating agents.
- NO a one-electron oxidizing agent and nitrosylation reagent.
- NO_2, a nitration reagent.
- Ferrocenium, $Fe(C_5H_5)_2$, and other cationic metallocenes.
- Selectfluor, a fluorination agent, and other N–F electrophilic fluorine sources.
- Bromonium and iodonium species, including py_2X (X = Br; X = I: Barluenga's reagent) and Ar_2I (diaryliodonium salts)
- Silver tetrafluoroborate and thallium tetrafluoroborate are convenient halide abstracting agents (although the thallium salt is highly toxic). Most other transition metal tetrafluoroborates only exist as solvates of water, alcohols, ethers, or nitriles.
- Transition metal nitrile complexes, e.g. $[Cu(NCMe)_4]BF_4$

An electrochemical cycle involving ferrous/ferric tetrafluoroborate is being used to replace thermal smelting of lead sulfide ores by the Doe Run Company.

Imidazolium and formamidinium salts, ionic liquids and precursors to stable carbenes, are often isolated as tetrafluoroborates.

Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate

Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate is an anion with chemical formula $[\{3,5\text{-}(CF_3)_2C_6H_3\}_4B]$, which is commonly abbreviated as $[BAr_4]$, indicating the presence of fluorinated aryl (Ar) groups. It is sometimes referred to as *Kobayashi's anion* in honour of Hiroshi Kobayashi who led the team that first synthesised it. More commonly it is affectionately nicknamed "BARF." The BARF ion is also abbreviated $BArF_{24}$, to distinguish it from the closely related $BArF_{20}$, $[(C_6F_5)_4B]$.

BARF has a tetrahedral geometry around the central boron atom but each of the four surrounding aryl groups is aromatic and planar. The motivation for its preparation was the search for an anion that coordinates more weakly than the then-available ions hexafluorophosphate, tetrafluoroborate, or perchlorate. Salts of this anion are known as solids and in both aqueous and non-aqueous solutions. BARF can be used in catalytic systems where the active site requires an anion which will not coordinate to the metal centre and interfere with the catalytic cycle, such as in the preparation of polyketones.

Synthesis of BARF compounds

The sodium salt is the starting point for most BARF derivatives. It is prepared by treating Grignard reagents derived from $XC_6H_3\text{-}3,5\text{-}(CF_3)_2$ (X = Br, I) with $NaBF_4$. A popular method is summarized in the following equation:

- $NaBF_4 + 4\ ArMgBr \rightarrow 4\ MgBrF + NaBAr_4$

Brookhart's acid is the salt of the BARF anion with the diethyl ether oxonium cation, $[(Et_2O)_2H]BAr_4$. It can be formed from the sodium salt in diethyl ether in the presence of hydrogen chloride as sodium chloride is insoluble in diethyl ether, facilitating cation exchange.

- $NaBAr_4 + HCl + 2\ Et_2O \rightarrow [(Et_2O)_2H]BAr_4 + NaCl$

BARF salts with hexakis(acetonitrile)metal(II) cations, $[M(CH_3CN)_6]$, are known for vanadium, chromium, manganese, iron, cobalt, and nickel. They are produced by salt metathesis reactions.

Properties

Non-coordinating anions are anions that interact only weakly with cations, a useful property when studying highly electrophilic cations. In coordination chemistry, the term can also be used to refer to anions which are unlikely to bind directly to the metal centre of a complex. Hexafluorophosphate is a non-coordinating anion in both senses of the term. Three widely used non-coordinating anions are hexafluorophosphate, tetrafluoroborateBF_4, and perchlorateClO_4; of these, the hexafluorophosphate ion has the least coordinating ability and it is deliberately used for this property. BARF was developed as a new non-coordinating anion in the 1990s, and is far less coordinating than even the hexafluorophosphate anion. Extremely Lewis acidic metal centers can, however, cleave the carbon-boron bond in BARF.

Chapter 4

Coordination Compounds

Protein–ligand complex

A **protein–ligand complex** is a complex of a protein bound with a ligand that is formed following molecular recognition between proteins that interact with each other or with various other molecules. Formation of a protein-ligand complex is based on molecular recognition between biological macromolecules and ligands, where ligand means any molecule that binds the protein with high affinity and specificity. Molecular recognition is not a process by itself since it is part of a functionally important mechanism involving the essential elements of life like in self-replication, metabolism, and information processing. For example DNA-replication depends on recognition and binding of DNA double helix by helicase, DNA single strand by DNA-polymerase and DNA segments by ligase. Molecular recognition depends on affinity and specificity. Specificity means that proteins distinguish the highly specific binding partner from less specific partners and affinity allows the specific partner with high affinity to remain bound even if there are high concentrations of less specific partners with lower affinity.

Interactions

- The protein-ligand complex is a reversible non-covalent interaction between two biological

(macro)molecules. In non-covalent interactions there is no sharing of electrons like in covalent interactions or bonds. Non-covalent binding may depend on hydrogen bonds, hydrophobic forces, van der Waals forces, π-π interactions, electrostatic interactions in which no electrons are shared between the two or more involved molecules. The molecules (protein and ligand) recognize each other also by stereospecificity i.e. by the form of the two molecules. Because of this real discriminative if not 'cognitive' property, Werner Loewenstein uses the term 'cognitive demon' or molecular demon referring to Maxwell's demon, the famous thought experiment. In fact, the proteins that form complexes are able to pick a substrate out of a myriad of different molecules. Jacques Monod attributed a teleonomic performance or function to these biological complexes. Teleonomy implies the idea of an oriented, coherent and constructive activity. Proteins therefore must be considered essential molecular agents in the teleonomic performances of all living beings.

Functions

Protein–ligand complexes can be found in almost any cellular process. Binding of a ligand causes a conformational change in the protein and often also in the ligand. This change initiates a sequence of events leading to different cellular functions. The complexes are formed by different molecules like macromolecules as in protein complexes, protein DNA or

protein RNA complexes as well as by proteins that bind smaller molecules like peptides, lipids, carbohydrates, small nucleic acids. They may have various functions within the cell: catalysis of chemical reactions (enzyme-substrate), defense of the organism through the immune system (antibodiesantigen complexes), signal transduction (receptor-ligand complexes) that consists of a transmembrane receptor that upon binding the ligand activates an intracellular cascade. Lipophilic hormonal receptor complexes can pass the nuclear membrane where transcription may be regulated.

Example

Protein-Ligand complex is essential in many of the cellular processes that occur within organisms. One of these examples is the Glucagon receptor (GCGR). Glucagon receptor (GCGR) is a family of G-protein coupled receptors (GPCRs) in humans that plays an important role in maintaining glucose concentration within the blood during periods of low energy state. Glucagon binding to GPCRcauses a conformational change in the intracellular domain, allowing interaction with the heterotrimeric Gs protein. The alpha Subunit of the Gs protein releases bound GDP and binds GTP. The alpha subunit-GTP complex dissociates from the beta and gamma dimer and interacts with adenylate cyclase. Binding of glucagon molecule activates many of the alpha subunit, which amplifies the hormonal signal. Then, the alpha subunit activates the adenylate cyclase, which converts ATP to cAMP. The alpha subunit deactivates itself within minutes by hydrolyzing GTP to GDP (GTPase activity). The alpha subunit reassociates with beta-gamma dimer to form an inactive

complex. A better understanding of the protein-ligand complex mechanisms may allow us for the treatment of some diseases such as type 2 diabetes. Glucagon receptor inhibitors are promising for the treatment of type 2 diabetes. Inhibitors of Glucagon receptors are either glucagon neutralizers or small molecular antagonists, and they all rely on the concept of protein-ligand complex interaction.

(Triphenylphosphine)iron tetracarbonyl

(Triphenylphosphine)iron tetracarbonyl is a coordination complex with the formula $Fe(CO)_4(PPh_3)$ (Ph = C_6H_5). A off-white solid, this complex is derived from iron pentacarbonyl by replacement of one carbonyl ligand by triphenylphosphine (PPh_3). The substitution is catalyzed by cobalt chloride. (Triphenylphosphine)iron tetracarbonyl is an intermediate in the synthesis of bis(triphenylphosphine)iron tricarbonyl. Both the mono- and bis(triphenylphosphine) complexes were originally described by Walter Reppe.

A-frame complex

A-frame complexes are coordination compounds that contain two bridging bidentate ligands and a single atom bridge. They have the formula $M_2(\mu\text{-}X)(bd)_2L_2$, where bd is a bidentate ligand like dppm, and X and L are a wide variety of ligands. The term was coined to describe products arising from the oxidative addition to Rh(I)Rh(I) complexes.

Scope of compounds

- A-frame complexes typically consist of a pair of square-planar metal centres. Consequently, this family of complexes is found for those metals that tend to adopt that geometry, Rh, Ir, Ni, Pd, Pt, and Au. In addition to dppm, the analogous tetramethyldiphosphine (dmpm) also forms such complexes as do some related ligands, such as diphenyl-2-pyridylphosphine. The bridging site can be occupied by a variety of ligands, including CO, SO, NO, CH_2, hydride, and chloride.

Preparation

A frame complexes are often produced by the addition of reagents of the type AX_2 to low valent complexes of dppm:

- $2\ M(0) + AX_2 + 2\ dppm \rightarrow M_2(\mu\text{-}A)(dppm)_2X_2$

Alternatively the group "A" can be added across a preformed M-M bond, as indicated by the oxidative addition of elemental sulfur:

- $Pd_2(dppm)_2Cl_2 + S \rightarrow Pd_2(\mu\text{-}S)(dppm)_2Cl_2$

Aluminoxane

Aluminoxanes are organoaluminium compounds with the formula $[RAlO]_m[R_2AlO_{0.5}]_n[R_2AlOH]_o$, where R = organic

substituent. The following structural rules apply: Al is tetrahedral and O is three-coordinate.

Methylaluminoxane is widely used in the polymerization of alkenes. These compounds are typically obtained by the partial hydrolysis of trialkylaluminium compounds. Aluminoxanes serve as activators for catalytic olefin polymerisation, such as the Ziegler–Natta catalyst. They also serve a function as scavenger for impurities (e.g. water) in reactions that are sensitive to these impurities. They usually are encountered as solutions. They are white solids.

Aurothioglucose

Aurothioglucose, also known as gold thioglucose, is a chemical compound with the formula $AuSC_6H_{11}O_5$. This derivative of the sugar glucose was formerly used to treat rheumatoid arthritis.

History

Throughout history, gold was used to cure diseases, although the efficacy was not established. In 1935, gold drugs were reported to be effective for the treatment of rheumatoid arthritis. Although many patients reacted positively to the drug, gold thioglucose was not uniformly effective.

Only one gold drug remains in active clinical use for this purpose in the United States: auranofin although sodium aurothiomalate (gold sodium thiomalate) and aurothioglucose

were still used until recently. In the United Kingdom, only sodium aurothiomalate and auranofin were used recently.

In 2001, aurothioglucose was withdrawn from the Dutch market, where it had been the only injectable gold preparation available since 1943, forcing hospitals to change medication for a large number of patients to aurothiomalate. The drug had been in use for more than 70 years, and four years later the reasons for its sudden disappearance remained unclear.

It was recently discontinued from the US market along with sodium aurothiomalate leaving only Auranofin as the only gold salt on the US market

Medicinal chemistry

- Main article: gold

Gold thioglucose features gold in the oxidation state of +I, like other gold thiolates. It is a water-soluble, non-ionic species that is assumed to exist as a polymer. Under physiological conditions, an oxidation-reduction reaction leads to the formation of metallic gold and sulfinic acid derivative of thioglucose.

- 2 AuSTg → 2 Au + TgSSTg
- TgSSTg + H_2O → TgSOH + TgSH
- 2 TgSOH → $TgSO_2H$ + TgSH
- Overall: 2 H_2O + 4 AuSTg → 4 Au + $TgSO_2H$ + 3 TgSH

(where AuSTg = gold thioglucose, TgSSTg = thioglucose disulfide, $TgSO_2H$ = sulfinic acid derivative of thioglucose)

Preparation

Gold thioglucose can be prepared by treating gold bromide with thioglucose solution saturated with sulfur dioxide. Gold thioglucose is precipitated with methanol and recrystallized with water and methanol.

Miscellaneous observations

In recent research, it was found that injection of gold thioglucose induces obesity in mice. Aurothioglucose has an interaction with the antimalarial medication hydroxychloroquine.

Benedict's reagent

Benedict's reagent (often called **Benedict's qualitative solution** or **Benedict's solution**) is a chemical reagent and complex mixture of sodium carbonate, sodium citrate, and copper(II) sulfate pentahydrate. It is often used in place of Fehling's solution to detect the presence of reducing sugars. The presence of other reducing substances also gives a positive result. Such tests that use this reagent are called the **Benedict's tests**. A positive test with Benedict's reagent is shown by a color change from clear blue to brick-red with a precipitate.

Generally, Benedict's test detects the presence of aldehydes, alpha-hydroxy-ketones, and hemiacetals, including those that occur in certain ketoses. Thus, although the ketose fructose is

not strictly a reducing sugar, it is an alpha-hydroxy-ketone and gives a positive test because the base in the reagent converts it into the aldosesglucose and mannose. Oxidation of the reducing sugar by the cupric (Cu) complex of the reagent produces a cuprous (Cu), which precipitates as insoluble red copper(I) oxide (Cu_2O).

It is named after American chemist Stanley Rossiter Benedict.

Composition and preparation

Benedict's reagent is a deep-blue aqueous solution. Each litre contains:

- 17.3g copper sulfate
- 173g sodium citrate
- 100g anhydrous sodium carbonate or, equivalently, 270g sodium carbonate decahydrate

Separate solutions of the reagents are made. The sodium carbonate and sodium citrate are mixed first, and then the copper sulfate is added slowly with constant stirring.

Sodium citrate acts as a complexing agent which keeps Cu in solution, since it would otherwise precipitate. Sodium carbonate serves to keep the solution alkaline. In the presence of mild reducing agents, the copper(II) ion is reduced to copper(I), which precipitates in the alkaline conditions as very conspicuous red copper(I) oxide.

Organic analysis

To test for the presence of monosaccharides and reducing disaccharide sugars in food, the food sample is dissolved in water and a small amount of Benedict's reagent is added. During a water bath, which is usually 4–10 minutes, the solution should progress through the colors of blue (with no reducing sugar present), orange, yellow, green, red, and then brick red precipitate or brown (if a high concentration of reducing sugar is present). A color change would signify the presence of a reducing sugar.

The common disaccharides lactose and maltose are directly detected by Benedict's reagent because each contains a glucose with a free reducing aldehyde moiety after isomerization.

Sucrose (table sugar) contains two sugars (fructose and glucose) joined by their glycosidic bond in such a way as to prevent the glucose undergoing isomerization to an aldehyde, or fructose to alpha-hydroxy-ketone form. Sucrose is thus a non-reducing sugar which does not react with Benedict's reagent. However, sucrose indirectly produces a positive result with Benedict's reagent if heated with dilute hydrochloric acid prior to the test, although it is modified during this treatment as the acidic conditions and heat break the glycosidic bond in sucrose through hydrolysis. The products of sucrose decomposition are glucose and fructose, both of which can be detected by Benedict's reagent as described above.

Starches do not react or react very poorly with Benedict's reagent due to the relatively small number of reducing sugar moieties which occur only at the ends of carbohydrate chains.

Other carbohydrates which produce a negative result include inositol.

Benedict's reagent can also be used to test for the presence of glucose in urine, elevated levels of which is known as glucosuria. Glucosuria can be indicative of diabetes mellitus, but Benedict's test is not recommended or used for diagnosis of the aforementioned condition. This is due to the possibility of a reaction in which the presence of other reducing substances such as ascorbic acid, drugs (levodopa, contrast used in radiological procedures) and homogentisic acid (alkaptonuria) creates a false positive.

As color of the obtained precipitate can be used to infer the quantity of sugar present in the solution, the test is semi-quantitative. A greenish precipitate indicates about 0.5 g% concentration; yellow precipitate indicates 1 g% concentration; orange indicates 1.5 g% concentration; and red indicates 2 g% or higher concentration.

Quantitative reagent

Benedict's quantitative reagent contains potassium thiocyanate and is used to quantitatively determine the concentration of reducing sugars. This solution forms a copper thiocyanate precipitate which is white and can be used in titration. The titration should be repeated with 1% glucose solution instead of the sample for calibration.

Net reaction

The net reaction between an aldehyde (or an alpha-hydroxy-ketone) and the copper(II) ions in Benedict's solution may be written as:

- $RCHO + 2\ Cu + 5\ OH^- \rightarrow RCOO^- + Cu_2O + 3\ H_2O$.

The hydroxide ions in the equation forms when sodium carbonate dissolves in water. With the citrate included, the reaction becomes:

- $RCHO + 2\ Cu(C_6H_5O_7)^- + 5\ OH^- \rightarrow RCOO^- + Cu_2O + 2\ C_6H_5O_{3-7} + 3\ H_2O$.

(Benzene)ruthenium dichloride dimer

(Benzene)ruthenium dichloride dimer is the organoruthenium compound with the formula $[(C_6H_6)RuCl_2]_2$. This red-coloured, diamagnetic solid is a reagent in organometallic chemistry and homogeneous catalysis.

Preparation, structure, and reactions

The dimer is prepared by the reaction of cyclohexadienes with hydrated ruthenium trichloride. As verified by X-ray crystallography, each Ru center is coordinated to three

chloride ligands and a η-benzene. The complex can be viewed as an edge-shared bioctahedral structure.

(Benzene)ruthenium dichloride dimer reacts with Lewis bases to give monometallic adducts:

- $[(C_6H_6)RuCl_2]_2 + 2\ PPh_3 \rightarrow 2\ (C_6H_6)RuCl_2(PPh_3)$

Related compounds

(cymene)ruthenium dichloride dimer, a more soluble analogue of (benzene)ruthenium dichloride dimer.

- (mesitylene)ruthenium dichloriide dimer, another more soluble derivative.

(Benzylideneacetone)iron tricarbonyl

(Benzylideneacetone)iron tricarbonyl is the organoiron compound with the formula $(C_6H_5CH{=}CHC(O)CH_3)Fe(CO)_3$. It is a reagent for transferring the $Fe(CO)_3$ unit. This red-colored compound is commonly abbreviated $(bda)Fe(CO)_3$.

Structure and bonding

$(bda)Fe(CO)_3$ is an example of a comnplex of an η-ketone. It is a piano stool complex. The compound is characterized by IR bands at 2065, 2005, and 1985 cm (cyclohexane solution), the

three bands being indicative of the low symmetry of the complex, which is chiral.

Synthesis, reactions, related reagents

It is prepared by the reaction of $Fe_2(CO)_9$ with benzylideneacetone.

(bda)$Fe(CO)_3$ reacts with Lewis bases to give adducts without displacement of the bda.

Another popular source of $Fe(CO)_3$ is $Fe_2(CO)_9$. Alternatively, $Fe(CO)_3$(cyclooctene)$_2$ is highly reactive, the trade-off being that it is thermally sensitive. Imine derivatives of cinnamaldehyde, e.g. $C_6H_5CH{=}CHC(H){=}NC_6H_5$, also form conveniently reactive $Fe(CO)_3$adducts, which have been shown to be superior in some ways to (bda)$Fe(CO)_3$.

Bis(acetonitrile)palladium dichloride

Bis(acetonitrile)palladium dichloride is the coordination complex with the formula $PdCl_2(NCCH_3)_2$. It is the adduct of two acetonitrile ligands with palladium(II) chloride. It is a yellow-brown solid that is soluble in organic solvents. The compound is a reagent and a catalyst for reactions that require soluble Pd(II). The compound is similar to bis(benzonitrile)palladium dichloride. It reacts with 1,5-cod to give dichloro(1,5-cyclooctadiene)palladium.

Bis(benzonitrile)palladium dichloride

Bis(benzonitrile)palladium dichloride is the coordination complex with the formula $PdCl_2(NCC_6H_5)_2$. It is the adduct of two benzonitrile (PhCN) ligands with palladium(II) chloride. It is a yellow-brown solid that is soluble in organic solvents. The compound is a reagent and a precatalyst for reactions that require soluble Pd(II). A closely related compound is bis(acetonitrile)palladium dichloride.

The complex is prepared by dissolving $PdCl_2$ in warm benzonitrile. The PhCN ligands are labile, and the complex reverts to $PdCl_2$ in noncoordinating solvents. According to X-ray crystallography, the two PhCN ligands are mutually trans.

Bis(dinitrogen)bis(1,2-bis(diphenylphosphino)ethane)molybdenum(0)

***trans*-Bis(dinitrogen)bis[1,2-bis(diphenylphosphino)ethane]molybdenum(0)** is a coordination complex with the formula $Mo(N_2)_2(dppe)_2$. It is a relatively air stable yellow-orange solid. It is notable as being the first discovered dinitrogen containing complex of molybdenum.

Structure

$Mo(N_2)_2(dppe)_2$ is an octahedral complex with idealized D_{2h} point group symmetry. The dinitrogen ligands are mutually trans across the metal center. The Mo-N bond has a length of 2.01 Å, and the N-N bond has a length of 1.10 Å. This length is close to the free nitrogen bond length, but coordination to the metal weakens the N-N bond making it susceptible to electrophilic attack.

Synthesis

The first synthetic route to $Mo(N_2)_2(DPPE)_2$ involved a reduction of molybdenum(III) acetylacetonate with triethylaluminum in the presence of dppe and nitrogen.

A higher yielding synthesis involves a four-step process. In the first step, molybdenum(V) chloride is reduced by acetonitrile (CH_3CN) to give $[MoCl_4(CH_3CN)_2]$. Acetonitrile is displaced by tetrahydrofuran (THF) to give $[MoCl_4(thf)_2]$. This Mo(IV) compound is reduced by tin powder to $[MoCl_3(thf)_3]$. The desired compound is formed in the presence of nitrogen gas, dppe ligand, and magnesium turnings as the reductant:

- $3\ Mg + 2\ MoCl_3(thf)_3 + 4\ Ph_2PCH_2CH_2PPh_2 + 4\ N_2 \rightarrow 2$ *trans*-$[Mo(N_2)_2(Ph_2PCH_2CH_2PPh_2)_2] + 3\ MgCl_2 + 6\ THF$

Reactivity

The terminal nitrogen is susceptible to electrophilic attack, allowing for the fixation of nitrogen to ammonia in the presence of acid. In this way, $Mo(N_2)_2(dppe)_2$ serves as a model for biological nitrogen fixation. Carbon-nitrogen bonds can also be formed with this complex through condensation reactions with ketones and aldehydes, and substitution reactions with acid chlorides. The terminal nitrogen can also be silylated.

Bis(triphenylphosphine)iron tricarbonyl

Tricarbonylbis(triphenylphosphine)iron(0) is a coordination complex with the formula $Fe(CO)_3(PPh_3)_2$ (Ph = C_6H_5). A yellow solid, this complex is derived from iron pentacarbonyl by replacement of two carbonyl ligands by triphenylphosphine (PPh_3). It can also be produced by borohydride-catalyzed substitution of iron pentacarbonyl. Protonation gives the ferrous hydride. This complex has a trigonal bipyramidal geometry with trans phosphines. (Triphenylphosphine)iron tetracarbonyl is an intermediate in the synthesis of this compound. Both the mono- and bis(triphenylphosphine) complexes were originally described by Walter Reppe.

Carbonation

Carbonation is the chemical reaction of carbon dioxide to give carbonates, bicarbonates, and carbonic acid. In chemistry, the

term is sometimes used in place of carboxylation, which refers to the formation of carboxylic acids.

In inorganic chemistry and geology, carbonation is common. Metal hydroxides (MOH) and metal oxides (M'O) react with CO_2 to give bicarbonates and carbonates:

- $MOH + CO_2 \rightarrow M(HCO_3)$
- $M'O + CO_2 \rightarrow M'CO_3$

In reinforced concrete construction, the chemical reaction between carbon dioxide in the air and calcium hydroxide and hydrated calcium silicate in the concrete is known as **neutralisation**.

Henry's law

Henry's law states that $P_{CO2}=K_B x_{CO2}$ where P_{CO2} is the partial pressure of CO2 gas above the solution. K_B is Henry's law constant. K_B increases as temperature increases. x_{CO2} is the mole fraction of CO2 gas in the solution. According to Henry's law carbonation increases in a solution as temperature decreases.

Since carbonation is the process of giving compounds like carbonic acid (liq) from CO_2 (gas) {i.e. making liquid from gasses} thus the partial pressure of CO_2 has to decrease or mole fraction of CO_2 in solution have to increase {$P_{CO2}/x_{CO2} = K_B$} and both these two conditions supports increase in carbonation.

Carboplatin

Carboplatin, sold under the trade name **Paraplatin** among others, is a chemotherapy medication used to treat a number of forms of cancer. This includes ovarian cancer, lung cancer, head and neck cancer, brain cancer, and neuroblastoma. It is used by injection into a vein.

Side effects generally occur. Common side effects include low blood cell levels, nausea, and electrolyte problems. Other serious side effects include allergic reactions and increased future risk of another cancer. Use during pregnancy may result in harm to the baby. Carboplatin is in the platinum-based antineoplastic family of medications and works by interfering with duplication of DNA.

Carboplatin was patented in 1972 and approved for medical use in 1989. It is on the World Health Organization's List of Essential Medicines.

Medical uses

Carboplatin is used to treat a number of forms of cancer. This includes ovarian cancer, lung cancer, head and neck cancer, brain cancer, and neuroblastoma. It may be used for some types of testicular cancer but cisplatin is generally more effective. It has also been used to treat triple-negative breast cancer.

Side effects

Relative to cisplatin, the greatest benefit of carboplatin is its reduced side effects, particularly the elimination of nephrotoxic effects. Nausea and vomiting are less severe and more easily controlled.

The main drawback of carboplatin is its myelosuppressive effect. This causes the blood cell and platelet output of bone marrow in the body to decrease quite dramatically, sometimes as low as 10% of its usual production levels. The nadir of this myelosuppression usually occurs 21–28 days after the first treatment, after which the blood cell and platelet levels in the blood begin to stabilize, often coming close to its pre-carboplatin levels. This decrease in white blood cells (neutropenia) can cause complications, and is sometimes treated with drugs like filgrastim. The most notable complication of neutropenia is increased probability of infection by opportunistic organisms, which necessitates hospital readmission and treatment with antibiotics.

Chemistry

In terms of its structure, carboplatin differs from cisplatin in that it has a bidentate dicarboxylate (the ligand is CycloButane DiCarboxylic Acid, CBDCA) in place of the two chlorideligands, which are the leaving groups in cisplatin. For this reason, "CBDCA" is sometimes used in the medical literature as an abbreviation referring to carboplatin. Carboplatin exhibits lower reactivity and slower DNA binding kinetics, although it forms the same reaction products *in vitro* at equivalent doses

with cisplatin. Unlike cisplatin, carboplatin may be susceptible to alternative mechanisms. Some results show that cisplatin and carboplatin cause different morphological changes in MCF-7 cell lines while exerting their cytotoxic behaviour. The diminished reactivity limits protein-carboplatin complexes, which are excreted. The lower excretion rate of carboplatin means that more is retained in the body, and hence its effects are longer lasting (a retention half-life of 30 hours for carboplatin, compared to 1.5-3.6 hours in the case of cisplatin).

Mechanism of action

Two theories exist to explain the molecular mechanism of action of carboplatin with DNA:

- Aquation, or the like-cisplatin hypothesis.
- Activation, or the unlike-cisplatin hypothesis.

The former is more accepted owing to the similarity of the leaving groups with its predecessor cisplatin, while the latter hypothesis envisages a biological activation mechanism to release the active Pt species.

History

Carboplatin was discovered at Michigan State University, and developed at the Institute of Cancer Research in London. Bristol-Myers Squibb gained Food and Drug Administration (FDA) approval for carboplatin, under the brand name

Paraplatin, in March 1989. Starting in October 2004, generic versions of the drug became available.

Research

Carboplatin has also been used for adjuvant therapy of stage 1 seminomatous testicular cancer. Research has indicated that it is not less effective than adjuvant radiotherapy for this treatment, while having fewer side effects. This has led to carboplatin based adjuvant therapy being generally preferred over adjuvant radiotherapy in clinical practice.

Carboplatin combined with hexadecyl chain and polyethylene glycol appears to have increased liposolubility and PEGylation. This is useful in chemotherapy, specifically non-small cell lung cancer.

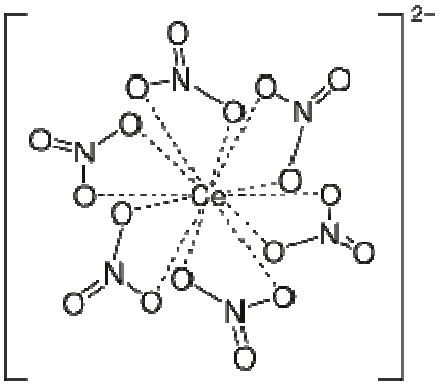
Ceric ammonium nitrate

Ceric ammonium nitrate (CAN) is the inorganic compound with the formula $(NH_4)_2Ce(NO_3)_6$. This orange-red, water-soluble ceriumsalt is a specialised oxidizing agent in organic synthesis and a standard oxidant in quantitative analysis.

Preparation, properties, and structure

The anion$[Ce(NO_3)_6]$is generated by dissolving Ce_2O_3 in hot concentrated HNO_3.

The salt consists of the anion $[Ce(NO_3)_6]$and a pair of NH_4 counter ions. The ammonium ions are not involved in the oxidising reactions of this salt. In the anion each nitrate group chelates the cerium atom in a bidentate manner as shown below:



- Hexanitratocerate anion

The anion $[Ce(NO_3)_6]$has T_h (idealized O_h) molecular symmetry. The CeO_{12} core defines an icosahedron.

Ce is a strong one-electron oxidizing agent. In terms of its redox potential (E° ~ 1.61 V vs. N.H.E.) it is even stronger oxidizing agent than Cl_2 (E° ~ 1.36 V). Few shelf-stable reagents are stronger oxidants. In the redox process Ce(IV) is converted to Ce(III), a one-electron change, signaled by the fading of the solution color from orange to a pale yellow (providing that the substrate and product are not strongly colored).

Applications in organic chemistry

In organic synthesis, CAN is useful as an oxidant for many functional groups (alcohols, phenols, and ethers) as well as C–

H bonds, especially those that are benzylic. Alkenes undergo dinitroxylation, although the outcome is solvent-dependent. Quinones are produced from catechols and hydroquinones and even nitroalkanes are oxidized.

CAN provides an alternative to the Nef reaction; for example, for ketomacrolide synthesis where complicating side reactions usually encountered using other reagents. Oxidative halogenation can be promoted by CAN as an *in situ* oxidant for benzylic bromination, and the iodination of ketones and uracil derivatives.

For the synthesis of heterocycles

Catalytic amounts of aqueous CAN allow the efficient synthesis of quinoxaline derivatives. Quinoxalines are known for their applications as dyes, organic semiconductors, and DNA cleaving agents. These derivatives are also components in antibiotics such as echinomycin and actinomycin. The CAN-catalyzed three-component reaction between anilines and alkyl vinyl ethers provides an efficient entry into 2-methyl-1,2,3,4-tetrahydroquinolines and the corresponding quinolines obtained by their aromatization.

As a deprotection reagent

CAN is traditionally used to release organic ligands from metal carbonyls. In the process, the metal is oxidised, CO is evolved, and the organic ligand is released for further manipulation. For example, with the Wulff–Dötz reaction an alkyne, carbon monoxide, and a chromium carbene are combined to form a

chromium half-sandwich complex and the phenol ligand can be isolated by mild CAN oxidation.

CAN is used to cleave *para*-methoxybenzyl and 3,4-dimethoxybenzyl ethers, which are protecting groups for alcohols. Two equivalents of CAN are required for each equivalent of *para*-methoxybenzyl ether. The alcohol is released, and the *para*-methoxybenzyl ether converts to *para*-methoxybenzaldehyde. The balanced equation is as follows:

- $2\ (NH_4)_2Ce(NO_3)_6 + H_3COC_6H_4CH_2OR + H_2O \rightarrow 4\ NH_4 + 2\ Ce + 12\ NO_3 + 2\ H + H_3COC_6H_4CHO + HOR$

Other applications

CAN is also a component of chromeetchant, a material that is used in the production of photomasks and liquid crystal displays.

Chloro(pyridine)cobaloxime

Chloro(pyridine)cobaloxime is a coordination compound containing a Co center with octahedral coordination. It has been considered as a model compound of vitamin B_{12} for studying the properties and mechanism of action of the vitamin. It belongs to a class of

bis(dimethylglyoximato)cobalt(III) complexes with different axial ligands, called cobaloximes. Chloro(pyridine)cobaloxime is a yellow-brown powder that is sparingly soluble in most solvents, including water.

Structure

The complex adopts a distorted octahedral geometry. Cobalt(III) is bound to two dimethylglyoximate ligands, i.e., mono-deprotonated dimethylglyoxime, in the equatorial plane. Completing the coordination sphere are chloride and a pyridine at the axial positions.

Reactions

The cobaloxime is slowly decomposed by acids and bases. With acids, the products of decomposition are dimethylglyoxime, cobalt salts, and pyridine; with bases, derivatives of other cobaloximes are formed, usually with the release of chloride ions.

The complex has no reaction with hydrogen gas, and cannot carry oxygen as salcomine does. It would, however, react with hydrogen in the presence of sodium hydroxide, a catalytic amount of platinum metal, or a reduced cobaloxime, therefore once the reduction occurs, the hydrogenation would occur much more rapidly as there is autocatalysis.

The reduction products of cobaloxime depends on the conditions. At pH near 7, a cobaloxime with a Co center is

formed. With a higher pH, the cobalt center would be further reduced to the Co state, which is supernucleophilic.

Preparation

The compound is usually prepared by mixing cobalt(II) chloride, dimethylglyoxime and pyridine in an ethanolic solution. This process afford the cobaloxime(II), which is subsequently oxidized by the oxygen in air:

- $4\ CoCl_2{\bullet}6H_2O + 8\ dmgH_2 + 8\ py + O_2 \rightarrow 4\ ClCo(dmgH)_2py + 4\ py{\bullet}HCl + 14\ H_2O$

Using cobalt(II) acetate in place of cobalt(II) chloride produce aceto(pyridine)cobaloxime. This acetate can be converted to the respective bromide, iodide, cyanate, cyanide, azide and thiocyanate.

- $(CH_3COO)Co(DH)_2py + NaX \rightarrow XCo(DH)_2py + NaCH_3COO$ (X = Br, I, CNO, CN, N_3 or SCN)

Reactions

The pyridine base in the axial position can also be replaced by other organic bases containing a *sp* hybridized N atom as well. Commonly used bases are morpholine, 4-methylpyridine, imidazole and benzimidazole. The derivatives are again prepared via diacetocobaloxime, followed by the addition of the desired base, such as imidazole.

- $(CH_3COO)_2Co(DH)_2 + imi \rightarrow (CH_3COO)Co(DH)_2imi$

Alkylation of Co

One of the methods used for producing the Co-C bond is to make use of the supernucleophilicity of the Co center. Chloro(pyridine)cobaloxime(III) is first reduced to Chloro(pyridine)cobaloxime(I) by sodium borohydride in alkaline solution, then an alkyl halide is added into the reaction mixture, and the desired Co-C bond is formed via a S_N2 reaction. This method can be used to produce cobaloximes containing a primary or a secondary alkyl substituent.

For derivatives with phenyl or vinyl substituent, the Grignard reaction is employed. However, since the dimethylglyoxime ligands contains two acidic H atoms in the oxime group, the Grignard reagent must be used in three-fold excess to compensate the loss.

Chloroauric acid

Chloroauric acid refers to inorganic compounds with the chemical formula$HAuCl_4 \cdot (H_2O)_x$. Both the trihydrate and tetrahydrate are known.

Both are orange-yellow solids consisting of the planar $[AuCl_4]$ anion. Often chloroauric acid is handled as a solution, such as those obtained by dissolution of gold in aqua regia. These solutions can be converted to other gold complexes or reduced to metallic gold or gold nanoparticles.

Properties

Structure

The tetrahydrate crystallizes as $H_5O_2 \cdot AuCl_4$ and two water molecules. The $AuCl_4$ anion has square planar molecular geometry. The Au–Cl distances are around 2.28 Å. Other d complexes adopt similar structures, e.g. $[PtCl_4]$.

Solute properties

Solid chloroauric acid is a hydrophilic (ionic) protic solute. It is soluble in water and other oxygen-containing solvents, such as alcohols, esters, ethers, and ketones. For example, in dry dibutyl ether or diethylene glycol, the solubility exceeds 1 mol/L. Saturated solutions in the organic solvents often are the liquid solvates of specific stoichiometry. Chloroauric acid is a strong monoprotic acid.

When heated in air, solid $HAuCl_4 \cdot nH_2O$ melts in the water of crystallization, quickly darkens and becomes dark brown.

Chemical reactions

Upon treatment with an alkali metal base, chloroauric acid converts to an alkali metal salt of tetrachloridoaurate. The related thallium salt is poorly soluble in all nonreacting solvents. Salts of quaternary ammonium cations are known. Other complex salts include $[Au(bipy)Cl_2][AuCl_4]$ and $[Co(NH_3)_6][AuCl_4]Cl_2$.

Partial reduction of chloroauric acid gives oxonium dichloridoaurate(1–). Reduction may also yield other gold(I) complexes, especially with organic ligands. Often the ligand serves as reducing agent as illustrated with thiourea, $(H_2N)_2CS$:

- $AuCl_4 + 4\ (H_2N)_2CS + H_2O \rightarrow Au[(H_2N)_2CS]_2 + (H_2N)_2CO + S + 2\ Cl + 2\ HCl$

Chloroauric acid is the precursor to gold nanoparticles by precipitation onto mineral supports. Heating of $HAuCl_4 \cdot nH_2O$ in a stream of chlorine gives gold(III) chloride (Au_2Cl_6). Gold nanostructures can be made from chloroauric acid in a two-phase redox reaction whereby metallic clusters are amassed through the simultaneous attachment of self-assembled thiol monolayers on the growing nuclei. $AuCl_4$ is transferred from aqueous solution to toluene using tetraoctylammonium bromide where it is then reduced with aqueous sodium borohydride in the presence of a thiol.

Production

Chloroauric acid is produced by dissolving gold in aqua regia (a mixture of concentrated nitric and hydrochloric acids) followed by careful evaporation of the solution:

- $Au + HNO_3 + 4\ HCl \rightarrow HAuCl_4 + NO + 2\ H_2O$

Under some conditions, oxygen can be used as the oxidant. For higher efficiency, these processes are conducted in autoclaves, which allows greater control of temperature and pressure. Alternatively, a solution of $HAuCl_4$ can be produced by electrolysis of gold metal in hydrochloric acid:

- $2\ Au + 8\ HCl \rightarrow 2\ HAuCl_4 + 3H_2$

To prevent the deposition of gold on the cathode, the electrolysis is carried out in a cell equipped with a membrane. This method is used for refining gold. Some gold remains in solution in the form of $[AuCl_2]$.

A solution of $HAuCl_4$ can also be obtained by the action of chlorine or chlorine water on metallic gold in hydrochloric acid:

- $2\ Au + 3\ Cl_2 + 2\ HCl \rightarrow 2\ HAuCl_4$

This reaction is widely used for extracting gold from electronic and other "rich" materials.

In addition to the above routes, many other ways exist to dissolve gold, differing in the choice of the oxidant (hydrogen peroxide, hypochlorites) or variations of conditions. It is possible also to convert the trichloride (Au_2Cl_6) or the oxide ($Au_2O_3 \cdot nH_2O$).

Uses

Chloroauric acid is the precursor used in the purification of gold by electrolysis.

Liquid–liquid extraction of chloroauric acid is used for the recovery, concentrating, purification, and analytical determinations of gold. Of great importance is the extraction of $HAuCl_4$ from hydrochloric medium by oxygen-containing extractants, such as alcohols, ketones, ethers and esters. The

concentration of gold(III) in the extracts may exceed 1 mol/L. Frequently used extractants for this purpose are dibutyl glycol, methyl isobutyl ketone, tributyl phosphate, dichlorodiethyl ether (chlorex).

In histology, chlorauric acid is known as "brown gold chloride", and its sodium salt $NaAuCl_4$ as "gold chloride", "sodium gold chloride" or "yellow gold chloride". The sodium salt is used in a process called "toning" to improve the optical definition of tissue sections stained with silver.

Health effects and safety

Chloroauric acid is a strong eye, skin, and mucous membrane irritant. Prolonged skin contact with chloroauric acid may result in tissue destruction. Concentrated chloroauric acid is corrosive to skin and must, therefore, be handled with appropriate care, since it can cause skin burns, permanent eye damage, and irritation to mucous membranes. Gloves are worn when handling the compound.

Chloroplatinic acid

Chloroplatinic acid (also known as **hexachloroplatinic acid**) is an inorganic compound with the formula $[H_3O]_2[PtCl_6](H_2O)_x$ ($0 \leq x \leq 6$). A red solid, it is an important commercial source of platinum, usually as an aqueous solution. Although often written in shorthand as H_2PtCl_6, it is the hydronium (H_3O) salt of the hexachloroplatinate anion ($PtCl_6$). Hexachloroplatinic acid is highly hygroscopic.

Production

Hexachloroplatinic acid may be produced via a variety of methods. The most common of these methods involves dissolution of platinum in aqua regia. Other methods include exposing an aqueous suspension of platinum particles to chlorine gas, or via electrolysis.

When produced by the aqua regia route, hexachloroplatinic acid is thought to arise by the following equation:

- $Pt + 4\ HNO_3 + 6\ HCl \rightarrow H_2PtCl_6 + 4\ NO_2 + 4\ H_2O$

The resulting orange/red solution can be evaporated to produce brownish red crystals. Some authors suggest that hexachloroplatinic acid produced using this method is contaminated with nitrosonium hexachloroplatinate. Newer literature indicates that this is not the case, and that once the nitric acid has been driven off, samples prepared via this method contain no detectable nitrogen.

Alternative methods have been investigated and described, often motivated by the avoidance of nitrogen contamination.

Reactions

When heated, hexachloroplatinic acid decomposes to platinum(IV) chloride.

- $(H_3O)_2PtCl_6 \cdot nH_2O \rightarrow PtCl_4 + 2\ HCl + (n + 2)\ H_2O$

Applications

Potassium determination

Chloroplatinic acid was popularized for the quantitative analysis of potassium. The potassium is selectively precipitated from solution as potassium hexachloroplatinate. Determinations were done in 85% (v/v) alcohol solutions with excess platinate ions, and the precipitated product was weighed. Potassium could be detected for solutions as dilute as 0.02 to 0.2% (m/v).

This method for determination of potassium was advantageous compared to the sodium cobaltinitrite method used previously, since it required a single precipitation reaction. Gravimetric analysis of precipitated products has been supplanted by modern instrumental analysis methods such as ion selective electrodes, flame photometry, ICP-AES or ICP-MS.

Purification of platinum

Upon treatment with an ammonium salt, such as ammonium chloride, chloroplatinic acid converts to ammonium hexachloroplatinate, which precipitates as a solid. Upon heating in an atmosphere of hydrogen, the ammonium salt converts to elemental platinum. Platinum is often isolated from ores or recycled from residues thus.

Catalysis

Like many platinum compounds, chloroplatinic acid is a catalyst (or precatalyst) for hydrogenation and related

reactions. As first reported by John Speier and colleagues from Dow Corning, it catalyzes the addition of hydrosilanes to olefins, i.e. hydrosilylation. Early demonstration reactions used isopropanol solutions of trichlorosilane ($SiHCl_3$) with pentenes. Prior work on the addition of silanes to alkenes required radical reactions that were inefficient. As well as with Karstedt's catalyst, Speier's catalyst enjoys widespread use for hydrosilylation, the main drawback is the deliquescent properties of the catalyst.

It is generally agreed that chloroplatinic acid is a precursor to the actual catalyst. A possible role for colloidal platinum or zero-valent complexes has also been considered.

Related compounds

Chloroplatinic acid prepared from aqua regia is proposed to contain nitrosonium hexachloroplatinate, $(NO)_2PtCl_6$. Nitrosonium hexachloroplatinate is obtained by the reaction of nitrosyl chloride (NOCl) and platinum metal. Nitrosonium hexachloroplatinate has been found to react vigorously with water and hydrochloric acid, making contamination of chloroplatinic acid prepared with aqua regia with nitrosonium hexachloroplatinate unlikely.

Chrome alum

Chrome alum or **Chromium(III) potassium sulfate** is the potassium double sulfate of chromium. Its chemical formula is $KCr(SO_4)_2$ and it is commonly found in its dodecahydrate form as $KCr(SO_4)_2 \cdot 12(H_2O)$. It is used in leather tanning.

Production and properties

Chromium alum is produced from chromate salts or from ferrochromium alloys. Concentrated aqueous solutions of potassium dichromate can be reduced, usually with sulfur dioxide but also with alcohols or formaldehyde, in the presence of sulfuric acid at temperatures <40 °C.

Alternatively and less commonly, ferrochromium alloys can be dissolved in sulfuric acid and, after precipitation of the ferrous sulfate, the chrome alum crystallizes upon addition of potassium sulfate. Chromium alum crystallizes in regular octahedra with flattened corners and is very soluble in water.

The solution reddens litmus and is an astringent. Aqueous solutions are dark violet and turns green when it is heated above 50 °C. In addition to the dodecahydrate, the hexahydrate $KCr(SO_4)_2 \cdot 6H_2O$, dihydrate $KCr(SO_4)_2 \cdot 2H_2O$, and the monohydrate $KCr(SO_4)_2 \cdot H_2O$ are known.

Uses

Chromium alum is used in the tanning of leather as chromium(III) stabilizes the leather by cross linking the collagen fibers within the leather. However, this application is obsolete because the simpler chromium(III) sulfate is preferred.

It was also used in gelatine emulsions in photographic film as hardener.

Chromium(II) acetate

Chromium(II) acetate hydrate, also known as **chromous acetate**, is the coordination compound with the formula $Cr_2(CH_3CO_2)_4(H_2O)_2$. This formula is commonly abbreviated $Cr_2(OAc)_4(H_2O)_2$. This red-coloured compound features a quadruple bond. The preparation of chromous acetate once was a standard test of the synthetic skills of students due to its sensitivity to air and the dramatic colour changes that accompany its oxidation. It exists as the dihydrate and the anhydrous forms.

$Cr_2(OAc)_4(H_2O)_2$ is a reddish diamagnetic powder, although diamond-shaped tabular crystals can be grown. Consistent with the fact that it is nonionic, $Cr_2(OAc)_4(H_2O)_2$ exhibits poor solubility in water and methanol.

Structure

The $Cr_2(OAc)_4(H_2O)_2$ molecule contains two atoms of chromium, two ligated molecules of water, and four acetatebridging ligands. The coordination environment around each chromium atom consists of four oxygen atoms (one from each acetate ligand) in a square, one water molecule (in an axial position), and the other chromium atom (opposite the water molecule), giving each chromium centre an octahedral geometry. The chromium atoms are joined together by a quadruple bond, and the molecule has D_{4h} symmetry (ignoring the position of the hydrogen atoms). The same basic structure is adopted by $Rh_2(OAc)_4(H_2O)_2$ and $Cu_2(OAc)_4(H_2O)_2$, although these species do not have such short M–M contacts.

The quadruple bond between the two chromium atoms arises from the overlap of four d-orbitals on each metal with the same orbitals on the other metal: the d_z orbitals overlap to give a sigma bonding component, the d_{xz} and d_{yz} orbitals overlap to give two pi bonding components, and the d_{xy} orbitals give a delta bond. This quadruple bond is also confirmed by the low magnetic moment and short intermolecular distance between the two atoms of 236.2 ± 0.1 pm. The Cr–Cr distances are even shorter, 184 pm being the record, when the axial ligand is absent or the carboxylate is replaced with isoelectronic nitrogenous ligands.

History

Eugène-Melchior Péligot first reported a chromium(II) acetate in 1844. His material was apparently the dimeric $Cr_2(OAc)_4(H_2O)_2$. The unusual structure, as well as that of copper(II) acetate, was uncovered in 1951.

Preparation

The preparation usually begins with reduction of an aqueous solution of a Cr(III) compound using zinc. The resulting blue solution is treated with sodium acetate, which results in the rapid precipitation of chromous acetate as a bright red powder.

- $2\ Cr + Zn \rightarrow 2\ Cr + Zn$
- $2\ Cr + 4\ OAc + 2\ H_2O \rightarrow Cr_2(OAc)_4(H_2O)_2$

The synthesis of $Cr_2(OAc)_4(H_2O)_2$ has been traditionally used to test the synthetic skills and patience of inorganic laboratory

students in universities because the accidental introduction of a small amount of air into the apparatus is readily indicated by the discoloration of the otherwise bright red product. The anhydrous form of chromium(II) acetate, and also related chromium(II) carboxylates, can be prepared from chromocene:

- $4\ RCO_2H + 2\ Cr(C_5H_5)_2 \rightarrow Cr_2(O_2CR)_4 + 4\ C_5H_6$

This method provides anhydrous derivatives in a straightforward manner.

Because it is so easily prepared, $Cr_2(OAc)_4(H_2O)_2$ is a starting material for other chromium(II) compounds. Also, many analogues have been prepared using other carboxylic acids in place of acetate and using different bases in place of the water.

Applications

Chromium(II) acetate has few practical applications. It has been used to dehalogenate organic compounds such as α-bromoketones and chlorohydrins. The reactions appear to proceed via 1e steps, and rearrangement products are sometimes observed.

Because the compound is a good reducing agent, it will reduce the O_2 found in air and can be used as an oxygen scrubber.

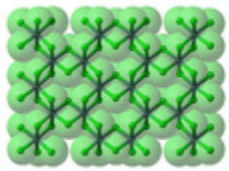
Chromium(III) chloride

Chromium(III) chloride (also called **chromic chloride**) describes any of several compounds of with the formula

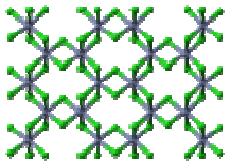
$CrCl_3 \bullet xH_2O$, where x can be 0, 5, and 6. The anhydrous compound with the formula $CrCl_3$ is a violet solid. The most common form of the trichloride is the dark green hexahydrate, $CrCl_3 \bullet 6H_2O$. Chromium chlorides find use as catalysts and as precursors to dyes for wool.

Structure

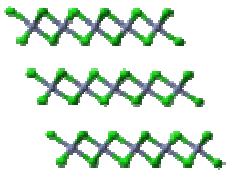
Anhydrous chromium(III) chloride adopts the YCl_3 structure, with Cr occupying one third of the octahedral interstices in alternating layers of a pseudo-cubic close packed lattice of Cl ions. The absence of cations in alternate layers leads to weak bonding between adjacent layers. For this reason, crystals of $CrCl_3$cleave easily along the planes between layers, which results in the flaky (micaceous) appearance of samples of chromium(III) chloride.



Space-filling model of cubic close packing of chloride ions in the crystal structure of $CrCl_3$



Ball-and-stick model of part of a layer



Stacking of layers

Chromium(III) chloride hydrates

Chromium(III) chlorides display the somewhat unusual property of existing in a number of distinct chemical forms (isomers), which differ in terms of the number of chloride anions that are coordinated to Cr(III) and the water of crystallization. The different forms exist both as solids, and in aqueous solutions. Several members are known of the series of $[CrCl_{3-n}(H_2O)_n]$. The main hexahydrate can be more precisely described as $[CrCl_2(H_2O)_4]Cl \bullet 2H_2O$. It consists of the cation trans-$[CrCl_2(H_2O)_4]$ and additional molecules of water and a chloride anion in the lattice. Two other hydrates are known, pale green $[CrCl(H_2O)_5]Cl_2 \bullet H_2O$ and violet $[Cr(H_2O)_6]Cl_3$. Similar behaviour occurs with other chromium(III) compounds.

Preparation

Anhydrous chromium(III) chloride may be prepared by chlorination of chromium metal directly, or indirectly by carbothermic chlorination of chromium(III) oxide at 650–800 °C

- $Cr_2O_3 + 3\ C + 3\ Cl_2 \rightarrow 2\ CrCl_3 + 3\ CO$

Dehydration with trimethylsilyl chloride in THF gives the solvate:

- $CrCl_3 \bullet 6H_2O + 12\ Me_3SiCl \rightarrow CrCl_3(THF)_3 + 6\ (Me_3Si)_2O + 12\ HCl$

It may also be prepared by treating the hexahydrate with thionyl chloride:

- $CrCl_3 \bullet 6H_2O + 6\ SOCl_2 \rightarrow CrCl_3 + 6\ SO_2 + 12\ HCl$

The hydrated chlorides are prepared by treatment of chromate with hydrochloric acid and methanol.

Reactions

Slow reaction rates are common with chromium(III) complexes. The low reactivity of the d Cr ion can be explained using crystal field theory. One way of opening $CrCl_3$ up to substitution in solution is to reduce even a trace amount to $CrCl_2$, for example using zinc in hydrochloric acid. This chromium(II) compound undergoes substitution easily, and it can exchange electrons with $CrCl_3$ via a chloride bridge, allowing all of the $CrCl_3$ to react quickly.

With the presence of some chromium(II), however, solid $CrCl_3$ dissolves rapidly in water. Similarly, ligand substitution reactions of solutions of $[CrCl_2(H_2O)_4]$ are accelerated by chromium(II) catalysts.

With molten alkali metalchlorides such as potassium chloride, $CrCl_3$ gives salts of the type M_3CrCl_6 and $K_3Cr_2Cl_9$, which is also octahedral but where the two chromiums are linked via three chloride bridges.

Complexes with organic ligands

$CrCl_3$ is a Lewis acid, classified as "hard" according to the Hard-Soft Acid-Base theory. It forms a variety of adducts of the type $[CrCl_3L_3]$, where L is a Lewis base. For example, it reacts with pyridine (C_5H_5N) to form an adduct:

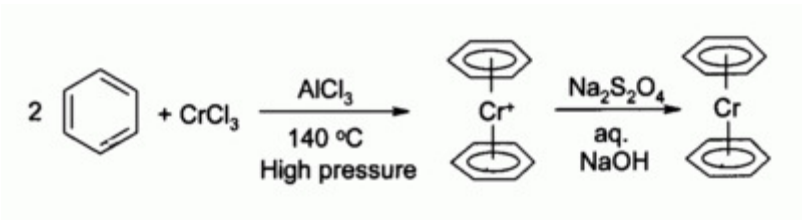
- $CrCl_3 + 3\ C_5H_5N \rightarrow CrCl_3(C_5H_5N)_3$

Treatment with trimethylsilylchloride in THF gives the anhydrous THF complex:

- $CrCl_3(H_2O)_6 + 12\ (CH_3)_3SiCl + 3\ THF \rightarrow CrCl_3(THF)_3 + 6\ ((CH_3)_3Si)_2O + 12\ HCl$

Precursor to organochromium complexes

Chromium(III) chloride is used as the precursor to many organochromium compounds, for example bis(benzene)chromium, an analogue of ferrocene:

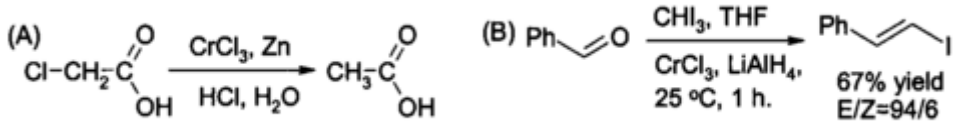


Phosphine complexes derived from $CrCl_3$ catalyse the trimerization of ethylene to 1-hexene.

Use in organic synthesis

One niche use of $CrCl_3$ in organic synthesis is for the *in situ* preparation of chromium(II) chloride, a reagent for the

reduction of alkyl halides and for the synthesis of (*E*)-alkenyl halides. The reaction is usually performed using two moles of $CrCl_3$ per mole of lithium aluminium hydride, although if aqueous acidic conditions are appropriate zinc and hydrochloric acid may be sufficient.



Chromium(III) chloride has also been used as a Lewis acid in organic reactions, for example to catalyse the nitroso Diels-Alder reaction.

Dyestuffs

A number of chromium-containing dyes are used commercially for wool. Typical dyes are triarylmethanes consisting of ortho-hydroxylbenzoic acid derivatives.

Precautions

Although trivalent chromium is far less poisonous than hexavalent, chromium salts are generally considered toxic.

Chromium(III) picolinate

Chromium(III) picolinate ($CrPic_3$) is a chemical compound sold as a nutritional supplement to treat type 2 diabetes and promote weight loss. This bright-red coordination compound is

derived from chromium(III) and picolinic acid. Large quantities of chromium are needed for glucose utilization by insulin in normal health, but deficiency is extremely common and has been observed in people receiving 100% of their nutrient needs intravenously, i.e., total parenteral nutrition diets. Chromium has been identified as regulating insulin by increasing the sensitivity of the insulin receptor. As such, chromium(III) picolinate has been proposed as a treatment for type 2 diabetes, although its effectiveness remains controversial due to conflicting evidence from human trials.

History

A study in 1989 suggested that chromium(III) picolinate may assist in weight loss and increase muscle mass which led to an increase in the usage of chromium(III) picolinate supplements, resulting in it being for a while the second most widely used supplement behind calcium. A 2013 Cochrane review was unable to find "reliable evidence to inform firm decisions" to support such claims. Research has generally shown that it improves insulin sensitivity by either prolonging its activity or up-regulating the production of mRNA to produce more insulin receptors.

Amongst the transition metals, Cr is the most controversial in terms of nutritional value and toxicity. This controversy centers on whether Cr provides any nutritional benefits. Furthermore, this controversy is amplified by the fact that no Cr-containing biomolecules have had their structure characterized, nor has the mode of action been determined. The first experiment that led to the discovery of Cr playing a role in glucose metabolism proposed that the biologically active

form of the metal existed in a protein called *glucose tolerance factor*, however, new evidence suggests that it is simply an artifact obtained from isolation procedures. The only accepted indicator of chromium deficiency is the reversal of symptoms that occurs when chromium(III) supplementation is administered to people on total parenteral nutrition.

Physicochemical properties

Chromium(III) picolinate is a pinkish-red compound and was first reported in 1917. It is poorly soluble in water, having a solubility of 600 μM in water at near neutral pH. Similar to other chromium(III) compounds, it is relatively inert and unreactive, meaning that this complex is stable at ambient conditions and high temperatures are required to decompose the compound. At lower pH levels, the complex hydrolyzes to release picolinic acid and free Cr.

Structure

Chromium(III) picolinate has a distorted octahedral geometry and is isostructural to cobalt (III) and manganese (III) counterparts. Chromium(III) is a hard lewis acid and as such has high affinity to the carboxylate oxygen and medium affinity to the pyridine nitrogen of picolinate. Each picolinate ligand acts as a bidentatechelating agent and neutralizes the +3 charge of Cr. Evidence that the Cr center coordinates to the pyridine nitrogen comes from a shift in the IR spectra of a C=N vibration at 1602.4 cm for free picolinic acid to 1565.9 cm for chromium(III) picolinate. The bond length between Cr and the nitrogen atom of the pyridine ring on picoliante ranges from

2.047 to 2.048 Å. The picolinate ligand coordinates to Cr only when deprotonated and this is evident by the disappearance of IR bands ranging from 2400–2800 cm (centered at 2500 cm) and 1443 cm, corresponding to the O-H stretching and bending, respectively, on the carboxyl functional group. Furthermore, this IR shift also indicates that only one oxygen atom from the carboxylate of picolinate coordinates to the Cr center. The Cr-O bond length ranges from 1.949 to 1.957 Å. The crystal structure has only been recently described in 2013. Water does not coordinate to the Cr center and is instead thought to hydrogen bond between other $Cr(Pic)_3$ complexes to form a network of $Cr(Pic)_3$ complexes.

Biochemistry of chromium(III) picolinate

Chromium has been identified as an essential nutrient in maintaining normal blood glucose levels and as such, it is proposed to interact with two naturally occurring molecules found within the body. These interactions are most likely to occur through coordination with hard ligands such as aspartate and glutamate, as Cr(III) itself is a hard metal.

Absorption and excretion of chromium(III) picolinate

Once chromium(III) picolinate is ingested and enters the stomach, acidic hydrolysis of the complex occurs when in contact with the stomach mucosa. The hydrolyzed Cr is present in the hexaaqua form and polymerizes to form an insoluble Cr(III)-hydroxide-oxide (the process of olation) once it reaches the alkaline pH of the small intestine. Approximately 2% of Cr

is absorbed through the gut as chromium(III) picolinate via unsaturated passive transport. Although absorption is low, $CrPic_3$ absorbs more efficiently than other organic and inorganic sources (i.e. $CrCl_3$ and chromium nicotinate) and thus accumulate at higher concentrations in tissues. This has been one major selling point for chromium(III) picolinate over other chromium(III) supplements. Organic sources tend to absorb better as they have ligands which are more lipophilic and usually neutralize the charge of the metal, thus permitting for easier passage through the intestinal membrane.

It has also been shown that dietary factors affect Cr absorption. Starch, simple sugars, oxalic acid, and some amino acids tend to increase the rate of absorption of chromium(III). This is a result of ligand chelation, converting hexaaqua Cr into more lipophilic forms. In contrast, calcium, magnesium, titanium, zinc, vanadium, and iron reduce the rate of absorption. Presumably, these ions introduce new metal-ligand equilibria, thus decreasing the lipophilic ligand pool available to Cr. Once absorbed into the bloodstream, 80% of the Cr from $CrPic_3$ is passed along to transferrin. The exact mechanism of release is currently unknown, however, it is believed not to occur by a single electron reduction, as in the case of Fe, due to the high instability of Cr. Administered Cr can be found in all tissues ranging from 10–100 μg/kg body weight. It is excreted primarily in the urine (80%) while the rest is excreted in sweat and feces.

Binding of chromium(III) to transferrin

Transferrin, in addition to chromodulin has been identified as a major physiological chromium transport agent, although a

recent study found that Cr in fact disables transferrin from acting as a metal ion transport agent. While transferrin is highly specific for ferric ions, at normal conditions, only 30% of transferrin molecules are saturated with ferric ions, allowing for other metals, particularly those with a large charge to size ratio, to bind as well. The binding sites consist of a C-lobe and an N-lobe which are nearly identical in structure. Each lobe contains aspartic acid, histidine, 2 tyrosine residues and a bicarbonate ion that acts as a bidentate ligand to allow iron or other metals to bind to transferrin in a distorted octahedral geometry. Evidence supporting the binding of Cr to transferrin comes from extensive clinical studies that showed a positive correlation between levels of ferritin and of fasting glucose, insulin, and glycated hemoglobin (Hb1Ac) levels.

Furthermore, an in vivo study in rats showed that 80% of isotopically labelled Cr ended up on transferrin while the rest were bound to albumin. An in vitro study showed that when chromium(III) chloride was added to isolated transferrin, the Cr readily bound transferrin, owing to changes in the UV-Vis spectrum. The formation constant for Cr in the C-lobe is 1.41 x 10 M and 2.04 x 10 M in the N-lobe, which indicates that Cr preferentially binds the C-lobe. Overall, the formation constant for chromium(III) is lower than that of the ferric ion. The bicarbonate ligand is crucial in binding Cr as when bicarbonate concentrations are very low, the binding affinity is also significantly lower.

Electron paramagnetic resonance (EPR) studies have shown that below pH 6, chromium(III) binds only to the N-lobe and that at near neutral pH, chromium(III) binds to the C-lobe as well. Chromium(III) can compete with the ferric ion for binding

to the C-lobe when the saturation greatly exceeds 30%. As such, these effects are only seen in patients suffering from hemochromatosis, an iron-storage disease characterized by excessive iron saturation in transferrin.

Mechanism of action

Low-molecular-weight chromium-binding substance (LMWCr; also known as chromodulin) is an oligopeptide that seems to bind chromium(III) in the body. It consists of four amino acid residues; aspartate, cysteine, glutamate, and glycine, bonded with four (Cr) centers. It interacts with the insulin receptor, by prolonging kinase activity through stimulating the tyrosine kinase pathway, thus leading to improved glucose absorption. It has been confused with glucose tolerance factor. Despite recent efforts to characterize chromodulin, the exact structure is still relatively unknown.

Although chromodulin's exact mechanism of action on the insulin receptor is currently unknown, one commonly described mechanism is presented below. This proposed mechanism has the highest amount of agreement with various experiments involving chromodulin.

Normally, chromodulin exists in the apochromodulin form, which is free of Cr(III) ions and has minimal activity on insulin receptors. The apochromodulin is stored in insulin sensitive cells in the nucleus. When blood glucose levels rise, insulin is released into the bloodstream and binds to an external α-subunit of the insulin receptor, a transmembrane protein. The insulin receptor consists of 2 extracellular α-subunits and 2 transmembrane β-subunits. As soon as insulin binds to the

insulin receptor, a conformational change in the receptor occurs, causing all 3 tyrosine residues (located in the β-subunits) to be phosphorylated. This activates the receptor and allows it to transmit the signal from insulin to the cell. As mentioned above, absorbed chromium(III) picolinate eventually gives up Cr to transferrin. In turn, transferrin transports Cr to insulin sensitive cells (i.e. adipocytes) where it binds to apochromodulin to form holochromodulin. Holochromodulin binds to the insulin receptor, which assists in maintaining the active conformation of the insulin receptor by prolonging the kinase activity of kinases or up-regulating the amount of insulin receptor mRNA levels, thus decreasing blood glucose levels. Experiments were able to show that chromium(III) was capable of up-regulating insulin-stimulated insulin signal transduction via affecting downstream molecules of the IR, as evidenced by enhanced levels of tyrosine phosphorylation of IRS-1, elevated Thr308 and Ser473phosphorylation of Akt, and increased PI3-K activity in a variety of cellular and animal models. The increased IRS-1 phosphorylation led to increased insulin receptor sensitivity while Akt and PI3-K led to enhanced GLUT4 translocation to the cell surface, thus causing greater uptake of glucose. It has also been shown that chromium(III) can alleviate insulin resistance by reducing endoplasmic reticulum (ER) stress. ER stress is defined as an accumulation of misfolded and unfolded proteins in the ER lumen. ER stress leads to stimulation of c-Jun terminal kinase (JNK), which in turn phosphorylates the serine residue of IRS, leading to suppression of insulin signaling cascade and less glucose uptake. Experimental findings suggest that chromium inhibits ER stress and hence the suppression of insulin signaling is uplifted. The exact mechanism is unknown.

Another way that Cr(III) may prolong the insulin receptor's kinase activity is through the oxidation of a critical active site cysteine residue on protein-tyrosine phosphatase 1B (PTP1B). Normally, PTP1B dephosphorylates phosphotyrosine residues by carrying out nucleophilic attack on the phosphate group via its cysteine residue, thus inactivating the insulin receptor. This process removes the phosphate group from the tyrosine residue to form a Cys—S—PO_3 group that is subsequently hydrolyzed by water to regenerate the cysteine residue, permitting for another round of action. Research has shown that chromium(III) may in fact cause irreversible inhibition of PTP1B. It is thought that Cr(III) is converted to Cr(VI) or Cr(V) (through the action of oxidoreductases) which then oxidize the thiol of the cysteine residue on PTP1B to sulfenic acid, consequently rendering it unable to attack the phosphate group on phosphotyrosine. However, this is only a plausible mechanism, and no direct evidence has been shown to support this hypothesis. When the signal cascade is turned off, holochromodulin is eliminated in urine since the formation constant is too large to remove Cr(III) directly. Experimental evidence has shown that the loss of chromodulin from cells is correlated with an increase in chromium concentrations in the urine after ingesting food rich in carbohydrates (i.e. glucose).

Health claims and debates

Body weight

Chromium(III) picolinate has been marketed in the United States as an aid to body development for athletes and as a means of losing weight. Reviews have reported either no effect

on either muscle growth or fat loss, or else a modest but statistically significant -1.1 kg (2.4 lb) weight loss in trials longer than 12 weeks. The European Food Safety Authority reviewed the literature and concluded that there was insufficient evidence to support a claim.

Diabetes

There are claims that the picolinate form of chromium supplementation aids in reducing insulin resistance and improving glucose metabolism, particularly in type 2 diabetics, but reviews showed no association between chromium and glucose or insulin concentrations for non-diabetics, and inconclusive results for diabetics. The authors of the second review mentioned that chromium picolinate decreased HbA1c levels by 0.7% in type 2 diabetes patients, they observed that poor quality studies produced larger positive outcomes than higher quality studies. Two reviews concluded that chromium(III) picolinate may be more effective at lowering blood glucose levels compared to other chromium-containing dietary supplements.

In 2005, the U.S. Food and Drug Administration (FDA) approved a qualified health claim for chromium picolinate as a dietary supplement relating to insulin resistance and risk of type 2 diabetes. Any company wishing to make such a claim must use the exact wording: "One small study suggests that chromium picolinate may reduce the risk of insulin resistance, and therefore possibly may reduce the risk of type 2 diabetes. FDA concludes, however, that the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes is highly uncertain." As part of

the petition review process, the FDA rejected other claims for reducing abnormally elevated blood sugar, risk of cardiovascular disease, risk of retinopathy or risk of kidney disease. In 2006 the FDA added that the "relationship between chromium(III) picolinate intake and insulin resistance is highly uncertain".

Variability of studies

There was no consistency observed in clinical results relating chromium(III) picolinate to adequate treatment of type 2 diabetes. This is due to the degree of glucose intolerance of patients that participate in the clinical studies. Glucose intolerance is a gradient and the intensity is affected by ethnicity, degree of obesity, age, distribution of body fat and many other factors. In some studies, low dosages of the supplement were given, however, a suitable amount of chromium(III) picolinate must be administrated to a person before any appreciable drop in glucose levels are observed due to differing levels of insulin resistance. Another important point to mention is that diabetes is not always caused by glucose intolerance. As mentioned before, Cr(III) has been shown to only influence glucose intolerance and not insulin levels. Furthermore, the environments in which the studies were performed were not consistent. The levels of stress, diets consumed by patients and patient genetics were variable among study subjects. This is also true of the controls amongst different studies in which the subjects having diabetes were already being treated with a wide variety of antidiabetic drugs, which can reduce the effects of chromium on affecting insulin activity. This could explain why animal studies tend to yield more positive results owing to the fact that these diabetic

animals were not treated with antidiabetic drugs for the control group. Also, as mentioned in the absorption and excretion section, the absorption/bioavailability of chromium(III) picolinate is influenced by the diet. Collectively, these different factors have contributed to the variability in the studies.

Safety and toxicity

Initial concerns were raised that chromium(III) picolinate is more likely to cause DNA damage and mutation than other forms of trivalent chromium, but these results are also debated. These concerns were based, in part, on studies in fruit flies, where chromium(III) picolinate supplementation generates chromosomal aberrations, impedes progeny development, and causes sterility and lethal mutations.

A study was published to assess the toxicity of Cr(III) picolinate on humans. The researchers that conducted this study used previous knowledge that Cr(III) is reduced to Cr(II) by cellular reductants such as NADH or cysteine. This reduced form of Cr(II) is shown to react with H_2O_2 to generate radical species which in turn oxidizeDNA base pairs. With this knowledge in mind, the researchers administered ten women with 400 μg of chromium(III) picolinate a day for an eight-week period. By measuring the amount of an oxidized DNA base pair, 5-hydroxymethyl uracil using antibody titers, the group could infer the amount of DNA base pair oxidation occurring in direct relation to chromium(III) picolinate. The results of the study suggested that chromium(III) picolinate itself does not cause significant chromosomal damage in vivo.

Generally speaking, it has been shown that chromium(III) picolinate is not toxic to humans. For most adults, it can be taken orally in doses up 1000 μg per day. This low toxicity has generally been associated with low absorbance of Cr(III) in the body through the lungs, skin and gastrointestinal tract, coupled with high excretion. Normally, 99% of chromium(III) taken can be recovered in the feces of the user. There have been isolated incidences of chromium(III) supplementation leading to kidney failure, however this relationship is unclear and has yet to be tested.

Regulation of chromium(III) picolinate

In 2004, the UK Food Standards Agency advised consumers to use other forms of trivalent chromium in preference to chromium(III) picolinate until specialist advice was received from the Committee on Mutagenicity. This was due to concerns raised by the Expert Group on Vitamins and Minerals that chromium(III) picolinate might be genotoxic (cause cancer). The committee also noted two case reports of kidney failure that might have been caused by this supplement and called for further research into its safety. In December 2004, the Committee on Mutagenicity published its findings, which concluded that "overall it can be concluded that the balance of the data suggest that chromium(III) picolinate should be regarded as not being mutagenic in vitro" and that "the available in-vivo tests in mammals with chromium(III) picolinate are negative". Following these findings, the UK Food Standards Agency withdrew its advice to avoid chromium(III)

picolinate, though it plans to keep its advice about chromium supplements under review.

In 2010, chromium(III) picolinate was approved by Health Canada to be used in dietary supplements. Approved labeling statements include: a factor in the maintenance of good health, provides support for healthy glucose metabolism, helps the body to metabolize carbohydrates and helps the body to metabolize fats.

Cisplatin

Cisplatin is a chemotherapy medication used to treat a number of cancers. These include testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain tumors and neuroblastoma. It is given by injection into a vein.

Common side effects include bone marrow suppression, hearing problems, kidney damage, and vomiting. Other serious side effects include numbness, trouble walking, allergic reactions, electrolyte problems, and heart disease. Use during pregnancy can cause harm to the baby. Cisplatin is in the platinum-based antineoplastic family of medications. It works in part by binding to DNA and inhibiting its replication.

Cisplatin was discovered in 1845 and licensed for medical use in 1978 and 1979. It is on the World Health Organization's List of Essential Medicines.

Medical use

Cisplatin is administered intravenously as short-term infusion in normal saline for treatment of solid and haematological malignancies. It is used to treat various types of cancers, including sarcomas, some carcinomas (e.g., small cell lung cancer, squamous cell carcinoma of the head and neck and ovarian cancer), lymphomas, bladder cancer, cervical cancer, and germ cell tumors.

Cisplatin is particularly effective against testicular cancer; its adoption has increased the cure rate from 10% to 85%.

In addition, cisplatin is used in Auger therapy.

Side effects

Cisplatin has a number of side effects that can limit its use:

- Nephrotoxicity (kidney damage) is a major concern. The dose should be reduced when the person's kidney function is impaired. Adequate hydration is used in an effort to prevent damage. Amifostine has been studied in an effort to prevent problems. Nephrotoxicity is a dose-limiting side effect.
- Neurotoxicity (nerve damage) can be anticipated by performing nerve conduction studies before and after treatment. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins. While triggering apoptosis through

interfering with DNA replication remains the primary mechanism of cisplatin, this has not been found to contribute to neurological side effects. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE-1. It is primarily found on cells of the peripheral nervous system, which are aggregated in large numbers near the ocular and aural stimuli-receiving centers. This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo. However, NHE-1 inhibition has been found to be both dose-dependent (half-inhibition = 30 μg/mL) and reversible.

- Nausea and vomiting: cisplatin is one of the most emetogenic chemotherapy agents, but this symptom is managed with prophylactic antiemetics (ondansetron, granisetron, etc.) in combination with corticosteroids. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone.
- Ototoxicity (hearing loss): there is at present no effective treatment to prevent this side effect, which may be severe, although there is ongoing investigation of acetylcysteine injections as a preventative measure. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs (such as the aminoglycoside antibiotic class) may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving

cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species.

- Electrolyte disturbance: Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin.
- Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis.

Pharmacology

Cisplatin interferes with DNA replication, which kills the fastest proliferating cells, which in theory are cancerous. Following 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-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. In 2008, researchers were able to show that the apoptosis induced by cisplatin on human colon cancer cells depends on the mitochondrial serine-protease Omi/Htra2. Since this was only demonstrated for colon carcinoma cells, it remains an open question if the Omi/Htra2 protein participates in the cisplatin-induced apoptosis in carcinomas from other tissues Omi/Htra2.

Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. These include 1,2-intrastrand d(GpG) adducts which form nearly 90% of the adducts and the less common 1,2-intrastrand d(ApG) adducts. 1,3-intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER). Other adducts include inter-strand crosslinks and nonfunctional adducts that have been postulated to contribute to cisplatin's activity. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. Omi/Htra2.

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. Many mechanisms of cisplatin resistance have been proposed including changes in cellular uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis and increased DNA repair.

Oxaliplatin is active in highly cisplatin-resistant cancer cells in the laboratory; however, there is little evidence for its activity in the clinical treatment of patients with cisplatin-resistant cancer. The drug paclitaxel may be useful in the treatment of cisplatin-resistant cancer; the mechanism for this activity is unknown.

Transplatin

Transplatin, the *trans* stereoisomer of cisplatin, has formula *trans*-$[PtCl_2(NH_3)_2]$ and does not exhibit a comparably useful pharmacological effect. Two mechanisms have been suggested to explain the reduced anticancer effect of transplatin. Firstly, the *trans* arrangement of the chloro ligands is thought to confer transplatin with greater chemical reactivity, causing transplatin to become deactivated before it reaches the DNA where cisplatin exerts its pharmacological action. Secondly, the stereo-conformation of transplatin is such that it is unable to form the characteristic 1,2-intrastrand d(GpG) adducts formed by cisplatin in abundance.

Molecular structure

Cisplatin is the square planarcoordination complex cis-$[Pt(NH_3)_2Cl_2]$. The prefix *cis* indicates the *cis* isomer in which two similar ligands are in adjacent positions. The systematic chemical name of this molecule is *cis*–diamminedichloroplatinum, where *ammine* with two m's indicates an ammonia (NH_3) ligand, as opposed to an organic amine with one m.

History

The compound *cis*-[$Pt(NH_3)_2Cl_2$] was first described by Michele Peyrone in 1845, and known for a long time as Peyrone's salt. The structure was deduced by Alfred Werner in 1893. In 1965, Barnett Rosenberg, Van Camp et al. of Michigan State University discovered that electrolysis of platinum electrodes generated a soluble platinum complex which inhibited binary fission in *Escherichia coli* (*E. coli*) bacteria. Although bacterial cell growth continued, cell division was arrested, the bacteria growing as filaments up to 300 times their normal length. The octahedral Pt(IV) complex *cis*-[$PtCl_4(NH_3)_2$], but not the *trans* isomer, was found to be effective at forcing filamentous growth of *E. coli* cells.

The square planar Pt(II) complex, *cis*-[$PtCl_2(NH_3)_2$] turned out to be even more effective at forcing filamentous growth. This finding led to the observation that *cis*-[$PtCl_2(NH_3)_2$] was indeed highly effective at regressing the mass of sarcomas in rats. Confirmation of this discovery, and extension of testing to other tumour cell lines launched the medicinal applications of cisplatin. Cisplatin was approved for use in testicular and ovarian cancers by the U.S. Food and Drug Administration on 19 December 1978. and in the UK (and in several other European countries) in 1979. Cisplatin was the first to be developed.

In 1983 pediatric oncologist Roger Packer began incorporating cisplatin into adjuvant chemotherapy for the treatment of childhood medulloblastoma. The new protocol that he developed led to a marked increase in disease-free survival rates for patients with medulloblastoma, up to around 85%.

The Packer Protocol has since become a standard treatment for medulloblastoma. Likewise, Cisplatin has been found to be particularly effective against testicular cancer, where its use improved the cure rate from 10% to 85%.

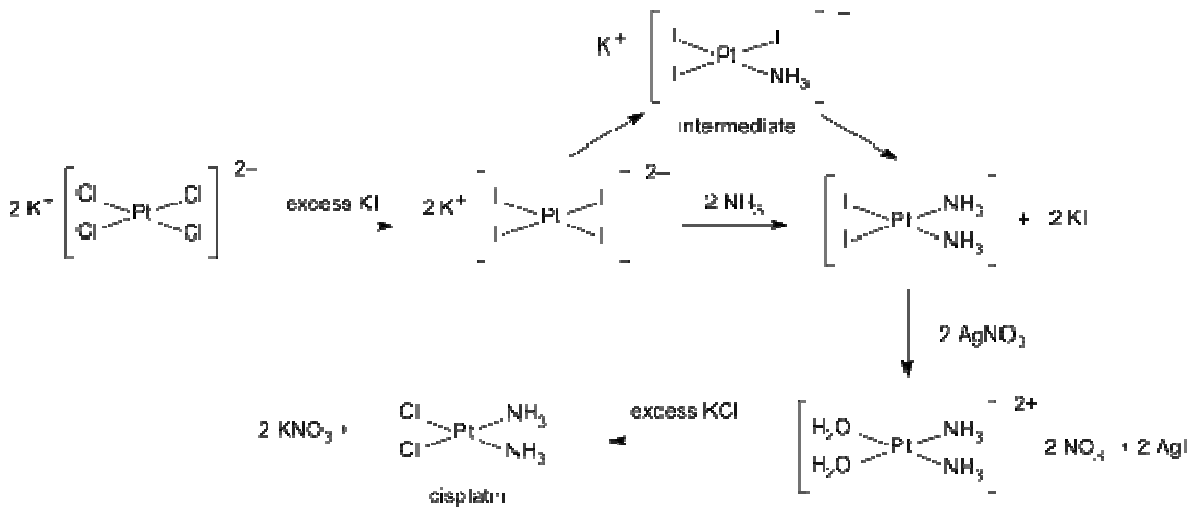
Recently, some researchers have investigated at the preclinical level new forms of cisplatin prodrugs in combination with nanomaterials in order to localize the release of the drug in the target.

Synthesis

Syntheses of cisplatin start from potassium tetrachloroplatinate. Several procedures are available. One obstacle is the facile formation of Magnus's green salt (MGS), which has the same empirical formula as cisplatin. The traditional way to avoid MGS involves the conversion of K_2PtCl_4 to K_2PtI_4, as originally described by Dhara.

Reaction with ammonia forms $PtI_2(NH_3)_2$ which is isolated as a yellow compound. When silver nitrate in water is added insoluble silver iodide precipitates and $[Pt(OH_2)_2(NH_3)_2](NO_3)_2$ remains in solution. Addition of potassium chloride will form the final product which precipitates In the triiodo intermediate the addition of the second ammonia ligand is governed by the trans effect.

A one-pot synthesis of cisplatin from K_2PtCl_4 has been developed. It relies on the slow release of ammonia from ammonium acetate.


2 K+
excess KI
2 K+
intermediate
2 NH3
+ 2 KI
2 AgNO3
2 KNO3 +
cisplatin
excess KCl
2 NO3 + 2 AgI

Chapter 5

Stubs

Alkoxide

An **alkoxide** is the conjugate base of an alcohol and therefore consists of an organic group bonded to a negatively charged oxygen atom. They are written as RO, where R is the organic substituent. Alkoxides are strong bases and, when R is not bulky, good nucleophiles and good ligands. Alkoxides, although generally not stable in protic solvents such as water, occur widely as intermediates in various reactions, including the Williamson ether synthesis. Transition metal alkoxides are widely used for coatings and as catalysts.

Enolates are unsaturated alkoxides derived by deprotonation of a C-H bond adjacent to a ketone or aldehyde. The nucleophilic center for simple alkoxides is located on the oxygen, whereas the nucleophilic site on enolates is delocalized onto both carbon and oxygen sites. Ynolates are also unsaturated alkoxides derived from acetylenic alcohols.

Phenoxides are close relatives of the alkoxides, in which the alkyl group is replaced by a derivative of benzene. Phenol is more acidic than a typical alcohol; thus, phenoxides are correspondingly less basic and less nucleophilic than alkoxides. They are, however, often easier to handle, and yield derivatives that are more crystalline than those of the alkoxides.

Structure

- Alkali metal alkoxides are often oligomeric or polymeric compounds, especially when the R group is small (Me, Et). The alkoxide anion is a good bridging ligand, thus many alkoxides feature M_2O or M_3O linkages. In solution, the alkali metal derivatives exhibit strong ion-pairing, as expected for the alkali metal derivative of a strongly basic anion.

Preparation

By metathesis reactions

Many alkoxides are prepared by salt-forming reactions from a metal chloride and sodium alkoxide:

- $n\ NaOR + MCl_n \rightarrow M(OR)_n + n\ NaCl$

Such reactions are favored by the lattice energy of the NaCl, and purification of the product alkoxide is simplified by the fact that NaCl is insoluble in common organic solvents.

For some electrophilic metal halides, conversion to the alkoxide requires no base. Titanium tetrachloride reacts with alcohols to give the corresponding tetraalkoxides, concomitant with the evolution of hydrogen chloride:

- $TiCl_4 + 4\ (CH_3)_2CHOH \rightarrow Ti(OCH(CH_3)_2)_4 + 4\ HCl$

The reaction can be accelerated by the addition of a base, such as a tertiary amine. Many other metal and main group halides can be used instead of titanium, for example $SiCl_4$, $ZrCl_4$, and PCl_3.

From reducing metals

Alkoxides can be produced by several routes starting from an alcohol. Highly reducing metals react directly with alcohols to give the corresponding metal alkoxide. The alcohol serves as an acid, and hydrogen is produced as a by-product. A classic case is sodium methoxide produced by the addition of sodium metal to methanol:

- $2\ CH_3OH + 2\ Na \rightarrow 2\ CH_3ONa + H_2$

Other alkali metals can be used in place of sodium, and most alcohols can be used in place of methanol. Another similar reaction occurs when an alcohol is reacted with a metal hydride such as NaH. The metal hydride removes the hydrogen atom from the hydroxyl group and forms a negatively charged alkoxide ion.

By electrochemical processes

Many alkoxides can be prepared by anodic dissolution of the corresponding metals in water-free alcohols in the presence of electroconductive additive. The metals may be Co, Ga, Ge, Hf, Fe, Ni, Nb, Mo, La, Re, Sc, Si, Ti, Ta, W, Y, Zr, etc. The conductive additive may be lithium chloride, quaternary ammonium halide, or other. Some examples of metal alkoxides obtained by this technique: $Ti(OCH(CH_3)_2)_4$, $Nb_2(OCH_3)_{10}$,

$Ta_2(OCH_3)_{10}$, $[MoO(OCH_3)_4]_2$, $Re_2O_3(OCH_3)_6$, $Re_4O_6(OCH_3)_{12}$, and $Re_4O_6(OCH(CH_3)_2)_{10}$.

Properties

Reactions with alkyl halides

The alkoxide ion can react with a primary alkyl halide in an SN_2 reaction to form an ether via the Williamson Ether Synthesis.

Hydrolysis and transesterification

Metal alkoxides hydrolyse with water according to the following equation:

- $2\ L_nMOR + H_2O \rightarrow [L_nM]_2O + 2\ ROH$

where R is an organic substituent and L is an unspecified ligand (often an alkoxide) A well-studied case is the irreversible hydrolysis of titanium ethoxide:

- $1/n\ [Ti(OCH_2CH_3)_4]_n + 2\ H_2O \rightarrow TiO_2 + 4\ HOCH_2CH_3$

By controlling the stoichiometry and steric properties of the alkoxide, such reactions can be arrested leading to metal-oxy-alkoxides, which usually are oligonuclear complexes. Other alcohols can be employed in place of water. In this way one alkoxide can be converted to another, and the process is properly referred to as alcoholysis (unfortunately, there is an issue of terminology confusion with transesterification, a

different process - see below). The position of the equilibrium can be controlled by the acidity of the alcohol; for example phenols typically react with alkoxides to release alcohols, giving the corresponding phenoxide. More simply, the alcoholysis can be controlled by selectively evaporating the more volatile component. In this way, ethoxides can be converted to butoxides, since ethanol (b.p. 78 °C) is more volatile than butanol (b.p. 118 °C).

In the transesterification process, metal alkoxides react with esters to bring about an exchange of alkyl groups between metal alkoxide and ester. With the metal alkoxide complex in focus, the result is the same as for alcoholysis, namely the replacement of alkoxide ligands, but at the same time the alkyl groups of the ester are changed, which can also be the primary goal of the reaction. Sodium methoxide, for example, is commonly used for this purpose, a reaction that is relevant to the production of "bio-diesel".

Formation of oxo-alkoxides

Many metal alkoxide compounds also feature oxo-ligands. Oxo-ligands typically arise via the hydrolysis, often accidentally, and via ether elimination:

- $2\ L_nMOR \rightarrow [L_nM]_2O + R_2O$

Additionally, low valent metal alkoxides are susceptible to oxidation by air

Formation of polynuclear and heterometallic derivatives

Characteristically, transition metal alkoxides are polynuclear, that is they contain more than one metal. Alkoxides are sterically undemanding and highly basic ligands that tend to bridge metals.

Upon the isomorphic substitution of metal atoms close in properties crystalline complexes of variable composition are formed. The metal ratio in such compounds can vary over a broad range. For instance, the substitution of molybdenum and tungsten for rhenium in the complexes $Re_4O_{6-y}(OCH_3)_{12+y}$ allowed one to obtain complexes $Re_{4-x}Mo_xO_{6-y}(OCH_3)_{12+y}$ in the range $0 \leq x \leq 2.82$ and $Re_{4-x}W_xO_{6-y}(OCH_3)_{12+y}$ in the range $0 \leq x \leq 2$.

Thermal stability

- Many metal alkoxides thermally decompose in the range ~100–300 °C. Depending on process conditions, this thermolysis can afford nanosized powders of oxide or metallic phases. This approach is a basis of processes of fabrication of functional materials intended for aircraft, space, electronic fields, and chemical industry: individual oxides, their solid solutions, complex oxides, powders of metals and alloys active towards sintering. Decomposition of mixtures of mono- and heterometallic alkoxide derivatives has also been examined. This method represents a prospective approach possessing an advantage of capability of obtaining functional materials with increased phase

and chemical homogeneity and controllable grain size (including the preparation of nanosized materials) at relatively low temperature (less than 500–900 °C) as compared with the conventional techniques.

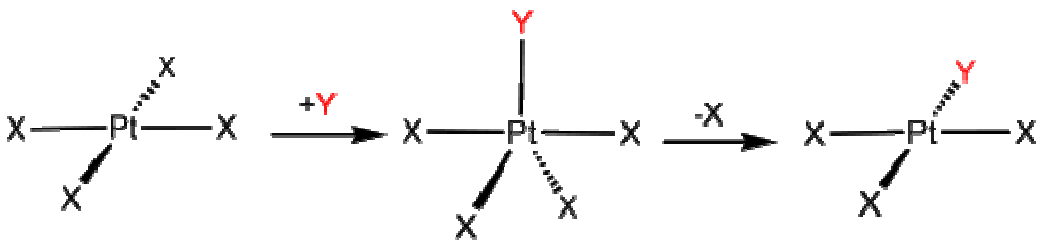
Associative substitution

Associative substitution describes a pathway by which compounds interchange ligands. The terminology is typically applied to coordination and organometallic complexes, but resembles the Sn2 mechanism in organic chemistry. The opposite pathway is dissociative substitution, being analogous to the Sn1 pathway. Intermediate pathways exist between the pure associative and pure dissociative pathways, these are called interchange mechanisms.

Associative pathways are characterized by binding of the attacking nucleophile to give a discrete, detectable intermediate followed by loss of another ligand. Complexes that undergo associative substitution are either coordinatively unsaturated or contain a ligand that can change its bonding to the metal, e.g. change in hapticity or bending of a nitrogen oxide ligand (NO). In homogeneous catalysis, the associative pathway is desirable because the binding event, and hence the selectivity of the reaction, depends not only on the nature of the metal catalyst but also on the substrate.

Examples of associative mechanisms are commonly found in the chemistry of 16e square planar metal complexes, e.g. Vaska's complex and tetrachloroplatinate. These compounds (MX_4) bind the incoming (substituting) ligand Y to form

pentacoordinate intermediates MX_4Y that in a subsequent step dissociates one of their ligands. Dissociation of Y results in no detectable net reaction, but dissociation of X results in net substitution, giving the 16e complex MX_3Y. The first step is typically rate determining. Thus, the entropy of activation is negative, which indicates an increase in order in the system. These reactions follow second order kinetics: the rate of the appearance of product depends on the concentration of MX_4 and Y. The rate law is governed by the Eigen–Wilkins Mechanism.



Associative interchange pathway

In many substitution reactions, well-defined intermediates are not observed, when the rate of such processes are influenced by the nature of the entering ligand, the pathway is called associative interchange, abbreviated I_a. Representative is the interchange of bulk and coordinated water in $[V(H_2O)_6]$. In contrast, the slightly more compact ion $[Ni(H_2O)_6]$ exchanges water via the I_d.

Effects of ion pairing

Polycationic complexes tend to form ion pairs with anions and these ion pairs often undergo reactions via the I_a pathway. The

electrostatically held nucleophile can exchange positions with a ligand in the first coordination sphere, resulting in net substitution. An illustrative process comes from the "anation" (reaction with an anion) of chromium(III) hexaaquo complex:

- $[Cr(H_2O)_6] + SCN \rightleftharpoons \{[Cr(H_2O)_6], NCS\}$
- $\{[Cr(H_2O)_6], NCS\} \rightleftharpoons [Cr(H_2O)_5NCS] + H_2O$

Special ligand effects

In special situations, some ligands participate in substitution reactions leading to associative pathways. These ligands can adopt multiple motifs for binding to the metal, each of which involves a different number of electrons "donated." A classic case is the indenyl effect in which an indenyl ligand reversibly "slips' from pentahapto (η) coordination to trihapto (η). Other pi-ligands behave in this way, e.g. allyl (η to η) and naphthalene (η to η). Nitric oxide typically binds to metals to make a linear MNO arrangement, wherein the nitrogen oxide is said to donate 3e to the metal. In the course of substitution reactions, the MNO unit can bend, converting the 3e linear NO ligand to a 1e bent NO ligand.

S_N1cB mechanism

The rate for the hydrolysis of cobalt(III) ammine halide complexes are deceptive, appearing to be associative but proceeding by an alternative pathway. The hydrolysis of $[Co(NH_3)_5Cl]$ follows second order kinetics: the rate increases linearly with concentration of hydroxide as well as the starting complex. Based on this information, the reactions would

appear to proceed via nucleophilic attack of hydroxide at cobalt. Studies show, however, that the hydroxide deprotonates one NH_3 ligand to give the conjugate base of the starting complex, i.e., $[Co(NH_3)_4(NH_2)Cl]$. In this monocation, the chloride spontaneously dissociates. This pathway is called the S_N1cB mechanism.

Eigen-Wilkins mechanism

The Eigen-Wilkins mechanism, named after chemists Manfred Eigen and R. G. Wilkins, is a mechanism and rate law in coordination chemistry governing associative substitution reactions of octahedral complexes. It was discovered for substitution by ammonia of a chromium-(III) hexaaqua complex. The key feature of the mechanism is an initial rate-determining pre-equilibrium to form an encounter complex ML_6-Y from reactant ML_6 and incoming ligand Y. This equilibrium is represented by the constant K_E:

- $ML_6 + Y \rightleftharpoons ML_6\text{-}Y$

The subsequent dissociation to form product is governed by a rate constant k:

- $ML_6\text{-}Y \rightarrow ML_5Y + L$

A simple derivation of the Eigen-Wilkins rate law follows:

- $[ML_6\text{-}Y] = K_E[ML_6][Y]$
- $[ML_6\text{-}Y] = [M]_{tot} - [ML_6]$
- $\text{rate} = k[ML_6\text{-}Y]$
- $\text{rate} = kK_E[Y][ML_6]$

Leading to the final form of the rate law, using the steady-state approximation ($d[ML_6\text{-}Y] / dt = 0$),

- $\text{rate} = kK_E[Y][M]_{tot} / (1 + K_E[Y])$

Eigen-Fuoss equation

A further insight into the pre-equilibrium step and its equilibrium constant K_E comes from the Fuoss-Eigen equation proposed independently by Eigen and R. M. Fuoss:

- $K_E = (4\pi a/3000) \times N_A \exp(-V/RT)$

Where a represents the minimum distance of approach between complex and ligand in solution (in cm), N_A is the Avogadro constant, R is the gas constant and T is the reaction temperature. V is the electrostatic potential energy of the ions at that distance:

- $V = z_1 z_2 e/4\pi a\varepsilon$

Where z is the charge number of each species and ε is the vacuum permittivity.

A typical value for K_E is 0.0202 dmmol for neutral particles at a distance of 200 pm. The result of the rate law is that at high concentrations of Y, the rate approximates $k[M]_{tot}$ while at low concentrations the result is $kK_E[M]_{tot}[Y]$.

The Eigen-Fuoss equation shows that higher values of K_E (and thus a faster pre-equilibrium) are obtained for large, oppositely-charged ions in solution.

Ate complex

An **ate complex** in chemistry is a salt formed by the reaction of a Lewis acid with a Lewis base whereby the central atom (from the Lewis acid) increases its valence and gains a negative formal charge. (In this definition, the meaning of valence is equivalent to coordination number).

Often in chemical nomenclature the phrase *ate* is suffixed to the element in question. For example, the ate complex of a boron compound is called a borate. Thus trimethylborane and methyllithium react to form the **ate compound** $LiB(CH_3)_4$, lithium tetramethylborate(1-). This concept was introduced by Georg Wittig in 1958. Ate complexes are common for metals, including the transition metals (groups 3-11), as well as the metallic or semi-metallic elements of group 2, 12, and 13. They are also well-established for third-period or heavier elements of groups 14–18 in their higher oxidation states.

Ate complexes are a counterpart to onium ions. Lewis acids form **ate ions** when the central atom reacts with a donor (2 e X-type ligand), gaining one more bond and becoming a negative-charged anion. Lewis bases form onium ions when the central atom reacts with an acceptor (0 e Z-type ligand), gaining one more bond and becoming a positive-charged cation.

-ate suffix

The phrase **-ate ion** or **ate ion** can refer generically to many negatively charged anions. **-ate compound** or **ate compound** can refer to salts of the anions or esters of the functional

groups. Chemical terms ending in -ate (and -ite) generally refer to the negatively charged anions, neutral radicals, and covalently bonded functional groups that share the same chemical formulas (with different charges). For example, the nitrate anion, NO_3; the nitrate functional group that forms nitrate esters, $–NO_3$ or $–ONO_2$; and the nitrate radical or nitrogen trioxide, NO_3.

Most numerous are oxyanions (oxyacids that have *lost* one or more protons to deprotonation) and the radicals and functional groups that share their names. The large family starts with borate, carbonate, nitrate, fluorate, aluminate, silicate, phosphate, sulfate, chlorate, titanate, vanadate, chromate, manganate, ferrate, percobaltate, germanate, arsenate, selenate, bromate, molybdate, pertechnate, perruthenate, stannate, antimonate, tellurate, iodate, perxenate, tungstate, plumbate, bismuthate. Also the partially deprotonated hydrogensulfate, hydrogenphosphate, dihydrogenphosphate, etc. Also phosphonate, sulfonate, etc. Also carboxylate ions such as formate, acetate, propionate, butyrate, isobutyrate; oxalate, etc. Also methanolate / methoxide, ethanolate / ethoxide, etc. Also cyanate, isocyanate, thiocyanate, fulminate. Sulfur oxoanions, thioacetate, thiolates. Chlorosulfate, chloroacetate, etc.

A lyate ion is a generic solvent molecule that has become a negative ion by *loss* of one or more protons.

The -ate suffix also applies to negative fluoroanions, fluorides which have *gained* one or more protons and twice as many electrons. Tetrafluoroborate, BF_4, is boron trifluoride, BF_3, which has gained one proton and two electrons.

Bond valence method

The **bond valencemethod** or mean method (or bond valence sum) (not to be mistaken for the valence bond theory in quantum chemistry) is a popular method in coordination chemistry to estimate the oxidation states of atoms. It is derived from the bond valence model, which is a simple yet robust model for validating chemical structures with localized bonds or used to predict some of their properties. This model is a development of Pauling's rules.

Theory

Introduction

Although the bond valence model is mostly used for validating newly determined structures, it is capable of predicting many of the properties of those chemical structures that can be described by localized bonds

In the bond valence model, the *valence of an atom*, V, is defined as the number of electrons the atom uses for bonding. This is equal to the number of electrons in its valence shell if all the valence shell electrons are used for bonding. If they are not, the remainder will form non-bonding electron pairs, usually known as *lone pairs*.

The *valence of a bond*, S, is defined as the number of electron pairs forming the bond. In general this is not an integral number. Since each of the terminal atoms contributes equal numbers of electrons to the bond, the bond valence is also

equal to the number of valence electrons that each atom contributes. Further, since within each atom, the negatively charged valence shell is linked to the positively charged core by an *electrostatic flux* that is equal to the charge on the valence shell, it follows that the bond valence is also equal to the electrostatic flux that links the core to the electrons forming the bond. The bond valence is thus equal to three different quantities: the number of electrons each atom contributes to the bond, the number of electron pairs that form the bond, and the electrostatic flux linking each core to the bonding electron pair.

The distortion theorem

Eq. 2 is used to derive the distortion theorem which states that the more the individual bond lengths in a coordination sphere deviate from their average, the more the average bond length increases provided the valence sum is kept constant. Alternatively if the average bond length is kept constant, the more the bond valence sum increases

The ionic model

The bond valence model can be reduced to the traditional ionic model if certain conditions are satisfied. These conditions require that atoms be divided into cations and anions in such a way that (a) the electronegativity of every anion is equal to, or greater than, the electronegativity of any of the cations, (b) that the structure is electroneutral when the ions carry charges equal to their valence, and (c) that all the bonds have a cation at one end and an anion at the other. If these conditions are satisfied, as they are in many ionic and covalent

compounds, the electrons forming a bond can all be formally assigned to the anion. The anion thus acquires a formal negative charge and the cation a formal positive charge, which is the picture on which the ionic model is based. The electrostatic flux that links the cation core to its bonding electrons now links the cation core to the anion. In this picture, a cation and anion are bonded to each other if they are linked by electrostatic flux, with the flux being equal to the valence of the bond. In a representative set of compounds Preiser et al. have confirmed that the electrostatic flux is the same as the bond valence determined from the bond lengths using Eq. 2.

The association of the cation bonding electrons with the anion in the ionic model is purely formal. There is no change in physical locations of any electrons, and there is no change in the bond valence. The terms "anion" and "cation" in the bond valence model are defined in terms of the bond topology, not the chemical properties of the atoms. This extends the scope of the ionic model well beyond compounds in which the bonding would normally be considered as "ionic". For example, methane, CH_4, obeys the conditions for the ionic model with carbon as the cation and hydrogen as the anion (or vice versa, since carbon and hydrogen have the same electronegativity).

For compounds that contain cation-cation or anion-anion bonds it is usually possible to transform these homoionic bonds into cation-anion bonds either by treating the atoms linked by the homoionic bond as a single complex cation (e.g., Hg_2), or by treating the bonding electrons in the homoionic bond as a pseudo-anion to transform a cation-cation bond into two cation - pseudo-anion bonds, e.g., Hg-e-Hg.

The covalent model

Structures containing covalent bonds can be treated using the ionic model providing they satisfy the topological conditions given above, but a special situation applies to hydrocarbons which allows the bond valence model to be reduced to the traditional bond model of organic chemistry. If an atom has a valence, V, that is equal to its coordination number, N, its bonding strength according to Eq. 3 is exactly 1.0 vu (valence units), a condition that greatly simplifies the model. This condition is obeyed by carbon, hydrogen and silicon. Since these atoms all have bonding strengths of 1.0 vu the bonds between them are all predicted to have integral valences with carbon forming four single bonds and hydrogen one. Under these conditions, the bonds are all single bonds (or multiples of single bonds). Compounds can be constructed by linking carbon and hydrogen atoms with bonds that are all exactly equivalent. Under certain conditions, nitrogen can form three bonds and oxygen two, but since nitrogen and oxygen typically also form hydrogen bonds, the resulting N-H and O-H bonds have valences less than 1.0 vu, leading through the application of Eq. 1, to the C-C and C-H bonds having valences that differ from 1.0 vu. Nevertheless, the simple bonding rules of organic chemistry are still good approximations, though the rules of the bond valence model are better.

Predicting bonding geometry

A chemical structure can be represented by a bond network of the kind familiar in molecular diagrams. The infinitely connected bond networks found in crystals can be simplified into finite networks by extracting one formula unit and

reconnecting any broken bonds to each other. If the bond network is not known, a plausible network can be created by connecting well matched cations and anions that satisfy Eq. 4. If the finite network contains only cation-anion bonds, every bond can be treated as an electric capacitor (two equal and opposite charges linked by electrostatic flux). The bond network is thus equivalent to a capacitive electrical circuit with the charge on each capacitor being equivalent to the bond valence. The individual bond capacitors are not initially known, but in the absence of any information to the contrary we assume that they are all equal. In this case the circuit can be solved using the Kirchhoff equations, yielding the valences of each bond. Eq. 2 can then be used to calculate bond lengths which are found to lie within a few picometres of the observed bond lengths if no additional constraints are present. Additional constraints include electronic anisotropies (lone pairs and Jahn-Teller distortions) or steric constraints, (bonds stretched or compressed in order to fit them into three-dimensional space). Hydrogen bonds are an example of a steric constraint.

The repulsion resulting from the close approach of the donor and acceptor atoms causes the bonds to be stretched, and under this constraint the distortion theorem predicts that the hydrogen atom will move off-center.

The bond valence is a vector directed along the bond since it represents the electrostatic field linking the ions. If the atom is unconstrained, the sum of the bond valence vectors around an atom is expected to be zero, a condition that limits the range of possible bond angles.

Strengths and limitations of the model

The bond valence model is an extension of the electron counting rules and its strength lies in its simplicity and robustness. Unlike most models of chemical bonding, it does not require a prior knowledge of the atomic positions and so can be used to construct chemically plausible structures given only the composition. The empirical parameters of the model are tabulated and are readily transferable between bonds of the same type. The concepts used are familiar to chemists and provide ready insight into the chemical restraints acting on the structure. The bond valence model uses mostly classical physics, and with little more than a pocket calculator, it gives quantitative predictions of bond lengths and places limits on what structures can be formed.

However, like all models, the bond valence model has its limitations. It is restricted to compounds with localized bonds; it does not, in general, apply to metals or aromatic compounds where the electrons are delocalized. It cannot in principle predict electron density distributions or energies since these require the solution of the Schoedinger equation using the long-range Coulomb potential which is incompatible with the concept of a localized bond.

History

The bond valence method is a development of Pauling's rules. In 1930, Bragg showed that Pauling's electrostatic valence rule could be represented by electrostatic lines of force emanating from cations in proportion to the cation charge and ending on

anions. The lines of force are divided equally between the bonds to the corners of the coordination polyhedron. Starting with Pauling in 1947 a correlation between cation–anion bond length and bond strength was noted. It was then shown later that if bond lengths were included in the calculation of bond strength, its accuracy was improved, and this revised method of calculation was termed the bond valence. These new insights were developed by later workers culminating in the set of rules termed the bond valence model.

Actinide oxides

- It is possible by bond valence calculations to estimate how great a contribution a given oxygen atom is making to the assumed valence of uranium. Zachariasen lists the parameters to allow such calculations to be done for many of the actinides. Bond valence calculations use parameters which are estimated after examining a large number of crystal structures of uranium oxides (and related uranium compounds); note that the oxidation states which this method provides are only a guide which assists in the understanding of a crystal structure.

Doing the calculations

It is possible to do these simple calculations on paper or to use software. A program which does it can be obtained free of charge. In 2020 David Brown published a nearly comprehensive set of bond valence parameters on the IuCr web site.

Bridging ligand

In coordination chemistry, a **bridging ligand** is a ligand that connects two or more atoms, usually metal ions. The ligand may be atomic or polyatomic. Virtually all complex organic compounds can serve as bridging ligands, so the term is usually restricted to small ligands such as pseudohalides or to ligands that are specifically designed to link two metals.

In naming a complex wherein a single atom bridges two metals, the bridging ligand is preceded by the Greek letter mu, μ, with a subscript number denoting the number of metals bound to the bridging ligand. μ_2 is often denoted simply as μ. When describing coordination complexes care should be taken not to confuse μ with η ('eta'), which relates to hapticity. Ligands that are not bridging are called **terminal ligands**.

Bonding

For doubly bridging (μ_2-) ligands, two limiting representation are 4-electron and 2-electron bonding interactions. These cases are illustrated in main group chemistry by $[Me_2Al(\mu_2\text{-}Cl)]_2$ and $[Me_2Al(\mu_2\text{-}Me)]_2$. Complicating this analysis is the possibility of metal–metal bonding. Computational studies suggest that metal-metal bonding is absent in many compounds where the metals are separated by bridging ligands. For example, calculations suggest that $Fe_2(CO)_9$ lacks an iron–iron bond by virtue of a 3-center 2-electron bond involving one of three bridging CO ligands.

Polyfunctional ligands

- Polyfunctional ligands can attach to metals in many ways and thus can bridge metals in diverse ways, including sharing of one atom or using several atoms. Examples of such polyatomic ligands are the oxoanions CO_{2-3} and the related carboxylates, PO_{3-4}, and the polyoxometalates. Several organophosphorus ligands have been developed that bridge pairs of metals, a well-known example being $Ph_2PCH_2PPh_2$.

Chelation

Chelation/ˈkiːˌleɪˈʃən/ is a type of bonding of ions and molecules to metal ions. It involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom. These ligands are called chelants, chelators, chelating agents, or sequestering agents. They are usually organic compounds, but this is not a necessity, as in the case of zinc and its use as a maintenance therapy to prevent the absorption of copper in people with Wilson's disease.

Chelation is useful in applications such as providing nutritional supplements, in chelation therapy to remove toxic metals from the body, as contrast agents in MRI scanning, in manufacturing using homogeneous catalysts, in chemical water treatment to assist in the removal of metals, and in fertilizers.

Chelate effect

The chelate effect is the greater affinity of chelating ligands for a metal ion than that of similar nonchelating (monodentate) ligands for the same metal.

The thermodynamic principles underpinning the chelate effect are illustrated by the contrasting affinities of copper(II) for ethylenediamine (en) vs. methylamine.

- $Cu + en \rightleftharpoons [Cu(en)]$ **(1)**

- $Cu + 2\ MeNH_2 \rightleftharpoons [Cu(MeNH_2)_2]$ **(2)**

In (**1**) the ethylenediamine forms a chelate complex with the copper ion. Chelation results in the formation of a five-membered CuC_2N_2 ring. In (**2**) the bidentate ligand is replaced by two monodentate methylamine ligands of approximately the same donor power, indicating that the Cu–N bonds are approximately the same in the two reactions.

The thermodynamic approach to describing the chelate effect considers the equilibrium constant for the reaction: the larger

the equilibrium constant, the higher the concentration of the complex.

- $[Cu(en)] = \beta_{11}[Cu][en]$ **(3)**

- $[Cu(MeNH_2)_2] = \beta_{12}[Cu][MeNH_2]$ **(4)**

Electrical charges have been omitted for simplicity of notation. The square brackets indicate concentration, and the subscripts to the stability constants, β, indicate the stoichiometry of the complex. When the analytical concentration of methylamine is twice that of ethylenediamine and the concentration of copper is the same in both reactions, the concentration [Cu(en)] is much higher than the concentration $[Cu(MeNH_2)_2]$ because $\beta_{11} \gg \beta_{12}$.

In nature

Numerous biomolecules exhibit the ability to dissolve certain metal cations. Thus, proteins, polysaccharides, and polynucleic acids are excellent polydentate ligands for many metal ions. Organic compounds such as the amino acids glutamic acid and histidine, organic diacids such as malate, and polypeptides such as phytochelatin are also typical chelators. In addition to these adventitious chelators, several

biomolecules are specifically produced to bind certain metals (see next section).

In biochemistry and microbiology

Virtually all metalloenzymes feature metals that are chelated, usually to peptides or cofactors and prosthetic groups. Such chelating agents include the porphyrin rings in hemoglobin and chlorophyll. Many microbial species produce water-soluble pigments that serve as chelating agents, termed siderophores. For example, species of *Pseudomonas* are known to secrete pyochelin and pyoverdine that bind iron. Enterobactin, produced by *E. coli*, is the strongest chelating agent known. The marine mussels use metal chelation esp. Fe chelation with the Dopa residues in mussel foot protein-1 to improve the strength of the threads that they use to secure themselves to surfaces.

In geology

In earth science, chemical weathering is attributed to organic chelating agents (e.g., peptides and sugars) that extract metal ions from minerals and rocks. Most metal complexes in the environment and in nature are bound in some form of chelate ring (e.g., with a humic acid or a protein). Thus, metal chelates are relevant to the mobilization of metals in the soil, the uptake and the accumulation of metals into plants and microorganisms. Selective chelation of heavy metals is relevant to bioremediation (e.g., removal of Cs from radioactive waste).

Medical applications

Nutritional supplements

In the 1960s, scientists developed the concept of chelating a metal ion prior to feeding the element to the animal. They believed that this would create a neutral compound, protecting the mineral from being complexed with insoluble salts within the stomach, which would render the metal unavailable for absorption. Amino acids, being effective metal binders, were chosen as the prospective ligands, and research was conducted on the metal–amino acid combinations. The research supported that the metal–amino acid chelates were able to enhance mineral absorption.

During this period, synthetic chelates such as ethylenediaminetetraacetic acid (EDTA) were being developed. These applied the same concept of chelation and did create chelated compounds; but these synthetics were too stable and not nutritionally viable. If the mineral was taken from the EDTA ligand, the ligand could not be used by the body and would be expelled. During the expulsion process the EDTA ligand randomly chelated and stripped another mineral from the body.

According to the Association of American Feed Control Officials (AAFCO), a metal–amino acid chelate is defined as the product resulting from the reaction of metal ions from a soluble metal salt with amino acids, with a mole ratio in the range of 1–3 (preferably 2) moles of amino acids for one mole of metal. The average weight of the hydrolyzed amino acids must be

approximately 150 and the resulting molecular weight of the chelate must not exceed 800 Da.

Since the early development of these compounds, much more research has been conducted, and has been applied to human nutrition products in a similar manner to the animal nutrition experiments that pioneered the technology. Ferrous bis-glycinate is an example of one of these compounds that has been developed for human nutrition.

Dental and oral application

Dentin adhesives were first designed and produced in the 1950s based on a co-monomer chelate with calcium on the surface of the tooth and generated very weak water-resistant chemical bonding (2–3 MPa).

Heavy-metal detoxification

Chelation therapy is an antidote for poisoning by mercury, arsenic, and lead. Chelating agents convert these metal ions into a chemically and biochemically inert form that can be excreted. Chelation using calcium disodium EDTA has been approved by the U.S. Food and Drug Administration (FDA) for serious cases of lead poisoning. It is not approved for treating "heavy metal toxicity".

Although beneficial in cases of serious lead poisoning, use of disodium EDTA (edetate disodium) instead of calcium disodium EDTA has resulted in fatalities due to hypocalcemia. Disodium EDTA is not approved by the FDA for any use, and all FDA-approved chelation therapy products require a prescription.

Pharmaceuticals

Chelate complexes of gadolinium are often used as contrast agents in MRI scans, although iron particle and manganese chelate complexes have also been explored. Bifunctional chelate complexes of zirconium, gallium, fluorine, copper, yttrium, bromine, or iodine are often used for conjugation to monoclonal antibodies for use in antibody-based PET imaging. These chelate complexes often employ the usage of hexadentate ligands such as desferrioxamine B (DFO), according to Meijs *et al.*, and the gadolinium complexes often employ the usage of octadentate ligands such as DTPA, according to Desreux *et al.* Auranofin, a chelate complex of gold, is used in the treatment of rheumatoid arthritis, and penicillamine, which forms chelate complexes of copper, is used in the treatment of Wilson's disease and cystinuria, as well as refractory rheumatoid arthritis.

Other medical applications

Chelation in the intestinal tract is a cause of numerous interactions between drugs and metal ions (also known as "minerals" in nutrition). As examples, antibioticdrugs of the tetracycline and quinolone families are chelators of Fe, Ca, and Mg ions.

EDTA, which binds to calcium, is used to alleviate the hypercalcemia that often results from band keratopathy. The calcium may then be removed from the cornea, allowing for some increase in clarity of vision for the patient.

Industrial and agricultural applications

Catalysis

Homogeneous catalysts are often chelated complexes. A representative example is the use of BINAP (a bidentate phosphine) in Noyori asymmetric hydrogenation and asymmetric isomerization. The latter has the practical use of manufacture of synthetic (–)-menthol.

Water softening

Citric acid is used to soften water in soaps and laundry detergents. A common synthetic chelator is EDTA. Phosphonates are also well-known chelating agents. Chelators are used in water treatment programs and specifically in steam engineering, *e.g.*, boiler water treatment system: *Chelant Water Treatment system.* Although the treatment is often referred to as "softening," chelation has little effect on the water's mineral content, other than to make it soluble and lower the water's pH level.

Fertilizers

Metal chelate compounds are common components of fertilizers to provide micronutrients. These micronutrients (manganese, iron, zinc, copper) are required for the health of the plants. Most fertilizers contain phosphate salts that, in the absence of chelating agents, typically convert these metal ions into

insoluble solids that are of no nutritional value to the plants. EDTA is the typical chelating agent that keeps these metal ions in a soluble form.

Etymology

The word chelation is derived from Greekχηλή, *chēlē*, meaning "claw"; the ligands lie around the central atom like the claws of a lobster. The term *chelate* was first applied in 1920 by Sir Gilbert T. Morgan and H. D. K. Drew, who stated: "The adjective chelate, derived from the great claw or *chele* (Greek) of the lobster or other crustaceans, is suggested for the caliperlike groups which function as two associating units and fasten to the central atom so as to produce heterocyclic rings."