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SEMESTR-VI

BIOINORGANIC CHEMISTRY

Bioinorganic chemistry is a field that examines the role of metals in biology. Bioinorganic chemistry includes the study of both natural phenomena such as the behavior of metal proteins as well as artificially introduced metals, including those that are non-essential, in medicine and toxicology. Many biological processes such as respiration depend upon molecules that fall within the realm of inorganic chemistry. As a mix of biochemistry and inorganic chemistry, bioinorganic chemistry is important which shows the electron-transfer proteins, substrate bindings and activation, atom and group transfer chemistry as well as metal properties in biological chemistry.

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

Different System in bioinorganic chemistry

Several distinct systems are of identifiable in bioinorganic chemistry. Major areas include:

Metal ion transport and storage

In this we include a different collection of ion channels, ion pumps (e.g. NaKATPase), vacuoles, siderophores, and other proteins and small molecules which control the concentration of metal ions in the cells. One issue is that many metals that are metabolically required are not readily available owing to solubility or scarcity. Organisms have developed a number of strategies for collecting such elements and transporting them.

Enzymology

Many reactions in life sciences involve water and metal ions are often at the catalytic centers (active sites) for these enzymes, i.e. these are metal proteins. Often the reacting water is a ligand. Examples of hydrolase enzymes are carbonic anhydrase, metallophosphatases, and metalloproteinases. Bioinorganic chemists seek to understand and replicate the function of these metal proteins.

Metal-containing electron transfer proteins are also common. They can be organized into three major classes:

iron-sulfur proteins (such as rubredoxins, ferredoxins, and Rieske proteins),

blue copper proteins, and cytochromes.

These electron transport proteins are complementary to the non-metal electron transporters nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). The nitrogen cycle make extensive use of metals for the redox interconversions.

Toxicity

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

Oxygen transport and activation proteins

Transition metal dioxygen complex

Aerobic life make extensive use of metals such as iron, copper, and manganese. Heme is utilized by red blood cells in the form of hemoglobin for oxygen transport and is perhaps the most recognized metal system in biology. Other oxygen transport systems include myoglobin, hemocyanin, and hemerythrin. Oxidases and oxygenases are metal systems found throughout nature that take advantage of oxygen to carry out important reactions such as energy generation in cytochrome c oxidase or small molecule oxidation in cytochrome P450 oxidases or methane monooxygenase. Some metalloproteins are designed to protect a biological system from the potentially harmful effects of oxygen and other reactive oxygen-containing molecules such as hydrogen peroxide. These systems include peroxidases, catalases, and superoxide dismutases. A complementary metalloprotein to those that react with oxygen is the oxygen evolving complex present in plants. This system is part of the complex protein machinery that produces oxygen as plants perform photosynthesis.

Bioorganometallic chemistry

Bioorganometallic systems feature metal-carbon bonds as structural elements or as intermediates. Bioorganometallic enzymes and proteins include the hydrogenases, FeMoco in nitrogenase, and methylcobalamin. These naturally occurring organometallic compounds. This area is more focused on the utilization of metals by unicellular organisms. Bioorganometallic compounds are significant in environmental chemistry.

Metals in medicine

A number of drugs contain metals. This theme relies on the study of the design and mechanism of action of metal-containing pharmaceuticals, and compounds that interact with endogenous metal ions in enzyme active sites. The most widely used anti-cancer drug is cisplatin. MRI contrast agent commonly contain gadolinium. Lithium carbonate has been used to treat the manic phase of bipolar disorder. Gold antiarthritic drugs, e.g. auranofin have been commercialized. Carbon monoxide-releasing molecules are metal complexes have been developed to suppress inflammation by releasing small amounts of carbon monoxide. The cardiovascular and neuronal importance of nitric oxide has been examined, including the enzyme nitric oxide synthase. (See also: nitrogen assimilation.) Besides, metallic transition complexes based on triazolopyrimidines have been tested against several parasite strains.

Biomineralization

Biomineralization is the process by which living organisms produce minerals, often to harden or stiffen existing tissues. Such tissues are called mineralized tissues.[6][7][8] Examples include silicates in algae and diatoms, carbonates in invertebrates, and calcium phosphates and carbonates in vertebrates. Other examples include copper, iron and gold deposits involving bacteria. Biologically-formed minerals often have special uses such as magnetic sensors in magnetotactic bacteria (Fe_3O_4), gravity sensing devices ($CaCO_3$, $CaSO_4$, $BaSO_4$) and iron storage and mobilization ($Fe_2O_3 \bullet H_2O$ in the protein ferritin). Because extracellular[9] iron is strongly involved in inducing calcification, its control is essential in developing shells; the protein ferritin plays an important role in controlling the distribution of iron.

Types of inorganic elements in biology

Alkali and alkaline earth metals

Like many antibiotics, monensin-A is an ionophore that tightly bind Na^+ (shown in yellow).[13]

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

Transition metals

The transition metals are usually present as trace elements in organisms, with zinc and iron being most abundant. These metals are used in some proteins as cofactors and are essential for the activity of enzymes such as catalase and oxygen-carrier proteins such as hemoglobin. These cofactors are bound tightly to a specific protein; although enzyme cofactors can be modified during catalysis, cofactors always return to their original state after catalysis has taken place. The metal micronutrients are taken up into organisms by specific transporters and bound to storage proteins such as ferritin or metallothionein when not being used.[21][22] Cobalt is essential for the functioning of vitamin B12.

Main group compounds

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

Metal toxicity

Metal toxicity or **metal poisoning** is the toxic effect of certain metals in certain forms and doses on life. Some metals are toxic when they form poisonous soluble compounds. Certain metals have no biological role, i.e. are not essential minerals, or are toxic when in a certain form.[1] In the case of lead, any measurable amount may have negative health effects.[2] Often heavy metals are thought as synonymous, but lighter metals may also be toxic in certain circumstances, such as beryllium and lithium. Not all heavy metals are particularly toxic, and some are essential, such as iron. The definition may also include trace elements when in abnormally high doses may be toxic. An option for treatment of metal poisoning may be chelation therapy, which is a technique which involves the administration of chelation agents to remove metals from the body.

Toxic metals sometimes imitate the action of an essential element in the body, interfering with the metabolic process resulting in illness. Many metals, particularly heavy metals are toxic, but some heavy metals are essential, and some, such as bismuth, have a low toxicity. Most often the definition of toxic metals includes at least cadmium, manganese, lead, mercury and the radioactive metals.[3] Metalloids (arsenic, polonium) may be included in the definition. Radioactive metals have both radiological toxicity and chemical toxicity. Metals in an oxidation state abnormal to the body may also become toxic: chromium(III) is an essential trace element, but chromium(VI) is a carcinogen.

Toxicity is a function of solubility. Insoluble compounds as well as the metallic forms often exhibit negligible toxicity. The toxicity of any metal depends on its ligands. In some cases, organometallic forms, such as methylmercury and tetraethyl lead, can be extremely toxic. In other cases, organometallic derivatives are less toxic such as the cobaltocenium cation.

Decontamination for toxic metals is different from organic toxins: because toxic metals are elements, they cannot be destroyed. Toxic metals may be made insoluble or collected, possibly by the aid of chelating agents, or through bioremediation. Alternatively, they can be diluted into a sufficiently large reservoir, such as the sea, because immediate toxicity is a function of concentration rather than amount.

Toxic metals can bioaccumulate in the body and in the food chain. Therefore, a common characteristic of toxic metals is the chronic nature of their toxicity. This is particularly notable with radioactive heavy metals such as radium, which imitates calcium to the point of being incorporated into human bone, although similar health implications are found in lead or mercury poisoning.

Types of poisoning

Arsenic poisoning

Arsenic poisoning is a medical condition caused by elevated levels of arsenic in the body. The dominant basis of arsenic poisoning is from ground water that naturally contains high concentrations of arsenic. A 2007 study found that over 137 million people in more than 70 countries are probably affected by arsenic poisoning from drinking water.

Cadmium poisoning

is an extremely toxic metal commonly found in industrial workplaces. Due to its low permissible exposure limit, overexposures may occur even in situations where trace quantities of cadmium are found. Cadmium is used extensively in electroplating, although the nature of the operation does not generally lead to overexposures. Cadmium is also found in some industrial paints and may represent a hazard when sprayed. Operations involving removal of cadmium paints by scraping or blasting may pose a significant hazard. Cadmium is also present in the manufacturing of some types of batteries. Exposures to cadmium are addressed in specific standards for the general industry, shipyard employment, construction industry, and the agricultural industry.[1]

Lead poisoning

Lead poisoning is a medical condition in humans and other vertebrates caused by increased levels of the heavy metal lead in the body. Lead interferes with a variety of body processes and is toxic to many organs and tissues including the heart, bones, intestines, kidneys, and reproductive and nervous systems. It interferes with the development of the nervous system and is therefore particularly toxic to children, causing potentially permanent learning and behavior disorders. Symptoms include abdominal cramping, constipation, tremors, mood changes, infertility, anemia, and toxic psychosis.

Mercury poisoning

Mercury poisoning is a disease caused by exposure to mercury or its compounds. Mercury (chemical symbol Hg) is a heavy metal occurring in several forms, all of which can produce toxic effects in high enough doses. Its zero oxidation state Hg^0 exists as vapor or as liquid metal, its mercurous state Hg_2^{2+} exists as inorganic salts, and its mercuric state Hg^{2+} may form either inorganic salts or organomercury compounds; the three groups vary in effects. Toxic effects include damage to the brain, kidney, and lungs. Mercury poisoning can result in several diseases, including acrodynia (pink disease), Hunter-Russell syndrome, and Minamata disease.

Symptoms typically include sensory impairment (vision, hearing, speech), disturbed sensation and a lack of coordination. The type and degree of symptoms exhibited depend upon the individual toxin, the dose, and the method and duration of exposure.

Chelation therapy

Chelation therapy is a medical procedure that involves the administration of chelating agents to remove heavy metals from the body. Chelation therapy has a long history of use in clinical toxicology and remains in use for some very specific medical treatments, although it is administered under very careful medical supervision due to various inherent risks.

Chelation therapy must be administered with care as it has a number of possible side effects, including death. In response to increasing use of chelation therapy as alternative medicine and in circumstances in which the therapy should not be used in conventional medicine, various health organizations have confirmed that medical evidence does not support the effectiveness of chelation therapy for any purpose other than the treatment of heavy metal poisoning. Over-the-counter chelation products are not approved for sale in the United States.

Medical uses

Chelation therapy is the preferred medical treatment for metal poisoning,[1][7] including acute mercury, iron (including in cases of sickle-cell disease and thalassemia),[8][9] arsenic, lead, uranium, plutonium and other forms of toxic metal poisoning. The chelating agent may be administered intravenously, intramuscularly, or orally, depending on the agent and the type of poisoning.

Chelating agents

There are a variety of common chelating agents with differing affinities for different metals, physical characteristics, and biological mechanism of action. For the most common forms of heavy metal intoxication – lead, arsenic, or mercury – a number of chelating agents are available. Dimercaptosuccinic acid (DMSA) has been recommended for the treatment of lead poisoning in children by poison control centers around the world. Other chelating agents, such as 2,3-dimercaptopropanesulfonic acid (DMPS) and alpha lipoic acid (ALA), are used in conventional and alternative medicine. Some common chelating agents are ethylenediaminetetraacetic acid (EDTA), 2,3-dimercaptopropanesulfonic acid (DMPS), and thiamine tetrahydrofurfuryl disulfide (TTFD). Calcium-disodium EDTA and DMSA are only approved for the removal of lead by the Food and Drug Administration while DMPS and TTFD are not approved by the FDA. These drugs bind to heavy metals in the body and prevent them from binding to other agents. They are then excreted from the body. The chelating process also removes vital nutrients such as vitamins C and E, therefore these must be supplemented.