What is the importance of chelates in biology?

Chelation is the formation or presence of two or more separate bindings between a polydentate (multiple bonded) ligand and a single central atom. Usually these ligands are organic compounds, and are called chelants, chelators, chelating agents, or sequestering agents.

The ligand forms a chelate complex with the substrate. Chelate complexes are contrasted with coordination complexes composed of monodentate ligands, which form only one bond with the central atom. The denticity of a central atom, of course, refers to the number of bonds formed by the central atom.

Chelants, according to ASTM-A-380, are " chemicals that form soluble, complex molecules with certain metal ions, inactivating the ions so that they cannot normally react with other elements or ions to produce precipitates or scale."

The chelate effect.

The chelate effect describes the enhanced affinity of chelating ligands for a metal ion compared to the affinity of a collection of similar nonchelating (monodentate) ligands for the same metal.

Consider the two equilibria, in aqueous solution, between the copper(II) ion, Cu2+ and ethylenediamine (en) on the one hand and methylamine, MeNH2 on the other.

Cu2+ + en

[Cu(en)]2+ (1)

Cu^{2+} + 2 $MeNH_2$ $[Cu(MeNH_2)_2]^{2+}$ (2)

In (1) the bidentate ligand ethylene diamine forms a chelate complex with the copper ion. Chelation results in the formation of a five-membered ring. In (2) the bidentate ligand is replaced by two monodentate methylamine ligands of approximately the same donor power, meaning that the enthalpy of formation of Cu-N bonds is approximately the same in the two reactions. Under conditions of equal copper concentrations and when the concentration of methylamine is twice the concentration of ethylenediamine, the concentration of the complex (1) will be greater than the concentration of the complex (2). The effect increases with the number of chelate rings so the concentration of the EDTA complex, which has six chelate rings, is much much higher than a corresponding complex with two monodentate nitrogen donor ligands and four monodentate carboxylate ligands. Thus, the phenomenon of the chelate effect is a firmly established empirical fact.

Cu^{2+} complexes with methylamine (left) and ethylenediamine (right)

The thermodynamic approach to explaining the chelate effect considers the equilibrium constant for the reaction: the larger the equilibrium constant, the higher the concentration of the complex.

Ethylene diamine tetra acetic acid,

Widely abbreviated as EDTA is a polyamino carboxylic acid and a colourless, water-soluble solid. Its conjugate base is named ethylenediaminetetraacetate. It is widely used to dissolve scale. Its usefulness arises because of its role as a hexadentate (“ six-toothed”) ligand

and chelating agent, i. e. its ability to " sequester" metal ions such as Ca^{2+} and Fe^{3+}. After being bound by EDTA, metal ions remain in solution but exhibit diminished reactivity. EDTA is produced as several salts, notably disodium EDTA and calcium disodium EDTA.

EDTA is used to bind metal ions in chelation therapy, e. g., for mercury and lead poisoning. It is used in a similar manner to remove excess iron from the body. This therapy is used to

treat the complication of repeated blood transfusions, as would be applied to treat thalassaemia. EDTA acts as a powerful antioxidant to prevent free radicals from injuring blood vessel walls.

Dentists use EDTA solutions to remove inorganic debris (smear layer) and prepare root canals for obturation. It serves as a preservative (usually to enhance the action of another preservative such as benzalkonium chloride or thiomersal) in ocular preparations and eyedrops. In evaluating kidney function, the complex $[Cr(edta)]^-$ is administered intravenously and its filtration into the urine is monitored. This method is useful for evaluating glomerular filtration rate.

EDTA is used extensively in the analysis of blood. It is an anticoagulant for blood samples for CBC/FBEs (complete blood count also known as full blood examination). Laboratory studies also suggest that EDTA chelation may prevent collection of platelets on the lining of the vessel [such as arteries] (which can otherwise lead to formation of blood clots, which itself is associated with atheromatous plaque formation or rupture, and thereby ultimately disrupts blood flow). These ideas are theoretical, and have so far been proven ineffective; however, a major clinical study of the effects of EDTA on coronary arteries is currently (2008) proceeding. EDTA played a role in the O. J. Simpson trial when the defense alleged that one of the blood samples collected from Simpson's estate was found to contain traces of the compound.

In nature

Virtually all biochemicals exhibit the ability to dissolve certain metal cations. Thus, proteins, polysaccharides, and polynucleic acids are excellent polydentate ligands for many metal ions. In addition to these adventitious chelators, several biomolecules are produced to specifically bind certain metals . Histidine, malate and phytochelatin are typical chelators used by plants.

Histidine (abbreviated as His or H) is one of the 22 proteinogenic amino acids. In terms of nutrition, histidine is considered an essential amino acid in human infants. After reaching several years of age, humans begin to synthesize it, at which point it becomes a non-essential amino acid. Its codons are CAU and CAC.

Histidine was first isolated by German physician Albrecht Kossel in 1896.

Malic acid is an organic compound with the formula HO2CCH2CHOHCO2H. This carboxylic diacid is the active ingredient in many sour or tart foods. Malic acid is found mostly in unripe fruits. Malic acid has two stereoisomers, a left-handed L-enantiomer and a right-handed D-enantiomer, but only the L isomer exist naturally. The salts and esters of malic acid are known as malates. The malate anion is an intermediate in the citric acid cycle.

Phytochelatins are oligomers of glutathione, produced by the enzyme phytochelatin synthase. They are found in plants, fungi, nematodes and all groups of algae including cyanobacteria. Phytochelatins act as chelators, and are important for heavy metal detoxification. They are abbreviated PC2 through PC11.

A mutant Arabidopsis thaliana lacking phytochelatin synthase is very sensitive to cadmium, but it grows just as well as the wild-type plant at normal concentrations of zinc and copper, two essential metal ions, indicating that phytochelatin is only involved in resistance to metal poisoning. Phytochelatin seems to be transported into the vacuole of plants, so that the metal ions it carries are stored safely away from the proteins of the cytosol.

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 pycocyanin and pyoverdin that bind iron. Enterobactin, produced by E. coli, is the strongest chelating agent known.

Porphyrins are a group of organic compounds of which many occur in nature. One of the best-known porphyrins is heme, the pigment in red blood cells. Heme is a cofactor of the protein hemoglobin. They are heterocyclic macrocycles composed of four modified pyrrole subunits interconnected at their Î± carbon atoms via methine bridges (= CH-). Porphyrins are aromatic

Hemoglobin (also spelled haemoglobin and abbreviated Hb or Hgb) is the iron-containing oxygen-transport metalloprotein in the red blood cells of vertebrates and the tissues of some invertebrates. Hemoglobin in the blood is what transports oxygen from the lungs or gills to the rest of the body (i. e. the tissues) where it releases the oxygen for cell use.

In mammals the protein makes up about 97% of the red blood cell’s dry content, and around 35% of the total content (including water). Hemoglobin has an oxygen binding capacity between 1. 36 and 1. 37 ml O2 per gram of hemoglobin, which increases the total blood oxygen capacity seventyfold.

Hemoglobin is involved in the transport of other gases: it carries some of the body’s respiratory carbon dioxide (about 10% of the total) as carbaminohemoglobin, in which CO2 is bound to the globin protein. The molecule also carries the important regulatory molecule nitric oxide bound to a globin protein thiol group, releasing it at the same time as oxygen.

Heme group

Chlorophyll (also chlorophyl) is a green pigment found in almost all plants, algae, and cyanobacteria. Chlorophyll absorbs light most strongly in the blue portion of the electromagnetic spectrum, followed by the red portion. However, it is a poor absorber of green and near-green portions of the spectrum, hence the green color of chlorophyll-containing tissues.

Chlorophyll was first isolated by Joseph Bienaimé Caventou and Pierre Joseph Pelletier in 1817.

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 micro-organisms. Selective chelation of heavy metals is relevant to bioremediation, e. g. removal of 137Cs from radioactive waste.

Applications

Chelators are used in chemical analysis, as water softeners, and are ingredients in many commercial products such as shampoos and food preservatives. 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.

Heavy metal detoxification.

Chelation therapy is the use of chelating agents to detoxify poisonous metal agents such as mercury, arsenic, and lead by converting them to a chemically inert form that can be excreted without further interaction with the body, and was approved by the U. S. Food and Drug Administration in

1991. In alternative medicine, chelation is used as a treatment for autism, though this practice is controversial due to no scientific plausibility, lack of FDA approval, and its potentially deadly side-effects.

Though they can be beneficial in cases of heavy metal poisoning, chelating agents can also be dangerous. The U. S. CDC reports that use of disodium EDTA instead of calcium EDTA has resulted in fatalities due to hypocalcemia.

Other medical applications

Antibiotic drugs of the tetracycline family are chelators of Ca2+ and Mg2+ ions.

EDTA is also used in root canal treatment as a way to irrigate the canal. EDTA softens the dentin facilitating access to the entire canal length and to remove the smear layer formed during instrumentation.

Chelate complexes of gadolinium are often used as contrast agents in MRI scans.

Copper-64 is a radioactive nuclide of copper which has unique decay properties making it useful in nuclear medicine for both imaging and therapy.

64Cu-ATSM (diacetyl-bis(N4-methylthiosemicarbazone)) has been shown to increase the survival time of tumor-bearing animals with no acute toxicity. Areas of low oxygen retention have been shown to be resistant to radiotherapy because hypoxia reduces the lethal effects of ionizing radiation. 64Cu was believed to kill these cells because of its unique decay properties. In this experiment, animal models having colorectal tumors with and without induced hypoxia were administered Cu-ATSM. Cu-ATSM is preferentially taken up by hypoxic cells over normoxic cells. The results demonstrated that this compound increased survival of the tumor bearing hamsters compared with controls. In the control groups, death due to tumor burden occurred within 4 weeks while animals with a dose greater than 6 mCi of the radioisotope tumor growth was inhibited and survival increased. The results also suggested that multiple doses and a single dose of 10 mCi were equally effective while the multiple dose regimen is safer for non-target tissue.

Radiotherapy of cancer cells using 64Cu can be applied in medical research and clinical practice. The advantages of radiotherapy with beta emitters of this energy are that there is enough to do substantial damage to the target cells but the mean range in tissue is less than a millimeter so non target tissues are unlikely to be harmed. In addition, 64Cu is a positron emitter making it a viable PET imaging radionuclide which can give real time images of the physiological processes in the system. These abilities in conjunction enable accurate monitoring of drug distribution and biokinetics simultaneously. Radiotherapeutic efficacy of Copper-64 depends highly upon the radioligand delivery to the target cells, so the development of bifunctional chelates is central to development of 64Cu's potential as a radiopharmaceutical. With sufficient development, 64Cu is likely to become a central element in nuclear medicine in the years to come.

A preliminary study of the bio availability of iron- and zinc-glycine chelates

Groups of rats were fed diets containing marginal levels of Fe and Zn as glycine chelates (tradename ' Chelazome', Albion Laboratories, Verona, New

Jersey, USA), or the same level of mineral as ferrous sulphate or zinc carbonate. The Fe diets were fed to weanling rats for 4 weeks and the Zn diets to young adult rats for 5 weeks. Blood Hb concentrations were significantly higher in the group fed Fe-chelazome than ferrous sulphate, 149 and 128 g/l respectively ($P < 0.001$), but PCV and liver Fe concentrations were similar between the two groups. No difference in plasma Zn, pancreas, testes or femur Zn concentrations were observed between the two Zn groups, indicating that Zn-chelazome has no advantage over zinc carbonate. The results of this preliminary study indicate that Fe-chelazome has a higher bioavailability than ferrous sulphate and merits further study.