THE FUNCTIONS OF METALS IN HUMAN WELL-BEING.

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Abstract

This brief overview provides insight into the vital contributions of metals to our existence. Their deficiency can contribute to various diseases in the human body, and numerous enzymes depend on them for catalytic functions. Additionally, metals have been utilized in the development of drugs aimed at treating conditions such as cancer, arthritis, and ulcers.

Keywords: metals, metal complexes, metal-containing drugs, metal-containing enzymes.

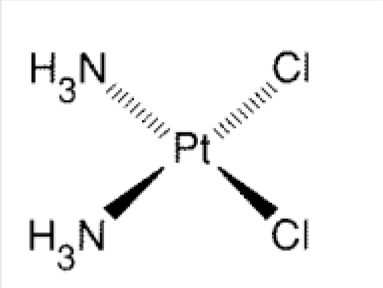
Introduction

Metal ions are essential for maintaining human health as numerous critical biological processes rely on their presence. The absence or scarcity of these ions may lead to diseases. However, certain metal ions, particularly heavy metals like mercury and lead, can be hazardous due to their toxic effects. Essential metal ions, while crucial for survival, can also become toxic in excess amounts.

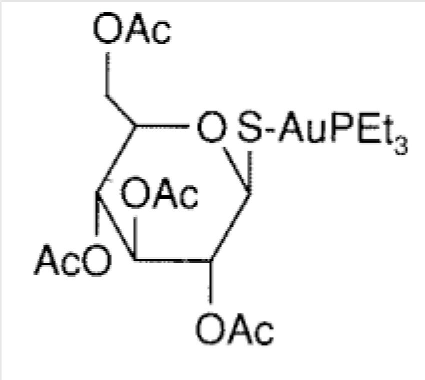
Notable among the metals deemed essential for normal biological functions in humans are sodium (Na), potassium (K), magnesium (Mg), and calcium (Ca) from the main group of elements. Transition metal group elements including vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), molybdenum (Mo), and cadmium (Cd) also play vital roles. Key metal ions usually existing in ion form include Fe, Co, Ni, Ca, Cu, Zn, and Cr.

Deficiency in iron (Fe) and cobalt (Co) leads to anemia, copper (Cu) deficiency is linked to brain and heart diseases along with anemia, zinc (Zn) deficiency results in growth retardation and skin changes, calcium (Ca) deficiency leads to bone deterioration, and chromium (Cr) deficiency reduces glucose tolerance. Consequently, contemporary medicinal bioinorganic chemistry focuses on studying diseases caused by the imbalance of various metal ions at the molecular level and finding remedies.

Metal ions play a crucial role in drug discovery, with notable examples being cisplatin (1) and auranofin (2), widely used in treating genitourinary and head and neck tumors, respectively. Metal ions also serve essential functions in various enzymes, influencing enzyme-catalyzed reactions by modifying electron flow in substrates or enzymes. In the absence of the appropriate metal ion, biochemical reactions catalyzed by specific metalloenzymes may proceed at a significantly slower pace. Metals also contribute to binding and orienting substrates in the active site of enzymes. This overview briefly presents descriptions of drugs containing metals and highlights enzymes that rely on metals for their essential functions.



1, Cisplatin or cis-DDP Cis-diamminedicchloroplatinum(II)



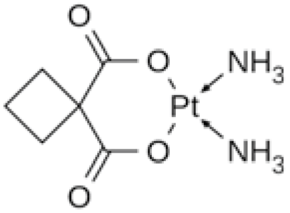
2, Auranofin 2,3,4,5-tetra-O-acetyl-1-1-β-D-thioglucose (triethylphosphine)gold(I)

Metal containing therapeutic agents

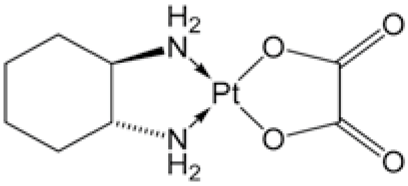
Platinum complexes

Apart from cisplatin (1), several drugs are formulated with platinum complexes. Cisplatin is employed in the treatment of germ-cell cancers, gestational trophoblastic tumors, epithelial ovarian cancer, small cell lung cancer, and for palliative care in cases of bladder, cervical, nasopharyngeal, esophageal, and head and neck cancers. However, certain cancers exhibit resistance to cisplatin, and it is associated with various side effects. Consequently, carboplatin (3) was developed with slightly lower toxicity, although its efficacy against cancer was not significantly superior to cisplatin. In fact, for some tumors, cisplatin remained therapeutically more effective than carboplatin.

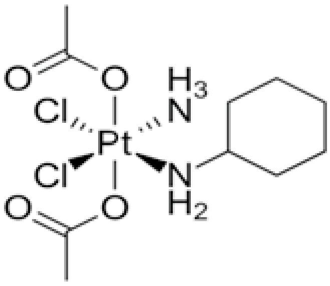
Further efforts to minimize toxicity and drug resistance led to the development of a new drug, oxaliplatin (4), which gained approval for use in the United States in August 2002 for colorectal cancer in combination with 5-fluorouracil (5-FU). Oxaliplatin had been in use in Europe for several years prior to its approval in the U.S. Satraplatin (5, JM216), another platinum-based antineoplastic agent, is currently under investigation for the treatment of advanced prostate cancer but has not yet received approval from the U.S. Food and Drug Administration. Despite the presumed inertness of Pt (IV) compounds, satraplatin undergoes rapid biotransformation in human red blood cells. Satraplatin serves as a direct analog of cisplatin (1). All direct structural analogs of cisplatin produce a similar array of adducts on target DNA, inducing comparable biological consequences and potentially offering a spectrum of clinical activity complementary to the parent drug, even if structurally dissimilar.



3. Carboplatin



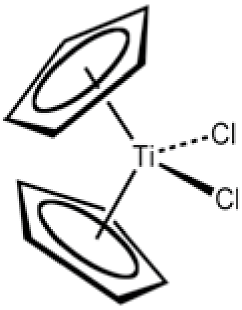
4. Oxaliplatin



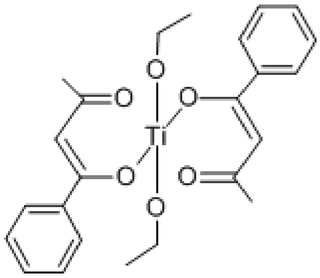
5, Satraplatin (JM-216)

Titanium complexes

Two titanium complexes identified for their anticancer properties are titanocene (6, MTK4) and budotitane (7, INN). Titanocene has demonstrated significant anticancer activity and was the first non-platinum complex to undergo clinical trials as a chemotherapeutic drug. Among non-platinum complexes, budotitane (INN) is among the most advanced and is currently undergoing clinical trials. Budotitane exhibits high activity against several transplantable tumors and demonstrates promising effects in an autochthonous colorectal tumor model, which is highly indicative of the clinical situation.



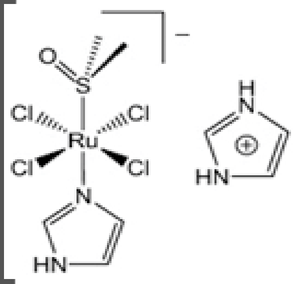
6, Titanocene (MTK4)



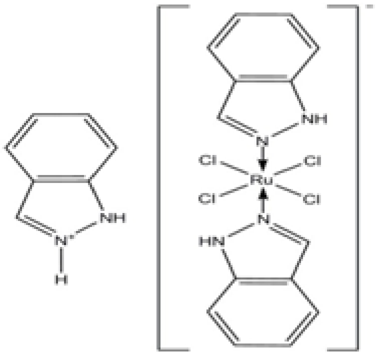
7, Budotitane (INN)

Ruthenium complexes

Ruthenium has yielded compounds showing significant promise, though no direct analogs have progressed to clinical use thus far. NAMI-A (8) and KP1019 (9) represent two ruthenium-based anticancer agents that have undergone clinical trials. NAMI-A demonstrates activity against lung metastasis in vivo and inhibits tumor cell invasion in vitro. On the other hand, KP1019 proves effective against metastatic tumors and tumors resistant to cisplatin. It displays potent cytotoxicity against primary tumors, especially in the context of colorectal cancer.



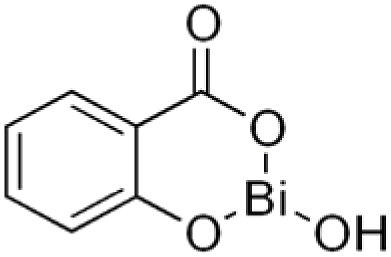
8, NAMI-A



9, KP1019

Bismuth complexes

Several compounds containing bismuth have been employed for their antacid and astringent characteristics in various gastrointestinal conditions. Bismuth subsalicylate (10, Pepto-Bismol) is a significant compound in this regard, serving as an antacid medication utilized to alleviate temporary discomforts of the stomach and gastrointestinal tract, including diarrhea, indigestion, heartburn, and nausea. Ongoing developments involve the exploration of additional compounds with similar applications.



10, Pepto-Bismol

Role of metals in enzymes

There exists a substantial number of enzymes that incorporate metals, and such enzymes are referred to as metalloenzymes. In these metalloenzymes, the metal ion forms a bond with the protein, typically at a labile coordination site, and is usually situated in a pocket whose shape accommodates the substrate. The configuration of the active site is of paramount importance in all enzymes. Metal ions in metalloenzymes catalyze reactions that are challenging to achieve in organic chemistry. Notable examples of metalloenzymes include carbonic anhydrase, Vitamin B12-dependent enzymes, nitrogenase, superoxide dismutase, chlorophyll-containing proteins, hydrogenases, ribozyme and deoxyribozyme, and matrix metalloproteinases. Furthermore, approximately half of all proteins contain a metal, which is essential for their proper functioning.

In enzymes, metal ions generally carry a positive charge, acting as electrophiles and engaging in charge-charge interactions with nucleophiles, which are typically negatively charged or neutral. The electrostatic environment in the active site, facilitated by metal ions, significantly aids in the proper binding of the substrate, enhancing enzyme action. Metal ions play a crucial role in the formation of the transition state of the catalyzed reaction and facilitate the release of the product. In many enzyme systems, a metal ion interacts with the oxygen of a water molecule, leading to the activation of the water molecule in situ. This activated water molecule, in turn, serves as a nucleophile in chemical or biochemical reactions, ensuring stereochemically controlled reactions within the enzyme's active site.

Metalloenzymes utilize specific three-dimensional arrangements of functional groups around the metal ion to ensure the specificity of the required biochemical reaction. Crystal structures of many metalloenzymes reveal a preferred configuration, often involving a carboxyl group where one oxygen atom is bound to the metal ion, and the other is bound to metal-bound water, forming a cyclic structure. Some enzymes, such as hemerythrin, alkaline phosphatase, and superoxide dismutases, feature two metal ions in their active site.

Taking the example of amide bond hydrolysis by metalloproteinases containing zinc, the Zn2+ ion is typically coordinated to three donor groups from the enzyme and a water molecule, adopting a tetrahedral geometry. In this context, Figure 1 illustrates the hydrolysis process in matrix metalloproteinases (MMPs), a prominent class of zinc-containing metalloproteinases. The coordinated water molecule undergoes nucleophilic attack on the scissile amide bond, resulting in the transfer of the proton (H+) to the amide nitrogen and the attachment of the carboxylate oxygen to Zn2+ in a tetrahedral manner. A proton transfer from glutamic acid to the amide nitrogen occurs simultaneously, followed by the collapse of the tetrahedral intermediate and the formation of a salt bridge between glutamic acid and the free amine of the cleaved substrate, ultimately leading to the generation of products.

Figure 2 demonstrates how an inhibitor can bind to zinc-containing enzymes. Using X-ray studies, it reveals the binding of an N-carboxyalkyl peptide inhibitor with a zinc-containing enzyme, stromelysin (MMP-3). In addition to several hydrogen bindings, zinc atoms play a stabilizing role in the binding of the inhibitor with the enzyme. Zinc, among all metals, has been found to perform various functions in biological systems due to its specific properties, as elucidated by Perkin.

i. Zinc is an element of borderline hardness,[41] and thus nitrogen, oxygen, and sulfur ligands interact favorably, leading its strong binding to proteins.
ii. The divalent zinc ion is exceptionally stable with respect to oxidation and reduction, and thus it does not participate in redox reactions.
iii. Zinc shows a strong preference in the enzymes for a tetrahedral coordination over an octahedral one, thereby enhancing both the Lewis acidity of the zinc center and the Brønsted acidity of a coordinated water molecule.
iv. As a result of d10 configuration of Zn^{2+}, zinc complexes are not subject to ligand field stabilization effects, and so coordination number and geometry are only dictated by ligand size and charge.
v. Anions such as OH-, OR-, and SR- retain their nucleophilic character when coordinated to zinc. Only Mn^{2+}, Fe^{3+}, and Cu^{2+} are better in this regard.

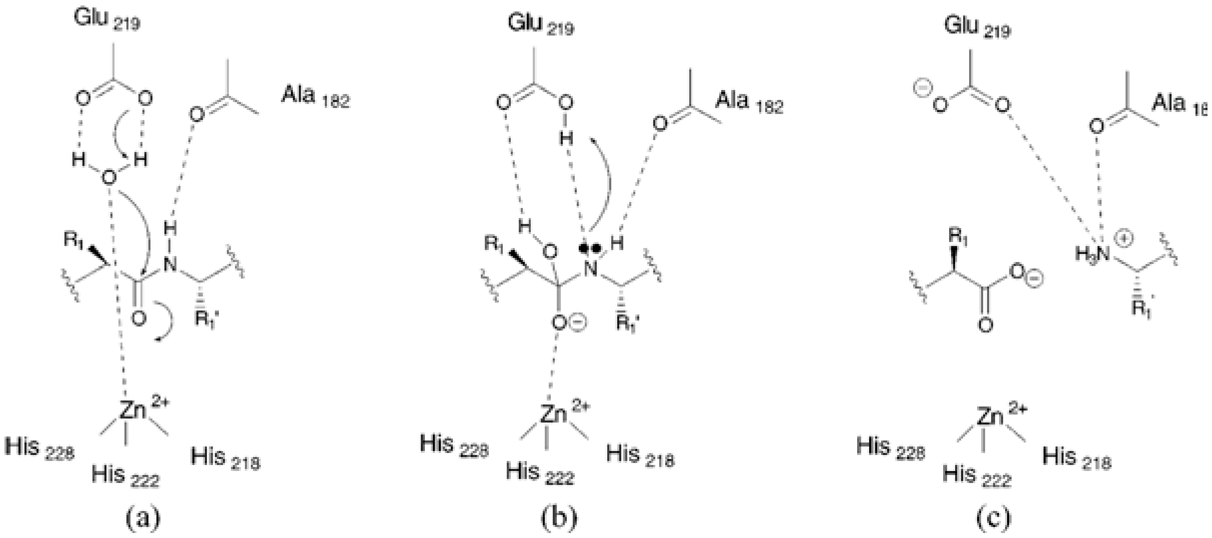


Fig. 11

Catalytic mechanism for MMPs.

a. The catalytic water molecule is hydrogen-bonded to the zinc atom and the carboxylate side chain of a glutamic acid residue and is therefore activated for nucleophilic attack
b. Coordination of the carbonyl carbon of the amide bond is followed by nucleophilic attack of the zinc-bound water to give the tetrahedral intermediate
c. Which collapses via acid-mediated catalysis to products? Reprinted with permission from ref 38.

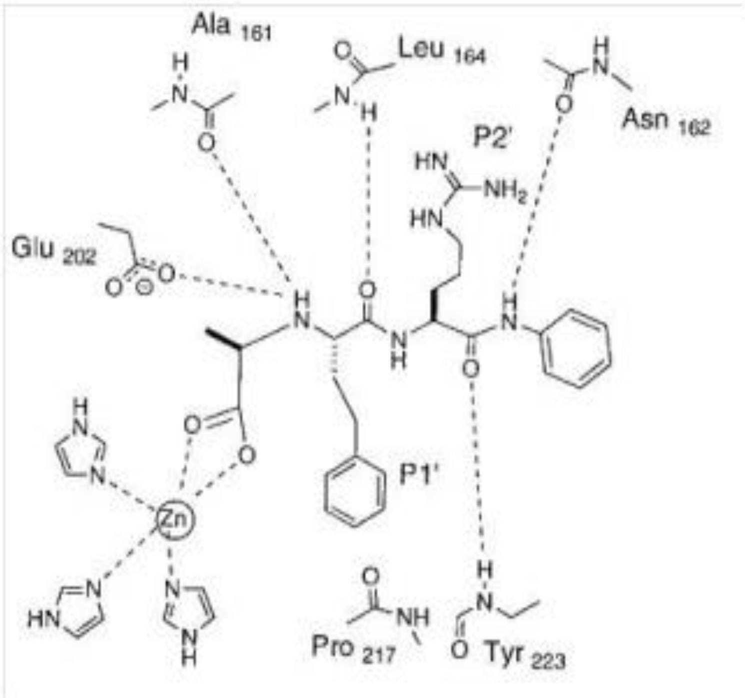


Figure 12 Binding of an MMP inhibitor with stromelysin (MMP-3) showing how the Zn atom participates in the bonding. In the figure P1′ and P2′ refer to the groups of the inhibitor or substrate that bind to the corresponding binding sites referred to by S1′ and S2′ in the enzyme. Reprinted with permission from ref 38.

Conclusion

Metals assume crucial roles in human life, and their deficiency can contribute to various diseases within the human body. Additionally, metals have been leveraged in the development of therapeutically valuable drugs for conditions such as cancer, arthritis, ulcers, and more. The presence of metals in enzymes significantly enhances their catalytic reactions.

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