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Review Article

Bioinorganic Chemistry Research in India

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Nature uses metal ions and metal containing biomolecules for carrying out crucial cellular processes. They are mostly associated with the protein core, or found in cofactors such as porphyrins, or in protein-bound clusters. A few processes and reaction which involve the metals are respiration, photosynthesis, complex DNA synthesis and repair mechanisms, circulation, muscle contraction, etc. Bioinorganic chemistry deals with the study of metal ions and their importance in biological system. This article encompasses the progress and current status in the understanding of metalloenzymes and biomimetic inorganic chemistry, especially in India. The broad aspects of metals in medicine; use of metal containing nanoparticles and complexes for therapeutic and diagnostic purposes; the array of methodologies employed to understand and mimic the structure and function of metallobiomolecules; metal containing compounds in bioremediation etc. are discussed. Further, the significance and a future prospect of the bioinorganic chemistry research are elucidated briefly.

Keywords: Biomolecules; Bioinorganic Chemistry; Hemoglobin; Plasma Membrane

Introduction

The main emphasis of bioinorganic chemistry is to understand the role of metals in biology; which include metalloproteins and their model systems, metal-nucleic acid interactions and the application of metal-based compounds in medicine (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994). The research activities in the area of metal ion transport and storage in biological systems include study on ion channels, ion pumps such as Na/K ATPase, several proteins and small molecules that can control the entry of metal ions into the cells (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994). As many metals are required for various biological functions, organisms employ a variety of strategies for transporting across the plasma membrane and storing them effectively in the cells (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994).

Metalloproteins constitute a large group of biomolecules that require metal ions for their biological function. Hemoglobin and myoglobin, the two well-known examples of metalloprotein in humans, play crucial roles in the oxygen transport and storage, respectively (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994). The unusual coordination environment at the heme sites of these proteins helps them bind molecular oxygen reversibly. The molecular oxygen is also used as a substrate for many enzymatic reactions involving metalloproteins. The monooxygenases such as cytochrome P450 and nitric oxidase synthase are involved in drug metabolism and synthesis of nitric oxide, respectively (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994). In addition, the mammalian electron transport chain (ETC) contains several key metalloproteins involved in generating electrochemical proton gradient. The dioxygen reactions play important roles in respiration. For example, cytochrome c oxidase (CcO), the terminal metalloenzyme in the respiratory ETC of mitochondria, consumes more than 90% of the respired dioxygen (Kaim and Schwederski, 1993; Lippard and Berg, 1994; Bertini *et al.*, 1994).

Metal-containing pharmaceuticals that can interact with the endogenous metal ions in enzyme active sites or metal complexes that can bind to nucleic acids attract significant attention in the treatment of

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various diseases (Guo and Sadler, 1999; Dabrowiak, 2017). Cisplatin, which is being used as a chemotherapeutic drug for cancers, gadolinium complexes as MRI contrast agents, lithium carbonate as a treatment option for manic phase of bipolar disorder, gold complexes as antiarthritic drugs, several carbon monoxide-releasing molecules, are some important examples where the metal-biomolecule interactions play key roles (Guo and Sadler, 1999; Dabrowiak, 2017). This article is not intended to provide a comprehensive picture of all the bioinorganic research activities in India, but to give an overview of a few recent developments in this area and future perspectives.

Bioinorganic Chemistry Research in India

The topic "bioinorganic chemistry" has been one of the thrust areas for the Inorganic Chemistry researchers in India. Many young and established researchers have delivered lectures in major international conferences such as International Conference on Biological Inorganic Chemistry (ICBIC) and Asian Biological Inorganic Chemistry (AsBIC) conference. At the national level, the Modern Trends in Inorganic Chemistry (MTIC), a biennial symposium series initiated in 1985, has become an important forum for the bioinorganic chemists to share their research. The bioinorganic chemistry activities in India focus on areas where the bioinspired metal-based chemistry can be applied to the broad areas of research related to energy, environment and human health. In the beginning of bioinorganic chemistry research in India, the influence of metal ions such as Cr(III) on the structural stability and state of aggregation of insulin and their possible role in glucose metabolism has been studied (Govindaraju *et al.*, 1989). A few metal-containing proteins involved in metabolic and catalytic pathways have been studied to understand the enzyme-substrate interaction, molecular recognition, drug metabolism (Prasad *et al.*, 2000). Extensive kinetics and spectroscopic studies have been carried out to understand the ligand binding in myoglobin and other related proteins (Mondal *et al.*, 1993).

The early research in understanding the chemistry of heme-containing proteins focused on synthesis and studies of porphyrin ligand systems. The coordination of porphyrin ligands and the photophysical properties of their metal complexes have been studied (Thanabal and Krishnan, 1982; Chandrashekar and Krishnan, 1982; Chandrashekar and Krishnan, 1981). Several modified porphyrins have been synthesized and studied for their chemical reactivity, structural diversity, aromaticity, anion receptor properties and their applications in photodynamic therapy (PDT) related to cancer treatment (Chandrashekar and Venkatraman, 2003; Amanullah *et al.*, 2019). Some of the expanded porphyrins, in which the pyrrole or heterocyclic rings are connected to each other through meso carbon bridges, have been synthesized and potential applications such as anion binding agents, photosensitizers for PDT, antisensing applications and MRI contrasting agents have been explored (Misra and Chandrashekar, 2008; Anju *et al.*, 2017). Research on synthetic porphyrins also helped to understand the chemistry of heme in mono- and multi-heme proteins and the role of noncovalent interactions that can control the heme reactivity and metal spin state (Ghosh and Rath, 2010; Sahoo *et al.*, 2015). The interaction of the redox active heme with amyloid β (Aβ) peptides and its relevance to Alzheimer's disease has been investigated (Pramanik and Dey, 2011). Although the normal physiological function of Aβ is not well understood, it is believed that these peptides of 36-42 amino acids length are involved in the formation of amyloid plaques in the brains of Alzheimer patients.

For many years, chemists have conducted research to understand the chemical processes of photosynthesis, which involves the splitting of water and conversion of the energy-rich products with carbon dioxide into stable storage molecules. In water splitting, oxygen, H^+ ions and electrons are generated. While oxygen is released from the photosystems, the electrons and H^+ ions are used for the synthesis of adenosine triphosphate (ATP) and NADPH, which are used in the follow-up light-independent reactions or dark reactions for the conversion of carbon dioxide and other compounds into glucose. The three major components of the dark reactions, commonly known as the Calvin cycle, involve carbon fixation, reduction reactions, and ribulose 1,5-bisphosphate (RuBP) regeneration. Chemists have developed efficient systems to split water (artificial photosynthesis) to generate hydrogen by using solar energy. Researchers from India have developed low-temperature as well as high-temperature processes based on the Mn(II)/

Mn(III) oxide system or yttrium-based rare earth manganites. They showed that the thermodynamics and kinetics of the water splitting are controlled by the inherent redox properties of the materials and the choice of the solar reactor may hold the key for the commercialization of thermochemical fuel production based on artificial photosynthesis (Rao and Dey, 2017).

In photosynthesis, the energy from sunlight is used by plants and certain microorganisms to produce glucose from carbon dioxide and water. The glucose generated in this process is converted into pyruvate, with the release of ATP by cellular respiration. Molecular oxygen is produced as by-product during the photosynthesis. The conversion of light energy into chemical energy is mediated by the green pigment known as chlorophyll present in plant leaves. Willstatter and Stoll suggested the binding of carbon dioxide to magnesium, which is complexed with chlorophyll. It has been reported that a carbon dioxide derivative with chlorophyll would form a bicarbonate-type additive compound (Willstatter and Stoll, 1918). Biomimetic studies from India have demonstrated that carbon dioxide molecule does bind to magnesium in chlorophyll in photosynthesis. This study suggested that carbon dioxide plays an important role not only in the light-independent reactions, but also in photosystems I and II in optimizing the photosynthesis (Bhuyan *et al.*, 2011).

The development of bioinspired model systems based on hydrogenase enzymes to understand the hydrogen production is also of current interest (Ahmed and Chattopadhyay *et al.*, 2018; Ahmed and Dey *et al.*, 2018). It is known that cytochrome c oxidase (CcO) catalyses the four-electron reduction of oxygen to water by receiving electrons from cytochrome c. The reduction works well at neutral pH and no partially reduced oxygen species, such as superoxide, hydrogen peroxide or hydroxyl radicals are produced by this enzyme under normal physiological conditions, although the formation of such species has been observed under various disease conditions. As the enzyme is very large with several metal-containing protein subunits, development of biomimetic systems for this enzyme is very challenging. Recently, the CcO-inspired research led to the development of several catalysts for the oxygen reduction reactions. These bioinspired molecules not only exhibited good catalytic activity, but also provided insights into the chemical mechanism and nature of intermediates produced in the reactions (Dey *et al.*, 2017; Amanullah *et al.*, 2019).

Functionally mimicking the redox active sites of metalloenzymes has been one of the active areas of research in the country. Development of enzyme mimetic molecules for the reduction of small molecules such as dioxygen, activation of C-H and C-X (X = Cl, Br or I) bonds and catalysis of electron transfer processes etc has attracted significant attention. Chemical models of Type 3 copper enzymes, such as tyrosinase and catechol oxidase using ligands that can provide bidentate alkylamine terminal coordination have been studied. It has been shown that the fine-tuning of the electronic properties of the scaffold ligands in a series of binuclear Cu(II) complexes controls the rate of catecholase activity (Mandal *et al.*, 2012). As many biological reactions involve water and the metal catalytic sites in the enzymes play crucial roles, biomimetic systems that functionally mimic the metal hydrolases have also been studied. The hydrolytic activity of model Zn(II) complexes for carbonic anhydrase, metallo-b-lactamase, phosphatases, phosphoesterase and metalloproteinases has been explored with an aim to understand and replicate the function of these metalloproteins. Biomimetic systems containing one or two zinc(II) ions supported by phenolate ligands were developed as functional mimics of metallo-β-lactamase. These complexes were shown to catalytically hydrolyze the b-lactam substrates such as oxacillin and penicillin G (Tamilselvi *et al.*, 2016; Tamilselvi and Mugesh, 2011). As antibiotic resistance to clinically employed β-lactam antibiotics currently poses a very serious threat to the clinical community and several metallo-β-lactamases play key roles in the resistance pathways, it is important to understand the mechanism by which these enzymes catalyze the hydrolysis of antibiotics. Therefore, functional enzyme mimetics will be very useful in understanding the mechanism of action of the enzymes.

Another area of research related to the application of bioinorganic chemistry in the bioremediation and environmental chemistry is the development of novel compounds as functional mimetics of enzymes that are involved in the degradation of environmental pollutants. Organophosphate-based nerve agents such as tabun,

sarin and VX were used as chemical warfare agents since World War II. Several other toxic organophosphates such as paraoxon and parathion are being used extensively as pesticides and insecticides. The toxicity of these compounds affects the nervous system, leading to cerebral edema and other neurological diseases. The irreversible inhibition of acetylcholinesterase (AChE), which is responsible for the breakdown of the neurotransmitter acetylcholine, is the main cause of toxicity. The importance of nerve agent detoxification led to the development of compounds that can efficiently hydrolyse the phosphotriester bonds. The initial studies on the hydrolysis of organophosphates were mainly focused on metal complexes having mono and binuclear Zn(II) and Cu(II) centres (Tamilselvi and Mugesh, 2010). Recently, nanomaterials that can catalyse the rapid conversion of the highly toxic phosphotriesters to less toxic diesters or monoesters have attracted significant attention (Vernekar *et al.*, 2016).

In addition to toxic organophosphates, organomercury compounds such as CH_3Hg^+ are highly toxic to humans. These compounds are neurotoxic environmental pollutants that preferentially accumulate in glia of the central nervous system. Therefore, the detoxification of organomercuric compounds is important in the bioremediation process. Mercury-resistance bacteria have evolved a unique mechanism for the detoxification of organomercury compounds. They utilize two enzymes – the organomercurial lyase (MerB) which catalyzes the cleavage of the stable Hg-C bond and the mercuric ion reductase (MerA), which reduces Hg(II) to less toxic elemental mercury, Hg(0). Although MerB successfully converts toxic $MeHg^+$ to Hg(II), studies to understand the role of amino acids present at the active site of the enzyme in demethylation of methyl mercury have just started emerging. An efficient detoxification of organomercurials by synthetic compounds will be of great importance as such compounds may be used for the treatment of patients suffering from organomercury poisoning. Recently, Indian researchers have developed a novel pathway for the detoxification of organomercurials by small molecules under physiologically and environmentally relevant conditions. It has been shown that the reactions produce less toxic insoluble HgS and HgSe nanoparticles and the nature of substituents plays a crucial role in the detoxification by facilitating the desulfurization and deselenization processes (Banerjee *et al.*, 2015). This study suggested that such compounds may also be useful in detoxifying other compounds based on toxic heavy metals such as Cu, Pb, Cd, and Sn.

Metalloenzymes are known as efficient catalysts for the activation inert C-H bonds. Particularly, non-heme metalloenzymes can mediate both mono- and dioxygenation reactions under mild conditions. Methane monooxygenase (MMO) is a typical example of non-heme enzyme that converts methane to methanol. Several iron-containing enzymes utilize molecular oxygen to mediate a series of reactions, which leads to the cleavage of strong C–H bonds. Researchers from India have studied iron(II) complexes to understand the nature of high-valent intermediates produced in reactions with molecular oxygen. It has been reported that olefin cis-dihydroxylation and aliphatic C-H bond oxygenation can be mediated by an electrophilic iron-oxygen oxidant, which can also selectively oxidize sulfides to sulfoxides and mediate the hydroxylation of C-H bonds of alkanes (Chatterjee and Paine, 2015). It has also been shown that a high-valent iron complex based on a substituted N4Py ligand system can oxygenate a relatively strong C–H bond of aliphatic substrates including that of cyclohexane (Singh *et al.*, 2019; Ghosh *et al.*, 2015; Singh *et al.*, 2015).

A few research groups work in the areas of bioinorganic chemistry related to human health. The interactions between metals and nucleic acids can control gene expression. The coordination ability of nucleobases towards metal ions has been explored. The use of supramolecular coordination complexes between nucleobases and metals have been considered for the transfer of molecular properties such as noncovalent interactions, i.e., van der Waals forces, electrostatic interactions, and hydrogen bonding, to design architectures for nanoscale applications (Purohit and Verma, 2010; Verma *et al.*, 2010). Photo- and biophysical studies on metal-DNA interactions revealed novel mode of binding and provided insights into the role of ligand in the metal complexes, which can alter the binding affinity (Ghosh *et al.*, 2011).

Metal-based compounds have attracted interest

in health science for several centuries. Egyptians used copper to sterilize water during 3000 BC and the Chinese empire used gold in a variety of medicines during 2500 BC. However, metals started making an impact on modern medicine only during early 1900s (Guo and Sadler, 1999; Dabrowiak, 2017). During the initial periods, a few metal complexes have been used treat various diseases, which include the use of $K[Au(CN)_2]$ for tuberculosis, the arsenic compound Salvarsan for the treatment of syphilis (sexually transmitted infection). Although cisplatin was discovered in 1845, its application as a chemotherapy medication to treat cancers started emerging in late 1900s. The compound was licensed for medical use in 1978-79 and it has become a part of the World Health Organization's List of Essential Medicines, indicating that cisplatin is one of the most effective and safe medicines needed in a health system. Cisplatin kills cancer cells by interfering with DNA replication (Guo and Sadler, 1999; Dabrowiak, 2017). A few other metal-based therapeutics have been successful in treating various diseases, which include gold(I) complexes such as gold thioglucose and auranofin for the treatment of arthritis, vanadium(IV) complexes as insulin mimetics, bismuth complexes for the treatment of ulcer, Li_2CO_3 for manic depression and platinum (IV) complexes for the treatment of ovarian cancer etc.

Although Pt(II)-based compounds such as cisplatin have been studied extensively as anticancer agents, the serious side effects and resistance to cisplatin prompted scientists to look for other metal-based compounds. Several metal complexes have been developed in research laboratories worldwide with promising anticancer properties. A few of these complexes are already in use in clinical practice for diagnosis and treatment and some of them are undergoing clinical trials. During last couple of decades, several transition metal complexes have been reported from India and these complexes have photodynamic therapeutic (PDT) and anti-metastasis activities. Some of the notable examples in this area include, the photodynamic effect of a cytotoxic iron(III) complex in cancer cells under near-IR light (Basu *et al.*, 2012), the anticancer activity of a novel water-soluble porphyrin THPP and its metalated derivative Zn-THPP having excellent triplet excited state quantum yields and singlet oxygen generation efficiency (Karunakaran *et al.*, 2013), cell death-inducing metal-amino acid complexes (Ramakrishnan *et al.*, 2009).

Recently, nanomaterials having metalloenzyme-like activity (nanozymes) attracted significant attention. Some of these materials have been shown to functionally mimic the antioxidant enzymes, such as catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD), which maintain the redox homeostasis in mammalian cells by controlling the level of reactive oxygen species (ROS) such as hydrogen peroxide and superoxide. A recent study showed that a manganese-based nanomaterial effectively internalizes into human cells and provides efficient cytoprotection in a Parkinson's disease model. This study suggested that such material can be considered as a potential candidate for therapeutic applications against oxidative stress-induced neurological disorders (Singh *et al.*, 2017). As high level of ROS is associated with various diseases and the production of ROS is mediated by redox active metal ions such as Fe(II) and Cu(II), compounds that can bind to the free metal ions and block the undesired reaction will be useful in controlling the ROS levels. It has been reported that certain Cu(II) selective chelators can relieve the copper-induced oxidative stress in a zebrafish larval model (Rakshit *et al.*, 2018).

Conclusions and Outlook

Metal complexes offer a versatile platform for the design of model systems to understand the chemistry of metalloproteins and enzymes and to functionally mimic the photosystems for water splitting. Although design and synthesis of simple metal complexes and study of their biophysical and photophysical properties helped to understand their ability to mimic the natural systems, it may become important to combine both chemistry and biology to understand the more complex life processes. Bioinorganic chemistry when combined with modern chemical biology and system biology can provide a valuable tool not only to get insight into the biochemical processes, but also to regulate the biological systems. The future research may involve understanding the role of metalloproteins and metal dysregulation in various diseases, including cardiovascular and metabolic diseases, cancer and neurodegenerative disorders and development of metal-based therapeutics for the above diseases.

Indian researchers worked on structural and functional models for cytochrome c oxidase, cytochrome P450 and peroxidases and have carried out mutational studies to understand the substrate specificity, and molecular mechanism. Synthetic heme/porphyrins have been developed to understand the structural diversity, electronic properties and photoinduced electron/energy transfer in both mammalian and bacterial proteins. Synthetic models for heme and non-heme enzymes helped understanding the reduction of molecular oxygen, e.g. cytochrome c oxidase models and activation of dioxygen for chemical reactions by biomimetic metal complexes. In the area of copper and zinc proteins, modelling of copper enzymes such as tyrosinase and catechol oxidase and functional models for mono and binuclear zinc(II) enzymes, particularly the zinc hydrolases have been studied. In the area of metal-nucleic acid interactions, DNA-binding, oxidative DNA cleavage, coordination mode of transition metal complexes, metal complexes as DNA binding agents – phototoxicity and anticancer agents – chemotherapeutic agents to phototherapeutic agents - cellular models for delivery and localization have been investigated. Studies were also focused on photodynamic properties of BODIPY dyes, nanomaterials and crystal engineering studies with metals and nucleobases. Clearly, the strength of bioinorganic chemistry researchers in India lies in the areas of coordination chemistry related to biological systems. The chemical knowledge gained from the model mechanistic studies is certainly important and researchers need to be encouraged to undertake multidisciplinary approaches in addressing more challenging, high-impact research problems.

A "top-down" approach involving identification of bioinorganic chemistry problems related to major human diseases/disorders is very important and such projects may involve collaborations with scientists having complementary expertise. The following areas may be considered: cardiovascular diseases, cancer, diabetes, infectious diseases - antibiotic resistance and neurodegenerative diseases. The specific research areas on the above themes may include metalloproteins/enzymes and understanding their biological functions, insights into biological processes at molecular levels, development of specific inhibitors with therapeutic effects, understanding metabolic pathways and the interlink between metalloproteins and signalling pathways, diagnostic tools, metal-based therapeutics and protection of human from potentially harmful substances. Bioinorganic chemistry related to energy and environment cannot be ignored.

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