

Solving 21st Century Problems in Biological Inorganic Chemistry Using Synthetic Models

Guest Editorial for the *Accounts of Chemical Research* special issue on “*Synthesis in Biological Inorganic Chemistry*”

Nature uses d-block elements to perform many functions. The ability of proteins to create environments that tune the redox and acid–base properties of these metal ions, control the pathways and timing by which substrates enter and products exit the active sites, and accelerate reaction rates far beyond what is attainable in the laboratory continues to amaze and confound chemists who try to emulate these achievements with synthetic models.

Here are presented 26 Accounts that display a diverse array of studies of synthetic models that explore the ability of metal centers to activate small molecules like hydrogen and oxygen, of metal chemistry to report on biological signaling events such as those performed by nitric oxide, and of novel small molecule and protein based ligands designed to reveal the versatility of a metal ion to perform chemical tasks.

Investigation of synthetic models is advantageous for determining the chemistry of metal ions in coordination environments that bear a close resemblance to those in a biological system in structure, spectroscopic features, and especially function. Ligand design involving the first or second coordination sphere, or both enables systematic variations to elucidate key factors that create special properties of the metal center at an active site. Ultimately, the goal is to generate systems able to effect biomimetic molecular transformations, learning in the process some of the tricks invented by nature to achieve what has otherwise seemed impossible. Bioinorganic principles are also employed for purposes beyond catalysis. These may include the development of sensors for metals or small molecules, tools to report on biological signaling agents, and drug development.

Models are essential in the scientific method. In bioinorganic model chemistry, the goal is to represent the biological environment of the metal with a synthetic mimic of what biopolymers have created. As a synthetic chemist, the design of ligands with a specific architecture and the utilization of organic chemistry methodology to synthesize them is the heart of this enterprise. The ligand defines the coordination sphere, bringing control to the intrinsic kinetic and thermodynamic properties of metal ions in their various oxidation states in solvents ranging from noncoordinating hydrocarbons to water. The ligand used in these bioinorganic studies replaces protein residues surrounding a metalloprotein active site. The goal is to achieve the physical properties, chemistry, and functions of the natural systems in a manner to elucidate some of the secrets by which nature manages the seemingly impossible.

The 26 Accounts in this special issue come from research laboratories around the world that are very active in bioinorganic modeling via synthesis. Still, they represent only a fraction of the work currently being undertaken. Late 20th and 21st century advancements, such as those in structural methodology, spectroscopy, theory and computation, and

experimental procedures, have provided greater information on living systems and thus about how chemical transformations that are very difficult to carry out in the laboratory occur in biology. Directly related to this topic are the recently highlighted societal concerns in the sphere of energy, which have helped to focus activity on chemistry for the public good. Consider the perhaps most important chemical reactions of societal interest; these include dioxygen reduction (the fuel cell reaction), water oxidation to O₂, carbon dioxide reduction to give potential fuels as products, water (proton) reduction giving dihydrogen, hydrocarbon functionalization (e.g., methane to methanol conversion), and nitrogen fixation (nitrogen reduction to ammonia). Every one of these reactions occurs in nature and involves metalloenzyme active sites. Of related interest is that in a quite recent discovery, certain copper enzymes are found to be capable of the oxidative breakdown of biomass, polysaccharides, and chitins.

The Accounts in this special issue cover many of the important topics discussed above. Among the small molecules whose “activation” or transformations are discussed are molecular oxygen (O₂) and its reduced derivatives, dihydrogen, water, hydrogen sulfide (H₂S), dinitrogen, and several nitrogen oxides, that is, nitric oxide (NO, nitrogen monoxide), nitrite ion, and HNO (nitroxyl). The metal ions discussed include Fe, Cu, Co, Mn, Ni, and Ru, the latter in connection with the process of water oxidation or in anticancer drug development. We hope the readers of these Accounts will find the range of subjects to be of great interest and hold the excitement of the field of synthetic biological inorganic chemistry, which we ourselves share.

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Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

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■ EDITOR'S NOTE

"Synthesis in Biological Inorganic Chemistry" was conceived during a conference call of senior editors of this journal early in 2014, shortly after I took over the reins as Editor-in-Chief from Joan Valentine. It was our intention to recognize the decades of service to the bioinorganic chemistry community through editorship of *Accounts* on Joan's part for the preceding 19 years, as well as the service of Steve Lippard who was Associate Editor of *Journal of the American Chemical Society* for nearly 25 years. Both stepped down from their editorial duties in 2013. Here we celebrate the progress and accomplishments of the community of chemists who, through their efforts to bridge the chemistry–biology interface via synthesis of metal complexes, have brought insight into the function of metal ions in biological systems. I greatly appreciate the efforts of Ken Karlin in bringing this issue to completion.

The cover art presents examples from the rich tapestries woven by the guest editors during their research careers: the copper–zinc active site of superoxide dismutase (Valentine), the diiron center of methane monooxygenase (Lippard), and a copper–iron model of mitochondrial cytochrome *c* oxidase (Karlin). We congratulate them on their outstanding achievements in bioinorganic chemistry and thank them for their decades of service to the community.