Inorganic Chemistry

Editorial

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Editorial for the Virtual Issue on Models of Metalloenzymes

Chemists have been inspired for decades by the novel structures, spectroscopic properties, and reactivity of metalloenzymes.[1] Many metalloenzyme active sites exhibit geometries that are unprecedented in inorganic chemistry, with spectroscopic features that are often entirely new and challenging to explain. They catalyze reactions under mild conditions with exquisite selectivity and efficiency, and these reactions are of fundamental significance, not only with respect to biological function but also more generally because of their environmental and societal impact (cf. energy, agriculture, drugs). Understanding metalloenzyme structure/function relationships and mechanisms of action is critical in order to be able to develop inhibitors, expand the substrate scope, or otherwise perturb the biological system. Such an understanding can also inform the development of new catalysts with myriad applications.

Multiple approaches are required in order to comprehend metalloenzyme structure, properties, function, and mechanism. Key among them is the synthetic modeling approach, whereby inorganic complexes that replicate aspects of the metalloenzyme active site are characterized and their reactivity is examined.[2] As a complement to direct studies of the enzymes, this approach can provide detailed, fundamental chemical insights into metal complex geometries, electronic structures, and reaction mechanisms. These insights can be a basis for postulating mechanisms, rationalizing spectroscopic properties, unraveling active site electronic structures, and designing new catalysts.

In this second virtual issue (http://pubs.acs.org/page/vi/2013/models-of-metalloenzymes.html) that follows the first on Quantum Molecular Magnets (http://pubs.acs.org/page/vi/2012/quantum-molecular-magnets.html), 22 selected articles were chosen to highlight advances in synthetic modeling of metalloenzymes from recent issues (mostly from 2012 to 2013) of the leading American Chemical Society journals *Inorganic Chemistry* and *Journal of the American Chemical Society*. The articles are available online in a single collection along with their synopses for comprehension by the nonspecialist. The findings described in the selected articles illustrate the breadth of the field and show how detailed study of small-molecule complexes can lead to provocative hypotheses about the structure and function of important metalloenzyme active sites, notwithstanding the fact that not all significant problems in synthetic bioinorganic chemistry can be addressed in such a relatively small collection. The exciting results in these articles also are of fundamental interest in their own right, as exemplars of forefront synthetic inorganic chemistry aimed at tackling notable challenges in the field.

The issue begins with two articles focused on nitric oxide (NO), a critical biological messenger molecule and pollutant. Work reported by Lehnert and co-workers[3] targets the conversion of NO to N_2O by the flavodiiron nitric oxide reductases, enzymes that act to defend organisms from the toxic effects of NO.[4] These authors describe the synthesis and structure of a rare example of a diiron complex with a nitrosyl bound to each metal ion and show that it evolves N_2O, but only upon reduction by two electrons. A similar pathway for N_2O evolution in the enzyme is proposed, involving reduction of the diiron active site by a nearby flavin cofactor. In the paper by Kozhukh and Lippard,[5] reactions of nitrogen oxides with zinc thiolate complexes are described, with the aim of understanding the role of zinc thiolate centers in nitric oxide synthase (NOS)[6] activity and regulation. Exposure of NOS to NO in the presence of air is thought to result in oxidation of the thiolate to an *S*-nitrosothiol and induce dissociation of zinc, which, in turn, disrupts the dimeric form of NOS and deactivates the enzyme. Kozhukh and Lippard show that (a) as proposed for NOS, reaction of zinc thiolate model complexes with NO/air, NO^+, or NO_2 induces formation of *S*-nitrosothiols and (b) zinc(II) salts react with *S*-nitrosothiols to yield NO and N_2O, suggesting a role for this process in rendering the aerobic deactivation of NOS reversible.

The next set of articles focuses on the characterization of metal−oxygen species relevant to intermediates in oxygenase and related enzymes. In work aimed at understanding the reactivity of nonheme mononuclear iron-oxo species that are the active species in many enzymes,[7] Nam, Fukuzumi, and co-workers[8] investigate the effects of protonation of the iron(IV)-oxo unit on the oxidation of toluene derivatives by $[(N4Py)Fe^{IV}(O)]^{2+}$ [N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine].[9] They show that protonation increases the rate of benzylic C−H bond attack and decreases the accompanying H/D kinetic isotope effect, consistent with a change in mechanism from hydrogen atom abstraction in the absence of added acid to proton-coupled electron transfer by the protonated $Fe^{IV}(OH)$ species. Diiron−oxygen species relevant to key intermediates involved in catalysis by nonheme diiron oxygenase enzymes such as soluble methane monooxygenase[10] are the subject of a contribution by Que, Lippard, and co-workers.[11] In this notable collaborative effort from laboratories that typically compete, the interconversions of diiron complexes with varying oxo, hydroxo, and aquo ligation are elucidated. For example, the formation of the diiron(IV) complex $[Fe_2(\mu\text{-}O)(OH)(O)(R_3TPA)_2]^{3+}$ (R_3TPA = [(3,5-dimethyl-4-methoxy)pyridyl-2-methyl]amine) is shown to occur upon reaction of H_2O_2 with a diiron(III) precursor having a (μ-oxo)(μ-hydroxo)diiron(III) core but not with the hydrated relative having a (μ-oxo)(hydroxo)(aqua)diiron(III) unit. These detailed reactivity studies shed important light onto the conditions required to generate key diiron(IV) enzymatic oxidants.

Dey and co-workers[12] describe advances in the functional modeling of cytochrome P450, a well-studied and biologically critical enzyme[13,14] that has served for decades as a paradigm for dioxygen activation by heme centers. In this new work, the P450 active site is mimicked by covalent attachment of heme iron units in site-isolated fashion to self-assembled monolayers of thiolates bound to gold surfaces. These modified electrodes

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were characterized spectroscopically and shown to be active catalysts for the oxidation of cyclohexane and toluene using O_2.

Dioxygen activation pathways at single copper active sites such as those found in the enzymes dopamine β-monooxygenase (DβM) and peptidylglycine α-hydroxylating monooxygenase (PHM)[15] are the topic of two papers in this collection. Itoh, Cramer, and co-workers provide detailed information on the kinetics of formation and reactivity of copper(II) superoxide complexes supported by *N*-[2-(2-pyridyl)ethyl]-1,5-diazacyclooctane ligands.[16] These complexes are distinguished from other 1:1 Cu/O_2 species[17] by virtue of their tetrahedral geometry and closely resemble a Cu/O_2 adduct characterized for PHM.[18] Kinetic parameters for the formation of the $S = 1$ copper(II) superoxide complex having an *i*Pr ligand substituent are consistent with an associative mechanism for its formation. Evaluation of the self-decay pathway followed by the complexes using density functional theory (DFT) calculations support a route involving hydrogen atom abstraction by the copper(II) superoxide from the benzylic position of the phenethylamine arm of the supporting ligand, followed by oxygenation by the oxygen proximal to the copper ion and O−O bond scission. These results provide key precedence for a similar reaction pathway for substrate oxidation by DβM and PHM.

Also relevant to reaction pathways proposed for DβM and PHM are copper(II) hydroperoxide species, a novel example of which is reported in the contribution by Karlin and co-workers.[19] They present spectroscopic and DFT evidence in support of the formation of a copper(II) hydroperoxide complex that is stabilized by intramolecular H-bonding from a ligand aniline moiety to the proximal oxygen atom. Such H-bonding illustrates a possible second-sphere interaction in the enzymes, of the sort that has been targeted for evaluation in a number of recent synthetic modeling efforts (vide infra).[20]

In a final example featuring the characterization of biologically relevant metal−oxygen species, Kovacs, Solomon, Rybak-Akimova, and co-workers report the first example of a (μ-peroxo)dimanganese(III) complex to be structurally characterized by X-ray crystallography.[21] This complex was identified as an intermediate in the reaction of a Mn(II) precursor with O_2 via low-temperature stopped-flow kinetics studies and was further characterized by resonance Raman spectroscopy. The $[Mn_2O_2]^{4+}$ core in the complex models moieties postulated as intermediates in oxygen evolution pathways by the manganese cluster in the oxygen-evolving complex (OEC) of photosystem II[22] and in manganese-enzyme-promoted DNA biosynthesis.[23]

In contrast to reaction pathways that involve activation of dioxygen via direct interaction with the metal ion in a metalloenzyme active site, in some oxygenases the metal ion apparently serves a different role, to activate a bound ligand for subsequent attack by O_2. Two contributions investigate this role in non-heme monoiron enzymes. Fiedler and co-workers tackle the challenge of preparing a model of a key intermediate proposed for extradiol catechol dioxygenases, enzymes that play a central role in the metabolism of aromatic compounds.[24] Studies of the various enzymes support the notion that this intermediate features a non-heme iron(II) site with a bound superoxide poised to attack a coordinated semiquinonate radical.[25] A key synthetic precedent for this notion is provided by the isolation of a 5-coordinated iron(II) (iminobenzo)-semiquinone complex, which is shown by spectroscopy and X-ray crystallography to contain a radical ligand bound to iron(II) instead of an anionic aminophenolate bound to iron(III), as seen in previously reported 6-coordinated complexes.[26]

Berreau and co-workers[27] target the acireductone dioxygenases, which act to cleave an aliphatic C−C bond of their substrate 1,2-dihydroxy-3-oxo-(*S*)-methylthiopentene through pathways with regioselectivities that differ depending on the identity of the active site metal ion.[28] In the nickel enzyme, oxidative cleavage results in the formation of formic acid, CO, and a carboxylic acid, whereby in the iron-containing enzyme, formic acid and an α-keto acid are generated. Differences in the mode of chelation of the substrate to the activating iron and nickel centers had previously been suggested to underly the regioselectivity differences.[26] Here, mechanistic studies of the reactions of O_2 with iron(II) complexes of a substrate analogue, 2-hydroxy-1,3-diphenylpropan-1,3-dione, led to an alternate explanation involving a difference in the course of hydration of a triketone intermediate in related nickel and iron complexes. This work illustrates how examination of synthetic models can reveal new mechanistic possibilities for metalloenzyme catalysis.

Mechanistic insights into CO_2 hydration by the highly efficient enzyme carbonic anhydrase[29] are provided in the work reported by Lightstone, Aines, and co-workers.[30] They couple stopped-flow kinetics and DFT studies to investigate a series of zinc(II) complexes of azamacrocyclic ligands. They draw a provocative conclusion, that "bicarbonate release, not CO_2 addition, may be the rate-limiting step in CO_2 hydration".[27] Some implications of this finding are presented for the design of new catalysts that operate at high rates to sequester CO_2, including the possible need for hydrogen-bond acceptors near, but not able to bind to, the metal ion.

Elusive and/or topologically complicated structures found in metalloenzyme active sites are the inspiration for several synthetic efforts presented in this virtual issue. For example, Meyer and co-workers[31] report the first structural definition and spectroscopic features of a diferrous complex with a $Fe_2(\mu\text{-}S)_2$ core, which models the "super-reduced" $[2Fe{-}2S]^0$ cluster identified in some ferrodoxins. Through this work, benchmarks are provided that may be useful for finding physiologically relevant examples of this unusual cluster in the future. Tatsumi and co-workers[32] describe the synthesis and structural characterization of a $[Fe_8S_x]$ cluster that features a light atom (O) within it, presented as progress toward the challenging goal of preparing a model of the nitrogenase FeMo cofactor. Goddard, Agapie, and co-workers[33] also study structurally complicated clusters but focus on the reactivity of cuboidal Mn_3MO_n moieties (M = Mn, Sc, Ca) that model the OEC. In addition to probing the oxidative capabilities of the complexes through experiment and theory, migration of O atoms within the clusters are examined that are relevant to proposed movements within the biological site. The synthetic successes presented in these three contributions illustrate the ability of talented inorganic chemists to prepare novel molecules that are both relevant to metalloenzyme active sites and of fundamental interest.

Other scientists have focused on ligand design as a strategy for metalloenzyme active site modeling. With the goal of understanding the function of the non-heme iron enzyme cysteine dioxygenase, Goldberg and co-workers[34] designed an N_4S-donor ligand akin to the well-studied N4Py ligand (vide supra) that features a thiolate cis to the putative O_2 binding site in an iron(II) complex, as postulated for the enzyme−substrate complex in the enzyme. Reaction of an iron(II) complex of the new ligand with O_2 was observed to yield a biologically relevant

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S-oxygenated product (a sulfinate). Reinaud and co-workers[35] target complex supramolecular assemblies as models of multicomponent moieties in enzymes through the use of an elaborate calix[6]arene ligand featuring N-donor azoles on both the small and large rims of the calix scaffold. Heterometallic clusters with Zn and/or Cu ions are prepared, metal ion migrations among the various binding sites are identified, and coordination mode changes are induced through addition of ligand guest molecules.

Second-sphere hydrogen-bonding interactions that model those thought to be critical for the function of many metalloenzymes are built into ligands reported by two groups. Okamura and co-workers use spectroscopic and electrochemical methods to probe the effects of hydrogen bonds of amide N−H groups to ligated thiolene S donors on the properties of bound Mo^{VI}=O units.[36] Correlations among the hydrogen bonding, Mo^{VI}=O bond strength, and redox potential are identified and related to observed reactivity in a series of complexes, providing important insight into second-sphere effects likely to occur in molybdenum-containing oxotransferase enzymes. Borovik and co-workers[37] use tripodal ligands with sulfonamide hydrogen-bond acceptors in efforts to understand the dual effects of hydrogen bonding and interactions with group II metal ions like calcium (found in the OEC) on the substrate reactivity. They report success in this approach through the isolation of novel cobalt complexes that feature aquo and hydroxo ligands stabilized by both hydrogen bonds and bound Ca^{II} ions. Particularly notable is the structural characterization of a complex with a $Co^{II}(\mu\text{-}OH_2)Ca^{II}OH_2$ core, which models key structural elements found in the OEC, such as transition metal and Ca^{II} ions within an extensive hydrogen-bonding network that is critical for function.

Finally, several contributions to this virtual issue describe the use of advanced spectroscopy and theory to understand electronic structures and bonding in metalloenzyme model complexes. Two papers focus on X-ray spectroscopy as an effective tool. DeBeer and co-workers[38] examine a series of manganese complexes through Kβ X-ray emission spectroscopy and theoretical calculations in order to provide benchmarks for studies of biological and other complex systems. Through their systematic study, they find that the valence-to-core regions of the spectra are sensitive indicators of manganese ion oxidation state, spin state, and ligand identity. A team led by Solomon, Hedman, and Hodgson[39] uses iron L-edge X-ray absorption spectroscopy to deeply probe the nature of the iron−oxygen bond in an oxygenated picket-fence iron porphyrin complex that models the oxygenated form of myoglobin and hemoglobin. Their findings support strong σ- and π-donor interactions from the bound dioxygen ligand that impact the spin polarization in the Fe-O_2 unit. Figg, Holland, and Cundari[40] report DFT calculations aimed at understanding how iron and K^+ work together to cleave N_2 into two nitride ligands in a system supported by β-diketiminate ligands that is relevant to nitrogenase.[41] They conclude that three reduced iron centers are required to activate the N_2 molecule and that the K^+ ion is key for stabilizing the bridging nitride and making N−N bond cleavage feasible. Silakov, Lubitz, and co-workers combine electron paramagnetic resonance (including ENDOR) and Mössbauer spectroscopy with DFT calculations to understand the electronic structure of a mixed-valent diiron complex prepared by Rauchfuss and co-workers that models a portion of the "H-cluster" in the [FeFe]hydrogenases.[42] The results of this in-depth study revealed differences between the spin delocalization in the model and in the enzyme, suggesting the operation of subtle protein influences that are challenging to replicate in synthetic complexes. Together, the work described in these papers illustrates how studies of synthetic model complexes can lead to deep insights into structure and bonding that underly diverse aspects of metalloenzyme chemistry.

While the diverse topics spanned by the articles featured in this virtual issue only partially reflect the breadth of the field, they, nonetheless, illustrate how the study of synthetic compounds can inform understanding of structure, bonding, and reactivity of metalloenzyme active sites. Moreover, such studies provide the underpinning for the development of new catalysts and often lead to the discovery of unforeseen molecules with novel and intrinsically interesting attributes. The interdisciplinary approaches used provide a deep understanding and make the field particularly attractive for students and postdoctoral researchers who desire the type of broad training required to address the most significant scientific challenges. I hope that readers will be inspired by the work presented here to delve into the field of bioinorganic chemistry further and to pursue their own creative ideas aimed at using synthetic inorganic chemistry to understand complex biological systems.

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Notes

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

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