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Preface: Forum on Dioxygen Activation and Reduction

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Through the photosynthetic action of cyanobacteria more than 2 billion years ago, dioxygen (O_2) converted the earth's atmosphere from a reducing medium to one that is powerfully oxidizing.[1] As a result, we are now awash in a sea of chemical instability, literally ready at all times to combust to yield carbon dioxide and water (H_2O). In other words, we are surrounded by enormous quantities of a gas that, from a thermodynamic point of view, is poised to react spontaneously with organic compounds and a wide variety of other reductants. While useful for generating heat, such reactions must be controlled if the oxidizing power of O_2 is to be harnessed for the production of more tractable forms of energy and more complex (partially and selectively oxidized) chemical compounds.

Luckily, kinetic and spin barriers inhibit the direct reaction of O_2 with organic materials and its reduction to H_2O, extending the time we can exist in our current metastable atmospheric state. Yet, at the same time, these barriers must be surmounted if the power of O_2 is to be exploited and controlled for the purposes of sustaining life, selectively oxidizing organic compounds, and generating electrical energy. Transition-metal ions hold the key to this conundrum: they are utilized by enzymes, in heterogeneous and homogeneous oxidation catalysis, and in fuel cells because of their ability to facilitate and control O_2 activation and reduction.

The articles collected in this Forum look at how transition-metal ions in such disparate systems function to activate and reduce O_2. Perspectives vary, from assessment of fundamental thermodynamic and mechanistic issues in the electroreduction of O_2 in fuel cells to evaluation of O_2 activation by metal-doped zeolites, metalloenzymes, and metal ions and synthetic complexes in solution. While the depth and breadth of the topic of this Forum preclude comprehensive coverage of the subject, this Forum on Dioxygen Activation and Reduction presents a stimulating sample of ongoing research and its many challenges that currently propel this subject forward. It is especially illuminating to consider these articles as complementary to those in a previous Forum on Making Oxygen;[2] many related issues are relevant to understanding and controlling how O_2 is both produced and utilized.

Improving the efficiency of the four-electron reduction of O_2 to H_2O in fuel cells is the central concern in two articles in this Forum. Gewirth and Thorum discuss a wide range of catalysts within the context of mechanistic hypotheses, with a particular emphasis on low-pH fuel cells. Analysis and evaluation of the factors that impact the activity and durability of various catalysts under working fuel cell conditions point to Pt-based nanoparticle catalysts as top performers, with the development of nonprecious metal systems like those operative in biology being a key goal for future research. Kjaergaard, Rossmeisl, and Nørskov propose a theoretical method for comparing the performance of the Pt-based and metalloenzyme catalysts for the four-electron reduction of O_2 to H_2O. The method involves calculation of the free energy of binding of various oxygen species to reactive metal ions on surfaces and within metalloenzyme active sites, such as cytochrome *c* oxidase or the multicopper oxidases. Provocative rationales for the lower overpotentials and improved performance of the enzymes relative to the heterogeneous Pt-based catalysts are presented.

In their contribution, Smeets, Woertink, Sels, Solomon, and Schoonheydt turn to heterogeneous systems of a different sort, namely, transition-metal ions embedded in zeolites. After a discussion on how Cu^{2+}, Fe^{3+}, and Co^{2+} bind to surface oxygens in zeolites, spectroscopic studies of intermediates generated from reactions of reduced forms of these systems with O_2 or O-atom-transfer reagents are presented. These studies have led to intriguing postulates of metal−superoxo and various binuclear oxygen−copper structures in systems active in selective oxidation catalysis.

A paper by Bakac presents a survey of the kinetics and thermodynamics of reactions of O_2 and reduced species (e.g., superoxide, peroxide, oxide) with metal complexes in H_2O. Particular emphasis is placed on reactions with Cr and Rh ions and on drawing comparisons with metal-free congeners ($ROO^\bullet$, ROOH, and $RO^\bullet$). Another focal point is the application of kinetic methods for the identification of highly reactive metal−oxygen intermediates that undergo a wide range of subsequent reactions, including electron transfer, H- and O-atom transfers, and O−O bond scission processes. Related reactions are discussed in the article by Neumann, which focuses on applications of polyoxometalates in oxidation catalysis. Specific attention is paid to unraveling the subtleties of oxygen activation by the Keggin-type compound

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(2) *Inorg. Chem.* **2008**, *47*, 1697−2232.

$H_5PV_2Mo_{10}O_{40}$ and the isolation of an iron(III) hydroperoxide species in a hexairon(II)-substituted polyoxometalate. Intriguing results of O_2 reactions with molecules that are hybrids of polyoxometalates and organometallic moieties also are discussed.

Detailed evaluations of metal−oxygen species derived from O_2 in the heme enzymes heme oxygenase (HO) and cytochrome P450 are presented in two articles. In the article on HO by Matsui, Iwasaki, Sugiyama, Unno, and Ikeda-Saito, a Fe-OOH species is proposed to play a key functional role in several steps along the complicated reaction pathway involving multiple self-oxygenations and degradation of the heme. The critical role of the distal hydrogen-bond network in facilitating O−O bond scission is emphasized. In another contribution, Rittle, Younker, and Green focus on a specific controversy regarding the nature of the oxidizing intermediate in catalysis by cytochrome P450. They argue on the basis of detailed UV−vis spectroscopic analysis that, in contrast to a previous report, an intermediate species generated by laser flash photolysis and identified as compound I, is not an iron(IV) oxo with an additional oxidizing equivalent delocalized over the porphyrin and thiolate ligands. This work leaves the identity of this oxidizing species open to question, setting the stage for future characterization efforts.

Three articles focus entirely on studies of synthetic models of metalloenzyme oxygen intermediates, the results of which deepen our mechanistic understanding of O_2 activation processes and provide detailed insights into the structures and properties of key intermediates derived from metal/O_2 reactions. Mukherjee, Cranswick, Paine, Fujisawa, and Que focus on iron(III) superoxo species, the precursor to the iron(IV) oxo unit most often thought to be the active oxidant in synthetic and enzymatic systems. After reviewing the important role of iron(III) superoxo species in non-heme enzymes, they provide evidence for the intermediacy of such a species in reactions of an iron(II) ketocarboxylate complex with O_2. Ligand effects on metal/O_2 reactivity is a common theme in articles by Halime, Kieber-Emmons, Qayyum, Mondal, Puiu, Chufán, Sarjeant, Hodgson, Hedman, Solomon, and Karlin and by Shook and Borovik. In studies of models of a key putative intermediate in cytochrome *c* oxidase, Halime et al. describe the characterization of two different bridging modes, μ-η^2:η^1 vs μ-η^2:η^2, in high-spin heme−peroxo−copper complexes with N-donor supporting ligands on the Cu ion of disparate denticity. In addition, they recount isolation of a low-spin variant and uncover interesting structure/reactivity differences of potential relevance for understanding how enzymatic reactions might be tuned. Shook and Borovik look at the role of secondary coordination sphere effects on metal/O_2 reactivity, with a particular focus on intramolecular hydrogen bonds involving metal−oxygen species. These hydrogen bonds play a key role in controlling reversible O_2 binding and subsequent activation to generate metal−oxo species in synthetic complexes, just as in metalloenzymes (cf. the article by Matsui et al.).

Further details on O_2 binding and O−O bond scission are probed in the article by Ashley and Roth, who discuss the use of O-isotope kinetic methods to obtain mechanistic information. Competitive isotope fractionation on samples prepared with natural abundance O_2 has been used to measure kinetic and equilibrium O-isotope effects that provide insight into O_2 coordination and activation steps in various transition-metal complexes and enzymes. Particularly insightful conclusions are drawn by using density functional theory calculations to interpret ground- and transition-state structures and how equilibrium isotope effects on reversible reactions relate to the kinetic isotope effects on the individual steps.

Taken together, the articles collected in this Forum illustrate the tremendous progress that is being made in efforts to understand how transition metals in diverse environments interact with O_2 and activate it for further reactions in a controlled way. While the systems described vary considerably, there are many common mechanistic features, as illustrated on the cover of this issue. For the most part, O_2 is activated by metal ions via two-electron reductions to form peroxymetal complexes, which are thermodynamically viable as intermediates. These species can then be further reduced to H_2O in a fuel cell, directly reacted with the substrates in selective oxygenation and oxidation reactions, or undergo O−O bond cleavage to generate even more active high-valent intermediates. In addition, a number of O_2-activating reactions may proceed through the one-electron reduction of O_2 to form a metal-bound superoxide that can then perform H-atom abstractions. While not as energetically favorable as the two-electron-reduction routes, the one-electron reduction of O_2 would be assisted by a relatively low reduction potential for the metal ion and strong superoxide metal bonding.

Finally, it should be noted that while all of the articles in this Forum have focused on the activation of O_2 by reaction with reduced metal ion(s), there are also a number of key catalytic processes where an oxidized metal center reacts with the substrate to activate it for the spin-forbidden reaction with O_2.[3] In some cases, this simply involves one-electron oxidation of the substrate and reduction of the metal ion (e.g., lipoxygenases), but in a number of important reactions, this is accomplished by substrate binding to an oxidized metal ion (e.g., catechol activation by the intradiol dioxygenases, cofactor formation in amine oxidase biogenesis).[4−6] There is clearly much to be understood in this highly interdisciplinary field that unites inorganic chemistry with biochemistry and materials science and is having an impact in biotechnology, health, catalysis, and advancing sources of sustainable energy.

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