JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Perspective
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Status of Reactive Non-Heme Metal–Oxygen Intermediates in Chemical and Enzymatic Reactions

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ABSTRACT: Selective functionalization of unactivated C–H bonds, water oxidation, and dioxygen reduction are extremely important reactions in the context of finding energy carriers and conversion processes that are alternatives to the current fossil-based oil for energy. A range of metalloenzymes achieve these challenging tasks in biology by using cheap and abundant transition metals, such as iron, copper, and manganese. High-valent metal–oxo and metal–dioxygen (superoxo, peroxo, and hydroperoxo) cores act as active intermediates in many of these processes. The generation of well-described model compounds can provide vital insights into the mechanisms of such enzymatic reactions. This perspective provides a focused rather than comprehensive review of the recent advances in the chemistry of biomimetic high-valent metal–oxo and metal–dioxygen complexes, which can be related to our understanding of the biological systems.

1. INTRODUCTION

Key metabolic functions, such as hydroxylation of methane in methanotrophs, desaturation of fatty acids in plants, DNA and RNA repairs, biosynthesis of β-lactam antibiotics, and sensing of hypoxia in mammalian cells to signal the formation of blood vessels, all require the controlled oxidation of organic substrates by metal-mediated activation of dioxygen (O_2).[1−5] Dioxygen activation by transition metal complexes to facilitate oxidative transformations is also industrially important in the context of making efficient use of the naturally abundant oxidant (i.e., O_2) in oxidation reactions.[6−8] As a consequence, great efforts have been focused on understanding the mechanisms of dioxygen activation in a number of heme and non-heme monooxygenase enzymes containing mononuclear and homo- and heterodinuclear active sites.[2,9−23] Despite the diversity of the active sites of the enzymes, a common mechanistic hypothesis for dioxygen activation has been established. In this unified scheme (Figure 1), the metal centers at the active sites first bind dioxygen to form a metal–superoxo intermediate (Figure 1A), thereby converting the kinetically inert ground state of O_2 to a more reactive doublet state of $O_2^{\bullet-}$. Subsequently, the generated metal–superoxo species picks up an electron (forming a metal–peroxo intermediate) and a proton to form a metal–hydroperoxo intermediate, which then undergoes O–O bond cleavage to afford a high-valent metal–oxo species (Figure 1A). Alternatively, the metal–superoxo species can abstract a hydrogen atom from the substrate to form the metal–hydroperoxo species (Figure 1A). In the dinuclear context, the corresponding intermediates are superoxo-bridged $M(O_2^{\bullet-})M$, peroxo-bridged $M(O_2^{2-})M$, and oxo-bridged high-valent $M_2(\mu\text{-}O)_2$ species (Figure 1B). Although the metal–oxo intermediates have been generally considered as the reactive species responsible for oxygenation reactions in heme and non-heme systems, arguments are also emerging in the mechanistic discussions of these systems as to whether the key oxidants should rather be described as metal–superoxo, –peroxo, or –hydroperoxo species.[24−29] For example, in cytochrome P_{450} enzymes (P_{450}), there is a long-standing controversy among scientists about the possibility of iron(III)–hydroperoxo species (Cpd 0) acting as an alternative oxidant to the high-valent iron(IV)–oxo porphyrin π-cation radical species (Cpd I). Indirect evidence collected from mutation and kinetic studies has suggested that Cpd 0 may indeed act as a second electrophilic oxidant, in particular in P_{450}-catalyzed sulfoxidation reactions.[30,31]

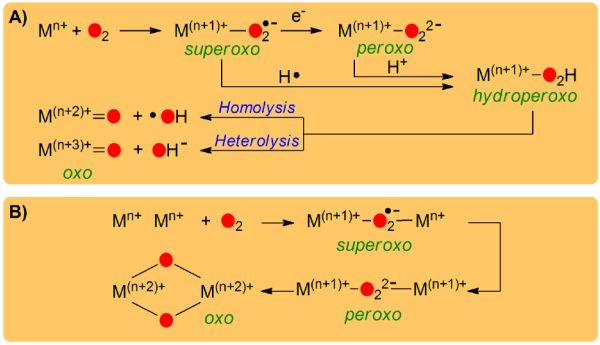

Figure 1. Unified mechanisms for dioxygen activation at (A) mononuclear and (B) dinuclear active sites.

However, a large number of experimental and theoretical results dispute the participation of this second oxidant in enzymatic and biomimetic oxidation reactions.[32−37] One reason for the long-standing controversy over one oxidant versus multiple oxidants in metal-mediated oxidation reactions is the lack of information on the chemical properties of the proposed metal–oxygen intermediates (e.g., metal–superoxo, –peroxo, –hydroperoxo, and –oxo), since these highly unstable intermediates are difficult to capture during oxidation reactions catalyzed by enzymes or their model compounds.

In this perspective, we summarize the information obtained to date in enzymatic and biomimetic systems that fuels this debate regarding the active oxidants in metal-mediated oxygenation reactions. The first part of this perspective provides some selected examples from enzymatic systems that highlight the

Received: July 31, 2014
Published: September 12, 2014

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

existing controversy with respect to the chemistry of metal−oxygen adducts (viz., superoxo, peroxo, hydroperoxo, and oxo) and their possible roles as active oxidants in various oxidation reactions (Figures 2−5). This is followed by an account of some recent advances in synthetic non-heme model chemistry, the results of which provide important insights into the structures (Figure 6), physiochemical properties, and reactivities (Figures 7−12) of the metal−oxygen intermediates generated at the active sites of oxidases and oxygenases. We do not provide a comprehensive review of the synthetic non-heme model complexes because of the brevity of this perspective; rather, we focus on some selected examples of unprecedented reactivity patterns exhibited by the synthetic metal−oxygen intermediates in order to highlight the key concepts and recent progress. Finally, we provide a perspective on potential future research directions and point out important unanswered questions with the goal of inspiring future studies in this highly active research field.

2. REACTIVE INTERMEDIATES IN BIOLOGICAL REACTIONS

2.1. Metal−Superoxo Species. Reductive activation of dioxygen at reduced metal cofactors generally results in a variety of two-electron oxidation processes leading to hydroxylation, halogenation, dehydrogenation, cyclization, and epoxidation products; the remaining two reducing equivalents required for the four-electron reduction of dioxygen are often provided by a cosubstrate or an exogenous electron donor.[1−5,9−32] However, four-electron oxidation of substrates by a single equivalent of dioxygen without the consumption of reducing cosubstrates has also been observed in a number of oxidases and oxygenases (Figure 2).[38−61] This alternative manifold for transition metal-mediated dioxygen activation would, however, require metal−superoxo species, which have been generally considered merely as pass-through points en route to high-valent metal−oxo intermediates that have been widely believed to be the only reactive species responsible for oxidation reactions. Indeed, convincing evidence for the involvement of a metal−superoxo intermediate in the C−H bond cleavage step was reported in *myo*-inositol oxygenase (MIOX), a mammalian enzyme that carries out the four-electron oxidation of *myo*-inositol to D-glucuronate (Figure 2, MIOX).[38−43] MIOX activates dioxygen at a mixed-valent diiron(II/III) cluster to form an $S = {}^1/_2$ diiron(III)−superoxo species, which was trapped and characterized by electron paramagnetic resonance (EPR) spectroscopy.[43] Since the decay of this species was retarded with the use of deuterated substrate, it was considered that the diiron(III)−superoxo intermediate must be involved in the cleavage of the labeled C−H bond,[38] which likely represents the first step in oxidation reactions. A similar hydrogen atom abstraction (HAA) process has been postulated in the mechanisms of other iron [e.g., isopenicillin-*N*-synthase (IPNS)] (Figure 2, IPNS) and copper [e.g., dopamine β-monooxygenase (DβM) and peptidylglycine α-hydroxylating monooxygenase (PHM)] enzymes,[44−49] although, unlike in MIOX, metal−superoxo intermediates have not been trapped in these enzymes. Notably, the three-dimensional structure of IPNS in complex with its substrate L-δ-aminoadipoyl-L-cysteinyl-D-valine (ACV) and nitric oxide, which is a dioxygen surrogate, shows the pendant oxygen atom of the iron-coordinated NO directed toward the α-hydrogen atom, which together with other kinetic and structural results provided indirect support for the hypothesis that the L-cysteine C−H bond cleavage is effected by the initial adduct of the iron(II) center and dioxygen.[50] For the DβM and PHM enzymes, evidence in favor of the involvement of the copper−superoxo species in the HAA process is limited to only theoretical and indirect kinetic studies, which support the idea that the HAA precedes any O−O cleavage step. However, experimental observation of the metal−dioxygen intermediates

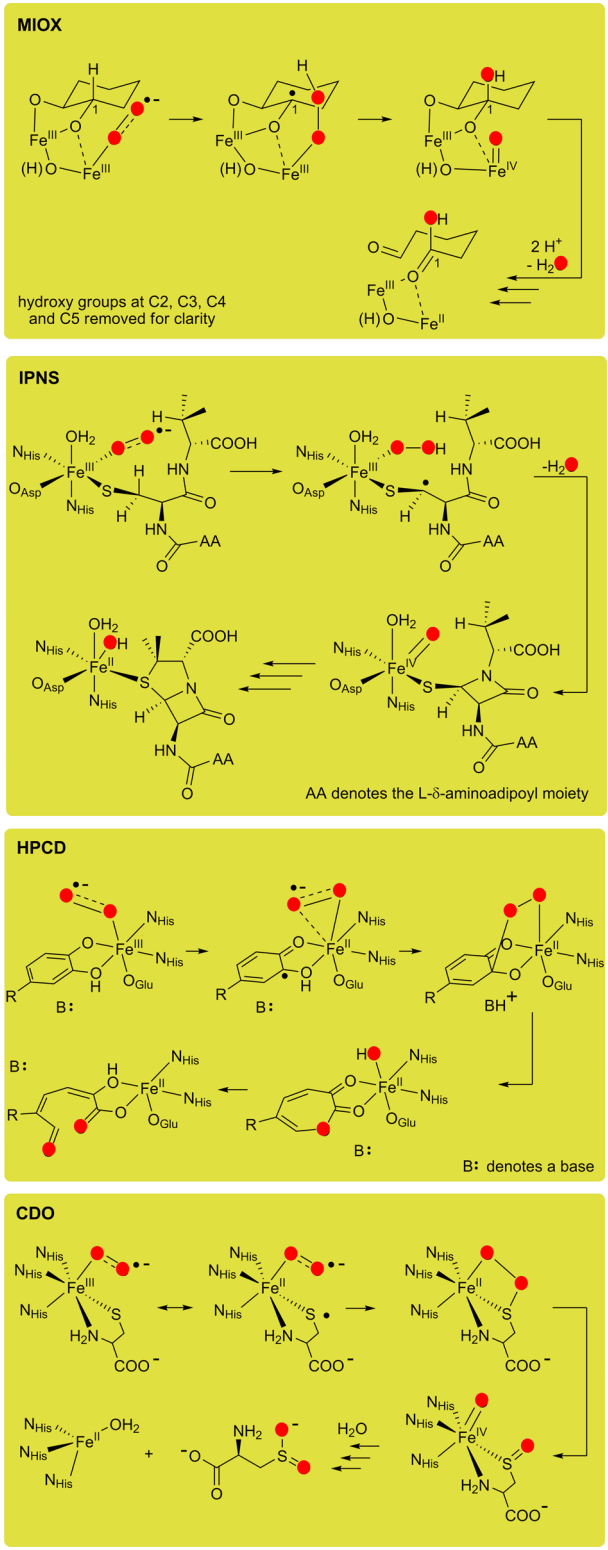

Figure 2. Proposed metal−superoxo intermediates in biological oxidation reactions.

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

in these enzymes is required in order to further evaluate the mechanistic possibilities.

In addition to C−H bond activation reactions, the metal−superoxo species generated can also initiate an internal electron transfer process from the bound substrate to generate adjacent substrate and oxygen radicals that can recombine to give the oxygenated products. One example in non-heme iron systems is homoprotocatechuate 2,3-dioxygenase (2,3-HPCD), an enzyme that cleaves the aromatic ring of its substrate with insertion of both oxygen atoms of O_2 into the product.[4,51,53] Kovaleva and Lipscomb recently presented a crystallographic tour de force of the catalytic mechanism regarding 2,3-HPCD by trapping three intermediates, namely, the iron(II)−superoxo, iron(II)−alkylperoxo, and enzyme−product complexes, thereby firmly establishing the mechanism shown in Figure 2, HPCD.[54] Thus, the net electron transfer from the catechol substrate through the iron(II) to dioxygen forms the semiquinonato iron(II)−superoxo species, which then yields the iron(II)−alkylperoxo species by radical coupling and eventually leads to the ring cleavage and oxygen insertion reactions to form the muconic semialdehyde adduct as the product. Although in the native 2,3-HPCD an iron(III)−superoxo intermediate that must precede the formation of the reactive semiquinonato iron(II)−superoxo intermediate has not been detected to date, the formation of an analogous $S = {}^5/_2$ manganese(III)−superoxo species was evidenced by EPR spectroscopy in manganese-substituted HPCD (Mn-HPCD).[55] Thus, in Mn-HPCD, the rapid electron transfer to form the reactive semiquinonato mangnese(II)−superoxo intermediate is not a concerted process, which is also possibly the case for native Fe-HPCD. Indeed, the use of an alternative substrate, 4-nitrocatechol, and mutation of the active-site His200 to Asn (H200N) led to the eventual trapping of the elusive iron(III)−superoxo intermediate; parallel-mode EPR and Mössbauer spectroscopic studies confirmed the presence of an antiferromagnetically coupled $S = 2$ iron(III)−superoxo unit.[56] A comparable mechanism has been suggested in cysteine dioxygenase (CDO) (Figure 2, CDO), where recombination of the oxygen radical and cysteinyl sulfur-based radical and a subsequent O−O bond cleavage step leads to the formation of an iron(IV)−oxo species and a sulfoxide intermediate.[57−61] A final oxygen atom transfer (OAT) then gives the cysteine sulfinic acid product. However, direct evidence for the suggested intermediates in the catalytic cycle of CDO is lacking, which makes a definitive complete assignment of the mechanism difficult.

2.2. Metal−Peroxo Species. When the metal−superoxo species do not participate directly in substrate oxidation reactions, they may be converted to metal−peroxo units upon one-electron reduction by a redox partner, which can be either an exogenous reductant or a second reduced metal center. Such metal−peroxo species are also considered to be active in carrying out a variety of nucleophilic and electrophilic enzymatic reactions (Figure 3). For example, a non-heme peroxo-bridged diiron(III) complex has been suggested as the active intermediate responsible for conversion of saturated or monounsaturated C_n fatty aldehydes to formate and the corresponding C_{n-1} alkanes or alkenes, respectively, in the diiron form of cyanobacterial aldehyde-deformylating oxygenases (Figure 3, ADO).[62,63] The proposed mechanism involves attack on the carbonyl of the bound substrate by the reduced O_2 moiety to form an $Fe_2^{III/III}$−peroxyhemiacetal complex, which undergoes reductive O−O bond cleavage that leads to C1−C2 radical fragmentation and formation of the alkane/alkene and formate products. Although studies of heme enzymes (i.e., P_{450}) and inorganic complexes

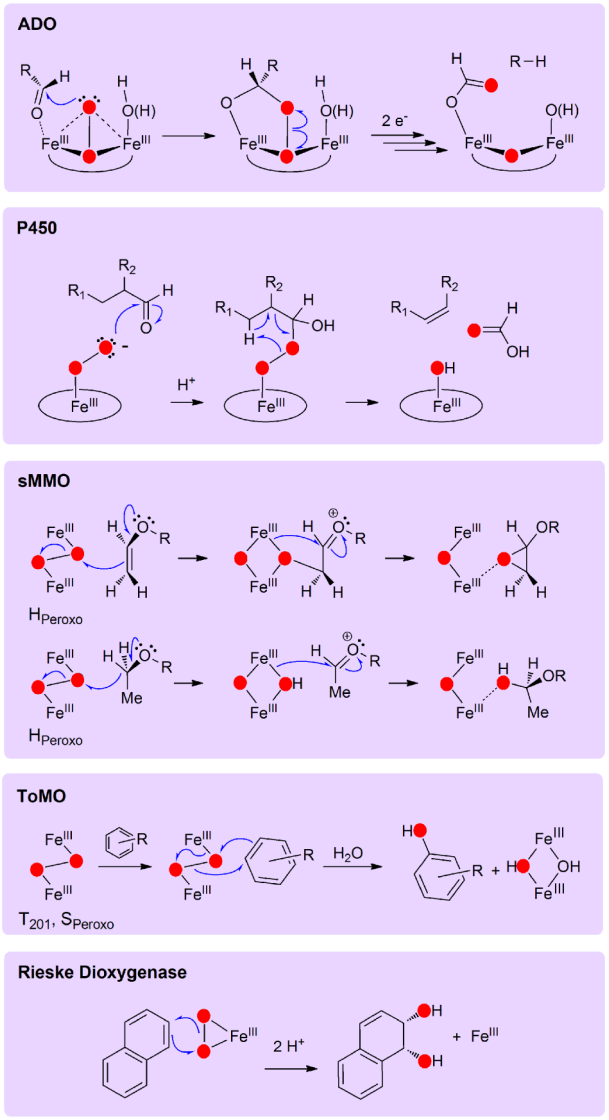

Figure 3. Proposed metal−peroxo intermediates in biological oxidation reactions.

have shown that metal-bound peroxides can also act as *nucleophiles* to attack (among other electrophiles) aldehydes, leading to the production of formate and oxidized coproducts (Figure 3, P_{450}),[64−69] the intriguing and (to date) unprecedented aspect of the proposed ADO mechanism is the breakdown of the peroxyhemiacetal intermediate to convert C2 of the substrate into a fully reduced (methyl) rather than partially oxidized (e.g., alcohol or olefinic methylene) center in the R−H product.

Electrophilic reactions by metal−peroxo complexes have also been suggested in biology. One example is the diiron(III)−peroxo species, H_{Peroxo}, which is the first spectroscopically characterized intermediate formed upon dioxygen activation at the reduced diiron(II) center of the hydroxylase component of soluble methane monooxygenase (sMMO).[70,71] Proton-promoted O−O bond scission and rearrangement of the diiron core in H_{Peroxo} leads to a bis(μ-oxo)diiron(IV) unit, termed Q, that is considered to be directly responsible for the oxidation of methane to methanol.[72,73] Relative reactivity studies of H_{Peroxo} and Q with various substrates have shown that H_{Peroxo} is a more electrophilic oxidant than Q, preferring to react by a two-electron, or a hydride abstraction, pathway (Figure 3, sMMO),

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

whereas one-electron oxidation processes are preferred by Q (see Figure 5, sMMO).[71,74] The reactivity difference between H_{Peroxo} and Q rather parallels the known differences between (μ-η^2:η^2-peroxo)dicopper(II) species, which react by two-electron processes, and high-valent di(μ-oxo)dicopper(III) centers,[11,21,23] which prefer sequential one-electron oxidations, in the dicopper complexes. However, one major difference between the reactions of H_{Peroxo} and Q with hydrocarbons is that large kinetic isotope effects, implicating H atom tunneling, are observed for Q but not for H_{Peroxo}.[75] A diiron(III)−peroxo species, $T_{201}S_{Peroxo}$, that is similar to H_{Peroxo} in methane monooxygenase has also been trapped in the catalytic cycle of toluene monooxygenase and is believed to be the key intermediate responsible for aromatic hydroxylation reactions (Figure 3, ToMO).[76]

In addition to the peroxo-bridged dinuclear complexes, the involvement of a mononuclear side-on iron(III)−peroxo complex in electrophilic oxidation reactions has also been discussed on the basis of the crystal structure of dioxygen-bound naphthalene dioxygenase (NDO) in the presence of the substrate, where both oxygen atoms are found to be similarly polarized and lined up for an attack on the double bond of the electron-rich aromatic substrate (Figure 3, Rieske Dioxygenase).[77] These observations have been interpreted to mean that cis dihydroxylation occurs via a concerted mechanism in which the O−O bond is cleaved simultaneously with the formation of the two C−O bonds; this interpretation also explains the characteristic cis-stereospecific addition of both oxygen atoms of substrates by NDO (Figure 3, Rieske Dioxygenase).[78] However, an alternative mechanism involving protonation of the side-on iron−peroxo species, leading to the formation of more reactive oxidants (e.g., iron−hydroperoxo or high-valent iron−oxo species), cannot be excluded (vide infra).

2.3. Metal−Hydroperoxo Species. Subsequent proton transfer to the metal−peroxo species affords a metal−hydroperoxo intermediate. Strong evidence for the oxidizing capability of the metal−hydroperoxo intermediate comes from studies on bleomycin (BLM), a glycopeptide anticancer drug that effectively carries out cleavage of single- and double-stranded DNA.[79−81] Activated BLM (ABLM), a low-spin (LS) ferric−hydroperoxo species (BLM−Fe^{III}−OOH), is the last intermediate detected before DNA cleavage (Figure 4, Bleomycin).[29,82−87] Solomon and co-workers[88] have used real-time circular dichroism kinetics to elegantly demonstrate that DNA accelerates the decay of ABLM, supporting a mechanism that involves direct HAA by ABLM. This study is consistent with the results of previous theoretical studies[89] by the same group on the reaction of ABLM with DNA, which revealed that direct HAA by the LS iron(III)−hydroperoxo complex is thermodynamically and kinetically favored over other proposed reaction pathways, such as heterolytic or homolytic O−O cleavage of the iron(III)−hydroperoxo species to form high-valent iron−oxo species.

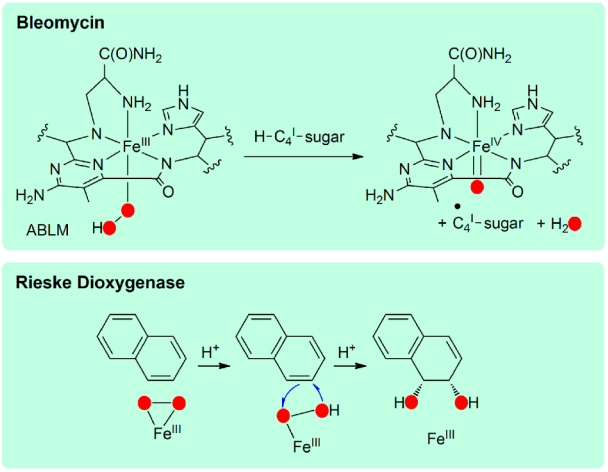

Figure 4. Proposed metal−hydroperoxo intermediates in biological oxidation reactions.

An iron(III)−hydroperoxo species has also been suggested as a key intermediate in the catalytic cycle of Rieske dioxygenases, which catalyze stereo- and regioselective electrophilic cis dihydroxylation of aromatic compounds (Figure 4, Rieske Dioxygenase). Notably, the crystal structure of dioxygen-bound carbazole 1,9a-dioxygenase, a member of the Rieske dioxygenase family, recently revealed an end-on binding mode of the (hydro)peroxo ligand in an iron(III) intermediate, which is in contrast to the side-on binding mode of the peroxo intermediate observed previously in NDO.[90] Accordingly, a mechanism was proposed wherein the peroxo group of the side-on iron(III)−peroxo species is protonated to give the end-on iron(III)−hydroperoxo species, which then performs the dihydroxylation step. In support of this mechanism, spectroscopic characterization of an iron(III)−hydroperoxo species in benzoate 1,2-dioxygenase has been reported;[91] however, a high-spin (HS) $S = {}^5/_2$ configuration was determined for this intermediate on the basis of EPR and Mössbauer studies. Notably, however, direct evidence for its involvement in biological oxidation reactions is still lacking. The open question is whether this HS iron(III)−hydroperoxo intermediate performs cis dihydroxylation directly or the O−O bond is first cleaved to generate a high-valent iron(V)−oxo−hydroxo species that performs the cis dihydroxylation.[92−97] While density functional theory (DFT) calculations favor the former mechanism,[96] isotope labeling studies provided evidence for the latter.[97]

2.4. Metal−Oxo Species. Cleavage of the O−O bond of the metal−hydroperoxo species leads to the generation of metal−oxo intermediates in the last step of the dioxygen activation process. Evidence that such species are involved in the reactions of heme peroxidases was reported three decades ago.[98,99] Recently, high-valent iron(IV)−oxo intermediates have also been trapped and spectroscopically characterized in several non-heme iron enzymes. For example, mononuclear non-heme Fe^{IV}=O cores have been detected in the catalytic cycles of α-KG-dependent oxygenases (taurine dioxygenase[100] and propyl-4-hydroxylase[101]), halogenases (cytochrome c_3 halogenases[102,103] with chlorine or bromine and SyrB2 halogenase[104,105]), and pterin-dependent hydroxylases (tyrosine[106] and phenylalanine hydroxylases[107]). Moreover, rapid freeze-quench studies of the R2 protein of the class-I ribonucleotide reductase (RNR R2) from *Escherichia coli* and methane monooxygenase (MMO) also provided evidence for intermediates X and Q, respectively, with X having an Fe^{III}−O−Fe^{IV} unit[108,109] and Q postulated to have an $Fe^{IV}_2(\mu\text{-}O)_2$ diamond core.[72] For non-heme enzymes, the iron(IV) center has been found to be in the HS $S = 2$ state in all cases, presumably because of the weak ligand field exerted by a combination of histidine and carboxylate ligands. This is in contrast to the heme enzymes, where the iron(IV) center is stabilized in the intermediate-spin ($S = 1$) state.

The reactivities of the mono- and dinuclear iron(IV)−oxo complexes have been explored in significant detail by

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

experimental and theoretical methods, and all of these studies have confirmed their strong HAA abilities (Figure 5). For

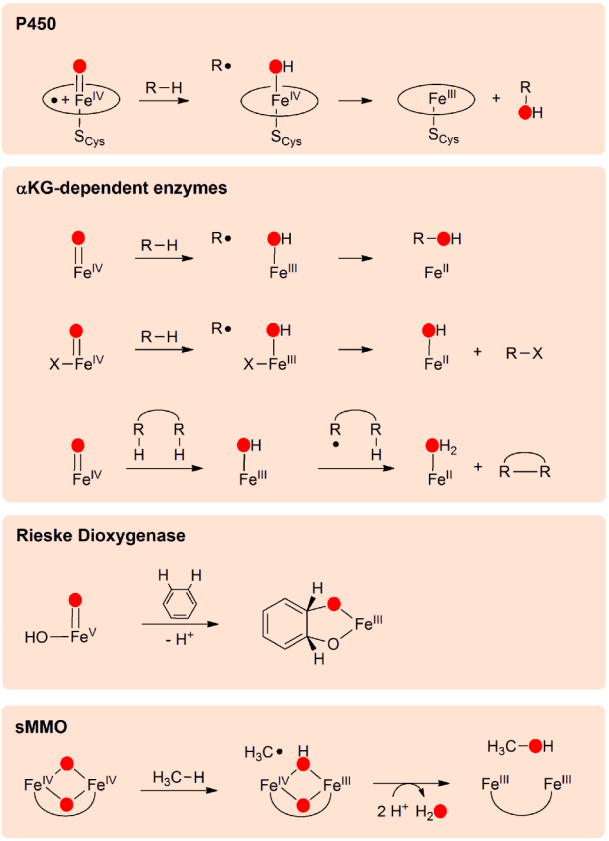

Figure 5. Proposed metal−oxo intermediates in biological oxidation reactions.

mononuclear Fe^{IV}=O cores, the real C−H bond-cleaving agent is suggested to be a ferric−oxyl (Fe^{III}−$O^{\bullet}$) species that is generated by lengthening of the Fe−oxo bond en route to the transition state leading to HAA.[110]

The dominance of high-valent iron(IV)−oxo cores in iron enzymes has led to the suggestion of the involvement of mono- or dinuclear copper−oxo cores in various copper-containing oxygenases.[44,46,111−113] However, direct evidence of mononuclear copper−oxo cores is lacking in both biological and biomimetic systems, although theoretical[111,112] and model[114,115] studies have supported their participation as active intermediates in various copper-mediated oxidation reactions. In contrast, a number of bis(μ-oxo)dicopper(III) cores have been identified in biomimetic systems,[21,116,117] and they are found to be active in various electrophilic oxidation reactions; however, the involvement of similar cores in biological systems is still a subject of great controversy.[21]

3. REACTIVE INTERMEDIATES IN CHEMICAL REACTIONS

The examples listed above demonstrate that the chemistry of the metal−dioxygen adducts (viz., superoxo, peroxo, hydroperoxo) formed in the course of dioxygen activation in non-heme enzymes is expanding rapidly and that their possible roles as active oxidants in various enzymatic reactions are presently a subject of great controversy. This is mainly because of their transient nature in many cases, which makes it extremely difficult to study their chemical and physical properties in the catalytic cycles of dioxygen activation by non-heme enzymes. In this context, biomimetic complexes can be useful in addressing some of the questions raised in the preceding section because of their simpler structures and the ease with which important data can be collected using various experimental and computational methods. Consequently, considerable efforts have been made by synthetic chemists to prepare viable models for the putative intermediates in the catalytic cycles of O_2-activating enzymes in order to understand the factors that control their geometric and electronic properties and chemical reactivities to form related active oxygen species or effect substrate oxidations. Some of the recent examples in biomimetic chemistry are summarized in this section.

3.1. Biomimetic Metal−Superoxo Complexes. In the past few decades, a number of metal−superoxo complexes with first-row transition metal ions, such as Cr, Mn, Co, Ni, and Cu, have been synthesized and thoroughly characterized to understand the structural and chemical properties of the transient iron− and copper−superoxo intermediates in enzymatic reactions.[67,118−126] In these studies, both the end-on and side-on binding modes of the superoxo ligands have been established. Moreover, the reactivities of these complexes have been extensively investigated in various oxidation reactions, providing justification of the involvement of the metal−superoxo cores in various enzymatic reactions.[127−136] For example, the versatility of the metal−superoxo species as reactive intermediates in various oxidation reactions was elegantly demonstrated in the recent synthesis of an end-on chromium(III)−superoxo complex bearing an N-methylated tetraazamacrocyclic (TMC) ligand, $[Cr^{III}(O_2)(14\text{-TMC})(Cl)]^+$ (**1**) (14-TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) (Figure 6, Superoxo).[120] The thermally stable complex **1** was reactive enough to be used in various oxidation reactions under stoichiometric conditions (Figure 7). For example, complex **1** can activate the weak C−H bonds of 1,4-cyclohexadiene, dihydroanthracene, and xanthene to form benzene, anthracene, and xanthone, respectively. Additionally, a large deuterium kinetic isotope effect (KIE) value of ∼50 was determined in the oxidation of 9,10-dihydroanthracene (DHA) and DHA-d_4 by **1**, which suggests tunneling behavior in the HAA reaction. This study, together with previous reports[124,126,128,129,137−139] on the reactivities of a number of synthetic copper(II)−superoxo complexes in ligand oxidation and the oxidation of organic compounds with weak C−H, O−H, and N−H bonds, provides direct experimental evidence to support the conclusion that metal−superoxo species can abstract H atoms from external substrates. Additionally, the electrophilic character of the superoxo unit in **1** was established by its ability to perform OAT reactions with phosphines and sulfides, affording oxidized organic products and $[Cr^{IV}(O)(14\text{-TMC})(Cl)]^+$ (Figure 7).[140] Notably, these OAT reactions support the proposed oxidant and mechanism in CDO, where an iron(III)−superoxo species attacks the sulfur atom of the cysteine ligand to give the sulfoxide and iron(IV)−oxo products.[62−66] Furthermore, reaction of **1** with nitric oxide also resulted in the generation of $[Cr^{IV}(O)(14\text{-TMC})(Cl)]^+$ along with the liberation of nitrogen dioxide (Figure 7).[136] In the latter reaction, the formation of nitrogen dioxide was confirmed by trapping experiments using 2,4-di-*tert*-butylphenol (DTBP) that led to the expected formation of nitrated 2,4-di-*tert*-butyl-6-nitrophenol (DTDP) and $[Cr^{III}(OH)(14\text{-TMC})(Cl)]^+$ products. Moreover, an intermediate was trapped by low-temperature UV−vis studies during the conversion of **1** to $[Cr^{IV}(O)(14$-

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

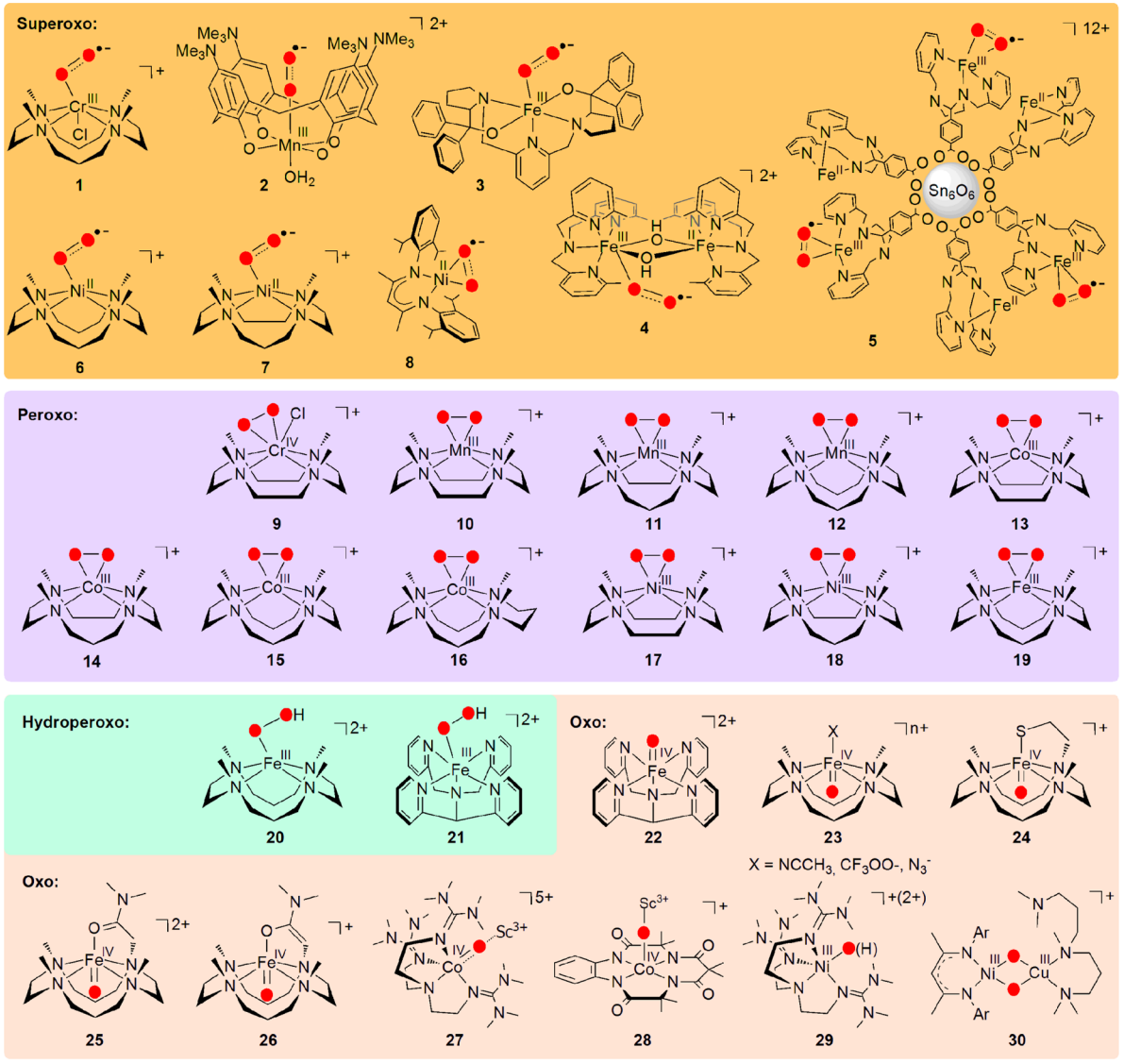

Figure 6. Biomimetic metal−superoxo, −peroxo, −hydroperoxo, and −oxo complexes. The Sn_6O_6 core of **5** has been simplified for clarity.

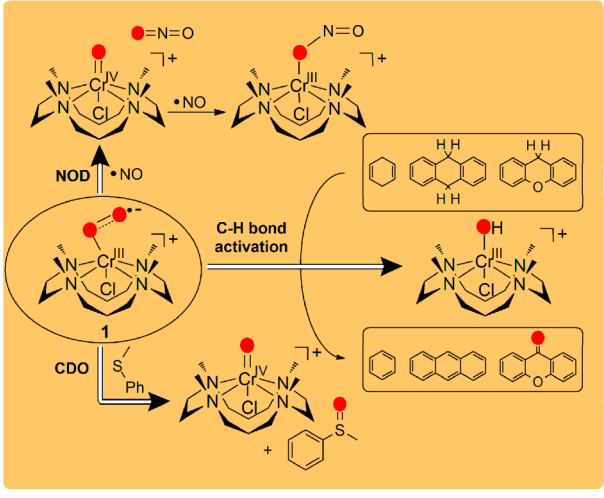

Figure 7. Cr(III)−superoxo complex **1** in various oxidation reactions.

TMC)(Cl)]$^+$ and has been assigned as a chromium(III)−peroxynitrite species on the basis of EPR studies. The reaction of **1** with NO therefore provides a spectroscopic snapshot of the catalytic mechanism of nitric oxide dioxygenase (NOD),[141−143] where an iron(III)−superoxo intermediate is proposed to react with NO to generate an iron(IV)−oxo species via homolytic O−O cleavage of a postulated iron(III)−peroxynitrite intermediate; however, unlike in NOD, no nitrate (NO_3^-) formation was observed upon NO activation by **1**.

Very recently, the formation of a stable manganese(III)−superoxo complex, $[Mn^{III}(L)(O_2)(H_2O)]^{2+}$ (**2**) (Figure 6, Superoxo) was reported in the reaction of a calix[4]arene ligand, $[H_4L][PF_6]_4$ (H_4L = 5,11,17,23-tetrakis(trimethylammonium)-25,26,27,28-tetrahydroxycalix[4]arene), with manganese acetate in the presence of dioxygen.[127] The crystal structure of **2** features an unprecedented linear end-on Mn−O_2 unit, which presumably originates from the electrostatic interactions between the terminal oxygen atom of the bound superoxide and the NMe_3^+ groups of the ancillary ligand. Complex **2** possesses an $S = {}^5/_2$ ground spin state resulting from ferromagnetic coupling of the $S = 2$ Mn(III) center with the superoxide radical; complex **2** thus represents a biomimetic model of the transient Mn(III)−superoxo species previously detected by EPR spectroscopy in the reaction of Mn-HPCD with dioxygen.[55] Complex **2** is reported

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

to be a highly efficient catalyst for the selective epoxidation of alkenes by dioxygen in the presence of isobutyraldehyde as a coreductant. Isotope labeling studies confirmed that the source of the epoxide oxygen is dioxygen rather than the superoxide unit of **2**. Thus, as suggested previously by Nam, Valentine, and co-workers,[144] the role of the Mn(III)−superoxo unit in **2** is merely to aid in the initiation step for the free radical autoxidation of aldehydes (presumably by HAA) and that acylperoxy radicals generated in the autoxidation reaction (or metal complexes formed by complexation of the acylperoxy radicals) are the active epoxidizing agent.

Although the isolation and spectroscopic characterization of mononuclear non-heme iron(III)−superoxo complexes were not known until very recently,[145] biomimetic studies have provided indirect evidence that such cores are capable of activating C−H bonds of organic substrates. Nam and co-workers reported that a non-heme $[Fe^{II}(14\text{-TMC})]^{2+}$ complex activates dioxygen and generates an iron(IV)−oxo complex in the presence of olefinic substrates (Figure 8).[146] A large KIE

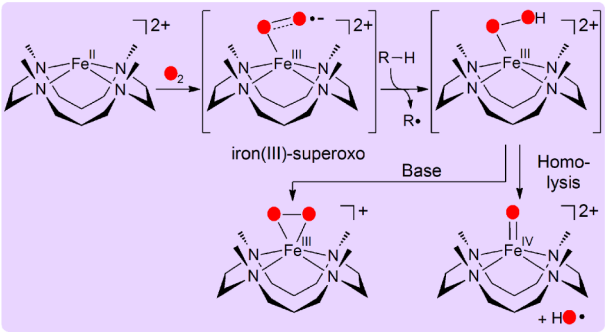

Figure 8. Proposed mechanism for the formation of an iron(IV)−oxo complex in the reaction of $[Fe^{II}(MeCN)(14\text{-TMC})]^{2+}$ and dioxygen in the presence of olefinic substrate. Iron(III)−superoxo and −hydroperoxo intermediates could not be trapped in this reaction.

value of 6.3 was determined for the rate of iron(IV)−oxo formation when cyclohexene and deuterated cyclohexene were used as substrates, which together with the dependence of the reaction on the C−H bond dissociation energy (BDE) of the substrate revealed that HAA takes place in the rate-determining step; a mechanism was proposed in which a putative iron(III)−superoxo intermediate is the active oxidant that abstracts a substrate H atom to form an iron(III)−hydroperoxo species, which then eventually is converted to the iron(IV)−oxo species (Figure 8). Although the iron(III)−hydroperoxo species could not be isolated in the reaction, indirect evidence of its formation was obtained by observing the formation of an iron(III)−peroxo complex when the reaction was performed in the presence of base (Figure 8). This study is therefore relevant to the chemistry of mononuclear non-heme enzymes such as IPNS and HEPD that are proposed to initiate oxidation of their substrates by HAA mediated by putative iron(III)−superoxo species to form iron(IV)−oxo species, which are then used in further oxidation reactions.[10,51]

The first synthetic example of a mononuclear iron(III)−superoxo complex in a non-heme ligand environment has, however, been reported by the groups of Bominaar, Que, Münck, and Lee.[145] A reversible bright-yellow fleeting intermediate **3** was generated by bubbling of O_2 into a tetrahydrofuran solution of Fe^{II}(BDPP) [where BDPP is the deprotonated 2,6-bis(((*S*)-2-(diphenylhydroxymethyl)-1-pyrrolidinyl)methyl)pyridine ligand] at −80 °C. Resonance Raman and Mössbauer spectroscopy were then employed to unambiguously assign **3** as a species containing a mononuclear iron(III)−superoxo core. While the former showed a resonance-enhanced vibration at 1125 cm^{-1} [assigned to ν(O−O) of a bound superoxide], the latter revealed the presence of a high-spin iron(III) center that is exchange-coupled to the superoxo ligand radical, like the $Fe^{III}-O_2^{\bullet-}$ pair found for the O_2 adduct of 4-nitrocatechol-bound HPCD.[56] Complex **3** was able to oxidize DHA to form anthracene, supporting the notion that $Fe^{III}-O_2^{\bullet-}$ species can carry out HAA from a C−H bond to initiate the four-electron oxidation of substrates proposed for some non-heme iron enzymes.[10]

Dinuclear iron−superoxo cores have also been trapped and spectroscopically characterized. Shan and Que[147] reported the trapping of a side-on iron(II)iron(III)−superoxo intermediate (**4** in Figure 6, Superoxo) by oxygenation of the diiron(II) precursor, $[Fe^{II}_2(\mu\text{-OH})_2(6\text{-Me}_3\text{-TPA})_2]^{2-}$, at −80 °C. Complex **4** was converted to the well-characterized 1,2-peroxo-bridged intermediate $[Fe^{III}_2(\mu\text{-O})(\mu\text{-1,2-O}_2)(6\text{-Me}_3\text{-TPA})_2]^{2-}$ upon warming to −60 °C and can also initiate HAA from DTBP at −80 °C, which is in stark contrast to the inability of the corresponding peroxo intermediate[148] to react with the same phenol even at −60 °C. Related chemistry has also been reported[149] for diiron(II) complexes of carboxylates that are appended to dendrimers, where binding of dioxygen resulted in the formation of an EPR-silent $Fe^{II}Fe^{III}$−superoxo product that exhibited two Mössbauer doublets corresponding to an antiferromagnetically coupled $Fe^{II}Fe^{III}$ center. In this case, the electrophilic properties of the superoxo unit were reflected in the reported HAA reactions of the intermediate with DHA and anthrone that led to the formation of oxygenated products.

Ray and co-workers recently reported the synthesis of a rare example of a room-temperature-stable side-on iron(II)iron(III)−superoxo complex (**5** in Figure 6, Superoxo) using iodosylbenzene (PhIO) as the oxidant and employing a novel hexanuclear non-heme ligand system supported on a stannoxane core.[150] On the basis of experimental and DFT studies, the reaction was best construed to proceed via a radical-coupled O−O bond-forming mechanism wherein the oxygen progressed through oxo, peroxo, and superoxo states. The iron(II)iron(III)−superoxo unit of **5** exhibited both nucleophilic and electrophilic reactions: it reacted with cyclohexanecarboxaldehyde (CCA) and benzoyl chloride to yield cyclohexene and benzoic acid, respectively, as well as with DTBP to form 2,2′,6,6′-tetra-*tert*-butyl-4,4′-biphenol. Notably, complex **4** represents the first example of a metal−superoxo species that exhibits a nucleophilic property; the only other example is a mononuclear copper−superoxo complex that has been recently demonstrated to perform a deformylation reaction with a number of aldehyde substrates.[151]

Few examples of monomeric nickel−superoxo complexes (**6**−**8** in Figure 6, Superoxo) have also been reported, and all of them were found to be capable of performing electrophilic oxidation reactions.[67,118,125,152] The reactivity of room-temperature-stable side-on nickel(II)−superoxo complex **8** involving a β-diketiminate ligand system, however, needs special mention here.[125,132] In addition to its ability to initiate oxidation of O−H and N−H groups from various exogenous substrates (Figure 9), **8** exhibited dioxygenase-like reactivity when exposed to para-substituted DTBPs, affording an unprecedented oxidation product incorporating two oxygen atoms from a single O_2 subunit.[132] The mechanism of this transformation is proposed to involve the mediation of a Ni^{III}−oxo species[132,153] formed via O−O bond

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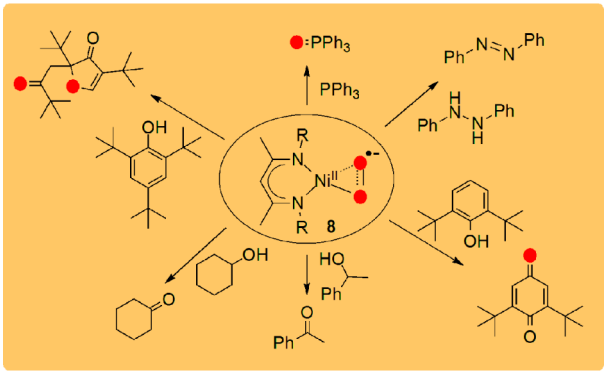

Figure 9. Ni(II)−superoxo complex **8** in various oxidation reactions.

homolysis of a Ni(II)−arylperoxo intermediate. The proposed mechanism parallels the generally accepted mechanism for metal-mediated activation of dioxygen to generate high-valent metal−oxo units by O−O bond homolysis/heterolysis of metal−(hydro)peroxo cores in various oxygenase and oxidase enzymes (Figure 1).[9,44] Notably, analogous reactions of iron−, cobalt−, and copper−superoxo complexes with para-substituted DTBPs have been previously reported to yield different oxidation products than that obtained with **8**, thereby underlying the importance of subtle electronic changes in the reactivity of the biologically relevant metal−dioxygen intermediates.[137,154−156]

3.2. Biomimetic Metal−Peroxo Complexes. In heme and non-heme iron, manganese, and copper enzymes, mono- and dinuclear metal−peroxo species have been proposed to play important roles as key intermediates in the oxidation of organic substrates.[157−162] Such metal−peroxo intermediates have been investigated extensively in biomimetic studies to understand the structural and chemical properties of the intermediates that are short-lived and thus difficult to study in enzymatic reactions. For instance, a variety of mono- and dinuclear manganese−peroxo complexes have been reported[65,163−169] as biomimetic models of the oxygen-evolving complex (OEC) of photosystem II, manganese superoxide dismutase (MnSOD), or catalase.[158−162] Similarly, mononuclear Fe(III)−O_2 complexes with heme and non-heme ligands have been synthesized in order to obtain deeper insights into the mechanisms of cytochrome P450 aromatases and Rieske dioxygenases.[78,170−174] The structures and reactivities of chromium−, cobalt−, nickel−, and copper−peroxo complexes have also been the subject of intense scrutiny.[120,135,175−178]

In these studies, the natures of the ancillary ligands and the metal ions have been shown to be important factors in regulating the stability of the metal−peroxo cores (see Figure 6, Peroxo). For example, the formation of the end-on Cr(III)−superoxo complex **1** and a side-on Cr(IV)−peroxo complex, $[Cr^{IV}(12\text{-}TMC)(O_2)Cl]^+$ (**9**) (12-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane), has been reported in the reactions of $[Cr^{II}(14\text{-}TMC)Cl]^+$ and $[Cr^{II}(12\text{-}TMC)Cl]^+$ with O_2, respectively.[69,120,135,175,179−181] In contrast, the electronic structure of the manganese−dioxygen complexes is independent of the nature of the ancillary ligand. This is evident from the stabilization of the manganese(III)−peroxo cores in the complexes $[Mn^{III}(12\text{-}TMC)(O_2)]^+$ (**10**), $[Mn^{III}(13\text{-}TMC)(O_2)]^+$ (**11**) (13-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclotridecane), and $[Mn^{III}(14\text{-}TMC)(O_2)]^+$ (**12**).[122,182] Cobalt has also been shown to have an inherent tendency to stabilize metal−peroxo cores in $[Co^{III}(12\text{-}TMC)(O_2)]^+$ (**13**), $[Co^{III}(13\text{-}TMC)(O_2)]^+$ (**14**), $[Co^{III}(14\text{-}TMC)(O_2)]^+$ (**15**), and $[Co^{III}(15\text{-}TMC)(O_2)]^+$ (**16**) (15-TMC = 1,4,8,12-tetramethyl-1,4,8,12-tetraazacyclotetradecane).[69,179] In the corresponding nickel chemistry, on the other hand, stabilization of nickel−superoxo complex **6** for 14-TMC and a nickel−peroxo complex for 12-TMC, $[Ni^{III}(12\text{-}TMC)(O_2)]^+$ (**17**), has been reported.[67] Additionally, the synthesis of Ni(II)−superoxo complex **7** and the Ni(III)−peroxo complex $[Ni^{III}(13\text{-}TMC)(O_2)]^+$ (**18**) bearing a common supporting ligand (13-TMC) in the presence of two different bases has also been reported.[152] Thus, the electronic nature of chromium− and nickel−dioxygen cores is similar to that of the copper−dioxygen core, whose electronic structure [e.g., copper(II)−superoxo vs copper(III)−peroxo] was also shown to vary depending on the supporting ligands of the copper complexes.[176−178]

Most of the reported mononuclear metal−peroxo compounds have presented negligible reactivity in electrophilic OAT reactions. However, side-on-bridged dicopper(II)−peroxo complexes are very unique among all of the known synthetic metal−peroxo intermediates in their ability to initiate electrophilic oxidation reactions, such as intramolecular aromatic and aliphatic ligand hydroxylation as well as intermolecular aliphatic and arene hydroxylation, HAA, and OAT reactions.[176−178,180,181] Accordingly, a bis(μ-oxo)dicopper(III) species, which is known to exist in equilibrium with the side-on-bridged dicopper(II) species in synthetic complexes,[116,117] has also been discussed as the reactive species responsible for the copper−peroxo-mediated C−H activation and group transfer reactions. Metal−peroxo cores have also exhibited a broad range of reactivity toward electrophiles. For example, the oxidation of CCA by metal−peroxo complexes resulted in the formation of cyclohexene and formate; the proposed mechanism involves attack on the carbonyl group by the M−O_2 moiety. Cyclohexanone has also been obtained as an alternate product in the reactions of the complexes $[Mn^{III}(\eta^2\text{-}O_2)(H_3bupa)]^-$ [where H_3bupa is the dianion of bis[(*N*′-*tert*-butylureayl)-*N*-ethyl](6-pivalamido-2-pyridylmethyl)amine] and $[Mn^{III}(\eta^2\text{-}O_2)(H_2bpaa)]$ with CCA.[165]

Further insights into the chemical properties of the metal−peroxo complexes have been provided in the NOD reaction. Although metal−superoxo intermediates are generally considered to be the active species responsible for the biological conversion of NO to NO_3^-, the NOD activity of a metal−peroxo complex has recently been demonstrated in a synthetic complex (Figure 10A).[175] The reaction of **9** with NO resulted in the quantitative formation of a Cr(III)−nitrato complex,[175] which is in contrast to the Cr(III)−nitrito product formed in the reaction of **1** and NO.[136]

Novel chemical properties of metal−peroxo cores have also been demonstrated very recently by Cho et al.[183] in a reactivity study of a side-on-bound iron(III)−peroxo complex, $[Fe^{III}(14\text{-}TMC)(O_2)]^+$ (**19** in Figure 6, Peroxo). Notably, **19** represents the only example to date of a structurally characterized mononuclear iron−peroxo species.[183] Moreover, the FeOO geometry of **19** is similar to that of the crystallographically characterized 1:1 Fe/O_2 adduct of NDO,[77] where dioxygen binds to an iron center in a side-on fashion at the active site (1.75 Å resolution, $r_{O-O} \approx 1.45$ Å); therefore, **19** represents a structural model of NDO. Complex **19** showed reactivity in the deformylation of aldehydes.[61] In addition, it reacted with nitrosonium hexafluorophosphate ($NO^+PF_6^-$) to generate an iron(III)−nitrato species via the formation of an iron(IV)−oxo complex and nitrogen dioxide.[184] It is notable that this is the first

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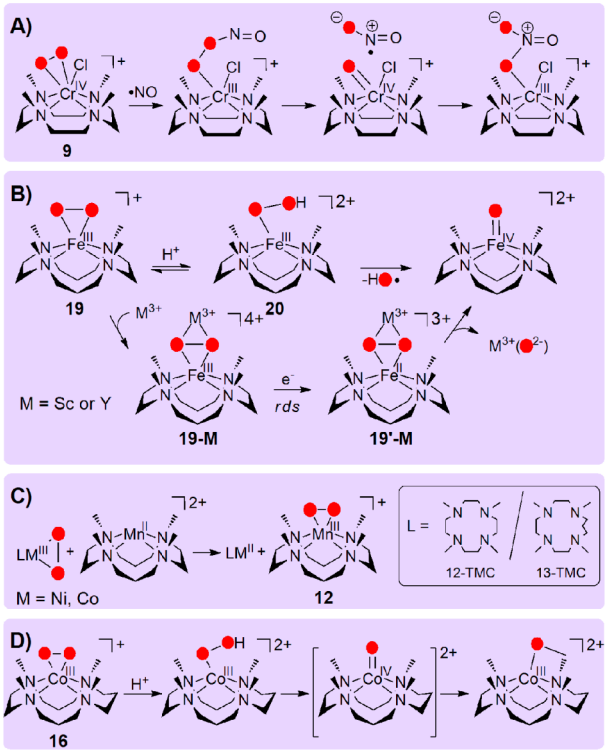

Figure 10. Biomimetic metal–peroxo complexes in (A) the reaction of nitric oxide, (B) the conversion to an iron(IV)–oxo complex upon the addition of a proton or binding of a Lewis acidic metal ion and reduction, (C) an O_2 transfer reaction, and (D) the conversion to a Co–O complex upon addition of a proton.

observation of a non-heme iron(III)–peroxo complex showing stepwise and stoichiometric NOD reactivity. Moreover, the latter reaction is essentially isoelectronic with the proposed reaction of iron(III)–superoxo species with NO in NODs.[141−143] Hence, the concept of mimicking the NOD reaction using a metal(III)–peroxo species and a nitrosonium ion, as established in this study, may provide the basis for a new approach that may be used to design isoelectronic pathways for enzymatic reactions.

Addition of a slight excess amount of $HClO_4$ to a solution of **19** resulted in the formation of the corresponding iron(IV)–oxo complex, $[Fe^{IV}(O)(14\text{-TMC})]^{2+}$, via the generation of iron(III)–hydroperoxo intermediate **20** (Figure 6, Hydroperoxo and Figure 10B). This reaction provides a synthetic precedent for the proton-assisted conversion of a metal–peroxo species to a high-valent metal–oxo species, which is considered to be a key step in the dioxygen activation mechanisms of various iron and copper monooxygenases. The reduction of **19** by ferrocene (Fc) in the presence of redox-innocent metal ions (e.g., Sc^{3+} and Y^{3+} ions) also led to the near-quantitative formation of $[Fe^{IV}(O)(14\text{-TMC})]^{2+}$;[185] a proposed mechanism involves initial binding of the metal ions to the peroxo unit of **19** followed by reduction and O–O bond heterolysis steps. In support of this mechanism, the iron(III)–peroxo complexes binding Sc^{3+} and Y^{3+} ions were characterized by various spectroscopic methods and unambiguously assigned as the heterodinuclear complexes Fe(III)–O_2–M(III) (**19-M**; M = Sc^{3+}, Y^{3+}) containing a peroxo ligand bound in a side-on fashion between two metal ions. Moreover, the conversion of **19-M** to the iron(IV)–oxo species could be monitored by UV–vis spectroscopy, and the rate of the reaction was shown to be dependent on the Lewis acidity of the redox-inactive metal ions and the concentration and oxidation potential of the electron donor. These results indicate that the reduction of **19-M** by the electron donor to form the one-electron-reduced species $[(TMC)Fe^{II}(O_2)]$–M^{3+} (**19′-M**) is the rate-determining step (r.d.s.), which is followed by rapid heterolytic O–O bond cleavage of the peroxide ligand of **19′-M** that results in the formation of the iron(IV)–oxo complex (Figure 10B); the role of the Lewis acidic metal ions is to increase the electrophilicity of the Fe–O_2 core, thereby assisting in the rate-determining reduction step. On the basis of this study, a similar role for the Cu(II) ion as a Lewis acid in the one-electron reduction of the iron(III) porphyrin–O_2–Cu(II) intermediate at the active site of cytochrome *c* oxidase[186,187] to give the S = 1 Fe(IV)–oxo and Cu(II) species via the intermediate formation of Fe(II)–O_2–Cu(II) can be envisioned, although no experimental evidence supporting this mechanism has been obtained to date.

An unprecedented O_2 transfer reaction mediated by structurally characterized side-on-bridged mononuclear cobalt– and nickel–peroxo complexes (e.g., **13**, **14**, and **17** in Figure 6) to $[Mn(II)(14\text{-TMC})]^{2+}$ resulted in the formation of the corresponding M(II) and $[Mn(III)(14\text{-TMC})(O_2)]^{+}$ complexes (Figure 10C).[67,69] Notably, this phenomenon of complete O_2 transfer between metal complexes bearing TMC ligands is in sharp contrast to the behavior of other systems involving different ancillary ligands, where the reactions of metal–O_2 complexes (e.g., Cu–O_2 and Ni–O_2) with a second metal ion (M or M′) lead to the formation of homo- or heterodinuclear complexes containing $[M_2(\mu\text{-}O)_2]^{n+}$, $[M_2(O_2)]^{n+}$, or $[MM'(\mu\text{-}O)_2]^{n+}$ cores.[131,176,188−190] Additionally, the rate of O_2 transfer from **13**, **14**, and **17** to $[Mn(14\text{-TMC})]^{2+}$ was found to be strongly dependent on the nature of the metal ion as well as on the ring size of the ancillary ligand; a reactivity order of **17** > **14** ≫ **13** was observed.[67,69]

Upon protonation of **16**, it could be cleanly converted into an end-on cobalt(III)–hydroperoxo complex, $[Co^{III}(15\text{-TMC})(OOH)]^{2+}$, which eventually decayed to a $[Co^{III}(15\text{-TMC}–CH_2–O)]^{2+}$ species by hydroxylation of a methyl group of the 15-TMC ligand (Figure 10D).[179] Kinetic studies and ^{18}O-labeling experiments showed that the aliphatic hydroxylation occurred via a transient Co^{IV}–oxo (or Co^{III}–oxyl) species formed by O–O bond homolysis of the cobalt(III)–hydroperoxo complex. Involvement of a transient cobalt–oxo species has also been suggested during the catalytic four-electron reduction of dioxygen via a rate-determining proton-coupled electron transfer to a dinuclear cobalt–1,2-peroxo complex.[191] Although direct evidence for the suggested cobalt–oxo intermediates is lacking in these reactions, Pfaff et al.[192] and Hong et al.[193] have recently reported the spectroscopic trapping of elusive cobalt(IV)–oxo intermediates in the $S = {}^3/_2$ and $S = {}^1/_2$ spin states, respectively, by the use of a stabilizing Lewis acid interaction of the cobalt–oxo group with redox-innocent metal ions (e.g., Sc^{3+} ion).

3.3. Biomimetic Metal–Hydroperoxo Complexes.

Although mononuclear metal–hydroperoxo species have been proposed as a "second electrophilic oxidant" in a variety of oxygenation reactions, including alkane hydroxylation and olefin epoxidation,[30,31,88−91] a number of well-characterized metal–hydroperoxo species were all found to be sluggish oxidants,[194−207] casting serious doubt on the proposed ability of such cores to initiate the oxidation of substrates. In particular, several LS Fe^{III}–OOH model complexes,[198−206] including $[(N4Py)Fe^{III}–OOH]^{2+}$ [**21** in Figure 6, Hydroperoxo; N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine], were found to be incapable of oxidizing alkanes, in contrast to the

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proposed role of ABLM,[88,89] which also contains an LS Fe^{III}–OOH core, in direct HAA from the strong C–H bond of a sugar (92 kcal/mol). However, in 2011 Valentine, Solomon, Nam, and co-workers demonstrated for the first time that complex **20** involving an HS Fe^{III}–OOH core, which is formed upon protonation of **19**, is capable of HAA from weak C–H bonds of xanthene and DHA to form xanthone and anthracene products, respectively.[183] Interestingly, **20** was found to be a stronger oxidant than the corresponding iron(III)–peroxo complex **19** in both nucleophilic and electrophilic oxidation reactions.[183,208] These results provide strong evidence that metal–hydroperoxo species can be alternative oxidants for high-valent metal–oxo complexes in OAT and HAA reactions.[183,208,209]

Further insights into the electrophilic property of the iron(III)–hydroperoxo intermediate were obtained in a combined theoretical and experimental study of the C–H bond activation of xanthene by the HS $[(TMC)Fe^{III}–OOH]^{2+}$ and LS $[(N4Py)Fe^{III}–OOH]^{2+}$ complexes.[209] In this study, both complexes were found to be capable of performing the direct HAA reaction, although complex **20** was slightly more reactive than **21**. Additionally, DFT calculations predicted significantly different reaction coordinates for the reactions of **20** and **21** with xanthene. For the LS Fe^{III}–OOH core in **21**, the transition state was found to be late in the O–O coordinate and early in the C–H coordinate; accordingly, the suggested mechanism involves initial homolysis of the O–O bond in $[(N4Py)Fe^{III}–OOH]^{2+}$ to form $[(N4Py)Fe^{IV}–O]^{2+}$ and $OH^{\bullet}$ with subsequent HAA by the hydroxyl radical (Figure 11). Notably, the transition state for

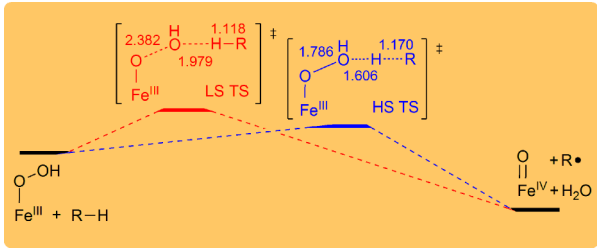

Figure 11. Reaction trajectories for the HAA reactions mediated by an iron(III)–hydroperoxo core on the low-spin (red) and high-spin (blue) surfaces.

HAA from xanthene by **21** is very similar to that of the direct HAA from DNA by ABLM. Interestingly, however, ABLM is more reactive than **21**, which has been attributed to the difference between the equatorial ligands in $[(N4Py)Fe^{III}–OOH]^{2+}$ and ABLM. ABLM has one negatively charged deprotonated amide, which has been suggested to contribute to the lower activation barrier for the HAA reaction by destabilizing the iron–hydroperoxo reactant and stabilizing the iron–oxo product. In contrast, for the HS Fe^{III}–OOH core in **20**, the transition state was found to be early in the O–O coordinate and further along in the C–H coordinate; thus, no O–O bond cleavage step precedes the HAA process. In addition, electron transfer from the substrate to the Fe^{III}–OOH core occurs only at the HS transition state (and not in the LS transition state), which was attributed to the theoretically predicted higher reduction potential of HS Fe^{III}–OOH than LS Fe^{III}–OOH. From these results, it was concluded that LS Fe^{III}–OOH complexes should be more reactive toward substrates with strong C–H bonds, whereas HS Fe^{III}–OOH complexes should be more reactive toward substrates with low ionization potentials and weak C–H bonds. These predictions are consistent with nature's preference for using an LS Fe^{III}–OOH core in ABLM in cleaving the strong C–H bond of DNA and an HS Fe^{III}–OOH core in oxidizing the electron-rich aromatic substrates in Rieske dioxygenases. It should be also noted that heme Fe^{III}–OOH species (e.g., Cpd 0) are unreactive in both OAT and HAA reactions.[32−37] This reactivity difference between heme and non-heme Fe^{III}–OOH species is an intriguing issue that should be investigated further.

3.4. Biomimetic Metal–Oxo Complexes. In the past decade, a number of synthetic non-heme metal–oxo complexes have been synthesized and characterized by various spectroscopic techniques as well as by X-ray crystallography.[174,210−229] In many cases, they have been found to be reactive toward substrates for HAA, OAT, and electron transfer reactions (Figure 12), corroborating their involvement in various metal-catalyzed

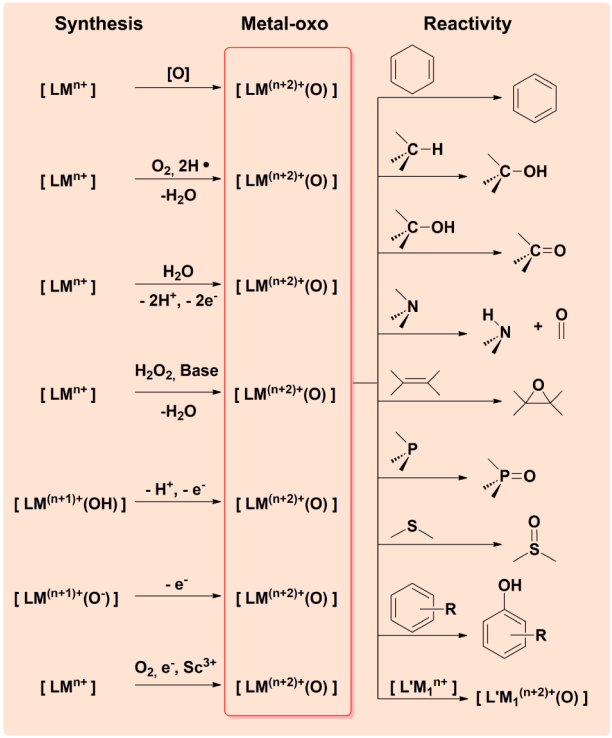

Figure 12. Syntheses of biomimetic high-valent terminal metal–oxo complexes and their reactivities with a variety of substrates. The common synthetic procedures involve the reaction of the reduced metal complexes $[LM^{n+}]$ with oxo transfer agents, [O], such as PhIO, N_2O, and peracids;[2,9,13,14,173,174,210−212,230,231] dioxygen in the presence of H atom donors or Sc^{3+} ion and a reductant;[146,229] water in the presence of an oxidant; and hydrogen peroxide and a base.[13] HAA from the reduced metal–hydroperoxo species or oxidation of the reduced metal–oxo complexes also lead to the generation of high-valent metal–oxo cores.[246]

oxidative transformations in chemistry and biology. Additionally, the oxidizing capabilities of the synthetic metal–oxo cores have been found to depend on the oxidation state of the metal as well as on the nature of the supporting and axial ligands. Moreover, binding of redox-inactive metal ions (acting as Lewis acids) to the metal–oxo moiety, interactions with entities from the secondary coordination sphere, and the presence of external electron-transfer agents have been reported to tune the oxidizing power of the metal–oxo complexes. In recent years, several review articles describing intense investigations into the chemistry of high-valent metal–oxo complexes have appeared, and there have been many excellent reports detailing their generation, structural and

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

spectroscopic characterization, and reactivity properties.[2,9,13,14,173,174,210−212,230,231] We are therefore extremely selective in our description of metal−oxo chemistry in this section, and we discuss only some recent examples from the literature, including those that have provided new insights into metal−oxo chemistry.

The general method of synthesizing non-heme metal−oxo complexes involves the reaction of the reduced metal precursor with an oxygen atom donor such as PhIO, N_2O, or a peracid (Figure 12).[2,9,13,14,173,174,210−212,230,231] In rare cases, they have been generated electrochemically[232,233] or photochemically[234] using water as the oxygen source. In several cases, dioxygen has also been used as an oxidant, which has helped to improve our understanding of the mechanism of dioxygen activation at mono- and dinuclear enzyme metal active sites. In iron-model chemistry, Nam, Fukuzumi, and co-workers recently demonstrated the generation of the iron(IV)−oxo complex $[Fe^{IV}(O)(N4Py)]^{2+}$ (**22** in Figure 6, Oxo) via oxidation of the corresponding iron(III)−hydroxo complex $[Fe^{III}(OH)(N4Py)]^{2+}$ using $[Ru^{III}(bpy)_3]^{3+}$ as the oxidant in acetonitrile containing water.[235] Interestingly, the rate of the formation of **22** was accelerated as much as 390-fold by the addition of a proton acceptor such as CF_3COO^-, p-$MeC_6H_4SO_3^-$ (TsO^-), o-$NO_2C_6H_4SO_3^-$ (NsO^-), 2,4-$(NO_2)_2C_6H_3SO_3^-$ ($DNsO^-$), or $CF_3SO_3^-$ (OTf^-). Moreover, the extent of acceleration increased with increasing basicity of the proton acceptor. This study therefore validates the proposed role of a conjugate base of aspartic acid as a proton acceptor during the formation of a Mn(V)−oxo core from Mn(III)−OH in the oxygen evolving cycle of Photosystem II.[159,236,237] In a separate study,[238] Nam, Fukuzumi, and co-workers also provided evidence for the occurrence of an unprecedented autocatalytic radical chain reaction in the synthesis of $[Fe^{IV}(O)(14\text{-TMC})(CH_3CN)]^{2+}$ (**23** in Figure 6, Oxo; X = CH_3CN) by reacting the corresponding iron(II) complex $[Fe^{II}(14\text{-TMC})]^{2+}$ with oxygen in the presence of isopropanol in acetonitrile. On the basis of a detailed kinetic study, the radical chain reaction was proposed to be initiated by HAA from isopropanol by the iron(IV)−oxo complex. Generation of iron(IV)−oxo complexes by O−O bond homolysis[239] of iron(III)−alkylperoxo species or O−O bond heterolysis[240] of iron(II)−hydro(alkyl)peroxo species has also been reported, further supporting the general mechanism of dioxygen activation in Figure 1.

Although some of the synthetic iron(IV)−oxo complexes are sufficiently powerful oxidants to oxidize even the strong C−H bonds of cyclohexane,[233,241] their reactivities are far lower than the extraordinary activity exhibited by enzymes. The factors that determine the reactivity of the iron(IV)−oxo unit are therefore of central interest, and extensive efforts have been directed toward the use of coordination complexes as synthetic models. However, these studies have shown puzzling reactivity patterns in many cases. For example, although all of the theoretical studies have led to the common conclusion that ferryl species are better oxidants in the quintet state than in the corresponding triplet state,[110,242,243] this has not been found to be the case experimentally. A limited number of recently synthesized S = 2 iron(IV)−oxo complexes have demonstrated comparable or even lower HAA and OAT rates than the corresponding S = 1 iron(IV)−oxo complexes.[244−248] Similarly, in contrast to a previous study[249] where an increasing HAA rate was shown to be correlated with increasing basicity of the axial ligand, the highly stable S = 1 iron(IV)−oxo complex $[Fe^{IV}(O)(L)]^{2+}$ [**25** in Figure 6, Oxo; L = 1,4,8-Me_3cyclam-11-$CH_2C(O)NMe_2$], was recently demonstrated to be a better HAA agent than its conjugate base $[Fe^{IV}(O)(L\text{-}H)]^+$ (**26** in Figure 6, Oxo) with a more basic axial ligand.[250] The complexity of the HAA reaction mediated by S = 1 iron(IV)−oxo cores has also been reflected in a recent study by Comba, Costas, Que, and co-workers,[233] which showed that the HAA rates of a series of iron(IV)−oxo complexes supported by pentadentate ligands are not correlated to their $Fe^{IV/III}$ redox potentials as determined by spectropotentiometric titration methods. This is again in contrast to a previous study on iron(IV)−oxo complexes binding different axial ligands, $[Fe^{IV}(O)(14\text{-TMC})X]^+$ (**23** in Figure 6, Oxo; X = CH_3CN, CF_3COO^-, N_3^-) and $[Fe^{IV}(O)(TMCS)]^+$ (**24** in Figure 6, Oxo; TMCS = 1-mercaptoethyl-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane), where a good correlation between the reactivities of the iron(IV)−oxo species in HAA reactions and their reduction potentials ($E_{p,c}$) was observed.[249] The above results highlight the shortcomings of our mechanistic understanding of reactions mediated by non-heme iron(IV)−oxo complexes.

Synthetic terminal iron−oxo species are highly susceptible to a variety of decomposition pathways, including dimerization to form oxo-bridged diiron complexes, intramolecular ligand oxidation, and solvent oxidation. In order to properly utilize the oxidizing equivalents of the iron(IV)−oxo core, it is necessary to prevent these side reactions. Long and co-workers have reported significant progress in this field through the use of metal−organic frameworks (MOFs) that feature site-isolated iron centers in a constrained, weak-field ligand environment.[251] In their study, they showed that the MOF Fe_2(dobdc) (dobdc^{4-} = 2,5-dioxido-1,4-benzenedicarboxylate) and its magnesium-diluted analogue $Fe_{0.1}Mg_{1.9}$(dobdc) can activate the C−H bonds of ethane and convert it into ethanol and acetaldehyde using nitrous oxide as the terminal oxidant. Although no intermediates could be trapped experimentally, electronic structure calculations indicated that the active oxidant is a high-spin S = 2 iron(IV)−oxo species. The unprecedented reactivity of the proposed iron−oxo core mitigated within the MOF has been attributed to the unique coordination environment containing solely O donors. Notably, although O donors are ubiquitous in biology, molecular iron−oxo complexes generally utilize nitrogen-based chelating ligands; only the tetracarbene complex recently reported by Meyer and co-workers contains a supporting ligand with non-N donor atoms.[252]

Terminal metal−oxo cores of cobalt, nickel, and copper are also attractive synthetic targets in the context of achieving selective functionalization of C−H bonds.[231] Theory and gas-phase reactivity studies have suggested that they should be powerful oxidants, perhaps even more reactive than the related iron−oxo complexes.[253−255] They have also been considered as potential reactive intermediates in various chemical and biological oxidation reactions.[231] However, despite significant experimental and theoretical work, no direct spectroscopic evidence for such species has been observed. All efforts to model $[M(O)]^{2+}$ (M = Co, Ni, Cu) cores in coordination complexes were hampered by the anticipated strong repulsion between the electron-rich oxo ligand and the late transition metal.[256] Ray and co-workers[192] employed a successful strategy of exploiting the stabilizing Lewis acid interactions of metal−oxo cores with Sc^{3+} ion, which was initially established in iron−oxo chemistry,[257] to provide direct evidence for the viability of a cobalt(IV)−oxo core. In this study, a highly reactive $S = {}^3/_2$ $\{Co^{IV}-O-Sc^{3+}\}$ unit supported by the TMG_3tren ligand (**27** in Figure 6, Oxo) was stabilized and characterized by a variety of spectroscopic and

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

reactivity studies.[192] In the absence of Sc^{3+} ion, the Co^{IV} oxidation state was found to be inaccessible. Notably, the same strategy was later used by the groups of Ray and Nam in the stabilization of the low-spin ($S = {}^1/_2$) $\{Co^{IV}-O-Sc^{3+}\}$ unit in **28** (Figure 6, Oxo).[193] The TMG_3tren ligand system has also been used to trap a reactive nickel intermediate in the reaction of a Ni(I) complex with *m*-chloroperoxybenzoic acid (*m*-CPBA),[153] which has been assigned as a Ni(III)−O(H) species (**29** in Figure 6, Oxo) on the basis of its C−H activation and oxo transfer abilities. The wider application of the use of Lewis acidic metal ions to stabilize reactive intermediates has also been demonstrated in the recent stabilization of an elusive formal Cu(III)−imido intermediate in the reaction of a Cu(I) complex with [*N*-(*p*-toluenesulfonyl)imino](2-*tert*-butylsulfonyl)phenyliodinane in the presence of scandium.[258] The imido ligand (NR^{2-}) is isoelectronic with the oxo ligand, and the two groups can often be interchanged in transition metal complexes. Accordingly, the report of the stabilization of the copper−imido core may validate the existence of the isoelectronic $Cu^{III}-O/Cu^{II}-O^{\bullet}$ units in coordination complexes.

Very recently, Limberg, Driess, Ray, and co-workers[189] reported the low-temperature trapping of a novel heterobimetallic Ni(III)Cu(III)bis(μ-oxo) intermediate (**30** in Figure 6, Oxo) during the one-electron reduction of a previously reported nickel−superoxo complex[125] using a Cu(I) triamine reductant.[259] Interestingly, the oxo groups of the $Ni^{III}(\mu\text{-}O)_2Cu^{III}$ core act as nucleophiles, in sharp contrast to the electrophilic oxo groups of the well-characterized mononuclear and homodinuclear oxo complexes of mid-to-late transition metals. In fact, the trapped $Ni^{III}(\mu\text{-}O)_2Cu^{III}$ complex represents the only example of a high-valent bis(μ-oxo)dimetal core involving nucleophilic oxo groups that can perform deformylation of aldehydes. Until this report, only metal-bound peroxides were believed to be sufficiently nucleophilic to attack aldehydes, leading to the production of formate and oxidized coproducts.[64,65,67,173,183] The present result suggests that a similar asymmetric bis(μ-oxo) core may also act as an active species in the catalytic cycle of cyanobacterial aldehyde decarbonylase,[62] where a heterodinuclear active site has also been proposed but has not yet been isolated.

A recent highlight in biomimetic copper chemistry is the ability of Cu-ZSM-5 to mediate the selective oxidation of methane in the presence of dioxygen under comparatively mild conditions.[260−265] Resonance Raman studies combined with theoretical calculations have shown that this impressive reactivity proceeds at a bent mono(μ-oxo)dicopper(II) core, $[Cu^{II}-O-Cu^{II}]^{2+}$, as the active site; the high reactivity of the $[Cu^{II}-O-Cu^{II}]^{2+}$ core has been attributed to the formation of a very stable O−H bond (90 kcal mol^{-1}) in the resulting Cu−(OH)−Cu complex formed by HAA from methane. In a subsequent theoretical study, it has been shown that the reactive mono(μ-oxo)dicopper(II) core with CH_4 is retained when the silicate ligand matrix of Cu-ZSM-5 is replaced by the protein environment within the active site of the particulate methane monooxygenase (pMMO) enzyme.[260−265] This result provides grounds to speculate that a (μ-oxo)dicopper(II) site is also the active species during the hydroxylation of methane by pMMO.[266−270] Examples of molecular $[Cu^{II}-O-Cu^{II}]^{2+}$ complexes are also known.[265,271−275] However, they have all been found to be sluggish oxidants in HAA and OAT reactions, in sharp contrast to their theoretically predicted high reactivity.

4. CONCLUSION AND PERSPECTIVE

For decades, scientists have been searching for efficient and cheap catalysts suitable for performing methane hydroxylation and water splitting reactions under ambient conditions in their efforts to find alternatives to fossil-based oil as energy carriers for energy conversion processes. The catalytic four-electron reduction of O_2 to water has also merited increasing attention because of its relevance to fuel cell technology. A range of metalloenyzmes achieve these challenging tasks in biology by using cheap and abundant first-row transition metals (e.g., iron, copper, and manganese). Such reactions are carried out under ambient conditions with high efficiency and stereospecificity. Artificial catalysts that are similarly efficient and based on inexpensive and abundant materials are of great interest. To engineer improved catalysts, there is a substantial impetus to characterize fully the active species, including all relevant higher oxidation states, intermediates, and transition states, in order to establish the mechanism(s) by which methane hydroxylation, water oxidation, or dioxygen activation/reduction are carried out in biology. However, biological intermediates are short-lived and highly reactive in most cases, thus making it difficult to study their chemical and physical properties in the catalytic cycles of metalloenzymes. The recent results presented here from the bioinorganic chemistry community lend credence to the participation of metal−superoxo, −peroxo, −hydroperoxo, and −oxo complexes in the above-mentioned processes. A number of metal−dioxygen and metal−oxo model complexes have now been synthesized using dioxygen as the oxidant via mechanisms reminiscent of the O_2 activation processes proposed in biology. Many of these complexes show intriguing reactivities, which in turn have provided vital insights into the biomimetic reactions. Among the most significant findings of these studies are the observed diversified reactivities of well-characterized metal−superoxo complexes, which have demonstrated that such intermediates are not mere pass-through points en route to the high-valent metal−oxo intermediates but may perform more important roles in biological and chemical oxidation reactions than earlier construed. Similarly, experimental evidence has also been provided in favor of the stronger oxidizing capabilities of metal−hydroperoxo cores, which support their proposed role as alternatives to high-valent metal−oxo complexes as oxidants in OAT and HAA reactions. Additionally, $Cu^{II}-O-Cu^{II}$ cores have appeared in the spotlight because of their proposed role as the active species in the challenging oxidation of methane to methanol at the surface of a Cu-grafted zeolite and in the active center of pMMO. Furthermore, the demonstrated stability of the Lewis acid adduct of the otherwise transient cobalt−oxo intermediate has paved the way for future studies that may lead to the identification of such intermediates under catalytic turnover conditions.

Unfortunately, the reactions exhibited by the model complexes are found to be noncatalytic, with activities falling far short of the activities of the biological catalysts. The low reactivity of the model complexes can be explained by the inability of synthetic chemists to exactly reproduce the biological ligands and protein environments. Although O-donor ligands are ubiquitous in biology, most of the model compounds are based on N-rich ligands. Notably, Long's demonstration of ethane oxidation by a transient MOF-based iron−oxo core highlights the importance of an oxygen-based coordination environment in metal−oxo-mediated oxidation reactions. The reactivities of the $S = 1$ iron(IV)−oxo complexes have also been found to be

dx.doi.org/10.1021/ja507807v | J. Am. Chem. Soc. 2014, 136, 13942−13958

complicated, and further systematic studies are required in order to unify all of the mechanistic observations into a single model that will allow qualitative prediction of their reactivity as a function of the supporting ligand. Additionally, new and innovative synthetic strategies are needed in order to obtain thus-far inaccessible metal−dioxygen and metal−oxo complexes that are of interest. Examples include stable superoxo complexes of iron and oxo complexes of cobalt, nickel, and copper. These goals may eventually lead to the development of cheap and efficient bioinspired/biomimetic catalysts for dioxygen activation/reduction, water oxidation, and methane hydroxylation under ambient conditions.

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The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge research support of this work by the NRF of Korea through CRI (NRF-2012R1A3A2048842 to W.N.) and GRL (NRF-2010-00353 to W.N.), the German Deutsche Forschungsgemeinschaft (Cluster of Excellence "Unifying Concepts in Catalysis", Grant EXC 314/1 to K.R.), and Cost Action (CM1305 ECOSTBio to K.R.).

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