ACCOUNTS of chemical research

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Tuning Reactivity and Mechanism in Oxidation Reactions by Mononuclear Nonheme Iron(IV)-Oxo Complexes

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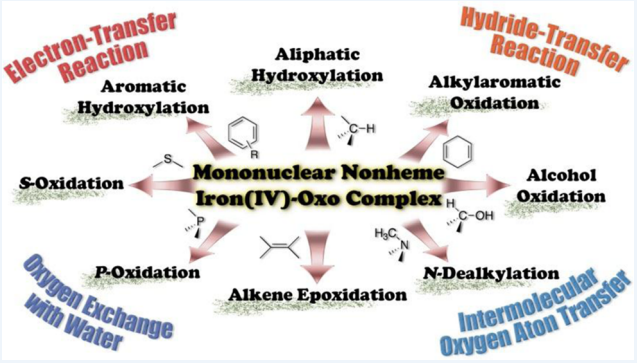
CONSPECTUS: Mononuclear nonheme iron enzymes generate high-valent iron(IV)-oxo intermediates that effect metabolically important oxidative transformations in the catalytic cycle of dioxygen activation. In 2003, researchers first spectroscopically characterized a mononuclear nonheme iron(IV)-oxo intermediate in the reaction of taurine: α-ketogultarate dioxygenase (TauD). This nonheme iron enzyme with an iron active center was coordinated to a 2-His-1-carboxylate facial triad motif. In the same year, researchers obtained the first crystal structure of a mononuclear nonheme iron(IV)-oxo complex bearing a macrocyclic supporting ligand, $[(TMC)Fe^{IV}(O)]^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecene), in studies that mimicked the biological enzymes. With these breakthrough results, many other studies have examined mononuclear nonheme iron(IV)-oxo intermediates trapped in enzymatic reactions or synthesized in biomimetic reactions. Over the past decade, researchers in the fields of biological, bioinorganic, and oxidation chemistry have extensively investigated the structure, spectroscopy, and reactivity of nonheme iron(IV)-oxo species, leading to a wealth of information from these enzymatic and biomimetic studies.



This Account summarizes the reactivity and mechanisms of synthetic mononuclear nonheme iron(IV)-oxo complexes in oxidation reactions and examines factors that modulate their reactivities and change their reaction mechanisms. We focus on several reactions including the oxidation of organic and inorganic compounds, electron transfer, and oxygen atom exchange with water by synthetic mononuclear nonheme iron(IV)-oxo complexes. In addition, we recently observed that the C−H bond activation by nonheme iron(IV)-oxo and other nonheme metal(IV)-oxo complexes does not follow the H-atom abstraction/oxygen-rebound mechanism, which has been well-established in heme systems.

The structural and electronic effects of supporting ligands on the oxidizing power of iron(IV)-oxo complexes are significant in these reactions. However, the difference in spin states between nonheme iron(IV)-oxo complexes with an octahedral geometry (with an $S = 1$ intermediate-spin state) or a trigonal bipyramidal (TBP) geometry (with an $S = 2$ high-spin state) does not lead to a significant change in reactivity in biomimetic systems. Thus, the importance of the high-spin state of iron(IV)-oxo species in nonheme iron enzymes remains unexplained. We also discuss how the axial and equatorial ligands and binding of redox-inactive metal ions and protons to the iron-oxo moiety influence the reactivities of the nonheme iron(IV)-oxo complexes. We emphasize how these changes can enhance the oxidizing power of nonheme metal(IV)-oxo complexes in oxygen atom transfer and electron-transfer reactions remarkably. This Account demonstrates great advancements in the understanding of the chemistry of mononuclear nonheme iron(IV)-oxo intermediates within the last 10 years.

1. INTRODUCTION

Mononuclear nonheme iron enzymes are highly versatile in nature and are involved in metabolically vital oxidative transformations.[1,2] These enzymes activate dioxygen to carry out a broad range of oxidative reactions, including hydroxylation, halogenation, desaturation, epoxidation, *cis*-dihydroxylation, and aromatic ring cleavage reactions. High-valent iron(IV)-oxo species have been implicated as reactive intermediates in the enzymatic reactions, and a number of high-spin $S = 2$ iron(IV)-oxo species have been trapped and characterized with various spectroscopic methods.[3] The nonheme iron(IV)-oxo species are competent oxidants capable of abstracting hydrogen atom (H-atom) in C−H bond activation reactions.[3]

In biomimetic studies, the first spectroscopic evidence for mononuclear nonheme iron(IV)-oxo species was reported by Wieghardt and co-workers in the ozonolysis of $[Fe^{III}(cyclam\text{-}acetato)(CF_3SO_3)]^+$ (cyclam-acetato = 1-(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane).[4] In 2003, the first X-ray crystal structure of a mononuclear nonheme iron(IV)-oxo

Received: October 30, 2013
Published: February 13, 2014

   dx.doi.org/10.1021/ar400258p | Acc. Chem. Res. 2014, 47, 1146−1154

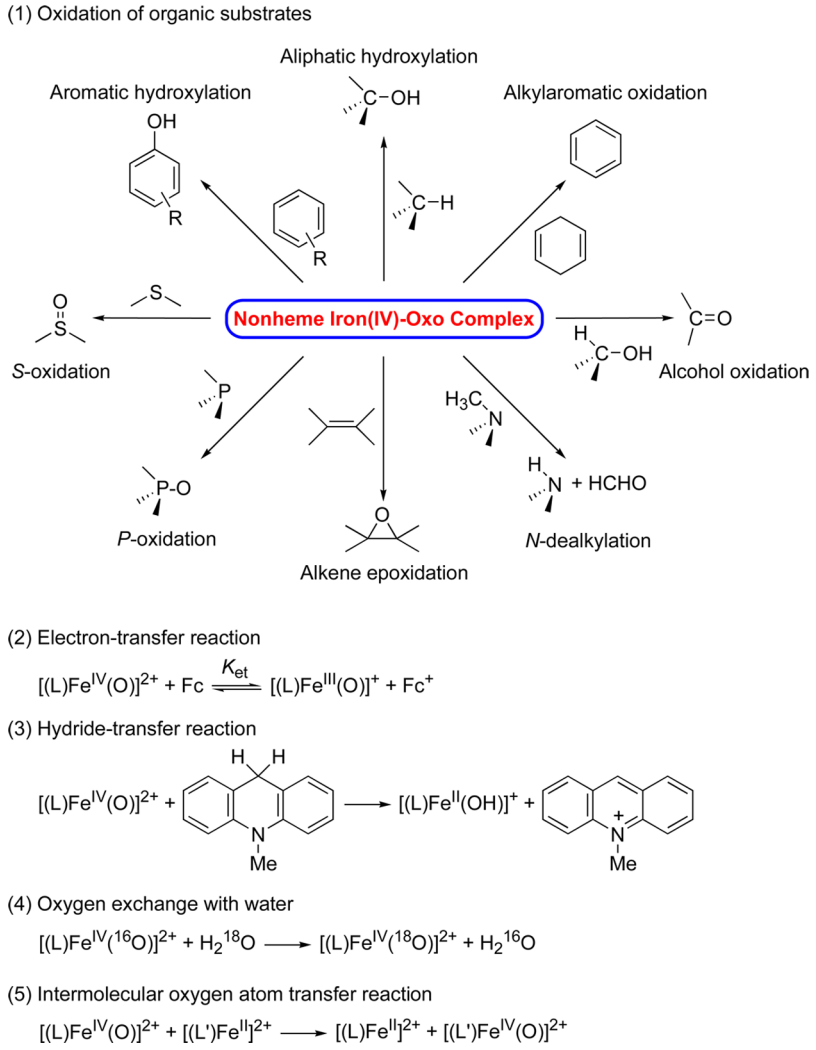


Figure 1. Reactions investigated with synthetic mononuclear nonheme iron(IV)-oxo complexes.

complex bearing a macrocyclic TMC ligand, [(TMC)-$Fe^{IV}(O)]^{2+}$, was reported with a thorough spectroscopic characterization.[5] Since then, a large number of mononuclear nonheme iron(IV)-oxo complexes have been synthesized using various supporting ligands and used in the structural and spectroscopic characterization and reactivity studies in oxidation reactions.[6,7]

The first isolated nonheme iron(IV)-oxo complex, [(TMC)-$Fe^{IV}(O)]^{2+}$, was prepared using iodosylbenzene (PhIO) as an oxidant in CH_3CN at −40 °C.[4] Other artificial oxidants, such as hydroperoxides (e.g., H_2O_2 and alkyl hydroperoxides), peracids, $KHSO_5$, NaOX (X = Cl or Br), O_3, R_3NO, and N_2O, were also used as single-oxygen atom donors to generate iron(IV)-oxo complexes under various reaction conditions such as in organic and aqueous solutions and at low and room temperatures.[6,7] Importantly, nonheme iron(IV)-oxo complexes were successfully generated by activating O_2 in alcoholic solvents or in the presence of electron donors and proton or olefin in CH_3CN.[8−13] Water (H_2O) was also used as an oxygen atom source in the generation of nonheme iron(IV)-oxo complexes in the presence of a strong oxidant.[14] More recently, Borovik and co-workers prepared a high-spin iron(IV)-oxo complex using the corresponding iron(III)-oxo or iron(III)-hydroxo complexes via one-electron oxidation or a proton-coupled electron-transfer (PCET) process, respectively.[15]

The success of generating and isolating nonheme iron(IV)-oxo complexes prompted studies on the reactivities of the intermediates in various oxidation reactions, such as aliphatic hydroxylation, olefin epoxidation, alcohol oxidation, C−H bond activation of alkylaromatics, *N*-dealkylation, aromatic hydroxylation, and the oxidation of sulfides and phosphines (Figure 1).[6] Other reactions, such as electron- and hydride-transfer,[16,17] oxygen atom exchange between the oxo group of nonheme iron(IV)-oxo complexes and water,[18] and intermolecular oxo-transfer from iron(IV)-oxo complexes to iron(II) complexes,[19,20] have also been investigated in detail (Figure 1). The structural and electronic effects of supporting ligands on the oxidizing power of the iron(IV)-oxo complexes were another topic that has been extensively investigated using nonheme iron(IV)-oxo complexes with an octahedral geometry (i.e., an $S = 1$ intermediate-spin state) or a trigonal bipyramidal (TBP) geometry (i.e., an $S = 2$ high-spin state).[15,21,22] The effects of axial and equatorial ligands[23,24] and the binding of redox-inactive metal ions[25] to the iron-oxo moiety on the reactivities of the nonheme iron(IV)-oxo complexes have attracted much attention in the electron-transfer and oxidation reactions. Thus, the chemistry of mononuclear nonheme iron(IV)-oxo intermediates in biomimetic studies has been advanced greatly in the past decade. In this Account, we summarize our recent results on the reactivity and mechanistic studies of mononuclear nonheme

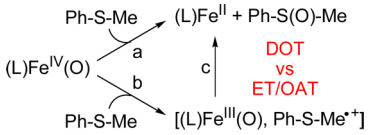
dx.doi.org/10.1021/ar400258p | *Acc. Chem. Res.* 2014, 47, 1146−1154

iron(IV)-oxo complexes that have been conducted using isolated and/or spectroscopically well-characterized nonheme iron(IV)-oxo complexes under stoichiometric reaction conditions. Factors affecting the chemical properties of the nonheme iron(IV)-oxo complexes, such as supporting and axial ligands and redox-inactive metal ions, are discussed as well.

2. OXIDATION REACTIONS BY NONHEME IRON(IV)−OXO COMPLEXES

The first example of oxygen atom transfer (OAT) from nonheme iron(IV)-oxo complexes to organic substrates was reported in the oxidation of PPh_3 by $[(TMC)Fe^{IV}(O)]^{2+}$ (Figure 1, *P*-oxidation).[5] PPh_3 is an easily oxidized substrate and has been often used in testing the electrophilic character of nonheme iron(IV)-oxo complexes with a low oxidizing power. Another substrate frequently used in OAT reactions is thioanisole (Figure 1, *S*-oxidation);[26] a direct oxygen transfer (DOT; Scheme 1, pathway a) rather than an electron transfer followed by an OAT (ET/OAT; Scheme 1, pathways b and c) was proposed for the sulfoxide formation.[27] In the oxidation of sulfides, reaction rates were dependent significantly on the electron-donating ability of *para*-substituents (e.g., Hammett ρ values between −1.4 and −2.5), and the negative ρ values indicate the electrophilic character of the iron-oxo moiety of the nonheme iron(IV)-oxo complexes.[26] When the sulfoxidation of thioanisoles by $[(N4Py)Fe^{IV}(O)]^{2+}$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis-(2-pyridyl)methylamine) was carried out in the presence of Sc^{3+} ion, the rate of the sulfoxidation was accelerated as much as 10^2-fold and the mechanism of sulfoxidation was switched from DOT to ET/OAT (vide infra).[27]

Scheme 1



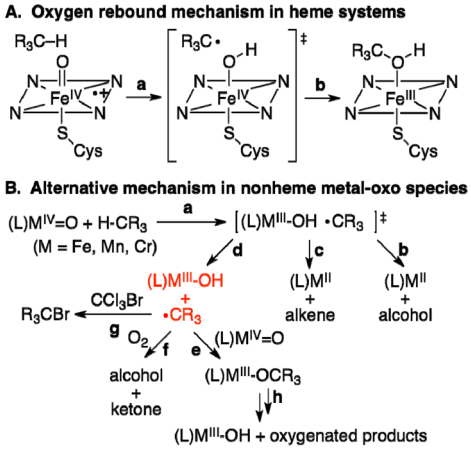
In aromatic hydroxylation reactions (Figure 1, aromatic hydroxylation), anthracene was oxidized to anthraquinone by $[(N4Py)Fe^{IV}(O)]^{2+}$ and $[(Bn\text{-}TPEN)Fe^{IV}(O)]^{2+}$ (Bn-TPEN = *N*-benzyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,2-diaminoethane), and a low kinetic isotope effect (KIE) value of ∼0.9 was determined kinetically in the hydroxylation of anthracene and deuterated anthracene.[28] The electron-donating ability of *para*-substituents on anthracene influences reaction rates significantly, affording a Hammett ρ value of −3.9. Such a large negative ρ value with the inverse KIE implies that the iron-oxo group attacks the aromatic ring via an electrophilic pathway.[28]

The most striking observation made in the oxidation of organic substrates by nonheme iron(IV)-oxo complexes was the hydroxylation of alkanes by $[(N4Py)Fe^{IV}(O)]^{2+}$ and $[(Bn\text{-}TPEN)Fe^{IV}(O)]^{2+}$ (Figure 1, aliphatic hydroxylation).[29] The iron(IV)-oxo complexes bearing pentadentate N5 ligands were thermally stable even at room temperature but capable of activating the C−H bonds of unactivated hydrocarbons. Since then, a number of nonheme iron(IV)-oxo complexes were shown to be a competent oxidant in the C−H bond activation of unactivated alkanes in organic and aqueous solutions.[30,31] One notable example is the highly reactive $[(Me_3NTB)Fe^{IV}(O)]^{2+}$ (Me_3NTB = tris((*N*-methyl-benzimidazol-2-yl)methyl)amine) complex which is even more reactive than iron(IV)-oxo porphyrin π-cation radical species (a model of cytochrome P450 compound I, Cpd I).[31] In the C−H bond activation of hydrocarbons, the reaction rates were proportional to the bond dissociation energies (BDE) of the substrates with a large KIE of >30, as reported in H-atom abstraction reactions by nonheme iron enzymes (e.g., KIE of ∼37 in TauD),[32] indicating that the C−H activation by nonheme iron(IV)-oxo species occurs via an H-atom abstraction mechanism.

Further insight into the C−H bond activation by nonheme iron(IV)-oxo complexes was obtained using alkylaromatic compounds having weak C−H bonds, specifically xanthene, 9,10-dihydroanthracene, 1,4-cyclohexadiene, and fluorene (Figure 1, Alkylaromatic oxidation). The alkylaromatic compounds were turned out to be excellent substrates in the mechanistic studies of C−H bond activation reactions, since many of the nonheme iron(IV)-oxo complexes possess a low oxidizing power.[5,23] A linear correlation between the second-order rate constants and the C−H BDE values of the substrates was observed in most of the reactions. In addition, high KIE values of ≥20 were obtained in the oxidation of alkylaromatic compounds by nonheme iron(IV)-oxo complexes irrespective of their spin states (e.g., intermediate-spin or high-spin states).[21,23,29]

Very recently, we have shown that the C−H bond activation by nonheme iron(IV)-oxo and manganese(IV)-oxo complexes does not follow the H-atom abstraction/oxygen-rebound mechanism proposed in heme systems. As shown in Scheme 2A, alkane hydroxylation by Cpd I is initiated by a rate-determining H-atom abstraction step by $(Porp)^{+\bullet}Fe^{IV}(O)$ species (Scheme 2A, pathway a), followed by an oxygen-rebound between the resulting $(Porp)Fe^{IV}(OH)$ and substrate radical species (Scheme 2A, pathway b). In this H-atom abstraction/oxygen-rebound mechanism, the formal oxidation state of Fe^{V} is reduced to Fe^{III} and the product formed is alcohol. In contrast to the heme systems, the metal complex products formed in the C−H bond activation by nonheme iron(IV)-oxo complexes were Fe^{III} species (Scheme 2B).[33] In addition, organic products were different from those typically obtained in the oxygen-rebound mechanism. These experimental results, with theoretical investigation into the C−H bond activation by nonheme iron(IV)-oxo and manganese(IV)-oxo species,[33] led us to propose that the dissociation (Scheme 2B, pathway d) of the substrate radical, which is formed via H-atom abstraction from hydrocarbons (Scheme 2B, pathway a), is more favorable than

Scheme 2



dx.doi.org/10.1021/ar400258p | Acc. Chem. Res. 2014, 47, 1146−1154

the oxygen rebound and desaturation processes (Scheme 2B, pathways b and c).

The alcohol oxidation by nonheme iron(IV)-oxo complexes have been conducted (Figure 1, alcohol oxidation), where benzyl alcohol and methanol were oxidized to benzaldehyde and formaldehyde, respectively.[34] As shown in the alkane hydroxylation reactions, a large KIE value of ∼50 was observed in the oxidation of benzyl alcohol by nonheme iron(IV)-oxo complexes, $[(TPA)Fe^{IV}(O)]^{2+}$ (TPA = tris(2-pyridylmethyl)-amine) and $[(N4Py)Fe^{IV}(O)]^{2+}$.[34] Such a large KIE value indicates that nonheme iron(IV)-oxo intermediates activate alcohols exclusively by an H-atom abstraction from the α-CH of benzyl alcohol and that this C−H bond cleavage is the rate-determining step.

Heme and nonheme iron enzymes participate in oxidative N-dealkylation reactions in nature. Therefore, oxidative N-dealkylation of *N*,*N*-dialkylamines was investigated using in situ-generated nonheme and heme iron(IV)-oxo complexes (Figure 1, *N*-dealkylation).[35] In the oxidative N-dealkylation of *N*,*N*-dimethylaniline by $[(N4Py)Fe^{IV}(O)]^{2+}$ and $[(TMC)Fe^{IV}(O)]^{2+}$, *N*-methylaniline was formed as a major product with the concurrent formation of CH_2O.[35] Based on the results of mechanistic studies, the oxidative N-dealkylation reactions by nonheme iron(IV)-oxo complexes were proposed to occur via an electron transfer-proton transfer (ET-PT) mechanism, not via an H-atom transfer (HAT). In the presence of Sc^{3+} ion, the electron transfer step is remarkably accelerated by binding of Sc^{3+} ion to the iron-oxo moiety (vide infra).[36]

It was demonstrated that an iron(IV)-oxo complex, $[(TPA)Fe^{IV}(O)]^{2+}$, reacts with cyclooctene to give cyclooctene oxide (Figure 1, alkene epoxidation).[37] Although it has been shown that nonheme iron-oxo complexes react with alkenes, mechanism(s) of the alkene oxidation by nonheme iron(IV)-oxo complexes remains elusive.

3. ELECTRON-TRANSFER AND HYDRIDE-TRANSFER REACTIONS

Among various redox reactions, electron transfer is the most essential, fundamental, and ubiquitous in biological and chemical systems. Thus, electron-transfer (ET) reactions of nonheme iron(IV)-oxo complexes were investigated using ferrocene (Fc) and its derivatives as electron donors (Figure 1, reaction 2). We have observed a one-electron reduction process and proposed the existence of an ET equilibrium for electron transfer from Fc to the iron(IV)-oxo to afford Fc^+ and iron(III)-oxo.[16] From the ET equilibrium, we determined the one-electron reduction potentials (E_{red}) of $[(TMC)Fe^{IV}(O)]^{2+}$ (E_{red} = 0.39 V vs SCE), $[(N4Py)Fe^{IV}(O)]^{2+}$ (E_{red} = 0.51 V vs SCE), and $[(Bn\text{-}TPEN)Fe^{IV}(O)]^{2+}$ (E_{red} = 0.49 V vs SCE).[16]

The driving force dependence of the rate constants (k_{et}) of electron transfer from various electron donors to nonheme iron(IV)-oxo complexes is well fitted by the Marcus equation of adiabatic outer-sphere electron transfer (eq 1),[16]

$$k_{et} = Z \exp[-(\lambda/4)(1 + \Delta G_{et}/\lambda)^2/k_B T] \quad (1)$$

where Z is the collision frequency taken as 1×10^{11} M^{-1} s^{-1}, λ is the reorganization energy of electron transfer, k_B is the Boltzmann constant, and T is the absolute temperature. ΔG_{et} is the free energy change of electron transfer, which is given by eq 2, where e is the elementary charge, and

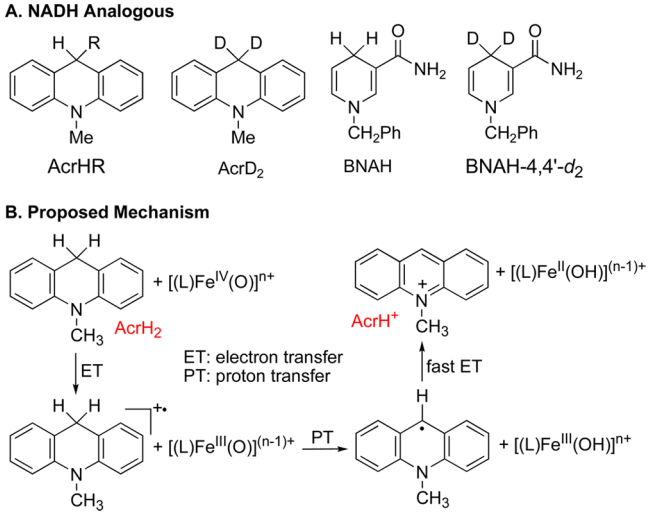
$$\Delta G_{et} = e[E_{ox}(D^{\bullet+}/D) - E_{red}(A/A^{\bullet-})] \quad (2)$$

E_{ox} and E_{red} are the one-electron oxidation potential (E_{ox}) of an electron donor (D) and the one-electron reduction potential (E_{red}) of an iron(IV)-oxo complex as an electron acceptor (A). The λ values of electron transfer from ferrocene derivatives to $[(L)Fe^{IV}(O)]^{2+}$ were determined by the driving force dependence of k_{et} using the Marcus theory of adiabatic outer-sphere electron transfer analysis (eq 1), increasing in the order of L = TMC (2.37 eV) < Bn-TPEN (2.55 eV) < N4Py (2.74 eV).[16] The large λ values of $[(L)Fe^{IV}(O)]^{2+}$ result from the significant elongation of the Fe−O bond upon the ET reduction.

More recently, we have shown the axial ligand effect on the one-electron reduction potentials of $[(TMC)Fe^{IV}(O)(X)]^{n+}$ (**1**-X) bearing different axial ligands (vide infra), such as **1**-$NCCH_3$ (E_{red} = 0.39 V vs SCE), **1**-$OOCCF_3$ (E_{red} = 0.13 V vs SCE), and **1**-N_3 (E_{red} = −0.05 V vs SCE).[38] The λ value determined from the driving force dependence of k_{et} using eq 1 decreases in the order of X = CH_3CN (2.37 eV) > CF_3COO^- (2.12 eV) > N_3^- (1.97 eV) as the E_{red} value decreases. Thus, the ET reduction becomes less favorable thermodynamically but more favorable kinetically with increasing axial ligand donor ability.

Dihydronicotinamide adenine dinucleotide (NADH) is the most important source of hydride ion (two electrons and a proton) in biological redox reactions, and there has been extensive discussion on the mechanism of hydride-transfer reactions of NADH and its analogues, such as concerted hydride-transfer vs sequential electron−proton−electron (equivalent to a hydride ion) transfer. In order to elucidate the mechanism of hydride transfer in nonheme iron systems, NADH analogues, such as 10-methyl-9,10-dihydroacridine ($AcrH_2$) and its derivatives, 1-benzyl-1,4-dihydronicotinamide (BNAH), and their deuterated compounds (Scheme 3A), were reacted with

Scheme 3



nonheme iron(IV)-oxo complexes such as $[(L)Fe^{IV}(O)]^{2+}$ (L = N4Py, Bn-TPEN, and TMC) (Figure 1, reaction 3).[17] In the reactions, the corresponding NAD^+ analogues and nonheme iron(II) complexes were formed as products. The detailed comparison of the hydride-transfer reactivity of $[(L)Fe^{IV}(O)]^{2+}$ with NADH analogues and that of *p*-chloranil, which is known to undergo hydride transfer via electron transfer, led us to propose that hydride transfer from NADH analogues to nonheme iron(IV)-oxo complexes also occurs via electron transfer from NADH analogues to the iron(IV)-oxo complexes, followed by the rate-limiting proton transfer from the radical cations of

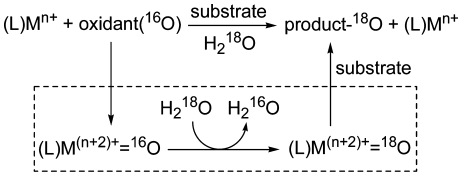
dx.doi.org/10.1021/ar400258p | Acc. Chem. Res. 2014, 47, 1146−1154

NADH analogues (Scheme 3B).[17] Then, rapid electron transfer from the deprotonated radicals to the Fe(III) complexes occurs to yield the corresponding NAD^+ analogues and the Fe(II) complexes as final products (Scheme 3B).[17]

4. OXYGEN-ATOM EXCHANGE WITH WATER AND OXO-TRANSFER BETWEEN IRON COMPLEXES

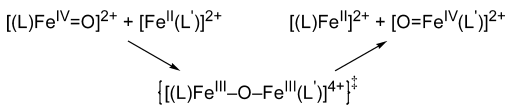
High-valent metal-oxo species are highly reactive and unstable in nature; therefore, it is difficult to detect them directly in catalytic oxidation reactions by enzymes and model compounds. One of frequently used indirect methods to propose the nature of the reactive intermediates is to carry out the catalytic oxidation reactions in the presence of ^{18}O-labeled water ($H_2{}^{18}O$), since metal-oxo complexes can exchange their O-atom with ^{18}O-labeled water prior to O-atom transfer to organic substrates (Scheme 4). Although most of the ^{18}O-labeled water experiments were performed under catalytic oxidation reactions, the first clear evidence for ^{18}O-atom exchange between metal-oxo complexes and $H_2{}^{18}O$ was obtained using the highly stable nonheme iron-oxo complexes, such as $[(TMC)Fe^{IV}(O)]^{2+}$ and $[(N4Py)Fe^{IV}(O)]^{2+}$ (Figure 1, reaction 4).[18] Interestingly, different from the previous assumption that the oxygen atom exchange between high-valent metal-oxo complexes and $H_2{}^{18}O$ was invariably fast, the determined oxygen atom exchange rates between nonheme iron(IV)-oxo species and $H_2{}^{18}O$ were slow.[18]

Scheme 4



A complete intermetal OAT between nonheme iron(IV)-oxo and iron(II) species was also observed (Figure 1, reaction 5).[19] For example, addition of $[Fe^{II}(TMC)]^{2+}$ to the solution of $[(N4Py)Fe^{IV}(O)]^{2+}$ afforded the formation of $[(TMC)Fe^{IV}(O)]^{2+}$ and $[Fe^{II}(N4Py)]^{2+}$, indicating that an OAT occurred between iron complexes via the formation of a μ-oxo-bridged iron(III) dimer (Scheme 5).[19,39] It has been shown that the OAT depends on the oxidizing power of the iron(IV)-oxo complexes in sulfoxidation reactions, such as $[(Bn\text{-}TPEN)Fe^{IV}(O)]^{2+} > [(N4Py)Fe^{IV}(O)]^{2+} > [(TMC)Fe^{IV}(O)]^{2+}$.[19,20]

Scheme 5



5. FACTORS AFFECTING REACTIVITIES OF NONHEME IRON(IV)–OXO COMPLEXES

The reactivity and stability of iron(IV)-oxo complexes are considered to be affected by several factors, such as supporting and axial ligands and spin state of iron(IV) ion. The iron(IV)-oxo complex bearing the macrocyclic TMC ligand, $[(TMC)Fe^{IV}(O)]^{2+}$, was relatively stable even at room temperature.[5] While this $[(TMC)Fe^{IV}(O)]^{2+}$ complex showed a low reactivity in OAT and HAT reactions,[5] nonheme iron(IV)-oxo complexes bearing TMC derivatives (e.g., the change of the TMC ring size or the replacement of *N*-methyl with *N*-benzyl on the cyclam framework) were much more reactive than that of $[(TMC)Fe^{IV}(O)]^{2+}$.[40,41] Nonheme iron(IV)-oxo complexes bearing pentadentate N5 ligands, such as N4Py and Bn-TPEN, were highly reactive in oxidation reactions despite their thermal stability. Another representative group of nonheme iron(IV)-oxo complexes was the one bearing a tripodal tetradentate N4 ligand, such as TPA and Me_3NTB.[31,37] These iron(IV)-oxo complexes turned out to be strong oxidants, and the $[(Me_3NTB)Fe^{IV}(O)]^{2+}$ complex was the most reactive species reported so far.[31] The topology of supporting ligands is another factor that affects the oxidizing power of nonheme iron(IV)-oxo complexes.[42] Recently, it has been shown that the rates of OAT from nonheme iron(IV)-oxo complexes increase linearly with the increase in their redox potentials ($Fe^{IV/III}$).[20] However, different from the OAT reaction (e.g., sulfoxidation), the reactivity of the nonheme iron(IV)-oxo complexes in HAT reactions does not follow the sulfoxidation pattern.[20] Although the redox potential of nonheme iron(IV)-oxo complexes is a factor that governs their reactivity in C–H bond activation reactions, there are other factors that influence their reactivity in C–H bond activation reactions.

It has been demonstrated in iron-oxo porphyrins that axial ligands bound *trans* to the iron-oxo moiety affect the reactivities of iron(IV)-oxo porphyrin π-cation radicals. Such an axial ligand effect has also been observed in nonheme iron(IV)-oxo systems.[23] When reactivities of nonheme iron(IV)-oxo complexes bearing different axial ligands, $[(TMC)Fe^{IV}(O)(X)]^{n+}$ (**1**-X) (**1**-$NCCH_3$, **1**-$OOCCF_3$, and **1**-N_3) and $[(TMCS)Fe^{IV}(O)]^+$ (**1′**-SR, TMCS = 1-(2-mercaptoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane)[43] (see Figure 2 for structures), were investigated in OAT and H-atom abstraction reactions, the reactivities were found to vary significantly by the axial ligands.[23] For example, in the oxidation of PPh_3 (i.e., OAT reaction), the reactivity order of **1**-$NCCH_3$ > **1**-$OOCCF_3$ > **1**-N_3 > **1′**-SR was observed, reflecting a decrease in the electrophilicity of iron(IV)-oxo moiety upon replacement of CH_3CN with an anionic axial ligand (Figure 3a, OAT). In contrast, the reactivity order was inverted in the oxidation of phenol O–H and alkylaromatic C–H bonds, such as **1′**-SR > **1**-N_3 > **1**-$OOCCF_3$ > **1**-$NCCH_3$ (Figure 3a, H-abstraction). In the latter reactions, a good correlation between the reactivities of iron(IV)-oxo species and their reduction peak potentials, $E_{p,c}$, was observed with the most reactive **1′**-SR complex exhibiting the lowest potential in C–H bond activation reactions. Such an axial ligand effect was also investigated experimentally and theoretically in the reactions of $[(TMC)Ru^{IV}(O)(X)]^{n+}$ and $[(TMP)^{+\bullet}Fe^{IV}(O)(X)]^+$, and the

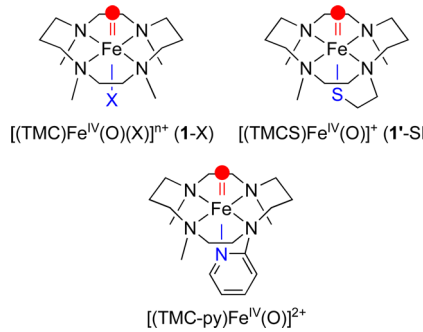


Figure 2. Schematic structures of $[(TMC)Fe^{IV}(O)(X)]^{n+}$ (1-X), $[(TMCS)Fe^{IV}(O)]^+$ (1′-SR), and $[(TMC\text{-}py)Fe^{IV}(O)]^{2+}$.

dx.doi.org/10.1021/ar400258p | Acc. Chem. Res. 2014, 47, 1146–1154

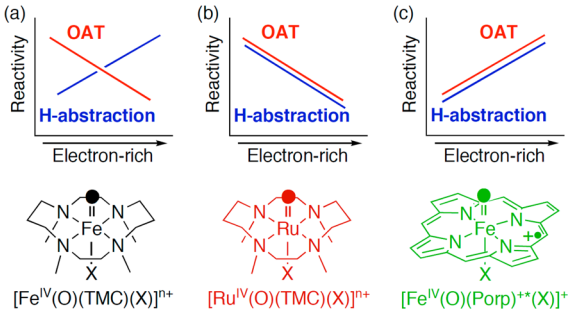


Figure 3. Schematic drawings showing the axial ligand effects in oxygen atom transfer (OAT) and H-atom abstraction (H-abstraction) reactions by high-valent metal-oxo complexes. Reprinted with permission from ref 45. Copyright 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

axial ligand effects were different depending on the metal ions and supporting ligands (Figure 3).[44,45]

More recently, Fukuzumi, Nam, and co-workers reported the effects of axial ligands on ET and PCET reactions of $[(TMC)Fe^{IV}(O)(X)]^{n+}$ (**1**-$NCCH_3$, **1**-$OOCCF_3$, and **1**-N_3); the electron-donating axial ligand retarded the ET reaction, whereas the rate of the PCET was accelerated by the electron-donating axial ligand.[38] In the ET reactions, **1** with a more electron-donating axial ligand becomes electron-richer, thereby showing the deceleration of the ET rate. In contrast, as observed in the C−H activation reactions, the enhanced reactivity of **1**-X bearing an electron-donating axial ligand was rationalized by an increased basicity of the O-atom of the iron-oxo intermediates, as proposed in heme systems.[46]

Although high-spin ($S = 2$) iron(IV)-oxo species are found in nonheme iron enzymes, most of the reactivity studies were performed with intermediate-spin ($S = 1$) iron(IV)-oxo models because it is only recently that high-spin iron(IV)-oxo complexes were successfully synthesized.[15,21] Theory has predicted that high-spin iron(IV)-oxo complexes should be more reactive than their intermediate-spin counterparts due to enhancement of exchange-stabilization;[47] however, the high-spin ($S = 2$) iron(IV)-oxo species synthesized so far showed reactivities comparable to those of intermediate-spin ($S = 1$) iron(IV)-oxo complexes. More information on the reactivity difference between high-spin and intermediate-spin iron(IV)-oxo complexes is needed to answer the question why nonheme iron enzymes use high-spin iron(IV)-oxo intermediates as active oxidants in their chemical reactions.

6. BINDING OF METAL IONS AND PROTONS TO HIGH-VALENT METAL−OXO COMPLEXES

In addition to the effects of supporting and axial ligands, binding of redox-inactive metal ions and protons to the oxo group results in remarkable change in the chemical properties of nonheme iron(IV)-oxo complexes.[27,36,48,49] First, binding of Sc^{3+} ion to the oxo group of $[(TMC)Fe^{IV}(O)]^{2+}$ was definitely shown by the X-ray crystal structure of $[(TMC)Fe^{IV}(O)-Sc(OTf)_4(OH)]$ (Figure 4).[48] The strong binding of Sc^{3+} ion to the oxo group resulted in elongation of the Fe−O bond length (1.754(3) Å) of the $Fe^{IV}(O)-Sc^{3+}$ complex; the Fe−O bond lengths of $[(TMC)Fe^{IV}(O)(NCMe)]^{2+}$,[5] $[(TMCS)Fe^{IV}(O)]^{+}$,[43] and $[(TMC\text{-}py)Fe^{IV}(O)]^{2+}$ (TMC-py =1-(2′-pyridylmethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane)[9] were 1.643(3) Å by X-ray crystallography, 1.70(2) Å by extended X-ray absorption fine structure (EXAFS) analysis, and 1.667(3) Å

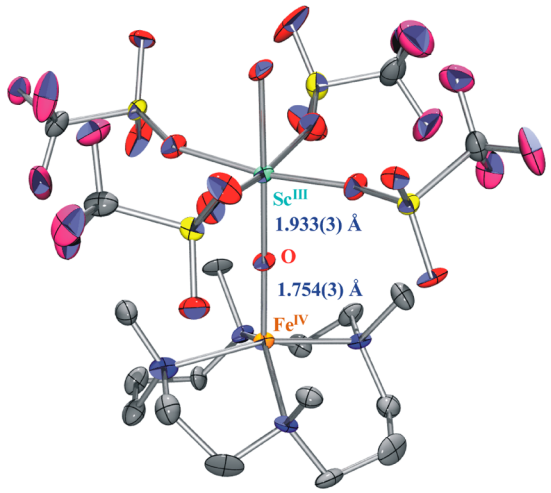


Figure 4. X-ray crystal structure of a Sc^{3+}-bound nonheme iron(IV)-oxo complex, $[(TMC)Fe^{IV}(O)\text{-}Sc^{III}(OTf)_4(OH)]$. Reprinted with permission from ref 48. Copyright 2010, Nature Publishing Group.

by X-ray crystallography, respectively. It is of interest to note that all four *N*-methyl groups of the TMC ligand in the $Fe^{IV}(O)-Sc^{3+}$ complex point to the same side of the oxo moiety (Figure 4),[48] which is different from the structures of $Fe^{IV}(O)$ complexes without binding Sc^{3+} ion, such as $[(TMC)Fe^{IV}(O)(NCMe)]^{2+}$ and $[(TMC\text{-}py)Fe^{IV}(O)]^{2+}$ (see Figure 2).[5,9,43]

The E_{red} values of $[(N4Py)Fe^{IV}(O)]^{2+}$ with and without Sc^{3+} ion were determined by redox titrations.[49] The E_{red} values increased with increasing concentration of Sc^{3+} ion in accordance with eq 3,

$$E_{red} = E^{\circ}_{red} + (2.3RT/F)\log(1 + K_1[Sc^{3+}] + K_1K_2[Sc^{3+}]^2) \quad (3)$$

where E°_{red} is the one-electron reduction potential without Sc^{3+} ion, and K_1 and K_2 are the formation constants of 1:1 and 1:2 complexes of $[(N4Py)Fe^{III}(O)]^{+}$ with one Sc^{3+} and two Sc^{3+} ions, respectively.[49] This indicates that the one-electron reduction of $[(N4Py)Fe^{IV}(O)]^{2+}$ is accompanied by binding of not only one but also two Sc^{3+} ions to $[(N4Py)Fe^{III}(O)]^{+}$.[49]

Manganese(IV)-oxo complexes, $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}$ and $[(N4Py)Mn^{IV}(O)]^{2+}$, also bind one and two Sc^{3+} ions.[50,51] The formation constants of $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}\text{-}(Sc^{3+})_1$ and $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}\text{-}(Sc^{3+})_2$ complexes were determined to be 4.0×10^3 and 1.2×10^3 M^{-1}, respectively.[50] The EXAFS results showed that the Mn−O bond length elongates from 1.69 to 1.74(2) Å, which is consistent with weakening of the Mn−O bond upon binding of Sc^{3+} ion.[51] The EXAFS data also revealed a Mn−Sc bond length of 3.45 Å, which clearly indicates that Sc^{3+} ion binds to the $Mn^{IV}(O)$ moiety. DFT calculations suggested that one Sc^{3+} ion binds directly to the O-atom of the $Mn^{IV}(O)$ complex, whereas the second Sc^{3+} ion is located at the secondary coordination sphere (Figure 5).[51]

The one-electron reduction potentials (E_{red}) of $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}$ and $[(N4Py)Mn^{IV}(O)]^{2+}$ in the absence and presence of $Sc(OTf)_3$ were determined by the redox titrations with appropriate electron donors whose one-electron oxidation potentials (E_{ox}) are known.[51] The E_{red} values of $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}$ and $[(N4Py)Mn^{IV}(O)]^{2+}$ exhibited large positive shifts from 0.78 and 0.80 V vs SCE in the absence of Sc^{3+} ion to 1.28 and 1.31 V vs SCE in the presence of one equiv (for N4Py) or two equiv (for Bn-TPEN) of Sc^{3+} ion, which

dx.doi.org/10.1021/ar400258p | *Acc. Chem. Res.* 2014, 47, 1146−1154

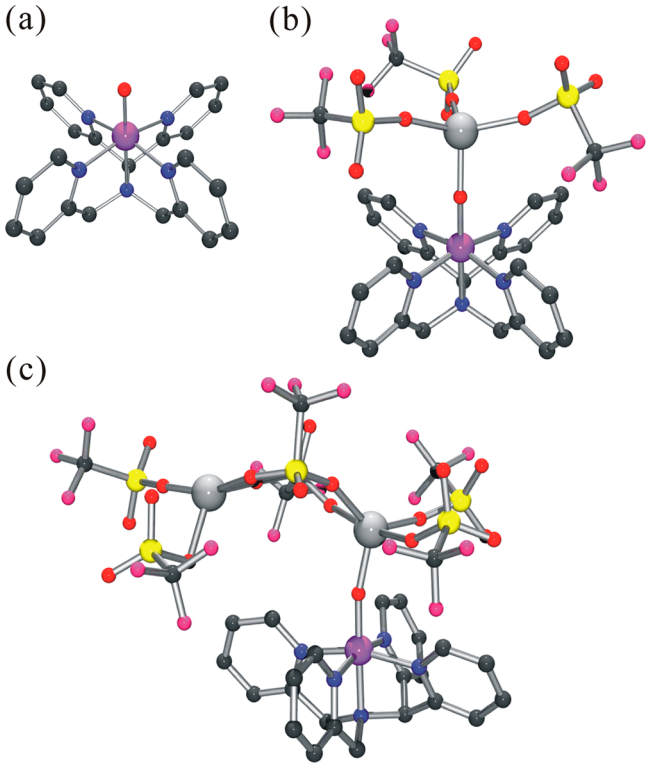


Figure 5. DFT-optimized structures of (a) $[(N4Py)Mn^{IV}(O)]^{2+}$, (b) $[(N4Py)Mn^{IV}(O)\text{-}Sc(OTf)_3]^{2+}$, and (c) $[(N4Py)Mn^{IV}(O)\text{-}Sc(OTf)_3\text{-}Sc(OTf)_3]^{2+}$. Reprinted with permission from ref 50. Copyright 2013 American Chemical Society.

correspond to the E_{red} values of the $[Mn^{IV}(O)]^{2+}$-Sc^{3+} complexes of $[(Bn\text{-}TPEN)Mn^{IV}(O)]^{2+}$ and $[(N4Py)Mn^{IV}(O)]^{2+}$, respectively.[51] The large shift of the E_{red} values by binding of Sc^{3+} ions may result from stronger binding of Sc^{3+} to the one-electron reduced species, $[Mn^{III}(O)]^{2+}$. Similarly, the E_{red} values of $[(N4Py)Fe^{IV}(O)]^{2+}$ exhibited large positive shifts by binding of protons of perchloric acid ($HClO_4$) in accordance with eq 3, where Sc^{3+} is replaced by H^+.[52,53]

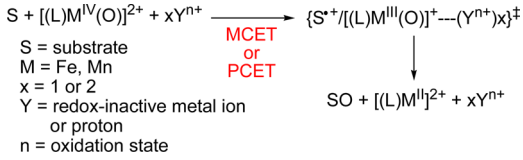
7. CHANGE OF MECHANISM FROM CONCERTED PATHWAYS TO PROTON-COUPLED OR METAL-ION-COUPLED ELECTRON-TRANSFER PATHWAYS

The positive reduction potentials of the Sc^{3+}-bound $Mn^{IV}(O)$ complex, ($[(N4Py)Mn^{IV}(O)]^{2+}$-$(Sc^{3+})_2$), resulted in remarkable enhancement of the ET reactivity of $[(N4Py)Mn^{IV}(O)]^{2+}$ by binding of Sc^{3+} ions. Not only the ET reactivity but also the sulfoxidation reactivity of $[(N4Py)Mn^{IV}(O)]^{2+}$ was enhanced greatly by binding of Sc^{3+} ions.[51] Both the rate constants of sulfoxidation of thioanisoles by $[(N4Py)Mn^{IV}(O)]^{2+}$-$(Sc^{3+})_2$ and electron transfer from electron donors to $[(N4Py)Mn^{IV}(O)]^{2+}$-$(Sc^{3+})_2$ fit well with the Marcus equation (eq 1) with λ = 2.16 eV.[51] Thus, the mechanism of sulfoxidation of thioanisoles by $[(N4Py)Mn^{IV}(O)]^{2+}$ is changed from a direct OAT pathway to a metal ion-coupled electron transfer (MCET)[20] pathway upon binding of Sc^{3+} ions. A similar change in the mechanism is observed in the case of $[(N4Py)Fe^{IV}(O)]^{2+}$, which undergoes a direct OAT from thioanisoles and HAT from benzyl alcohols and *N*,*N*-dimethylanilines without metal ions, whereas the rate was much enhanced by Sc^{3+} due to Sc^{3+}-coupled electron transfer from these substrates to $[(N4Py)Fe^{IV}(O)]^{2+}$-$(Sc^{3+})_2$.[27,36] The MCET reactivity of $[(N4Py)Fe^{IV}(O)]^{2+}$ with various metal ions has been shown to increase with increasing the Lewis acidity of metal ions.[49]

Large positive shifts in E_{red} of $[(N4Py)Fe^{IV}(O)]^{2+}$ by binding of protons (e.g., addition of $HClO_4$) also resulted in the change of mechanism from HAT to PCET in the oxidation of toluene derivatives.[53] The change of the mechanism is clearly demonstrated by the drastic change in deuterium kinetic isotope effect from k_H/k_D = 31 in the absence of $HClO_4$ to k_H/k_D = 1.0 in the presence of $HClO_4$.[53] The dependence of rate constants of oxygenation of toluene derivatives by $[(N4Py)Fe^{IV}(O)]^{2+}$ in the presence of $HClO_4$ was also well evaluated in light of the Marcus theory of outer-sphere electron transfer (eq 1).[53]

The general scheme of MCET and PCET of metal(IV)-oxo complexes is depicted in Scheme 6, where M^{n+} denotes metal

Scheme 6



ions (e.g., Sc^{3+}) or protons. The binding of metal ions and protons to $[(L)M^{IV}(O)]^{2+}$ resulted in large positive shifts in the one-electron reduction potentials, which makes electron transfer from substrates to metal ion- or proton-bound $[(L)M^{IV}(O)]^{2+}$ species thermodynamically feasible depending on the one-electron oxidation potentials of substrates. When the free energy change of MCET or PCET is smaller than 0.4 eV, MCET or PCET becomes the rate-determining step instead of concerted pathways such as OAT and C−H bond cleavage, judging from the dependence of the rate constants on the driving force of electron transfer in accordance with the Marcus theory of electron transfer (eq 1).[27,53] In the case of sulfoxidation, MCET or PCET may be followed by fast oxygen ($O^{\bullet-}$) transfer from $[(L)M^{III}(O)]^{+}$ to radical cations of thioanisole derivatives to yield the sulfoxides and $[(L)M^{II}]^{2+}$.[27,52] In the case of C−H bond cleavage, MCET or PCET may be followed by deprotonation of radical cations of substrates and oxygen rebound or further oxidation of the deprotonated radicals by $[(L)M^{IV}(O)]^{2+}$.[53]

In conclusion, high-valent metal-oxo complexes are not strong oxidants as indicated by the relatively low one-electron reduction potentials.[16] However, binding of metal ions and protons resulted in remarkable positive shifts in one-electron reduction potentials. Such large positive shifts in E_{red} resulted in change of mechanism from OAT and HAT without binding of metal ions or protons to MCET and PCET by binding of metal ions and protons, respectively. Thus, the reactivities of high-valent metal-oxo complexes are finely controlled not only by the supporting and axial ligands but also by binding of metal ions and protons to the metal-oxo moiety.

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■ ACKNOWLEDGMENTS

The authors are indebted to the past and present students, postdoctoral fellows, and collaborators whose names appear in the list of references. Financial support from the NRF/MEST of Korea through CRI (2-2012-1794-001-1) and GRL (2-2013-4213-001-1) programs and the Grant-in-Aid from MEXT of Japan is greatly acknowledged.

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