High-Valent Iron(IV)–Oxo Complexes of Heme and Non-Heme Ligands in Oxygenation Reactions

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ABSTRACT

High-valent iron(IV)–oxo species have been implicated as the key reactive intermediates in the catalytic cycles of dioxygen activation by heme and non-heme iron enzymes. Our understanding of the enzymatic reactions has improved greatly via investigation of spectroscopic and chemical properties of heme and non-heme iron(IV)–oxo complexes. In this Account, reactivities of synthetic iron(IV)–oxo porphyrin π-cation radicals and mononuclear non-heme iron(IV)–oxo complexes in oxygenation reactions have been discussed as chemical models of cytochrome P450 and non-heme iron enzymes. These results demonstrate how mechanistic developments in biomimetic research can help our understanding of dioxygen activation and oxygen atom transfer reactions in nature.

1. Introduction

Heme and non-heme iron enzymes catalyze a diverse array of important metabolic transformations that require the binding and activation of dioxygen.[1–5] Our understanding of the catalytic reactions of the enzymes, especially the nature of active oxidizing species, has improved recently with the intensive mechanistic studies of the enzymes and their model compounds. One example is the fact that a catalytic cycle of dioxygen activation and oxygen atom transfer by cytochrome P450 enzymes (CYP 450) has been proposed (Figure 1a), and high-valent iron(IV)–oxo porphyrin π-cation radicals, termed compound I and two oxidizing equivalents above the resting ferric state (see the structure in Figure 1a), are believed to transfer their oxygen atom to organic substrates. Very recently, a high-valent iron(IV)–oxo porphyrin π-cation radical has been characterized in CYP 450, but its detailed physical and chemical properties remained elusive in future studies.[6] In iron porphyrin models, a number of iron(IV)–oxo porphyrin π-cation radicals have been synthesized and characterized with various spectroscopic techniques, and their reactivities have been extensively investigated in various oxygenation reactions, including alkane hydroxylation and olefin epoxidation, in an effort to unveil mechanistic details of dioxygen activation and oxygen atom transfer reactions by CYP 450.[1,7]

High-valent iron(IV)–oxo species have been invoked as key reactive intermediates in non-heme iron enzymes as well.[4,8,9] Very recently, non-heme iron(IV)–oxo intermediates have been identified as active oxidizing species in the catalytic cycles of *Escherichia coli* taurine:α-ketogultarate dioxygenase (TauD) (Figure 1b), prolyl-4-hydroxylase, and halogenase CytC3.[10–12] The intermediates were characterized with various spectroscopic techniques, such as Mössbauer, resonance Raman, and X-ray absorption spectroscopies, showing that the intermediates have a high-spin ($S = 2$) iron(IV)–oxo unit with double bond character between the iron ion and oxygen atom. The activation of C–H bonds by the iron(IV)–oxo species was proposed to occur via a hydrogen atom abstraction mechanism (i.e., KIE of ~37).[13] In biomimetic studies, the first indirect evidence for the existence of a mononuclear non-heme iron(IV)–oxo intermediate was reported by Wieghardt and co-workers, but the structure was characterized only with Mössbauer spectroscopy.[14] In 2003, Münck, Nam, Que, and their co-workers reported the isolation of a mononuclear non-heme iron(IV)–oxo complex bearing a macrocyclic ligand.[15] The intermediate has been well-characterized with various spectroscopic techniques and X-ray crystallography, revealing that the intermediate has an iron(IV)–oxo unit with Fe–O double bond character and a low-spin ($S = 1$) Fe^{IV} oxidation state. Since then, a number of mononuclear non-heme iron(IV)–oxo complexes bearing tetradentate N4 and pentadentate N5 and N4S ligands have been synthesized and studied in the oxidation of various substrates, such as PPh_3, thioanisoles, *N,N*-dialkylanilines, aromatic compounds, alkylaromatic compounds, olefins, alcohols, and alkanes.[8,15–28] Thus, the success of generating and isolating mononuclear non-heme iron(IV)–oxo complexes opened a new area in the biomimetic studies of non-heme iron enzymes. In this Account, we describe our recent results from the reactivity studies of heme and non-heme iron(IV)–oxo complexes in the oxygenation of organic substrates and their reaction mechanisms.

2. High-Valent Iron–Oxo Porphyrin Complexes

In 1979, Groves and co-workers published the first article on the catalytic olefin epoxidation and alkane hydroxylation by a synthetic iron(III) porphyrin complex, Fe(TPP)Cl (TPP = *meso*-tetraphenylporphyrin), and iodosylbenzene (PhIO).[29] In the reactions, olefins and alkanes were preferentially oxidized to the corresponding epoxides and alcohols, respectively. Since then, iron(III) porphyrin complexes bearing functional aryl groups at *meso* positions have been synthesized and used as catalysts in a variety of oxidation reactions, with the intention of

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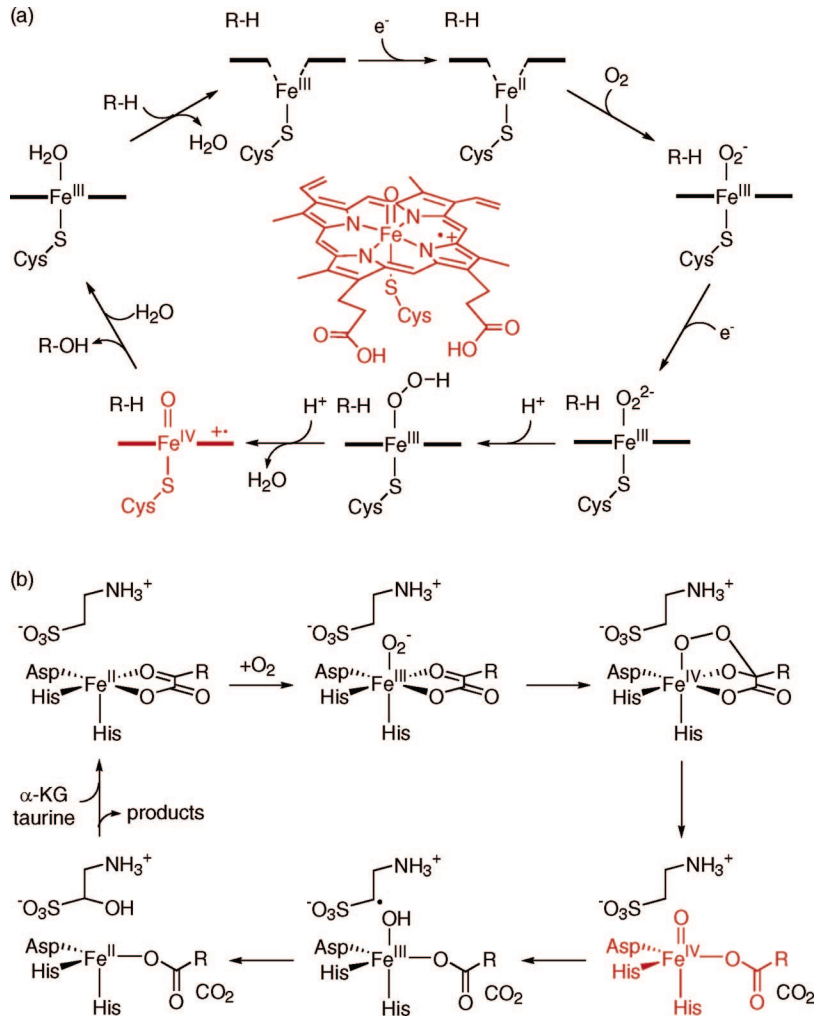
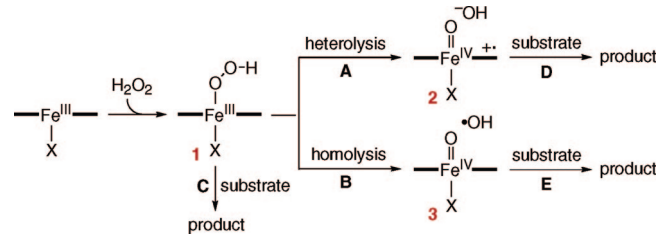


FIGURE 1. Proposed catalytic cycles of CYP 450 (a) and TauD (b).

developing biomimetic catalysis which shows shape selectivity and regio-, stereo-, and enantioselectivity with a high efficiency under mild conditions; iron(III) porphyrins with electron-withdrawing substituents on the phenyl groups, such as Fe(TPFPP)Cl [TPFPP = *meso*-tetrakis(pentafluorophenyl)porphyrin], Fe(TDFPP)Cl [TDFPP = *meso*-tetrakis(2,6-difluorophenyl)porphyrin], and Fe(TDCPP)Cl [TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin], exhibited good catalytic activities in oxygenation reactions with very high turnover numbers and a resistance against the destruction of porphyrin ligands.[30,31] The electron-deficient iron porphyrins were also excellent catalysts in the oxygenation of hydrocarbons by H_2O_2, a biologically relevant and environmentally benign oxidant, in protic and aprotic solvents.[32–34] In the catalytic oxygenation reactions, iron(IV)–oxo porphyrin π-cation radicals (**2**), which are formed via O–O bond heterolysis of iron(III)–hydroperoxo species (**1**), have been proposed as reactive species (Scheme 1, pathways A and D). In addition to the porphyrin ligand effect, the catalytic oxygenation of hydrocarbons by H_2O_2 was also markedly affected by the anionic axial ligands of iron(III) porphyrins and the presence of base added externally, indicating that the electron donating ability of the axial ligands as well as the electron richness of porphyrin ligands is an important

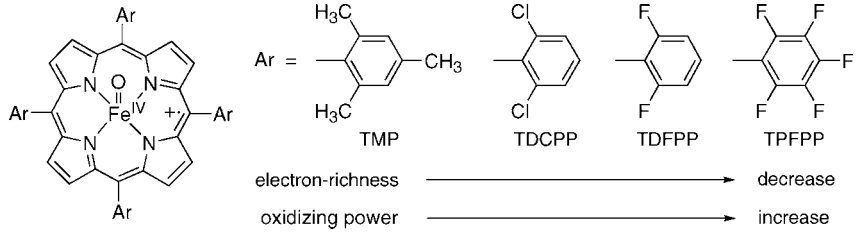
Scheme 1. Proposed Mechanisms for the Reactions of Iron Porphyrin Complexes



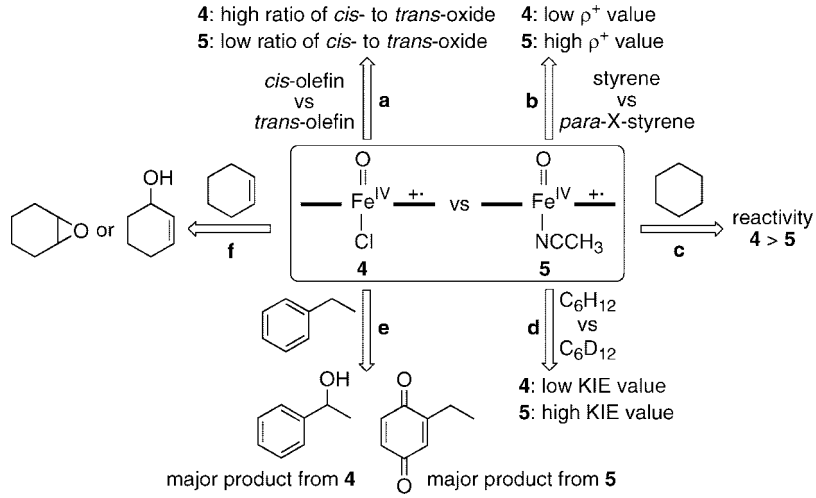
factor in activating the hydroperoxide O–O bond by iron porphyrin catalysts.[35,36]

Our research team has also been involved in elucidating mechanisms of O–O bond cleavage of (Porp)Fe^{III}-OOR (R = acyl, H, and alkyl) intermediates under various reaction conditions (Scheme 1, pathways A and B). While our current understanding of the O–O bond cleavage mechanism is quite advanced in the case where peroxyacids are used as oxidants, in which the O–O bond of peroxyacids is cleaved heterolytically by the iron porphyrin complexes,[37] the situation is less clear in the cases of biologically important oxidants such as hydrogen peroxide and alkyl hydroperoxides. Traylor and co-workers proposed that the O–O bond of **1** is heterolytically cleaved to

Scheme 2. Correlation between Electron Richness of Iron–Oxo Complexes and Their Reactivities



Scheme 3. Effects of Axial Ligands on the Reactivities of Iron(IV)–Oxo Porphyrin π-Cation Radicals[44]

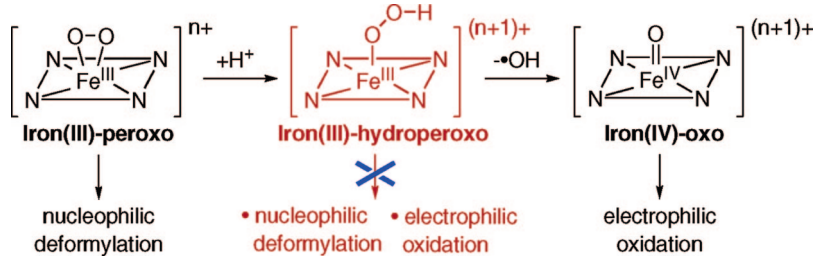


form **2** as reactive species in the epoxidation of olefins by H_2O_2 and *tert*-alkyl hydroperoxides in protic solvents (Scheme 1, pathway A).[32] In contract, Bruice and co-workers provided evidence that the initial step of the O–O bond cleavage of **1** is homolysis in aqueous and aprotic solvents, resulting in the formation of **3** and a hydroxyl radical (Scheme 1, pathway B).[38] Recently, we have provided experimental results which show that the hydroperoxide O–O bond can be cleaved both heterolytically and homolytically, depending on the conditions such as the electronic nature of iron porphyrin complexes (i.e., electronic properties of porphyrin and axial ligands) and the substituent of hydroperoxides, ROOH [R = C(O)R′, H, and CR_3 for peracids, H_2O_2, and alkyl hydroperoxides, respectively].[39] Other factors such as solvents also influence the modes of O–O bond cleavage (e.g., heterolysis in protic solvents and homolysis in aprotic solvents).

2.1. Reactivities of Iron(IV)–Oxo Porphyrins. In 1981, Groves and co-workers reported the synthesis and characterization of an iron(IV)–oxo porphyrin π-cation radical intermediate in the reaction of Fe(TMP)Cl (TMP = *meso*-tetramesitylporphyrin) and *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 and CH_3OH at –78 °C; the green species, formulated as $[(TMP)^{+\bullet}Fe^{IV}{=}O]^+$ on the basis of various spectroscopic measurements, was found to be a competent oxidant in olefin epoxidation.[40] Since then, iron(IV)–oxo porphyrin π-cation radicals bearing electron-rich and -deficient porphyrins and with different axial ligands have been prepared and studied in various oxidation reactions, in an effort to understand the electronic effects of porphyrin and axial ligands on the chemical properties of the iron–oxo intermediates.[41] As electron-deficient iron(III) porphyrin complexes are better catalysts in catalytic oxygenation reactions,[30,31] iron(IV)–oxo porphyrin π-cation radicals bearing electron-deficient porphyrin ligands exhibit high reactivities in hydrocarbon oxygenations.[41] This result indicates that the oxidizing power of iron–oxo porphyrins is controlled by the electronic nature of porphyrin ligands and that iron–oxo species with electron-deficient porphyrins are more powerful oxidants in the oxygenation of organic substrates (Scheme 2).[42]

The axial ligands bound *trans* to the iron–oxo moiety also markedly influence the reactivities of iron(IV)–oxo porphyrin π-cation radicals in olefin epoxidation and alkane hydroxylations. For example, Gross and Nimri reported a pronounced axial ligand effect on the epoxidation of olefins by $(TMP)^{+\bullet}Fe^{IV}(O)(X)$, in which $(TMP)^{+\bullet}Fe^{IV}(O)(X)$ complexes bearing ligating anionic ligands (e.g., F^-, Cl^-, and $CH_3CO_2^-$) showed a greater reactivity than those bearing nonligating anions (e.g., $CF_3SO_3^-$ and ClO_4^-) in the epoxidation of styrenes.[43] Very recently, we have demonstrated that iron(IV)–oxo porphyrin π-cation radicals, $(TPFPP)^{+\bullet}Fe^{IV}(O)(Cl)$ (**4**) and $(TPFPP)^{+\bullet}Fe^{IV}(O)(NCCH_3)$ (**5**) (Scheme 3), exhibit diverse reactivity patterns depending on the identity of axial ligands, such as in the selectivity of *cis*- versus *trans*-olefins (reaction a) and of styrene versus *para*-substituted styrenes (reaction b) in olefin epoxidation, the oxidizing power in alkane C–H bond activation (reaction c), the kinetic isotope effect (reaction d), and the regioselectivity of aromatic ring oxidation versus C–H bond hydroxylation in ethylbenzene hydroxylation (reaction e) and of C=C epoxidation versus C–H bond hydroxylation (reaction f) in olefin oxygenation.[44] These results demonstrate un-

Scheme 4. Reactions of Mononuclear Non-Heme Iron Intermediates[52]



ambiguously that iron(IV)–oxo porphyrin π-cation radicals can exhibit diverse reactivity patterns under different circumstances. Theoretical calculations provided plausible explanations for the role of axial ligands in tuning the reactivities of iron–oxo species,[45,46] in which the electron donating ability of axial ligands influences the Fe–O bond strength in the transition state[45] or the spin states of iron(IV)–oxo intermediates.[46] Since the electron donating property of the axial thiolate ligands in CYP 450 and chloroperoxidase (CPO) is believed to play a key role for the unique spectroscopic features of CPO and the strong oxidizing power of CYP 450 in the activation of C–H bonds,[47] continued extensive research is in progress to elucidate the axial ligand effects on the chemical and physical properties of iron(IV)–oxo intermediates in heme enzymes.

2.2. Multiple-Oxidants Hypothesis. In addition to the iron(IV)–oxo porphyrin π-cation radicals, oxidant–iron(III) porphyrin adducts (**1**) are proposed as active oxidants in electrophilic oxygenation reactions (see Scheme 1). Thus, there has been an intriguing, current controversy over the involvement of an iron(III)–hydroperoxo species as a "second electrophilic oxidant" in oxygenation reactions by heme and non-heme iron enzymes and their model compounds.[48–51] The primary evidence for proposing the multiple-oxidants hypothesis was that products and/or product distributions derived from the catalytic oxidations by CYP 450 and iron porphyrin models were different depending on reaction conditions such as catalysts (e.g., CYP 450 and their mutants), oxidants (e.g., H_2O_2, peracids, and iodosylarenes), and axial ligands of iron porphyrin catalysts (e.g., ligating and nonligating anions).[44,49,51] However, as we have discussed in the previous section, iron(IV)–oxo porphyrin π-cation radicals can exhibit diverse reactivity patterns under different circumstances, leading us to postulate that the different products and/or product distributions observed in iron porphyrin-catalyzed oxygenation reactions do not arise from the involvement of multiple oxidizing species but from a single oxidant under different environmental circumstances.[44] More strong experimental evidence for excluding the possibility of a "second electrophilic oxidant" in oxygen atom transfer reactions was obtained from the reactivity studies of iron(III)–hydroperoxo species in nucleophilic and electrophilic reactions, by using in situ-generated mononuclear non-heme iron(III)–hydroperoxo complexes that have been well characterized with various spectroscopic techniques.[52] In this study, non-heme iron(III)–hydroperoxo intermediates did not exhibit any reactivities in both nucleophilic (e.g., aldehyde deformylation) and electrophilic (e.g., oxidation of sulfide and olefin) reactions (Scheme 4), demonstrating that non-heme iron(III)–hydroperoxo species are sluggish oxidants and that the oxidizing power of the intermediates cannot compete with that of iron(IV)–oxo complexes. Similarly, reactivity, spectroscopic, and theoretical studies of a non-heme iron (III)–alkylperoxo complex, $[(TPA)Fe^{III}\text{-}OO^tBu]^{2+}$, revealed that this intermediate is not capable of oxygenating substrates and that a high-valent iron(IV)–oxo intermediate, which is generated via O–O bond homolysis of the Fe(III)-OOR species, is an active oxidant that effects the oxygenation of organic substrates.[53]

3. Mononuclear Non-Heme Iron(IV)–Oxo Complexes

While the first paper on the synthesis and characterization of an iron(IV)–oxo porphyrin π-cation radical appeared in 1981,[40] the first well-characterized mononuclear non-heme iron(IV)–oxo complex was reported in 2003.[15] The late discovery of the non-heme iron–oxo species was due to the difficulty in characterizing non-heme iron(IV)–oxo intermediates by routine spectroscopies like a UV–vis spectrophotometry; the generation of iron(IV)–oxo porphyrin π-cation radicals exhibits distinct UV–vis spectral changes of Soret and Q-bands in heme models. Nonetheless, the first high-resolution structure of an iron(IV)–oxo species was obtained in non-heme iron models (Figure 2);[15,23] the success of growing single crystals for X-ray crystallography analysis results from their greater thermal stability. With non-heme iron(IV)–oxo complexes firmly established by crystallography, significant progress has been made in the chemistry of non-heme iron(IV)–oxo intermediates over the past 4 years; ~15 non-heme iron(IV)–oxo complexes appeared in the literature in that time. In this Account, the reactivities of mononuclear non-heme iron(IV)–oxo complexes in a variety of oxidation reactions are discussed with a brief introduction about the synthesis and characterization of the intermediates.

3.1. Generation and Characterization of Non-Heme Iron(IV)–Oxo Complexes. Wieghardt and co-workers reported for the first time the generation of an iron(IV)–oxo intermediate in the reaction of $[Fe^{III}(cyclam\text{-}acetato)(CF_3SO_3)]^+$ and O_3 in acetone and water at –80 °C; the green species was characterized as a low-spin ($S = 1$) Fe(IV)–oxo intermediate based on Mössbauer analysis.[14] Subsequently, Münck, Nam, Que, and their coworkers reported the first X-ray crystal structure of a

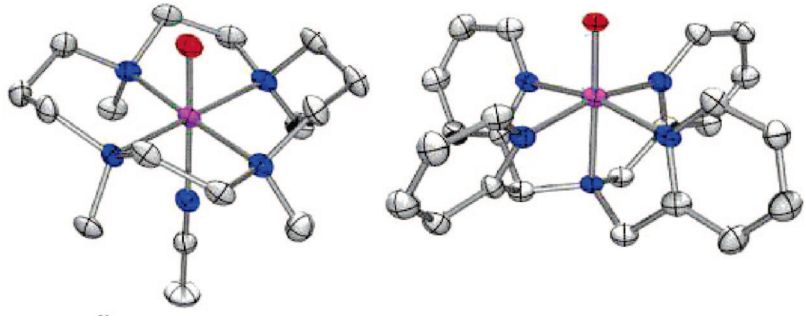


FIGURE 2. X-ray crystal structures of $[Fe^{IV}(TMC)(O)(NCCH_3)]^{2+}$ (left) and $[Fe^{IV}(N4Py)(O)]^{2+}$ (right). Atom colors: gray for carbon, blue for nitrogen, red for oxygen, and purple for iron. This figure is adapted from ref 8.

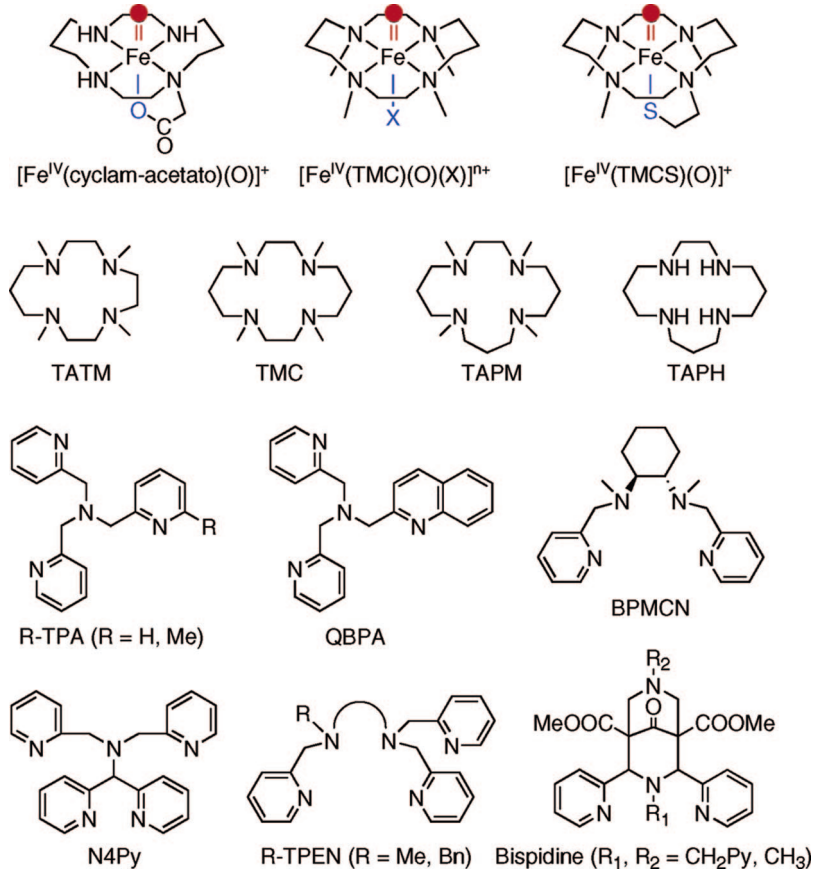


FIGURE 3. Structures of iron(IV)–oxo complexes and ligands. Abbreviations: cyclam-acetate, 1,4,8,11-tetraazacyclotetradecane 1-acetate;[14] TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane;[15] TMCS, 1-mercaptoethyl-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane;[22] TATM, 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclotridecane; TAPM, 1,4,8,12-tetramethyl-1,4,8,12-tetraazacyclopentadecane;[25] TAPH, 1,4,8,12-tetraazacyclopentadecane;[25] TPA, tris(2-pyridylmethyl)amine;[16] QBPA, (2-quinolylmethyl)bis(2-pyridylmethyl)amine; BPMCN, *N*,*N*-bis(2-pyridylmethyl)-*N*,*N*-dimethyl-*trans*-1,2-diaminocyclohexane; N4Py, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine;[17] R-TPEN, *N*-R-*N*,*N*′,*N*′-tris(2-pyridylmethyl)ethane-1,2-diamine;[17,27,28] Bispidine, 3,7-dimethyl-9,9′-dihydroxy-2,4-di(2-pyridyl)-3,7-diazabicyclononane-1,5-dicarboxylate.[55,60]

mononuclear non-heme iron(IV)–oxo complex that was generated in the reaction of $Fe^{II}(TMC)(CF_3SO_3)_2$ and PhIO in CH_3CN at –40 °C (Figure 2).[15] The pale green intermediate, characterized with various spectroscopic methods, such as UV–vis spectroscopy, electrospray ionization mass spectrometry, EPR, Mössbauer, resonance Raman, and magnetic circular dichroism, was assigned as $[(TMC)Fe^{IV}{=}O]^{2+}$ with a low-spin ($S = 1$) Fe(IV) center and a 1.646 Å Fe–O distance.[15,21,54] Since then, a handful of non-heme iron(IV)–oxo complexes have been synthesized using macrocyclic tetradentate N4, tripodal tetradentate N4, and pentadentate N5 and N4S ligands (Figure 3 for ligand structures).[5,8,14–28,55] The structural analysis of the intermediates by X-ray crystallography for $[(TMC)Fe^{IV}{=}O]^{2+}$ and $[(N4Py)Fe^{IV}{=}O]^{2+}$ (Figure 2) and extended X-ray absorption fine structure (EXAFS) for others revealed a short Fe–O bond distance of ~1.64 Å, indicating double-bond character between the iron ion and the oxygen atom.[15,23] The Fe–O double-bond character was further supported by ν(Fe–O) frequencies (e.g.,

Scheme 5. Generation of Iron(IV)–Oxo Complexes Using Different Oxidants

(a) Single oxygen atom donors

$$[(L)Fe^{II}]^{n+} + X\text{-}O \longrightarrow [(L)Fe^{IV}{=}O]^{n+} + X$$

(b) Hydroperoxides

$$[(L)Fe^{II}]^{n+} + ROOH \xrightarrow{Oxid.} [(L)Fe^{III}\text{-}OOR]^{n+} \longrightarrow [(L)Fe^{IV}{=}O]^{n+} + RO\bullet$$

(c) Molecular oxygen

$$2\,[(L)Fe^{II}]^{n+} + O_2 \longrightarrow [(L)Fe^{III}\text{-}O\text{-}O\text{-}Fe^{III}(L)]^{2n+} \longrightarrow 2\,[(L)Fe^{IV}{=}O]^{n+}$$

$\sim$830 cm^{-1}) of $[Fe^{IV}(TMC)(O)(X)]^{n+}$ complexes.[15,21] Mössbauer analysis indicates a low-spin ($S = 1$) Fe(IV) oxidation state for all of the synthetic non-heme iron(IV)–oxo complexes except $[(H_2O)_5Fe^{IV}{=}O]^{2+}$ which has a high-spin ($S = 2$) state of Fe(IV) in acidic aqueous media.[57] In enzymes, an iron(IV)–oxo intermediate identified in TauD has a 1.62 Å Fe–O distance and a high-spin ($S = 2$) Fe(IV) center.[10] Interestingly, low-spin Fe(IV)–oxo complexes exhibit characteristic near-IR absorption bands between 650 and 1050 nm with low extinction coefficients (ε_{max} of 250–400 M^{-1} cm^{-1}),[8] and it turns out that the IR features serve as a convenient spectral signature in forecasting the formation of low-spin iron(IV)–oxo species.

Various oxygen atom donors were used in generating the iron(IV)–oxo complexes, such as PhIO,[15,17,18,21,25,55] peracids (e.g., *m*-CPBA and peracetic acid),[15,16,18,22,28] $KHSO_5$,[18] O_3,[14,56] and NaOX (X = Cl or Br)[27] as single-oxygen atom donors, hydroperoxides (e.g., H_2O_2 and *tert*-butyl hydroperoxide),[15,18,57] and molecular oxygen (Scheme 5).[19] While two-electron oxidation of Fe(II) to the Fe(IV)–oxo species was proposed in the reactions of single-oxygen atom donors (reaction a),[15,16] Fe(III)–OOR species was homolytically cleaved to form Fe(IV)–O species in the reactions of hydroperoxides (reaction b).[53,57] In the case of O_2 activation (reaction c), we found that the structures of iron(II) complexes and solvents (e.g., alcohols) are important factors in generating iron(IV)–oxo species by activating O_2.[19] A mechanism was proposed in which two molecules of an iron(II) complex react with O_2 to give two molecules of an iron(IV)–oxo species. This mechanism is similar to the O_2 activation by iron(II) porphyrins[58] and relevant to the catalytic cycle of methane monooxygenases (MMOs).[59] In the latter reaction, a dinuclear non-heme iron(II) complex activates O_2 to form a di(μ-oxo)diiron(IV) intermediate that effects the hydroxylation of organic substrates, including CH_4.

The stability of non-heme iron(IV)–oxo complexes is dependent on ligand structures. For example, $[(TMC)Fe^{IV}{=}O]^{2+}$ and $[(N4Py)Fe^{IV}{=}O]^{2+}$ are thermally stable even at room temperature,[15,17] whereas $[(TPA)Fe^{IV}{=}O]^{2+}$ is stable only at low temperatures (e.g., −40 °C).[16] Also, the stability of iron(IV)–oxo species is markedly dependent on the pH of reaction solutions;[18,56,60] $[(N4Py)Fe^{IV}{=}O]^{2+}$ is stable at low pH (i.e., pH 5–6) but decays at a fast rate with an increase in the pH of the reaction solutions.[18] Further, iron–oxo complexes exhibit different reactivities in oxidation reactions, depending on the ligand structures. While $[(TMC)Fe^{IV}{=}O]^{2+}$ oxygenates Ph_3P to Ph_3PO,[15,21] $[(N4Py)Fe^{IV}{=}O]^{2+}$ shows the capability of oxidizing the C–H bonds of cyclohexane at room temperature.[17] Furthermore, as we have observed in iron(IV)–oxo porphyrin π-cation radicals,[43,44] the reactivity of non-heme iron(IV)–oxo complexes is markedly influenced by the axial ligands bound *trans* to the iron–oxo group.[21,22,61] As a conclusion, we have demonstrated that the stability and reactivity of non-heme iron(IV)–oxo intermediates are sensitive to the structure of iron complexes, the axial ligand bound to iron ion, and the pH of reaction solutions. With the results, we were able to investigate the reactivities of nonheme iron(IV)-oxo complexes in a variety of oxidation reactions in detail.

3.2. Non-Heme Iron(IV)–Oxo Complexes in Oxidation Reactions. The first clear example that non-heme iron(IV)–oxo complexes are capable of transferring their oxygen atom to organic substrates was the oxidation of Ph_3P by $[(TMC)Fe^{IV}{=}O]^{2+}$, yielding Ph_3PO quantitatively (Figure 4, *P*-oxidation).[15] Subsequently, it was demonstrated that an iron(IV)–oxo complex, $[(TPA)Fe^{IV}{=}O]^{2+}$, reacts with cyclooctene to give cyclooctene oxide at –40 °C (Figure 4, alkene epoxidation).[16] Similarly, Girerd and co-workers reported the epoxidation of olefins by $[(Bn\text{-}TPEN)Fe^{IV}{=}O]^{2+}$, in which cyclooctene oxide and *trans*-stilbene oxide were produced in the epoxidation of cyclooctene and *cis*-stilbene, respectively.[27] More recently, we have shown that non-heme iron(IV)–oxo complexes, $[(TPA)Fe^{IV}{=}O]^{2+}$, $[(Bn\text{-}TPEN)Fe^{IV}{=}O]^{2+}$, $[(TPA)Fe^{IV}{=}O]^{2+}$, and $[(TMC)Fe^{IV}{=}O]^{2+}$, are capable of oxygenating sulfides to the corresponding sulfoxides (Figure 4, *S*-oxidation).[18,19,52] In the sulfide oxidation, the relative reactivities of the iron–oxo species were in the following order: $[(TPA)Fe^{IV}{=}O]^{2+}$ > $[(Bn\text{-}TPEN)Fe^{IV}{=}O]^{2+}$ > $[(N4Py)Fe^{IV}{=}O]^{2+}$ > $[(TMC)Fe^{IV}{=}O]^{2+}$.[52] The reaction rates were significantly dependent on the electron donating ability of *para* substituents (i.e., Hammett ρ values between −1.4 and −2.5).[18,52]

The most striking observation made in oxygenation reactions by non-heme iron(IV)–oxo complexes was the hydroxylation of alkanes by $[(N4Py)Fe^{IV}{=}O]^{2+}$ and $[(Bn\text{-}TPEN)Fe^{IV}{=}O]^{2+}$ (Figure 4, aliphatic hydroxylation).[17] The iron(IV)–oxo complexes bearing pentadentate N5 ligands were thermally stable even at room temperature but capable of hydroxylating C–H bonds as strong as those in cyclohexane. More significantly, a large KIE of >30 was observed in the hydroxylation of ethylbenzenes, C_8H_{10} and C_8D_{10}.[17] Such a large KIE implies that the C–H bond activation by non-heme iron(IV)–oxo species occurs via a hydrogen atom abstraction mechanism (Scheme 6).[62] In non-heme iron enzymes, large isotope effects were observed in H-atom abstraction reactions by the iron(IV) intermediates of the monoiron TauD (i.e., KIE of $\sim$37)[13] and the diiron MMO (i.e., KIE of >50).[63]

A large KIE of $\sim$50 was also observed in the oxidation of benzyl alcohol by non-heme iron(IV)–oxo complexes, $[(TPA)Fe^{IV}{=}O]^{2+}$ and $[(N4Py)Fe^{IV}{=}O]^{2+}$ (Figure 4, alcohol oxidation).[20] Such a large KIE value indicates that non-heme iron(IV)–oxo intermediates activate alcohols exclusively by H-atom abstraction from the α-CH group of

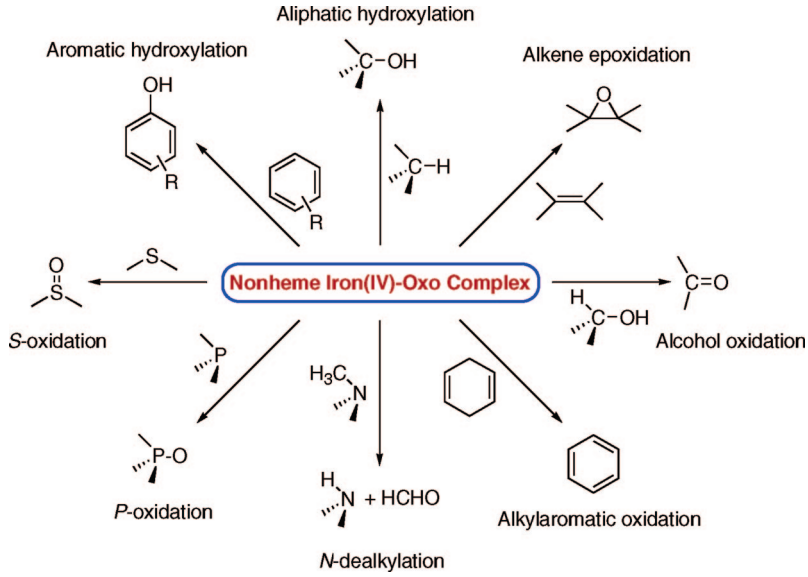
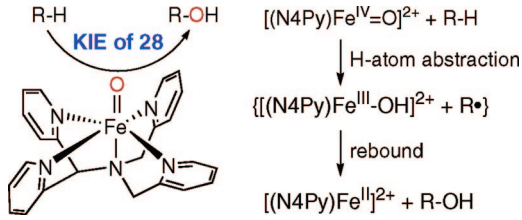
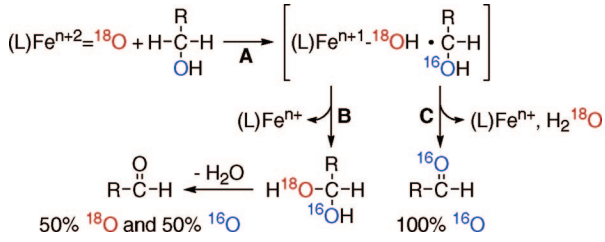


FIGURE 4. Oxidation reactions mediated by mononuclear non-heme iron(IV)–oxo complexes.

Scheme 6. Alkane Hydroxylation by an Iron(IV)–Oxo Complex[17]



Scheme 7. Proposed Mechanism for Alcohol Oxidation by Iron(IV)–Oxo Species[20]

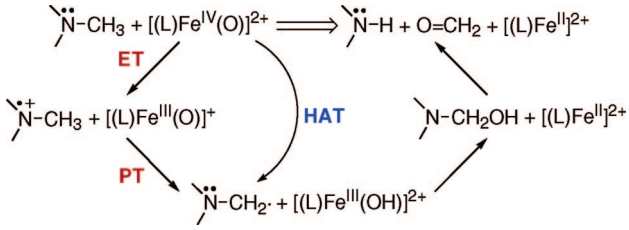


benzyl alcohol (Scheme 7, pathway A) and that C–H bond cleavage is the rate-determining step. The mechanism of the alcohol oxidation was further investigated with an ^{18}O-labeled iron(IV)–oxo complex, [(N4Py)Fe^{IV}=^{18}O]$^{2+}$, to understand whether the final step of the alcohol oxidation occurs via a *gem*-diol dehydration or a dual-hydrogen abstraction process. The product formed in the ^{18}O-labeled experiment contained only a trace amount of ^{18}O, supporting the possibility that the alcohol oxidation by non-heme iron(IV)–oxo complexes occurs via a dual-hydrogen abstraction mechanism (Scheme 7, pathway C), not via a *gem*-diol dehydration process (Scheme 7, pathway B).[20]

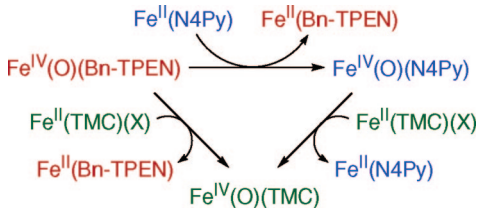
In contrast to the alkane hydroxylation and alcohol oxidation, we have obtained a low KIE value of ~0.9 in the hydroxylation of aromatic compounds by non-heme iron(IV)–oxo complexes (Figure 4, aromatic hydroxylation).[64] In the hydroxylation of anthracene by [(N4Py)Fe^{IV}=O]$^{2+}$ and [(Bn-TPEN)Fe^{IV}=O]$^{2+}$, anthraquinone was produced in high yields. We also found the electron donating ability of *para* substituents on anthracene influences reaction rates significantly, affording a large Hammett ρ value of –3.9. Such a large negative ρ value implies that the iron–oxo group attacks the aromatic ring via an electrophilic pathway. Further, the calculated k_H/k_D values of ~0.9, determined kinetically in the hydroxylation of anthracene and deuterated anthracene, indicate an inverse KIE in the aromatic ring oxidation reactions; the observation of the inverse KIE is consistent with the sp^2-to-sp^3 hybridization change during the addition of an electrophilic iron–oxo group to the sp^2 center of the aromatic ring to form a σ adduct.[65] On the basis of the large negative Hammett ρ and inverse KIE values, we have proposed that the aromatic ring oxidation does not occur via a hydrogen atom abstraction mechanism but involves an initial electrophilic attack on the π-system of the aromatic ring to produce a tetrahedral radical or cationic σ-complex.[64,65]

Non-heme iron enzymes participate in oxidative N-dealkylation reactions in nature, and high-valent iron(IV)–oxo species have been invoked as an active oxidant that effects the oxygenation of organic substrates.[66] We therefore performed oxidative N-dealkylation of *N*,*N*-dialkylamines with non-heme iron(IV)–oxo complexes. In the oxidative N-dealkylation of *N*,*N*-dimethylaniline by [(N4Py)Fe^{IV}=O]$^{2+}$ and [(TMC)Fe^{IV}=O]$^{2+}$, *N*-methylaniline was produced as a major product with the concurrent formation of CH_2O.[26] Detailed mechanistic studies were carried out in an effort to understand whether the oxidative N-dealkylation occurs via an electron transfer–proton transfer (ET–PT) mechanism or a hydrogen atom transfer (HAT) (Scheme 8).[67] On the basis of the results of a linear free energy correlation (e.g., Hammett ρ values of approximately –2.5), inter- and intramolecular kinetic isotope effects (e.g., KIE values of <5), and product analysis with mechanistic probes, the oxidative N-dealkylation reactions by non-heme iron(IV)–oxo complexes were proposed to occur via an ET–PT mechanism (Scheme 8).[26]

Scheme 8. Proposed Mechanisms for Oxidative N-Demethylation by Fe(IV)–Oxo Complexes[26]



Scheme 9. Oxygen Atom Transfer between Nonheme Iron Complexes[24]



In addition to the oxygenation of organic substrates, we have reported the first example of the transfer of an oxygen atom between non-heme iron(IV)–oxo and iron(II) complexes (i.e., complete intermetal oxygen atom transfer).[24] This observation is contrary to the case of iron porphyrins, in which the reaction of iron(IV)–oxo and iron(II) porphyrins resulted in the generation of μ-oxo-bridged iron(III) porphyrin dimers (i.e., incomplete intermetal oxygen atom transfer).[68] The oxygen atom transfer was found to depend on the oxidizing power of the iron(IV)–oxo complexes (Scheme 9); the oxidizing power of iron(IV)–oxo complexes was determined to be on the order of $[(\text{Bn-TPEN})\text{Fe}^{\text{IV}}{=}\text{O}]^{2+}$ > $[(\text{N4Py})\text{Fe}^{\text{IV}}{=}\text{O}]^{2+}$ > $[(\text{TMC})\text{Fe}^{\text{IV}}{=}\text{O}]^{2+}$ in sulfide oxidation reactions.[52] Detailed investigations aimed at illustrating the mechanism of complete intermetal oxygen atom transfer from iron(IV)–oxo to iron(II) complexes are currently underway in this laboratory.

4. Concluding Remarks

In this Account, efforts to understand the reactivities and mechanisms of iron(IV)–oxo porphyrin π-cation radicals and non-heme iron(IV)–oxo complexes in oxygenation reactions over the past 7 years have been reviewed. In the part of iron(IV)–oxo porphyrin π-cation radicals, we have demonstrated that there are significant porphyrin and axial ligand effects on the catalytic oxygenation of hydrocarbons by hydroperoxides, the activation of the hydroperoxide O–O bond, and the oxidizing power of iron–oxo complexes in oxygenation reactions. A current controversy about the multiple-oxidants hypothesis in catalytic oxygenation reactions (i.e., ferric–hydroperoxide species as a "second electrophilic oxidant") has been addressed, and we have proposed that ferric–hydroperoxo species are not active oxidants in electrophilic oxidation reactions.

Our non-heme iron(IV)–oxo studies were initiated with the success of obtaining the first crystal structure of a mononuclear non-heme iron(IV)–oxo complex with the groups of Que and Münck. Despite a short history of non-heme iron(IV)–oxo species, significant developments were made in characterizing the intermediates and understanding their reactivities in a variety of oxygenation reactions. The reactions depicted in Figure 4 clearly demonstrate that mononuclear non-heme iron(IV)–oxo complexes are involved in diverse oxygenation reactions. The next challenging target in biomimetic studies of non-heme iron enzymes is to understand the reactivities of the recently discovered non-heme iron(V)–oxo intermediate.[69]

As mentioned above, we have observed the great advances in elucidating the chemistry of heme and non-heme iron(IV)–oxo complexes. However, continued extensive research is needed to clarify the currently unanswered questions in both enzymatic and biomimetic reactions, such as the role(s) of the axial–thiolate ligand of $(\text{Porp})^{+\bullet}\text{Fe}^{\text{IV}}(\text{O})(\text{S-Cys})$ in activating C–H bonds of hydrocarbons by CYP 450, the involvement of multiple oxidants in the catalytic oxygenation of organic substrates by heme and non-heme iron complexes, and the effect(s) of the heme and non-heme ligands and the axial ligands on the reactivities of iron(IV)–oxo species in oxygenation reactions. Especially, it is of interest to understand why enzymes with iron active sites utilize heme and non-heme ligands in oxygenation reactions [e.g., the role(s) of heme and non-heme ligands in governing and tuning the oxidizing power of iron–oxo intermediates]. Without a doubt, our next Account will provide exciting discoveries to answer the currently unanswered questions and new mechanistic insights into the oxygenation reactions by heme and non-heme iron(IV)– and iron(V)–oxo complexes.

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