

The Road to Non-Heme Oxoferryls and Beyond[†]

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ABSTRACT

Oxoiron(IV) species are often implicated in the catalytic cycles of oxygen-activating non-heme iron enzymes. The paucity of suitable model complexes stimulated us to fill this void, and our synthetic efforts have afforded a number of oxoiron(IV) complexes. This Account provides a chronological perspective of the observations that contributed to the generation of the first non-heme iron(IV)–oxo complexes in high yield and summarizes their salient properties to date.

1. Introduction

Oxoferryl species are often postulated as the key oxidizing intermediates in the dioxygen activation mechanisms of iron enzymes.^{1–4} Evidence that such species were involved in the reactions of heme peroxidases was found as many as 40 years ago, and extensive spectroscopic investigations have established the existence of the Fe^{IV}=O unit in many cases. By extension, it is widely accepted that an oxoferryl species is a key intermediate in the mechanism of cytochrome P450.^{1,5} However the evidence for its existence is not as compelling as for the heme peroxidases, and efforts persist to put this mechanistic hypothesis on firmer ground.

Non-heme iron oxygenases also activate dioxygen but catalyze an array of oxidative transformations more diverse than those associated with their heme counterparts.^{2–4} To date, high-valent iron intermediates have been trapped in five cases, and structures proposed for these species are shown in Figure 1. In the 1990s, rapid freeze-quench studies of the R2 protein of the class I ribonucleotide reductase (RNR R2) from *Escherichia coli* and methane monooxygenase (MMO) provided evidence for intermediates **X** and **Q**,² respectively, with **X** having an Fe^{III}–O–Fe^{IV} unit^{6,7} and **Q** postulated to have an Fe^{IV}₂(μ-O)₂ diamond core.⁸ Within the last four years, Fe^{IV}=O intermediates have been characterized for taurine/2-oxoglutarate dioxygenase (TauD), prolyl 4-hydroxylase,

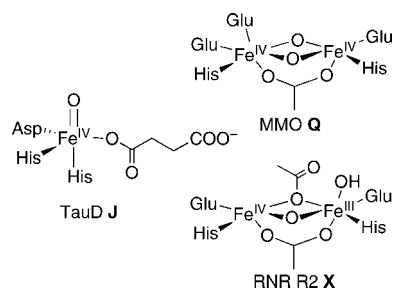


FIGURE 1. Structures proposed for high-valent intermediates of TauD,¹⁰ MMO,⁸ and RNR R2.^{6,7}

and the halogenase CytC3, monoiron enzymes that require 2-oxoglutarate as a cosubstrate.^{9–12} In all cases, the iron(IV) center has been found to be in the high-spin $S = 2$ state, presumably due to the weak ligand field exerted by a combination of histidine and carboxylate ligands.

2. Precedents in the 1990s

The pioneer in the coordination chemistry of iron(IV) with biomimetic non-heme ligands was T. J. Collins, in whose group was developed a series of oxidatively robust tetra-amido macrocyclic ligands (TAMLs; Figure 2) that in their tetraanionic forms were capable of supporting high-valent metal centers.¹³ This effort led in 1990 to the isolation of [Fe^{IV}(TAML1)Cl][–], the first and only example to date of a crystallographically characterized high-spin iron(IV) complex.¹⁴ Subsequently, Collins' work resulted in a number of exciting developments and applications that have been reviewed recently.¹⁵ Among those particularly relevant to this Account are the formation of an oxo-bridged di-iron(IV) complex from the reaction of O₂ and an iron(III) precursor reported in 2005¹⁶ and the trapping and characterization of the first oxoiron(V) complex reported in 2007.¹⁷

Also in the 1990s, Ingold and co-workers obtained indirect evidence that oxoiron(IV) species could form in solution from studies of Fe(TPA)-catalyzed alkane functionalization with ^tBuOOH as an oxidant.¹⁸ In subsequent experiments, the putative (TPA)Fe^{IV}=O species could be intercepted intermolecularly by the addition of thioanisole to form the corresponding sulfoxide¹⁹ (Figure 3, R = H) or intramolecularly when a 6-Ph substituent was introduced (Figure 3, R = Ph) to afford a hydroxylated arene ring.^{20,21} On the other hand, direct evidence of the existence of oxoiron(IV) species could be obtained by ESIMS (electrospray ionization mass spectrometry) analysis of metastable Fe^{III}–OOH species supported by neutral tetra- and pentadentate nitrogen ligands, revealing (L)Fe^{IV}=O fragments derived from the molecular ions in the gas phase.^{22,23}

The most compelling precedent that an oxoiron(IV) center could be supported by a neutral TPA ligand came from the generation and characterization of a family of

Larry Que grew up in Manila and went to the University of Minnesota for graduate studies, receiving his Ph.D. in chemistry in 1973. After a postdoctoral stint with Richard Holm at the Massachusetts Institute of Technology, he returned to Minnesota to work in Eckard Münck's lab where his long-term interest in how biological non-heme iron centers activate dioxygen was kindled. This interest continued to grow in his independent career that led first to Cornell University and then back again to Minnesota. His interactions with Eckard continued in this period and only grew stronger with time. Larry's achievements in high-valent non-heme iron chemistry could not have been realized without Eckard's enthusiastic collaboration over these 33 years. (*Thank you very much, Eckard; not only are you an outstanding scientist, you have also been a wonderful mentor and staunch friend.*)

[†] In celebration of Eckard Münck and his 2007 Alfred Bader Award in Bioinorganic Chemistry.

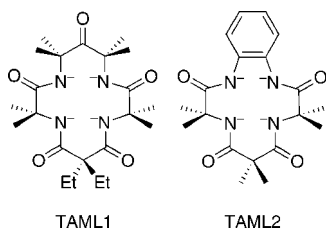


FIGURE 2. Structures of TAML ligands.

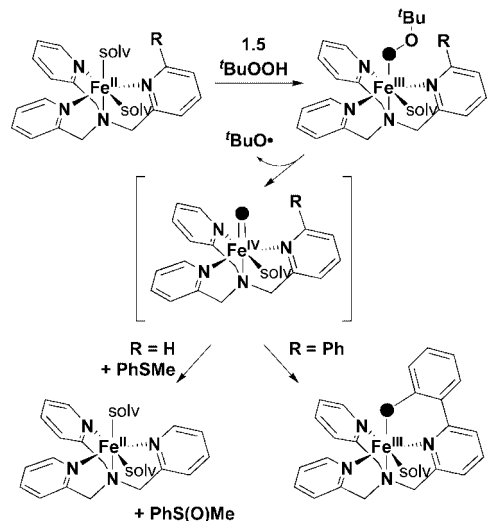


FIGURE 3. Reactions of $[\text{Fe}^{\text{II}}(\text{TPA})(\text{NCCH}_3)_2]^{2+}$ complexes with $^t\text{BuOOH}$.

$[\text{Fe}_2(\mu\text{-O})_2(5\text{-R}_3\text{-TPA})_2](\text{ClO}_4)_3$ complexes, initially investigated by R. Leising and Y. Dong²⁴ and crystallographically characterized subsequently by H. Hsu²⁵ (Figure 4). The crystal structure of the R = Et complex revealed a diiron complex with a centrosymmetric $\text{Fe}_2(\mu\text{-O})_2$ diamond core. Despite the fact that it was formally an iron(III)iron(IV) complex, Mössbauer analysis showed the two irons to be electronically identical,²⁴ requiring the $[\text{Fe}_2(\mu\text{-O})_2]^{3+}$ core to be valence-delocalized, with each iron having an oxidation state of 3.5.

3. Non-Heme Oxoiron(IV) Complexes Generated and Identified

Given these precedents in the 1990s, an obvious question that may occur to the reader is why it has taken so long to prepare mononuclear non-heme oxoiron(IV) complexes. The biggest impediment to progress in identifying and trapping a transient iron(IV)–oxo species was the lack of a convenient spectroscopic signature that would readily signal its presence in a reaction mixture. Although oxoiron(IV) porphyrin complexes had been well characterized for some time,²⁶ their UV–vis spectra were dominated by intense porphyrin ligand transitions that obscured weaker bands that may be associated with the $\text{Fe}^{\text{IV}}=\text{O}$ unit. The expected silence of the d^4 electronic configuration made EPR useless as an initial probe. While Mössbauer spectroscopy is often the tool of choice for establishing iron oxidation state,²⁷ this technique when applied to millimolar samples requires ^{57}Fe -enriched complexes to be synthesized. This presents a significant experimental

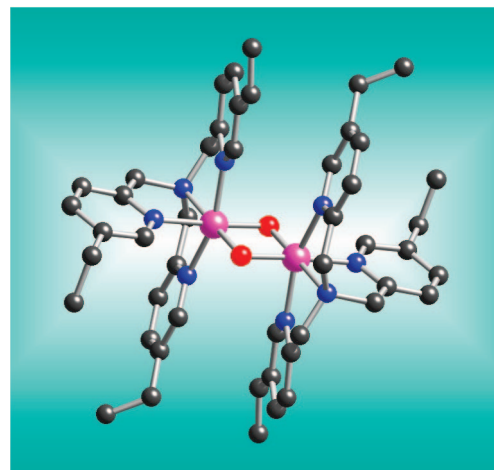


FIGURE 4. Crystal structure of the $[\text{Fe}_2(\mu\text{-O})_2(5\text{-Et}_3\text{-TPA})_2]^{3+}$ cation based on crystallographic data reported in ref 24.

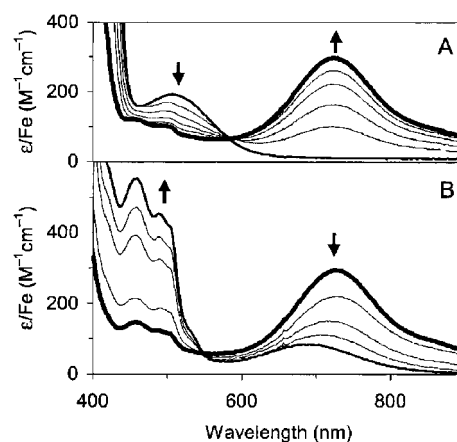


FIGURE 5. Reaction of $[\text{Fe}^{\text{II}}(\text{TPA})(\text{NCMe})_2]^{2+}$ with stoichiometric peracid in MeCN at $-40\text{ }^\circ\text{C}$ to form a new transient species with a λ_{max} of 720 nm (A) and its subsequent decay at $10\text{ }^\circ\text{C}$ (B). Reprinted with permission from ref 28. Copyright 2003 National Academy of Sciences.

barrier, as ^{57}Fe is not inexpensive and a procedure for synthesis on a submicromole scale must be developed. Typically, the synthesis of ^{57}Fe -enriched complexes is carried out only after there is some compelling evidence that something will be learned from the Mössbauer experiment.

In 1998, R. Ho in my lab carried out the reaction of $[\text{Fe}^{\text{II}}(\text{TPA})(\text{NCMe})_2]^{2+}$ with stoichiometric peracid in MeCN at $-40\text{ }^\circ\text{C}$ and observed a transient absorbance at 720 nm (Figure 5A). However, the new band had a low intensity with an estimated ϵ of $\sim 200\text{ M}^{-1}\text{ cm}^{-1}$ assuming all iron in the sample was converted to the new species. The appearance of the near-IR band led us to suspect the formation of a new species, but we had no clue at that time that it might be an oxoiron(IV) complex, given our naive expectation that an oxoiron(IV) unit should give rise to an intense oxo-to-iron(IV) charge transfer band in the visible region.

Four years later, W. Nam of Ehwa Womans University came to spend his sabbatical at the University of Minnesota. The students he brought along to Minnesota and mine worked together to make the observations that led

to the generation of the first well-characterized oxoiron(IV) complexes. M. H. Lim re-examined the reaction of $[\text{Fe}^{\text{I}}(\text{TPA})(\text{NCMe})_2]^{2+}$ with stoichiometric peracid in MeCN at -40°C and reproduced the earlier observations.²⁸ She further found conditions that allowed the new species with a λ_{max} at 720 nm to persist for 24 h at this temperature and noted its subsequent decay at higher temperatures. The decay product had a visible spectrum (Figure 5B) easily attributed to a complex with a (μ -oxo)(μ -carboxylato)diiron(III) core that had been characterized in our lab since the late 1980s.²⁹ Very importantly, the conversion of the 720 nm species to this byproduct showed isosbestic behavior. This key observation led us to realize that the new species did not in fact possess an intense chromophore and that it represented a substantial fraction of what was present in the reaction solution!

Further spectroscopic work identified the new species as an oxoiron(IV) complex.²⁸ ESIMS analysis of solutions containing the 720 nm species showed the most prominent ion to have an m/z value (461) and isotope distribution pattern consistent with the composition $[\text{Fe}(\text{O})(\text{TPA})(\text{ClO}_4)]^+$. With strong preliminary evidence for a novel intermediate, the ^{57}Fe -enriched iron(II) precursor complex was quickly synthesized and a ^{57}Fe -enriched sample of the new species was generated to ascertain the iron oxidation state of the new species. Its Mössbauer spectrum revealed a quadrupole doublet representing a large fraction (80%) of the sample with an isomer shift of 0.01 mm/s and a quadrupole splitting of 0.92 mm/s, parameters that can be assigned to an iron(IV) center. Subsequent high-field analysis assigned the iron center to be $S = 1 \text{ Fe}^{\text{IV}}$. In this manner was the first high-yield synthesis of a non-heme oxoiron(IV) complex ascertained.

With a convenient near-IR spectral signature in hand, work on other oxoiron(IV) complexes proceeded, and a number of complexes were subsequently generated.³⁰ J.-U. Rohde, J.-H. In, and M. Hee Lim collaborated on the corresponding TMC complex and found that the oxoiron(IV) species formed very readily by treatment of $[\text{Fe}^{\text{II}}(\text{TMC})(\text{OTf})_2]$ with PhIO. This oxoiron(IV) complex was unexpectedly quite stable, having a lifetime of at least a month at -40°C ($t_{1/2} \sim 10 \text{ h}$ at 25°C), which allowed diffraction-quality crystals to be obtained.³¹ The crystal structure of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCMe})]^{2+}$ shown in Figure 6 (top) represents the first for this class of complexes. Subsequently, J. Kaizer also obtained diffraction-quality crystals for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$, another thermally stable complex ($t_{1/2} \sim 60 \text{ h}$ at 25°C) (Figure 6, bottom).^{32,33} The $\text{Fe}=\text{O}$ units in the two complexes exhibit bond lengths of 1.646 and 1.636 Å, respectively, comparable to those of oxoiron(IV) porphyrin intermediates^{34,35} and flanked by the 1.813(3) Å distance of Borovik's oxoiron(III) complex³⁶ and the 1.58 Å distance of Collins' oxoiron(V) complex.¹⁷ DFT calculations paint a picture of a highly covalent iron-oxo double bond with significant unpaired spin density on the oxo atom.³⁷⁻³⁹

Figure 7 shows a sampling of the tetradentate and pentadentate non-heme ligands that can support the $S = 1$ oxoiron(IV) unit.^{28,31,32,40-48} These complexes can in

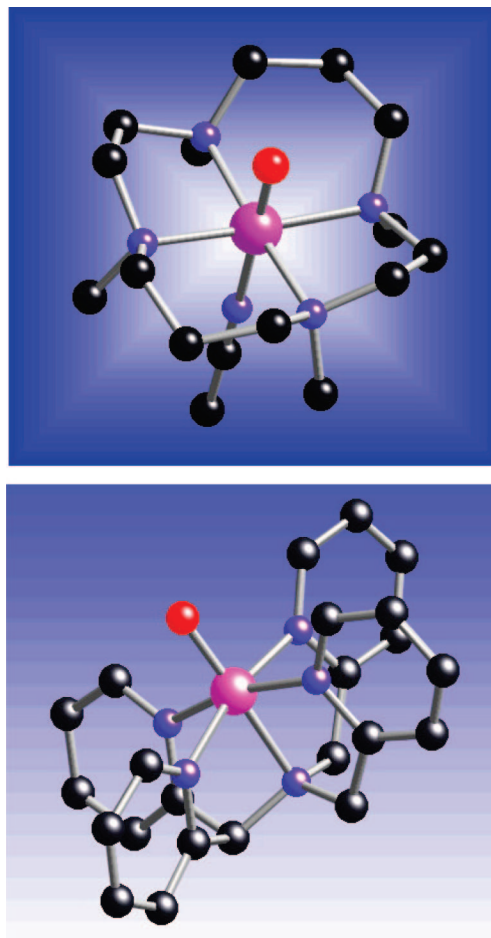


FIGURE 6. Structures of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCCH}_3)]^{2+}$ (top) and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$ (bottom) based on crystallographic data reported in refs 31 and 33, respectively.

general be prepared by the reaction of the iron(II) precursor with an oxygen atom donor such as a peracid or PhIO but can in some cases be obtained from the decomposition of corresponding $\text{Fe}^{\text{III}}\text{-OOR}$ species by O–O bond homolysis.^{42,49} For several complexes that have not been crystallized, EXAFS analysis has been used to establish the presence of a short ($\sim 1.65 \text{ \AA}$) $\text{Fe}=\text{O}$ bond.^{42,43,50,51} From this collection of ligands, it is clear that the $\text{Fe}^{\text{IV}}=\text{O}$ unit can be supported by a combination of four amine and/or pyridine ligands in a planar or nonplanar arrangement, with the oxo either *cis* or *trans* to a fifth variable ligand site in the case of a tetradentate ligand. The fifth ligand can be NCMe, an amine, a carboxylate, a halide (or pseudohalide), or a thiolate, affording complexes with a range of properties. Our oxoiron(IV) work was in fact preceded by that of Wieghardt and co-workers, who first observed this new type of complex in 2000 in the reaction of the iron(III) complex of the pentadentate cyclam acetate ligand with O_3 at -80°C .⁴⁰ However, the low yield of complex formation ($<25\%$) prevented a definitive structural assignment.

Mössbauer spectroscopy played an absolutely essential role by establishing the iron oxidation state of this new class of complexes. A. Stubna and E. Münck at Carnegie Mellon University were enthusiastic collaborators in our

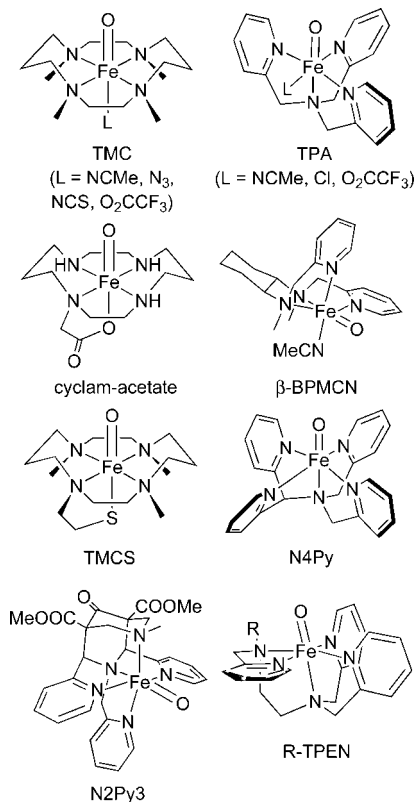


FIGURE 7. Sampling of the oxoiron(IV) complexes prepared since 2000.

efforts. With a d^4 electronic configuration, a mononuclear iron(IV) center would be expected to exhibit a simple quadrupole doublet in dilute solution at 4.2 K. This was indeed observed for the non-heme oxoiron(IV) complexes, and the quadrupole doublets were characterized with isomer shifts that range from 0.2 mm/s for the amine-rich TMC complexes to -0.04 mm/s for the pyridine-rich N4Py complex (Table 1). However, the isomer shift value alone is insufficient for establishing the oxidation and spin state of the iron center. By application of a large magnetic field, the quadrupole doublet splits into many more peaks due to magnetic hyperfine interactions between the d electrons and the ^{57}Fe nucleus that further characterize the iron center. Analysis of these features allows an $S = 1$ and an $S = 2$ iron(IV) center to be distinguished.

We now turn to the nature of the near-IR band that is found in all non-heme $S = 1$ oxoiron(IV) centers characterized thus far and serves as a convenient spectroscopic signature. As shown in the bottom panel of Figure 8, this feature has a moderate extinction coefficient of $\sim 400 \text{ M}^{-1} \text{ cm}^{-1}$ and shifts from 824 nm for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCMe})]^{2+}$ to 739 nm for $[\text{Fe}^{\text{IV}}(\text{O})(\text{BnTPEN})]^{2+}$ and to 695 nm for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$. On the basis of a MCD analysis of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCMe})]^{2+}$ by A. Decker and E. Solomon of Stanford University,³⁸ these bands were assigned to three of the five ligand field transitions expected of a low-spin iron(IV) center with C_{4v} symmetry. The progressive blue shift observed upon replacement of amine ligands with pyridines is consistent with increasing ligand field strength in the series TMC, BnTPEN, and N4Py. Upon replacement of the axial MeCN with azide or thiolate, some of these

transitions red-shift (Figure 11 bottom), as would be expected for the replacement of the strong field MeCN ligand with weaker field anionic ligands.^{52,53}

It is interesting to note that the visible regions of dicationic TMC, BnTPEN, and N4Py complexes show no intense feature that one might attribute to an oxo-to-iron(IV) charge transfer transition (Figure 8, top). This transition presumably is at higher energy than what we had naively expected. Indeed, the onset of intense transitions in the near-UV region can be observed below 400 nm. However, when the axial MeCN ligand of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCCH}_3)]^{2+}$ is replaced by pseudohalides like azide or thiocyanate, an intense feature near 400 nm appears that must be ligand-to-metal charge transfer (LMCT) in nature.⁵³ The assignment for this band is unclear at present. Laser excitation into this band for the azide complex results in the observation of an enhanced Raman mode at 812 cm^{-1} {vs 834 cm^{-1} for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCCH}_3)]^{2+}$ obtained by IR}, with an ^{18}O isotope shift expected for the $\nu(\text{Fe}=\text{O})$ mode, but no vibrational feature that can be associated with the azide ligand.⁵³ While this observation may lead one to associate the near-UV band with the oxo-to-iron(IV) LMCT band, two observations suggest caution in making this assignment. Such an assignment would then require an energy shift of approximately 10000 cm^{-1} for the oxo-to-iron(IV) LMCT band upon replacement of MeCN ($\lambda_{\text{max}} = 282 \text{ nm}$) with the pseudohalides ($\lambda_{\text{max}} = 407 \text{ nm}$ for azide). Furthermore, the corresponding azide-to-iron(IV) LMCT transition might also be expected to appear in this region, as observed for $[\text{Fe}^{\text{IV}}(\text{TMC-acetate})\text{N}_3]^{2+}$.^{54,55} Clearly, more work is needed to clarify this question.

The ligand exchange chemistry discussed above suggests that a synthetic complex with the $\text{RS-Fe}^{\text{IV}}=\text{O}$ unit like that proposed in cytochrome P450 cycle⁵ might be obtainable via replacement of the axial MeCN of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCMe})]^{2+}$ with a thiolate ligand. This substitution was accomplished by the use of a pentadentate ligand named TMCS, first synthesized by J. Halfen at the University of Wisconsin Eau Claire to serve as a model for the superoxide reductase active site,⁵⁶ wherein one of the methyl groups on the TMC ligand was replaced with a mercaptoethyl tail (Figure 7). Stimulated by discussions with W. Nam, M. Bukowski found conditions for generating $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCS})]^+$ in high yield from the reaction of $[\text{Fe}^{\text{II}}(\text{TMCS})]^+$ with peracid.⁴³ Its visible spectrum shown in the bottom panel of Figure 8 exhibits characteristic ligand field transitions in the near-IR region. In addition, there are two more intense bands near 500 nm, which cannot yet be assigned, due to photoreduction that occurred in resonance Raman experiments. EXAFS analysis revealed a short Fe–O bond of 1.70 Å and an Fe–S bond of 2.33 Å, establishing the presence of the unique combination of an oxidizing $\text{Fe}=\text{O}$ unit and a reducing thiolate group in a synthetic complex.

The oxoiron(IV) complexes obtained thus far exhibit a large range of thermal stabilities with lifetimes at room temperature ranging from less than seconds to days. The most thermally stable are exemplified by the macrocyclic

Table 1. Properties of Selected $S = 1$ Non-Heme Oxoiron(IV) Complexes

	$r(\text{Fe}-\text{O})$ (\AA) ^a	λ_{max} (nm)	ϵ ($\text{M}^{-1} \text{cm}^{-1}$)	$\delta_{\text{Fe}^{\text{IV}}}$ (mm/s)	ΔE_{Q} (mm/s)	ref
[Fe ^{IV} (O)(TMC)(NCMe)] ²⁺	1.646(3)	282	10000	0.17	1.24	31
		820	400			
[Fe ^{IV} (O)(TMC)(N ₃)] ⁺	1.70	407	360	0.17	0.70	53
		850	130			
		1050	110			
[Fe ^{IV} (O)(TMC)(NCS)] ⁺	1.67	387	3500	0.18	0.55	53
		850	200			
		1010	170			
[Fe ^{IV} (O)(TMC)(O ₂ CCF ₃)] ⁺	1.66	836	250	0.19	0.22	52
[Fe ^{IV} (O)(TMCS)] [±]	1.70	460	1300			43
		570	1100			
		850	230			
		1050				
[Fe ^{IV} (O)(TPA)(NCMe)] ²⁺	1.67	724	300	0.01	0.92	28
[Fe ^{IV} (O)(TPA)(O ₂ CCF ₃)] ⁺	1.66	745	300	0.02	0.92	51
[Fe ^{IV} (O)(TPA)(Cl)] ⁺	1.65	778	300	0.04	0.95	51
[Fe ^{IV} (O)(TPA)(Br)] ⁺	1.66	800	400	0.06	0.95	51
[Fe ^{IV} (O)(BPMCN)(NCMe)] ²⁺	1.66	753	280	0.07	1.02	42
[Fe ^{IV} (O)(N4Py)] ²⁺	1.636(3)	695	400	-0.04	0.39	32, 33
[Fe ^{IV} (O)(BnTPEN)] ²⁺	1.67	739	400	0.01	0.87	32
[Fe ^{IV} (O)(N2Py3)] ²⁺		715	400	0.015	0.68	46
aqueous Fe ^{IV} =O ^b				0.38	-0.33	57
TauD intermediate J ^b	1.62			0.31	-0.88	10
prolyl hydroxylase intermediate J ^b				0.30	-0.82	11
halogenase CytC3 intermediate J ^b				0.30	-1.09	12
				0.22	-0.70	

^a Values in bold type are derived from X-ray crystallography, while other values are derived from EXAFS analysis. ^b These intermediates have $S = 2$ iron(IV) centers.

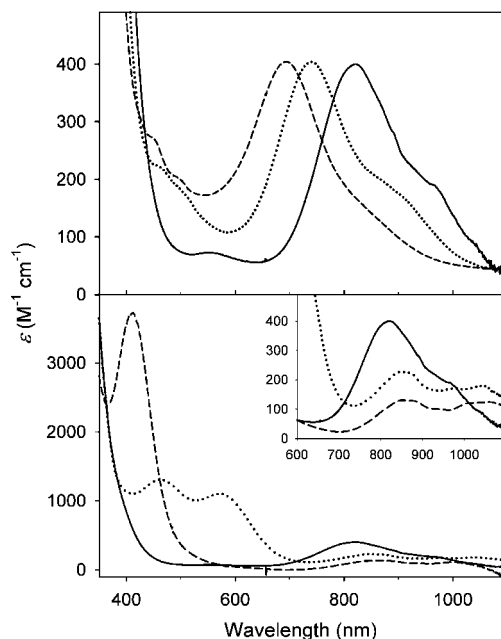


FIGURE 8. Electronic spectra of oxoiron(IV) complexes: (top) [Fe^{IV}(O)(TMC)(NCCH₃)]²⁺ (—), [Fe^{IV}(O)(BnTPEN)]²⁺ (···), and [Fe^{IV}(O)(N4Py)]²⁺ (---) and (bottom) [Fe^{IV}(O)(TMC)(NCCH₃)]²⁺ (—), [Fe^{IV}(O)(TMC)(N₃)]⁺ (- - -), and [Fe^{IV}(O)(TMCS)]⁺ (···). The inset shows the expanded near-IR regions.

TMC and the pentadentate N4Py and BnTPEN complexes, which have half-lives at 25 °C of 10, 60, and 6 h, respectively.^{32,52} In contrast, the complexes of nonplanar tetradentate TPA and β -BPMCN ligands are much less stable and typically studied at lower temperatures, as they have half-lives of 10 min or less at 25 °C. The difference between the two sets of complexes is the absence of an available coordination site *cis* to the oxo group in the more

stable complexes. The presence of a *cis*-labile ligand in the case of the TPA complex may have promoted thermal decay to its (μ -oxo)(μ -carboxylato)diiron(III) thermodynamic sink that was so useful for its identification (Figure 5B).

Interestingly, replacement of the MeCN ligand in [Fe^{IV}(O)(TMC)(NCMe)]²⁺ and [Fe^{IV}(O)(TPA)(NCMe)]²⁺ with anionic ligands resulted in the destabilization of the oxoiron(IV) complexes.^{43,51–53} This observation is counterintuitive, as it belies the conventional wisdom that increasing negative charge should stabilize high oxidation states. However, the flip side of a decreased stability is a greater reactivity. The reactivity properties of these non-heme oxoiron(IV) complexes will not be discussed in detail here but are the focus of W. Nam's Account in this issue.

One aspect of the oxoiron(IV) reactivity I would like to highlight in this Account is the ability of [Fe^{IV}(O)(N4Py)]²⁺ and [Fe^{IV}(O)(BnTPEN)]²⁺ to attack the aliphatic C–H bonds of a range of hydrocarbon substrates, despite their high thermal stability.³² N.-Y. Oh of W. Nam's group observed that [Fe^{IV}(O)(N4Py)]²⁺ converted to [Fe^{II}(N4Py)(NCMe)]²⁺ in the nearly quantitative oxidation of triphenylmethane to triphenylmethanol (see Figure 1 of ref 32). E. Klinker then collected the data to show a correlation between the measured second-order rate constants for C–H bond cleavage, normalized on a per hydrogen atom basis, with bond dissociation energies (BDEs) of the target C–H bond on the substrate (Figure 9). Remarkably, even cyclohexane, with a C–H bond strength of 99.3 kcal/mol, can be oxidized by these oxoiron(IV) complexes, albeit slowly. This linear correlation strongly implicates the cleavage of the C–H bond as the rate-determining step. In support, respective KIE values of 30 and 50 were observed for the oxidation of

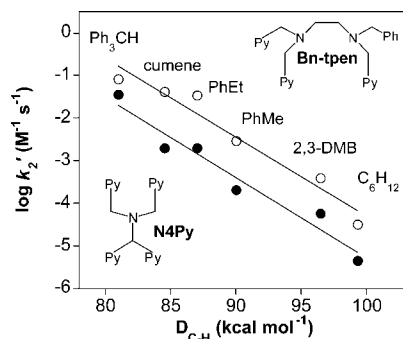


FIGURE 9. Correlations of the logarithms of second-order rate constants (normalized on a per hydrogen basis) of the reactions of $[\text{Fe}^{\text{IV}}(\text{O})\text{L}]$ complexes with hydrocarbon substrates with C–H bond dissociation energies. Reprinted with permission from ref 32. Copyright 2004 American Chemical Society.

ethylbenzene. Notably, the BnTPEN complex is 1 order of magnitude more reactive than the N4Py complex, which in turn is more reactive than the TMC complex, in line with the oxo transfer reactivity scale determined by Nam and co-workers.⁵⁸

Some quantitative insight into the oxidizing capabilities of this class of oxoiron(IV) complexes was recently obtained from the determination of the redox potential of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$.⁵⁹ The electrochemical behavior of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$, however, was not straightforward to figure out. Sastri et al. reported the cyclic voltammetry of this complex and found a reduction wave ($E_{p,c}$) in a MeCN solution to be near -0.5 V versus ferrocene with no corresponding oxidation wave.⁵⁸ The $E_{p,c}$ value seemed to us quite negative for a $\text{Fe}^{\text{IV/III}}$ potential, considering that the $\text{Fe}^{\text{III/II}}$ potential of the iron(II) precursor $[\text{Fe}^{\text{II}}(\text{N4Py})(\text{NCMe})]^{2+}$ was found to be $+0.61$ V.⁶⁰ As an alternative strategy, M. Collins on sabbatical from Viterbo University carried out bulk electrolysis in aqueous MeCN in my lab to generate $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$ from its iron(II) precursor. Electrolysis at potentials slightly above $+0.61$ V generated $[\text{Fe}^{\text{III}}(\text{N4Py})(\text{OH})]^{2+}$, as indicated by the appearance of a yellow chromophore ($\lambda_{\text{max}} = 320$ nm). At even higher potentials, the yellow color converted to the pale green color ($\lambda_{\text{max}} = 695$ nm) characteristic of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$.³² Its $\text{Fe}^{\text{IV/III}}$ potential of $+0.90$ V versus ferrocene was then determined by spectropotentiometry by following the disappearance of the 320 nm band and the appearance of the 695 nm band as a function of applied potential (Figure 10). This redox potential is significantly more positive than those of oxoiron(IV) centers supported by anionic ligands such as tetramesitylporphyrinate (0.69 V)⁶¹ and trisureaylate (0.34 V),⁶² thereby providing a strong rationale for the greater alkane oxidation reactivity of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$.

4. Further Challenges

All the synthetic mononuclear oxoiron(IV) complexes characterized thus far with one exception have $S = 1$ Fe^{IV} centers, unlike the $S = 2$ centers found for the oxoiron(IV) intermediates of TauD, prolyl hydroxylase, and halogenase CytC3.^{9–12} In general, the synthetic complexes have N_5O

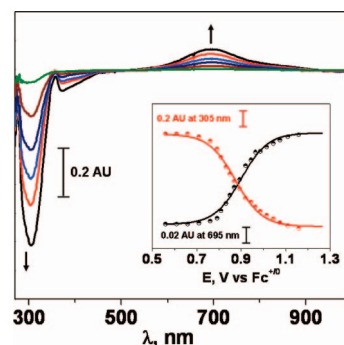


FIGURE 10. Difference spectral changes observed in the conversion of $[\text{Fe}^{\text{III}}(\text{OH})(\text{N4Py})]^{2+}$ to $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$ in wet MeCN as a function of applied potential. The inset shows the plot of ΔA vs potential for the respective bands at 305 and 695 nm. Reprinted with permission from ref 59. Copyright 2006 American Chemical Society.

ligand sets that favor a low-spin iron(IV) configuration, and introducing one or two carboxylate ligands appears to be insufficient to cause a shift to the high-spin state.^{51,52,63} The only mononuclear complex characterized to date is the fleeting species obtained from the reaction of $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$ and ozone in acidic aqueous media called **Z** by Bakac and co-workers.⁵⁷ Species **Z** is formulated as $[(\text{H}_2\text{O})_5\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ and can be recognized by its unique Mössbauer properties in low and high applied fields that distinguish it from the low-spin oxoiron(IV) complexes discussed above.

In the 1990s, we found that an $S = 2$ oxoiron(IV) center can be supported by sterically hindered tetradentate N_4 ligands within a diiron framework.^{64,65} These complexes are a variation of the earlier described iron(III)iron(IV) TPA complexes with valence-delocalized $S = 3/2$ $\text{Fe}_2(\mu\text{-O})_2$ cores.^{24,25} By introducing α -methyl substituents onto the TPA ligand, one could generate iron(III)iron(IV) complexes with $S = 1/2$ ground states that were derived from antiferromagnetic coupling of valence-localized high-spin iron(III) and iron(IV) ions. The resonance Raman spectrum of the 6-Me₃-TPA complex exhibited a feature at 840 cm^{-1} that was assigned to the $\text{Fe}=\text{O}$ stretch {compared with 834 cm^{-1} for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCMe})]^{2+}$ },³¹ thereby providing evidence for the isomerization of the $\text{Fe}_2(\mu\text{-O})_2$ core to a ring-opened $\text{Fe}^{\text{III}}\text{-O-Fe}^{\text{IV}}=\text{O}$ structure having a terminal $\text{Fe}^{\text{IV}}=\text{O}$ unit.⁶⁵ Thus, related mononuclear high-spin $\text{Fe}^{\text{IV}}=\text{O}$ complexes should be synthetically accessible.

The search for non-heme oxoiron(IV) complexes has also led to the characterization of $[\text{Fe}^{\text{IV}}(\beta\text{-BPMCN})(\text{OH})(\text{OO}^t\text{Bu})]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{TMC-acetate})\text{X}]^{2+}$ ($\text{X} = \text{N}_3, \text{F}$, and Cl) by the Que and Wieghardt groups, respectively (Figure 11).^{42,54,55} These non-oxoiron(IV) complexes demonstrate that two anionic ligands can substitute for the oxo group to stabilize an iron(IV) center supported by a neutral N_4 ligand set. These complexes set the stage for even more interesting chemistry.

There are of course iron oxidation states beyond iron(IV). In our efforts to model Rieske dioxygenases,⁴ K. Chen and M. Costas identified the first non-heme iron complexes to catalyze the *cis* dihydroxylation of olefins.^{66,67} In these experiments, H_2^{18}O labeling results strongly implicated an $\text{Fe}^{\text{V}}(\text{O})(\text{OH})$ oxidant. Just prior to the

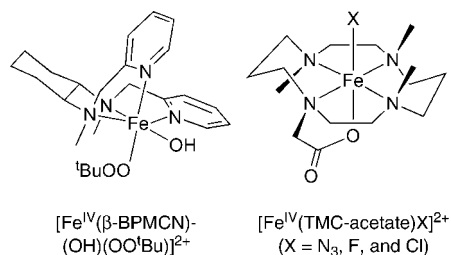


FIGURE 11. Proposed structures of non-heme iron(IV) complexes without an oxo group.

submission of this Account, a paper appeared in which Collins and co-workers reported spectroscopic evidence for an oxoiron(V) complex.¹⁷ The Fe^V=O unit supported by the tetraanionic TAML2 ligand persisted for hours at -60 °C (Figure 2). This exciting result, coupled with Wieghardt's generation of a nitridoiron(VI) species,⁶⁸ demonstrates that high-valent iron chemistry is alive and well and at the threshold of further discoveries.

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