Dioxygen Activation

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Proton- and Reductant-Assisted Dioxygen Activation by a Nonheme Iron(II) Complex to Form an Oxoiron(IV) Intermediate**

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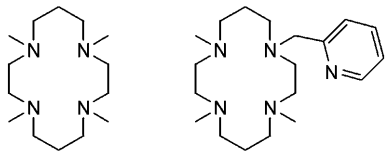
Dedicated to Professor Jan Reedijk

Dioxygen activation by mononuclear iron oxygenases in general requires two electrons and protons to facilitate reductive cleavage of the O–O bond and formation of a high-valent iron oxidant.[1,2] For enzymes with an iron(III) resting state, the oxidant is postulated to have a formally Fe^{V} oxidation state, for example, $Fe^{IV}(O)$(porphyrin radical) for cytochrome P450[1] and $Fe^{V}(O)(OH)$ for the Rieske dioxygenases.[2] On the other hand, enzymes with an iron(II) resting state often require a tetrahydropterin or an α-keto acid cofactor to form an $Fe^{IV}(O)$ intermediate.[2] Such intermediates have recently been trapped and characterized for several enzymes.[3]

In model nonheme iron systems, there has been significant recent progress in the generation and characterization of $Fe^{IV}(O)$ complexes, most of which were prepared by reaction of iron(II) precursors with oxygen-atom donors (e.g., peroxides, peroxy acids, and ArIO).[4] The one exception is the formation of $[Fe^{IV}(O)(TMC)(CH_3CN)]^{2+}$ (**1**)[5] by reaction of its iron(II) precursor with O_2 in the presence of alcohols or ethers, reported by Nam and co-workers.[6] The mechanism for the formation of **1** under these conditions is not well established, but it was postulated to result from O–O bond homolysis of a (μ-1,2-peroxo)diiron(III) intermediate, resembling the mechanism postulated for formation of $[Fe^{IV}(O)(TPP)]$ by oxygenation of $[Fe^{II}(TPP)]$.[5,7] In the latter case, coordination of imidazole *trans* to the peroxo ligand promoted oxoiron(IV) formation. By extension, it seems plausible that binding of the added alcohol or ether to iron may also promote the formation of **1**, as $[Fe^{II}(TMC)(OTf)_2]$ in the absence of such additives is air-stable.[6] In the course of our work, we appended a pyridine moiety to the TMC framework to obtain the pentadentate ligand TMC-py (Scheme 1). Its iron(II) and oxoiron(IV) complexes were synthesized and structurally characterized. Interestingly, the oxoiron(IV) complex could be generated by oxygenation of the iron(II) complex, but only in the presence of an electron source (BPh_4^-) and a proton source.



Scheme 1. Cyclam ligands used in this study.

In our initial exploration of the chemistry of **1**, attempts to coordinate pyridine *trans* to the oxo unit by replacement of the MeCN ligand proved to be unsuccessful, perhaps due to the steric constraints imposed by the binding pocket. To enhance the probability of pyridine coordination we synthesized the TMC-py ligand in which one of the TMC methyl groups is replaced by a 2-pyridylmethyl arm and prepared the corresponding iron(II) complex $[Fe^{II}(TMC\text{-}py)]X_2$ (**2**$(X)_2$; X = OTf or PF_6). X-ray analysis of single crystals of **2**$(PF_6)_2$ obtained from MeCN/MeOH confirmed coordination of TMC-py as a pentadentate ligand (Figure S1 and Table S2, Supporting Information),[8] with the cyclam macrocycle adopting a *trans*-I configuration[9] and the pyridine residue bound at the apical position of a distorted square pyramid ($\tau = 0.45$[10]).

The reaction of **2** with PhIO in MeCN solution at room temperature gave pale brown-green complex **3** in about 95 %

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yield with λ_{max} at 834 nm ($\varepsilon_{max} = 260\,M^{-1}cm^{-1}$; Figure 1, left). Complex **3** can also be generated with 3 equiv H_2O_2, but in lower yield (ca. 65%). The observed near-IR bands are very similar to those of **1**[11] and assigned to ligand-field transitions,

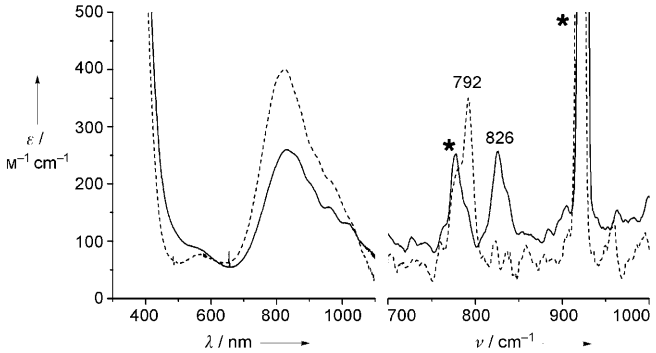


Figure 1. Left: electronic spectra of **1** (-----) and **3** (——) in MeCN. Right: resonance Raman spectra ($\lambda_{ex} = 407$ nm) of ^{16}O-**3** (——) and ^{18}O-**3** (-----) recorded in frozen solution with samples mounted on a brass cold finger. Asterisks designate features from the CH_3CN solvent. The Raman samples were prepared by reaction of a 10 mM solution of **2**$(OTf)_2$ in acetonitrile with 2 equiv of $PhI(OAc)_2$, in the presence of 100 equiv of $H_2{}^{16}O$ and $H_2{}^{18}O$, respectively.

which are diagnostic of the formation of a low-spin ($S = 1$) oxoiron(IV) center.[12] Consistent with this assumption, the electrospray mass spectrum of **3** exhibited a peak at m/z 554.1 and an isotope distribution pattern in agreement with its formulation as $\{[Fe^{IV}(O)(TMC\text{-}py)](OTf)\}^+$ (calcd m/z: 554.2; Figure S2, Supporting Information). Furthermore, the resonance Raman spectrum of **3** showed a ν(Fe=O) band at 826 cm^{-1} that shifted by 34 cm^{-1} to 792 cm^{-1} on ^{18}O labeling, as expected from Hooke's Law (Figure 1, right). The observed frequency is 13 cm^{-1} lower than that observed for **1** by FTIR spectroscopy, and this presumably reflects the differing coordinative properties of axial pyridine and MeCN ligands.[11] Mössbauer studies on **3** yielded a doublet with an isomer shift δ of 0.18 mm s^{-1} and a quadrupole splitting ΔE_Q of 1.08 mm s^{-1} (Figure 2a), parameters similar to those of **1** ($\delta = 0.17$ mm s^{-1}, $\Delta E_Q = 1.24$ mm s^{-1}).[11] High-field studies (Figure S4, S5, and Table S1, Supporting Information) showed that **3** exhibits zero-field splitting and hyperfine parameters similar to those reported for **1**.[11]

The high purity of **3** and its stability ($t_{1/2} = 7$ h at 25 °C) allowed the growth of diffraction-quality crystals at −20 °C from MeOH/Et_2O (Table S3, Supporting Information). The structure obtained (Figure 3) is only the third high-resolution crystal structure of an oxoiron(IV) complex reported to date[8] and conclusively demonstrates that the TMC-py ligand retains its pentadentate binding mode, and the cyclam ring its *trans*-I stereochemistry, on oxidation of **2** to **3**. Complex **3** has an Fe=O distance of 1.667(3) Å, which is 0.02–0.03 Å longer than those of 1.646(3) Å reported for **1**[11] and 1.639(5) Å for $[Fe^{IV}(O)(N4Py)]^{2+}$ (**5**).[5,13] The Fe–N_{amine} bonds in **3** have an average length of 2.083 Å, close to that of **1** (2.091 Å). In contrast, the Fe–N_{py} bond length in **3** is 2.118(3) Å, which is 0.06 Å longer than the axial Fe–N_{NCMe} bond in **1**,[11] despite the fact that pyridine is a much better

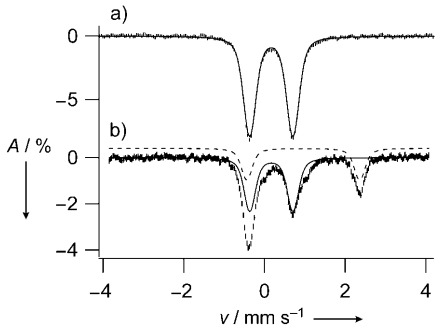


Figure 2. Mössbauer spectra recorded at 4.2 K in a parallel applied field of 45 mT for **3** generated a) by treating **2** in MeCN with PhIO to afford a sample that contained >95% **3** and b) by treating **2** in MeCN with O_2 in the presence of 1 equiv BPh_4^- and 1 equiv $HClO_4$. Solid and dashed lines indicate contributions of **3** (56% of Fe) and starting material **2** (32%), respectively.

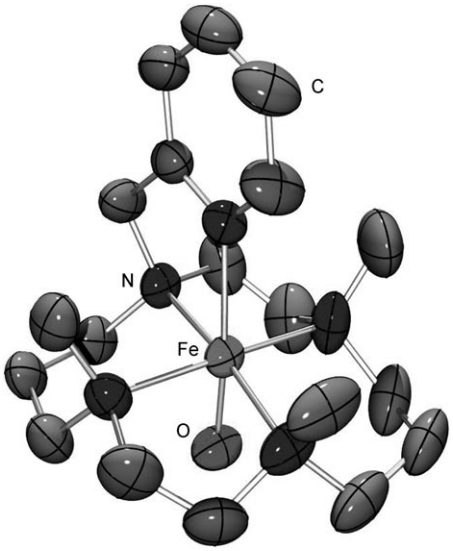


Figure 3. Thermal ellipsoid drawing of $[Fe^{IV}(O)(TMC\text{-}py)](OTf)_2$ (**3**) showing 50% probability ellipsoids. The second enantiomorph, hydrogen atoms, counterions, and noncoordinating solvent molecules have been omitted for clarity. Selected bond lengths [Å]: Fe–O, 1.667(3), Fe–N_{py} 2.118(3), Fe–N_{amine} (av) 2.083.

Lewis base than MeCN. This observation may be attributed to the geometric constraints imposed by tethering of the pyridyl donor to the cyclam ring, which is also manifested in deviation of the O=Fe–N_{py} bond angle from linearity (169.77(13)°). Furthermore, the Fe–N_{py} bond in **3** is significantly longer than the equatorial Fe–N_{py} bonds of **5** (av 1.96 Å),[13] which most probably reflects the *trans* effect of the oxo ligand. Metrical parameters obtained from a DFT geometry optimization for **3** (Figure S7 and Table S4, Supporting Information) are in good agreement with the X-ray structure. Of particular note is the close reproduction of the nonlinear O=Fe–N_{py} bond angle and associated elongation of the Fe–N_{py} bond length.

The susceptibility of **2** to oxidation by O_2 was then investigated. While **2** was found to be air-stable at 25 °C in MeCN, it was converted to **3** within minutes in the presence of 1 equiv BPh_4^- and 1 equiv $HClO_4$, as indicated by the growth

of the ligand-field band at 834 nm (Figure S3, Supporting Information). The Mössbauer spectrum of a ^{57}Fe-enriched sample obtained under these conditions (Figure 2b) showed the presence of three components: **3** (56%), unconverted **2** (32%), and an unidentified high-spin ferric byproduct (ca. 12%). Thus, the amount of **3** formed by oxygen activation represented about 80% of the **2** that was oxidized, a yield that is comparable to those for two oxoiron(IV) porphyrin complexes obtained by reductive activation of corresponding oxyheme precursors.[14]

The yield of **3** obtained by oxygen activation depended on the amount of BPh_4^- and $HClO_4$ added to the oxygenated solution (Figure 4) and was found to be maximal for samples

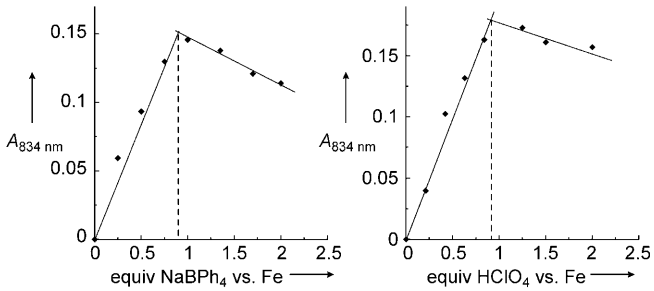
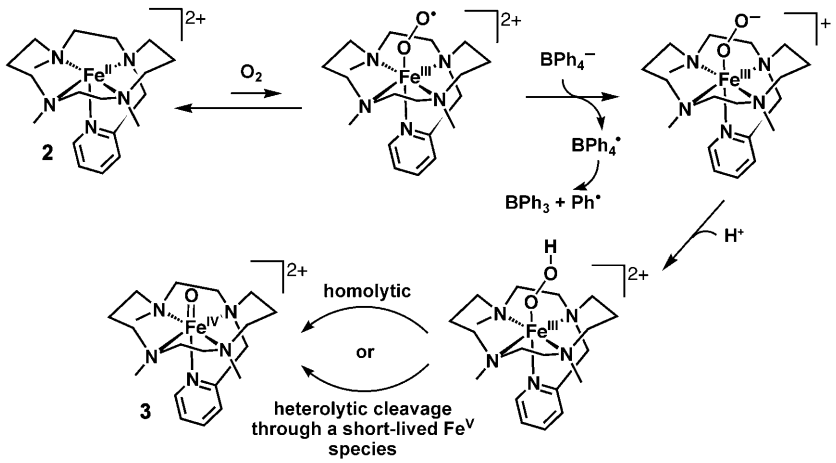


Figure 4. Conversion of **2** to **3** by reaction with O_2 in the presence of BPh_4^- and H^+ in CH_3CN solution at 25°C. Left: amount of **3** formed as a function of the amount of BPh_4^- added to a solution containing 1 equiv of both **2** and $HClO_4$. Right: amount of **3** formed as a function of $HClO_4$ added to a solution containing 1 equiv of both **2** and BPh_4^-.

containing a 1:1:1 ratio of **2**/BPh_4^-/H^+. Under these conditions, **3** exhibited a four-fold shorter lifetime ($t_{1/2} \approx 100$ min) than when prepared with H_2O_2 or PhIO. Studies of the reaction mixture by NMR spectroscopy showed that BPh_4^- had decomposed to form phenol (1 equiv) and biphenyl (0.75 equiv) byproducts, presumably derived from phenyl radicals formed on one-electron oxidation of BPh_4^-. Thus, BPh_4^- acts as a reductant in this reaction.[15] Additionally, we also found that ascorbic acid could be used as both an electron and a proton source in the conversion of **2** to **3** and that introduction of 0.5 equiv of ascorbic acid in an ethanol suspension to an oxygenated solution of **2** in a 1:1 mixture of MeCN and EtOH afforded **3** in about 55% yield.

Comparison of the dioxygen reactivity of **2** with that of the precursor to **1**, [Fe^{II}(TMC)(OTf)](OTf) (**4**), reveals similarities and differences. Like **2**, **4** was unreactive towards O_2 in MeCN solvent at room temperature but was converted to **1** in 75% yield within minutes in the presence of 1 equiv each of H^+ and BPh_4^-. However, unlike **2**, which is air-stable in MeCN/EtOH (1:1), **4** readily reacted with O_2 to form **1** in nearly quantitative yield in MeCN/EtOH (1:1) and other MeCN/(alcohol or ether) solvent mixtures.[6]

In the latter case, Nam and co-workers proposed that dioxygen activation occurs via a (1,2-peroxo)diiron(III) species akin to that proposed for Fe(porphyrin) autoxidation,[7,16] but no detailed studies substantiating this mechanism have been reported. The fact that dioxygen activation by **4** occurs only in the presence of an alcohol or ether cosolvent raises the possibility that this additive coordinates to the iron(II) center to promote binding and activation of the *trans*-bound O_2. Consistent with this notion is the air stability of **2** in MeCN/EtOH (1:1), because **2** differs from **4** in having only one available coordination site, which is presumably reserved for binding of O_2 and its subsequent activation. In the presence of H^+ and BPh_4^-, we propose instead a reductive activation mechanism for conversion of **2** to **3** (Scheme 2), in which the initially formed Fe^{III}(OOH) intermediate subsequently decomposes rapidly by O–O bond cleavage to form **3**. The O–O bond cleavage may proceed in a homolytic fashion, but we have yet to obtain evidence for formation of a hydroxyl radical. Alternatively, heterolytic cleavage to yield a short-lived oxoiron(V) species, followed by its rapid reduction cannot be ruled out at this stage. Although the proposed Fe^{III}(OOH) intermediate has not to date been observed in the reaction of **2** with dioxygen, our mechanistic proposal is precedented by the trapping and characterization of an Fe^{III}(OOH) species supported by a related pentadentate ligand with amine, pyridine, and pivaloylamido functionalities in the reaction of its iron(II) complex with O_2 in the presence of BPh_4^- and H^+.[17] This intermediate could alternatively be prepared from the reaction of the same Fe^{II} complex with H_2O_2, which allowed its unambiguous identification.[18]



Scheme 2. Proposed dioxygen activation mechanism.

In summary, we have described a new oxoiron(IV) complex **3** in terms of its spectroscopic properties and high-resolution crystal structure and have demonstrated its formation by reaction of its iron(II) precursor **2** with oxo-transfer agents or with O_2 in the presence of a reductant and an acid. In the latter case, the requirement of a proton and an electron source is consistent with the intermediacy of a hydroperoxoiron(III) species, which bears strong parallels to the mechanistic paradigm for formation of high-valent iron

oxo species, as postulated for enzymatic systems such as cytochrome P450 and the Rieske dioxygenases.[1,2] Although the mechanism of formation of **3** by reaction of **2** with O_2 requires greater definition and is the subject of ongoing investigations, this study represents the first example in a synthetic system of the activation of dioxygen facilitated by protons and electrons to yield high-valent nonheme iron oxo species.

Experimental Section

2$(OTf)_2$: Under argon, a solution of TMC-py (0.50 g, 1.50 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of $Fe(OTf)_2(CH_3CN)_2$ (0.62 g, 1.43 mmol) in tetrahydrofuran (10 mL). A precipitate began to form within minutes. After stirring overnight, the volume of solvent was reduced to ca. 10 mL and the mixture filtered. The solid obtained was washed with THF (2×5 mL) and dried under vacuum to give the product as a cream-colored powder (0.74 g, 75%). Elemental analysis (%) calcd for $C_{21}H_{35}F_6FeN_5O_6S_2$: C 36.69, H 5.13, N 10.19; found: C 36.44, H 5.14, N 9.97. **2**$(PF_6)_2$ was prepared in a similar fashion. A solution of $FeCl_2{\cdot}2H_2O$ (0.121 g, 0.74 mmol) in MeOH (5 mL) was added to a solution of TMC-py (0.248 g, 0.74 mmol) in minimal MeOH. The yellow solution was stirred overnight and then filtered. Addition of $NaPF_6$ (0.250 g, 1.49 mmol) in MeOH to the filtrate resulted in formation of a pale precipitate, which was collected by filtration and dried under vacuum to afford the product in 46% yield. Elemental analysis (%) calcd for $C_{19}H_{35}F_{12}FeN_5P_2$: C 33.59, H 5.19, N 10.31; found: C 33.41, H 5.15, N 9.95.

3$(OTf)_2$: An excess of solid iodosobenzene was added to a solution of **2**$(OTf)_2$ in acetonitrile/methanol. After stirring the resultant mixture at room temperature for 20 min, the residual iodosobenzene was removed by filtration to leave an olive-green solution of **3**. Crystals of **3**$(OTf)_2$ suitable for X-ray crystallography were grown at −20 °C from a methanol solution layered with diethyl ether.

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[5] Abbreviations: TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, TMC-py = 1-(2′-pyridylmethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane, TPP = dianion of *meso*-tetraphenylporphyrin, N4Py = *N*,*N*-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine.
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[8] Single-crystal structure and refinement data for **2**$(PF_6)_2$: $C_{19}H_{35}F_{12}FeN_5P_2$, $M_r = 679.31$, monoclinic, space group $P2_1/c$, $a = 9.8438(4)$, $b = 9.7471(5)$, $c = 28.3527(13)$ Å, $\alpha = 90$, $\beta = 90.803(2)$, $\gamma = 90°$, $V = 2720.1(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.651$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, $\mu = 0.771$ mm^{-1}), $T = 100(1)$ K. A total of 48672 ($R_{int} = 0.0468$) independent reflections with $2\theta < 30.71°$ were collected. The resulting parameters were refined to converge at $R_1 = 0.0839$ ($I > 2\sigma(I)$) for 392 parameters and 8407 independent reflections ($wR_2 = 0.2237$); max./min. residual electron density 0.733/−0.658 e Å^{-3}; GOF = 1.074. Single-crystal structure and refinement data for **3**$(OTf)_2$: $C_{22}H_{39}F_6FeN_5O_8S_2$, $M_r = 735.55$, triclinic, space group $P\bar{1}$, $a = 9.6920(8)$, $b = 12.2001(10)$, $c = 13.9646(17)$ Å, $\alpha = 95.294(4)$, $\beta = 108.020(4)$, $\gamma = 98.922(4)°$, $V = 1533.8(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.593$ Mg m^{-3}, synchrotron radiation ($\lambda = 0.49594$ Å, $\mu = 0.232$ mm^{-1}), $T = 100(2)$ K. A total of 6096 ($R_{int} = 0.0275$) independent reflections with $2\theta < 18.09°$ were collected. The resulting parameters were refined to converge at $R_1 = 0.0632$ ($I > 2\sigma(I)$) for 627 parameters and 6096 independent reflections ($wR_2 = 0.1877$); max./min. residual electron density 1.150/−0.517 e Å^{-3}; GOF = 1.052. Further experimental details are provided in the Supporting Information. CCDC 683058 and 685380 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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