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Near-Stoichiometric Conversion of H_2O_2 to Fe^{IV}=O at a Nonheme Iron(II) Center. Insights into the O−O Bond Cleavage Step

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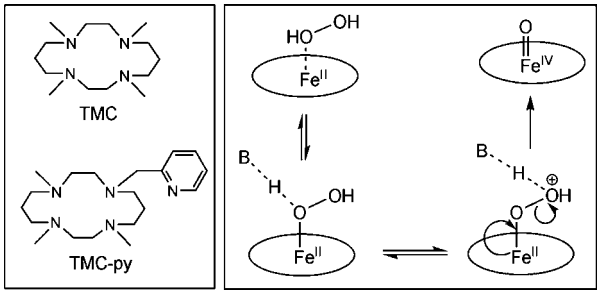
The reaction between iron(II) and H_2O_2 has attracted great interest ever since Fenton discovered that this combination could produce a strong oxidant in acidic aqueous media.[1] Despite the fact that this chemistry was first observed over a century ago, debate continues as to whether HO• or an Fe^{IV}=O species represents the reactive oxidant that is formed by O−O bond cleavage, homolytically for HO• and heterolytically for Fe^{IV}=O.[1] The involvement of the latter is supported by recent DFT studies[1d] and a kinetic reinvestigation.[1e] An understanding of the factors affecting the reaction between iron(II) and H_2O_2 is also of relevance to several nonheme iron enzymes, such as the tetrahydropterin-dependent hydroxylases and isopenicillin N synthase (IPNS), where the key Fe^{IV}=O oxidants are proposed to arise by O−O bond heterolysis of iron(II)-peroxo precursors.[2] However, the chemical feasibility of such a two-electron-transformation may be questioned because reactions of Fe(II) with H_2O_2, with very few exceptions,[3] afford one-electron oxidized Fe(III) products.[2a] As a consequence, we have sought to establish whether a synthetic iron(II) complex can react stoichiometrically with H_2O_2 to yield an oxoiron(IV) species. The heterolytic O−O bond cleavage that a stoichiometric reaction entails was proposed by Bautz et al. to occur upon treatment of an Fe^{II}(bispidine) system with H_2O_2 in aqueous media,[3a] but the observed maximum yield of only 60% for the Fe^{IV}=O complex makes it difficult to invoke the heterolytic mechanism unequivocally. This uncertainty can now be eliminated for the analogous reaction with $[Fe^{II}(TMC)]^{2+}$ (**1**)[4] (Scheme 1), described herein, where H_2O_2 can be converted to the Fe^{IV}=O species in high yield.

Scheme 1[a]



[a] Left: Ligands used in this study.[4] Right: Proposed mechanism for the base-catalyzed formation of **2** from **1** and H_2O_2.

Previously **1** was reported to react at −40 °C with 3 equiv of H_2O_2 in CH_3CN to generate $[Fe^{IV}(O)(TMC)(CH_3CN)]^{2+}$ (**2**) in ∼70% yield after 3 h.[5] During our reinvestigation of this system, we found that the reaction between equimolar amounts of **1** and H_2O_2 in the presence of 2,6-lutidine showed an increased yield of **2** to ∼85 ± 3% (Figure 1, inset). Furthermore, the titration of **1** with substoichiometric H_2O_2 in the presence of 1.0 equiv of 2,6-lutidine afforded a linear increase in the yield of **2**, which plateaued at ∼90% with slightly more than 1 equiv of H_2O_2 added, indicating a 1:1 stoichiometry between **1** and H_2O_2 (Figure 1).[6]

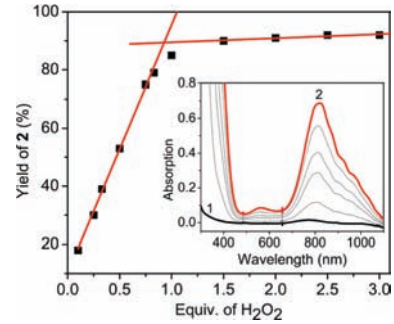


Figure 1. Yield of **2** vs equiv of H_2O_2 added. Experimental conditions: 2.0 mM **1**, 2.0 mM 2,6-lutidine, −40 °C in CH_3CN. The yield of **2** was determined from its absorption at 820 nm (ϵ = 400 M^{-1} cm^{-1}). Inset: Spectral changes observed during the formation of **2** (b = 1 cm).

In addition to enhancing the yield of **2**, 2,6-lutidine also accelerated its rate of formation 10-fold. The addition of only 0.1 equiv of 2,6-lutidine was sufficient to afford **2** in ∼90% yield, but the maximal pseudo-first-order rate constant for the formation of **2** (k_{obs}) was obtained with more than 0.5 equiv of 2,6-lutidine (Figure 2 left). Further kinetic studies with 5−25 equiv of H_2O_2 revealed that the rate for the formation of **2** was first-order in both **1** and H_2O_2. A second-order rate constant (k_2) of 2.3(1) × 10^2 M^{-1} s^{-1} at −40 °C was obtained from the slope of the plot of k_{obs} vs $[H_2O_2]$ (Figure 2 right). Analysis of the Eyring plot for the temperature dependence of this pseudo-first-order reaction afforded $\Delta H^{\ddagger}$ = 29(2) kJ/mol and $\Delta S^{\ddagger}$ = −144(10) J/(mol·T) (Figure S1). These values compare favorably with those obtained from the reaction of $[Fe^{II}(bispidine)]^{2+}$ with H_2O_2 to form $[Fe^{IV}(O)(bispidine)]^{2+}$ where rate-determining heterolytic O−O bond scission was proposed but deviate significantly from those of synthetic Fe^{III}−OOH(R) systems that undergo homolytic O−O bond cleavage.[3a]

The effects of 2,6-lutidine (pK_a = 6.7) suggest its key role as an acid−base catalyst, similar to that played by the distal histidine in horseradish peroxidase (HRP), where it has been established that the active site base facilitates proton transfer from the proximal to the distal oxygen of bound H_2O_2 to promote *heterolytic* O−O bond cleavage.[7] As shown in Figure S2, 2,4,6-collidine (pK_a = 7.3) and pyridine (pK_a = 5.2) also facilitate the formation of **2** with ∼90% yield at comparable rates. Weaker bases such as 3-bromopyridine (pK_a = 2.84) or 2-acetylpyridine (pK_a = 2.68) also accelerated the reaction, but a *very large excess* of either base was necessary for k_{obs} to plateau. Significantly weaker bases like 2-bromopyridine (pK_a = 0.79) and 2,6-diacetylpyridine (pK_a = 0.12) were ineffective. These trends are similar to those found for HRP Compound I formation, where mutation of the distal His residue to a less basic

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Glu or to Ala/Val/Gln decreased the rate of Compound I formation by factors of 10^4 and 10^6, respectively.[7a,b] The important role played by protons was further illustrated by the effect of replacing H_2O_2/H_2O with D_2O_2/D_2O, for which a large H/D KIE of 3.7(4) was observed (Figure 2 right). For comparison, sizable solvent H/D KIEs were also observed for HRP Compound I formation (1.6 ± 0.1)[8a] and in the reactions of Fe(III) porphyrins with peracids (~2),[8b] supporting a mechanistic parallel between heme and nonheme iron centers.

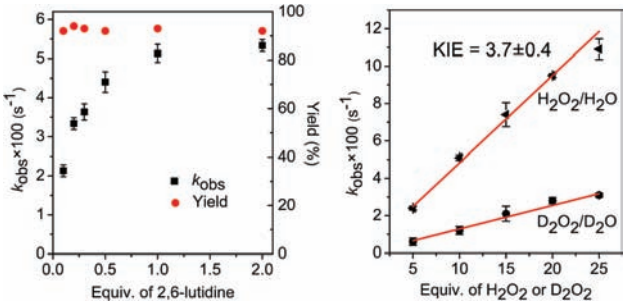

Figure 2. Left panel: Dependence of the pseudo-first-order rate constant for formation of **2** (k_{obs}) *and* yield of **2** on [2,6-lutidine] (conditions: 1.0 mM **1** in CH_3CN and 20 equiv of H_2O_2 at −40 °C). Right panel: [H_2O_2/D_2O_2] dependence of k_{obs} (conditions: 2.0 mM **1**, 2.0 mM 2,6-lutidine in CH_3CN at −40 °C). See SI for further experimental details.

In the three published [Fe^{II}(TMC)X] structures, the four methyl groups of the TMC ligand in each complex are oriented *syn* to each other, and each X ligand binds *syn*, within the four-methyl pocket.[9] In the structure of **2**, the *syn* site has an MeCN ligand while the *anti* site is occupied by the oxo atom.[5] This requires H_2O_2 to interact with the iron center of **1** at the *anti* site, with the *syn* ligand presumably being MeCN.[10] The effect of the *syn* ligand was examined by investigation of the reaction of H_2O_2 with [Fe^{II}(TMC-py)]$^{2+}$ (**3**)[4] (Scheme 1), where the appended pyridine occupies the *syn* site. In this case, 2,6-lutidine also exerted a beneficial effect, increasing the yield of [Fe^{IV}(O)(TMC-py)]$^{2+}$ (**4**) from ~65%[11] to >90% with stoichiometric H_2O_2 and enhancing the reaction rates 5-fold (see SI). Interestingly, the reaction of H_2O_2 with **3** was ~30-fold slower than with **1** under the same conditions (see SI), which we ascribe to a less Lewis acidic iron(II) center in **3** that has a lower affinity for H_2O_2 than **1**.

We have thus identified for the first time a synthetic iron(II) complex that reacts with *stoichiometric* H_2O_2 to generate an oxoiron(IV) complex in nearly quantitative yield. A sizable H/D KIE of 3.7 was observed, highlighting the importance of proton transfer in the cleavage reaction. The observed stoichiometry and KIE is best rationalized by invoking *heterolytic* O−O bond cleavage of an iron-bound H_2O_2 that is facilitated by an acid−base catalyst (Scheme 1).[12] This mechanism bears a strong resemblance to the heterolytic O−O bond cleavage postulated to occur at the nonheme iron centers of the tetrahydropterin-dependent hydroxylases and IPNS in the course of O_2 activation.[2]

The near-stoichiometric conversion of H_2O_2 to Fe^{IV}═O in the formation of **2** is unprecedented and can be ascribed to two factors. The first is the relatively poor hydrogen-atom abstraction ability of **2**,[13] which minimizes the reaction between nascent **2** and residual H_2O_2. The second factor is the demonstrated lack of reactivity between **1** and **2**,[5] allowing **2** to accumulate without comproportionation to Fe^{III} species (Figure 1). Our results also show that the conversion of **1** to **2** can be quite facile, suggesting that under the right conditions the two-electron oxidation of Fe^{II} to Fe^{IV}═O should not be such an uncommon event.

Such a transformation has, on the basis of DFT studies,[1d] been proposed to be the first step of the Fenton reaction, but this argument has been weakened by the fact that the putative [Fe^{IV}(O)$(H_2O)_5$]$^{2+}$ species has yet to be experimentally observed *in situ*.[1] However, it has been generated independently by reaction of O_3 with Fe^{2+} in aqueous acidic solution[14a,b] and was found to be very reactive. Unlike **2**, [Fe^{IV}(O)$(H_2O)_5$]$^{2+}$ reacts rapidly not only with substrates but also with residual Fe^{II} to yield Fe^{III} *and* H_2O_2 to generate HO_2• and HO• radicals.[14] Thus it may be possible to reconcile the conflicting views of the Fenton reaction mechanism by considering the points we have raised in demonstrating the feasibility of the Fe^{II}-to-Fe^{IV}═O conversion.

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Supporting Information Available: Detailed experimental procedures and Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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