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Near-Stoichiometric Conversion of H_2O_2 to $\text{Fe}^{\text{IV}}=\text{O}$ at a Non-Heme Iron(II) Center. Insights Into the O-O Bond Cleavage Step

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Abstract

Near-quantitative formation of an oxoiron(IV) intermediate $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ (**2**) from stoichiometric H_2O_2 was achieved with $[\text{Fe}^{\text{II}}(\text{TMC})]^{2+}$ (**1**) (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraaza-cyclotetradecane). This important outcome is best rationalized by invoking a direct reaction between **1** and H_2O_2 followed by a heterolytic O–O bond cleavage facilitated by an acid-base catalyst (2,6-lutidine in our case). A sizable H/D KIE of 3.7 was observed for the formation of **2**, emphasizing the importance of proton transfer in the cleavage step. Pyridines with different $\text{p}K_a$ values were also investigated, and less basic pyridines were found to function less effectively than 2,6-lutidine. This study demonstrates that the reaction of Fe(II) with H_2O_2 to form $\text{Fe}(\text{IV})=\text{O}$ can be quite facile. Two factors promote the near-stoichiometric conversion of H_2O_2 to $\text{Fe}(\text{IV})=\text{O}$ in this case: a) the low reactivity between **1** and **2** and b) the poor H-atom abstracting ability of **2**, which inhibits subsequent reaction with residual H_2O_2 . Both factors inhibit formation of the Fe(III) byproduct commonly found in reactions of Fe(II) complexes with H_2O_2 . These results may shed light into the nature of the O–O bond cleaving step in the activation of dioxygen by nonheme iron enzymes and in the first step of the Fenton reaction.

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 $\text{HO}\cdot$ or an $\text{Fe}^{\text{IV}}=\text{O}$ species represents the reactive oxidant that is formed by O–O bond cleavage, homolytically for $\text{HO}\cdot$ and heterolytically for $\text{Fe}^{\text{IV}}=\text{O}$.¹ The involvement of the latter is supported by recent DFT studies^{1d} and a kinetic re-investigation.^{1e} An understanding of the factors affecting the reaction between iron(II) and H_2O_2 is also of relevance to several non-heme iron enzymes, such as the tetrahydropterin-dependent hydroxylases and isopenicillin N synthase (IPNS), where the key $\text{Fe}^{\text{IV}}=\text{O}$ oxidants are proposed to arise by O–O bond heterolysis of iron(II)-peroxo precursors.² However, the

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Supporting Information Available: Detailed Experimental Procedures and Figure S1 and Figure S2. This material is available free of charge via the internet at <http://pubs.acs.org>.

chemical feasibility of such a two-electron-transformation may be questioned because reactions of Fe(II) with H₂O₂, 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 H₂O₂ 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 H₂O₂ 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 H₂O₂ can be converted to the Fe^{IV}=O species in high yield.

Previously **1** was reported to react at -40 °C with 3 equiv. H₂O₂ in CH₃CN to generate [Fe^{IV}(O)(TMC)(CH₃CN)]²⁺ (**2**) in ~70% yield after three hours.⁵ During our re-investigation of this system, we found that the reaction between equimolar amounts of **1** and H₂O₂ 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 sub-stoichiometric H₂O₂ in the presence of 1.0 equiv. 2,6-lutidine afforded a linear increase in the yield of **2**, which plateaued at ~90% with slightly more than 1 equiv. H₂O₂ added, indicating a 1:1 stoichiometry between **1** and H₂O₂ (Figure 1).⁶

Besides enhancing the yield of **2**, 2,6-lutidine also accelerated its rate of formation tenfold. The addition of only 0.1 equiv. 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. H₂O₂ revealed that the rate for the formation of **2** was first order in both **1** and H₂O₂. A second order rate constant (*k*₂) of 2.3(1) × 10² M⁻¹s⁻¹ at -40 °C was obtained from the slope of the plot of *k*_{obs} vs. [H₂O₂] (Figure 2 right). Analysis of the Eyring plot for the temperature dependence of this pseudo-first order reaction afforded Δ*H*[‡] = 29(2) kJ/mol and Δ*S*[‡] = -144(10) J/(mol•T) (Figure S1). These values compare favorably with those obtained from the reaction of [Fe^{II}(bispidine)]²⁺ with H₂O₂ to form [Fe^{IV}(O)(bispidine)]²⁺ where rate-determining heterolytic O–O bond scission was proposed, but deviate significantly from synthetic Fe^{III}–OOH(R) systems that undergo homolytic O–O bond cleavage.^{3a}

The effects of 2,6-lutidine (p*K*_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 H₂O₂ to promote *heterolytic* O–O bond cleavage.⁷ As shown in Figure S2, 2,4,6-collidine (p*K*_a = 7.3) and pyridine (p*K*_a = 5.2) also facilitate the formation of **2** with ~90% yield at comparable rates. Weaker bases such as 3-bromopyridine (p*K*_a = 2.84) or 2-acetylpyridine (p*K*_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 (p*K*_a = 0.79) and 2,6-diacetylpyridine (p*K*_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 Glu or to Ala/Val/Gln decreased the rate of Compound I formation by factors of 10⁴ and 10⁶, respectively.^{7a,b} The important role played by protons was further illustrated by the effect of replacing H₂O₂/H₂O with D₂O₂/D₂O, 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.

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 a MeCN ligand while the *anti* site is occupied by the oxo atom.⁵ This requires H₂O₂ 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 H₂O₂ 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 H₂O₂ and enhancing the reaction rates fivefold (See SI). Interestingly, the reaction of H₂O₂ 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 H₂O₂ than **1**.

We have thus identified for the first time a synthetic iron(II) complex that reacts with *stoichiometric* H₂O₂ to generate an oxoiron(IV) complex in nearly quantitative yield. A sizeable 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 H₂O₂ 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 O₂ activation.²

The near-stoichiometric conversion of H₂O₂ 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 H₂O₂. 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)(H₂O)₅]²⁺ species has yet to be experimentally observed *in situ*.¹ However, it has been generated independently by reaction of O₃ with Fe²⁺ in aqueous acidic solution^{14a,b} and was found to be very reactive. Unlike **2**, [Fe^{IV}(O)(H₂O)₅]²⁺ reacts rapidly not only with substrates, but also with residual Fe^{II} to yield Fe^{III} and H₂O₂ to generate HO₂• 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Yield of **2** vs. equiv. H₂O₂ added. Experimental conditions: 2.0 mM **1**, 2.0 mM 2,6-lutidine, -40 °C in CH₃CN. The yield of **2** was determined from its absorption at 820 nm ($\epsilon = 400 \text{ M}^{-1}\text{cm}^{-1}$). Inset: Spectral changes observed during the formation of **2** ($b = 1 \text{ cm}$).

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. H_2O_2 at -40°C). Right panel: $[\text{H}_2\text{O}_2/\text{D}_2\text{O}_2]$ 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.

Scheme 1.

Left: Ligands used in this study.⁴ Right: Proposed mechanism for the base-catalyzed formation of **2** from **1** and H₂O₂.