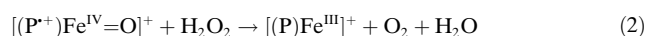
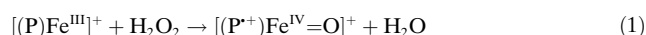


The Reaction of a High-Valent Nonheme Oxoiron(IV) Intermediate with Hydrogen Peroxide**

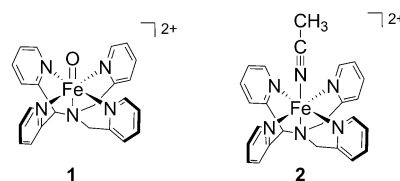
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Reactive oxygen species (ROS) are versatile small molecules that under normal homeostatic control are essential for physiological signaling, whereas an improper balance can lead to aging and age-related diseases.^[1–4] A main regulatory mechanism for the ROS hydrogen peroxide (H₂O₂) is associated with heme enzymes called catalases.^[5,6] These metalloenzymes dismutate two molecules of H₂O₂ via the proposed reaction pathways shown in Equations (1) and (2).^[5–8] Initial oxidation of the Fe^{III} resting state with H₂O₂ generates a high-valent oxoiron(IV) porphyrin π -cation radical, also known as compound I, [(P^{•+})Fe^{IV}=O]⁺, where P = porphyrinate dianion [Eq. (1)]. The reaction of compound I with a second molecule of H₂O₂ results in the return to the resting state of the enzyme with the release of water and dioxygen [Eq. (2)]. Considering the reactivity of compound I toward H₂O₂ in heme enzymes, a similar interaction with H₂O₂ has not been reported for oxoiron(IV) intermediates involved in the catalytic cycles of mononuclear nonheme iron enzymes.^[9–11]



Although the different iron coordination spheres, distal pocket environments, and spin states of the oxoiron(IV) intermediates found in heme and nonheme iron enzymes afford specific oxidative reactivities, similar reactions can occur in both enzyme families, for example C–H bond activation in the nonheme iron enzyme taurine α -ketoglutarate dioxygenase (TauD) and heme-based cytochrome P450 enzymes.^[9–18] These comparable reactions lead to the question of whether and possibly how nonheme oxoiron(IV) species play a role similar to that of catalases in modulating the fate of

H₂O₂. The feasibility of such reactions may first be validated through the use of biomimetic complexes, which also have provided vast insights into the mechanisms of other chemical reactions underlying biological functions of oxoiron(IV) and other iron–oxygen intermediates (for example, organic transformations, electron transfer, and interaction with reactive nitrogen species (RNS)).^[13,16,19–22] Examples of interactions of oxometal complexes with H₂O₂ have been reported, and these generally involve coordination of peroxide to the metal center or exchange of the oxo ligand with peroxide.^[23–27] Alternatively, the direct reaction of H₂O₂ with terminal or bridging oxo ligands through hydrogen atom transfer, generating O₂, has been described for only a few complexes of V, Cr, Mn, and Ru.^[23,27–31] In iron chemistry, reaction of oxoiron(IV) complexes with H₂O₂ has been suggested to occur at intermediate steps upon mixing of Fe^{II} or Fe^{III} complexes with H₂O₂ or O₃, although direct reactivity is difficult to discern owing to the possible existence of multiple species and reaction pathways in these cases.^[32–39] Progress in recent years has made a number of oxoiron(IV) complexes available that can be generated independently of H₂O₂ by artificial oxidants,^[16] thus providing an opportunity to investigate their reactivity toward H₂O₂. Expanding upon investigations of the chemistry between high-valent intermediates found in heme enzymes and H₂O₂,^[7,18,40–42] herein we present evidence of the direct and relatively rapid reaction of a mononuclear nonheme oxoiron(IV) complex, [Fe^{IV}O(N4Py)]²⁺ (**1**; N4Py = *N,N*-bis(2-pyridylmethyl)-*N*-[bis(2-pyridyl)methyl]amine; Scheme 1),^[43,44] with H₂O₂. To the best of our knowledge, this reaction demonstrates for the first time direct H₂O₂ reactivity of a terminal Fe^{IV}=O group of a nonheme iron complex.



Scheme 1. Structures of **1** and **2**.

Starting from [Fe^{II}(N4Py)(CH₃CN)]²⁺ (**2**; Scheme 1), the generation of **1** was carried out with iodosylbenzene (PhIO),^[43,44] which provided oxidation of the Fe^{II} center independently of H₂O₂. As shown in Figure 1a, the characteristic absorption band of **1** ($\lambda_{\text{max}} = 692 \text{ nm}$) disappeared upon the addition of H₂O₂ to a CH₃CN solution of **1** at -20°C , indicating its direct reaction with H₂O₂. The nearly full decay (ca. 94%) of **1** required 0.5 equiv of H₂O₂ with a half-life of

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however, the signal was very weak, indicating that this complex was not present in a substantial amount. The low accumulation of **3** in the reaction of **1** with 0.5 equiv of H₂O₂ could be due to its fast conversion to [Fe^{III}(N4Py)(CH₃CN)]³⁺ (**4**) and self-decay to **2** in CH₃CN or to the possible equilibrium between **3** and the oxo-bridged dimer [(Fe^{III}(N4Py))₂(μ-O)]⁴⁺ (**5**), which is EPR silent (X-band, perpendicular mode) and does not absorb in the visible region (Scheme 2).^[47,48]

To determine kinetic parameters, the reaction of **1** with H₂O₂ was studied under pseudo-first-order conditions. The observed rate constant (*k*_{obs}) for the decomposition of **1** increased linearly with the concentration of H₂O₂ (Figure 3a), whereas no significant change in *k*_{obs} values was observed for varying concentrations of **1** (Supporting Infor-

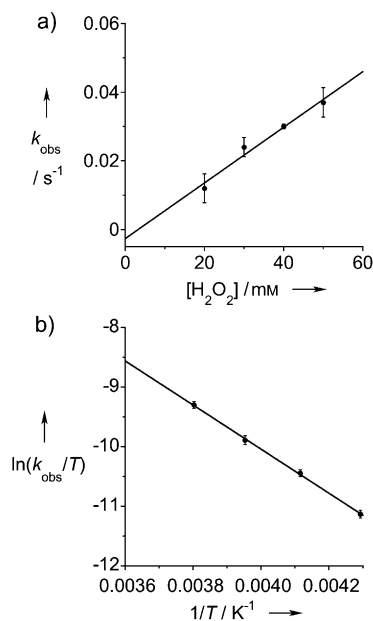
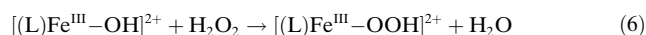


Figure 3. Kinetic and thermodynamic results for the reaction of 1.0 mM **1** in CH₃CN with H₂O₂. a) Plot of the pseudo-first-order rate constant *k*_{obs} versus [H₂O₂] (20–50 mM) to determine the second-order rate constant *k*₂ at –20°C. b) Eyring plot for the reaction of **1** with 20 equiv of H₂O₂ (*T* = 233–263 K).

mation, Figure S6). This behavior indicated a bimolecular reaction with a *k*₂ value of (0.80 ± 0.02) L mol⁻¹ s⁻¹.^[50] Thermodynamic parameters were determined from an Eyring plot for experiments in the temperature range from –40 to –10°C, affording an enthalpy of activation ΔH^\ddagger of (30.8 ± 0.7) kJ mol⁻¹ and an entropy of activation ΔS^\ddagger of (–158 ± 2) J mol⁻¹ K⁻¹ (Figure 3b). In contrast to the reaction of **1** with 0.5 equiv of H₂O₂, the absorption spectra of reactions with an excess of H₂O₂ showed an additional feature at 532 nm that is indicative of [Fe^{III}(N4Py)(OOH)]²⁺ (**6**), which was confirmed by EPR spectroscopy (Supporting Information, Figure S7). These spectroscopic data were consistent with those previously reported for **6**.^[47,51] In the H₂O₂ reaction of **1**, complex **6** may be expected to form from the reaction of **3** with H₂O₂ [Eq. (6)], but pathways involving other Fe^{III} or Fe^{II} species

and ·OOH or excess H₂O₂ are also possible (Supporting Information, Scheme S1).^[47]



For comparison, the reaction of another oxoiron(IV) complex, [Fe^{IV}O(tmc)(CH₃CN)]²⁺ (**7**; tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane),^[52] with H₂O₂ was investigated. The reactivity of this complex in the same solvent (CH₃CN) was significantly lower than that of **1**, yielding a *k*₂ value of (3.5 ± 0.2) × 10⁻² L mol⁻¹ s⁻¹ at 25°C (Supporting Information, Figure S8). This result is consistent with the lower reactivity of **7** (compared to **1**) previously observed in oxidation reactions of organic substrates.^[16,43] On the other hand, the H₂O₂ reactivity of **1** is comparable to that of the oxoruthenium(IV) complex [Ru^{IV}O(bpy)₂(py)]²⁺. When the reaction of **1** with an excess of H₂O₂ was carried out at 25°C, a *k*' value of about 8 L mol⁻¹ s⁻¹ was obtained (*k*' = *k*_{obs}/[H₂O₂]), while a similar value had been reported for the Ru complex, albeit in a different solvent (*k*' = (12.7 ± 1.3) L mol⁻¹ s⁻¹ (25°C, H₂O, pH 7.92)).^[28b] Previous reactivity studies of nonheme oxoiron(IV) complexes have largely been focused on organic substrates. For C–H bond activation mediated by nonheme oxoiron(IV) complexes (including **1**), the bond dissociation energy (BDE) and *k*₂' typically are inversely correlated (*k*₂' = *k*₂/*n*, where *n* is the number of available protons for hydrogen atom transfer).^[16] Complex **1** showed a higher reactivity toward H₂O₂ (*k*₂' = (0.40 ± 0.01) L mol⁻¹ s⁻¹, –20°C) than in C–H bond activation reactions (*k*₂' = 4.6 × 10⁻⁶–0.037 L mol⁻¹ s⁻¹, 25°C, BDE = 81–99 kcal mol⁻¹),^[43] even though the BDE of the O–H bond in H₂O₂ (89.5 kcal mol⁻¹)^[53] falls in the range of the C–H BDEs of the hydrocarbon substrates used. The divergence from the correlation of BDE and *k*₂' is consistent with the greater reactivity of O–H bonds over C–H bonds in HAT mechanisms.^[46] Taken together, complex **1** exhibits significantly greater H₂O₂ reactivity than **7** and is also more reactive toward H₂O₂ than in hydrocarbon C–H bond activation.

The nature of the reaction of the nonheme oxoiron(IV) complex **1** with H₂O₂ presents a new view of iron redox chemistry and potentially of ROS detoxification and/or production. In the context of reactive metal-oxygen intermediates and also the oxidation of organic substrates catalyzed by metalloenzymes or synthetic metal complexes, H₂O₂ is commonly an oxidant.^[6,7,15,16,18] In our study with a nonheme iron model complex, we have demonstrated that H₂O₂ can also function as a reductant resulting in O₂ production. The reaction is related to the HAT mechanism proposed for catalase compound I; however, both mechanisms differ in the ratio of oxoiron(IV) reactant to O₂ product; that is, 2:1 versus 1:1 [Scheme 2, Eqs. (3) and (4)].^[5–7] Our results indicate that the reactivity of oxoiron(IV) species with H₂O₂ or ·OOH within the active site of mononuclear nonheme iron enzymes may be feasible and could be involved in the detoxification or generation of ROS (O₂ versus ·OOH production) depending on the environmental conditions. Although H₂O₂ reactivity has not been documented for oxoiron(IV) intermediates in nonheme iron enzymes, to the best of our knowledge, it is intriguing to

consider this interaction as a possible mechanism in biological systems.

In conclusion, the direct reaction of H₂O₂ with a nonheme oxoiron(IV) complex, generated independently of H₂O₂, was investigated and found to be relatively rapid. Nearly full decay of **1** was achieved with 0.5 equiv of H₂O₂ (2:1) resulting in the formation of an Fe^{III} complex, **2**, and O₂ (Scheme 2). The 2:1 stoichiometry and O₂ generation are consistent with a mechanism involving two HAT steps from H₂O₂ to the Fe^{IV}=O group of **1**. Determination of the bimolecular rate constant under pseudo-first-order conditions revealed that the reaction of **1** with H₂O₂ was more facile than its previously reported reactions with hydrocarbon substrates. In the presence of an excess of H₂O₂, the hydroperoxoiron(III) complex **6** was formed in the course of the reaction, but this was not observed for low equivalents of H₂O₂. The overall observations described herein indicate that if H₂O₂ (and/or ·OOH) can directly react with nonheme oxoiron(IV) intermediates in enzymes, it may be converted into the hydroperoxy radical or O₂ [Eqs. (3) and (4)] and could thus either disrupt or contribute to ROS homeostasis. Therefore, our findings on the interaction of a nonheme oxoiron(IV) complex with H₂O₂ may provide new insight into the reactivity of ROS with high-valent iron centers in both biomimetic complexes and metalloenzymes.

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2.13, and 1.96), which is possibly attributable to $[\text{Fe}^{\text{III}}(\text{N4Py})(\text{CH}_3\text{CN})]^{3+}$ (**4**) or $[\text{Fe}^{\text{III}}(\text{N4Py})(\text{H}_2\text{O})]^{3+}$ (Scheme 2; Supporting Information, Figure S5). Furthermore, Fe^{III} species present upon oxidation of **2** with PhIO ($g = 4.3$) may be due to incomplete formation of **1**. See: a) H. Kotani, T. Suenobu, Y.-M. Lee, W. Nam, S. Fukuzumi, *J. Am. Chem. Soc.* **2011**, *133*, 3249; b) A. Decker, J.-U. Rohde, E. J. Klinker, S. D. Wong, L. Que, Jr., E. I. Solomon, *J. Am. Chem. Soc.* **2007**, *129*, 15983.

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0.5 equiv of D_2O_2 was added to a 1.0 mM solution of **1** in CH_3CN at -20°C , a circa 70% decay of **1** was observed.

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