Mononuclear nonheme ferric-peroxo complex in aldehyde deformylation†

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A mononuclear nonheme ferric-peroxo complex bearing a macrocyclic tetradentate N4 ligand, \([\text{TMC})\text{Fe}^{III}{\text{O}}_2]^+\), was prepared and used in mechanistic studies of aldehyde deformylation; a catalytic aldehyde deformylation by a nonheme iron(II) complex, \([\text{Fe}^{II}(\text{TMC})]^2+\), and molecular oxygen is reported as well.

Ferric-peroxo complexes are frequently implicated as key intermediates in oxidation reactions catalyzed by heme and nonheme iron enzymes. In heme iron enzymes, the participation of a ferric-peroxo species as an active oxidant has been invoked in many cytochrome P450-catalyzed reactions including the aromatization of androgen to estrogen by cytochrome P450 aromatase and the cleavage of the C-17 side chain of progestosterone to form androstenedione by progestosterone 17α-hydroxylase-17,20-lyase. Evidence for the ferric-peroxo species behaving as a nucleophile and attacking an aldehyde carbon has been obtained from mechanistic studies of the enzymes and synthetic ferric-peroxo porphyrin complexes.

In nonheme iron enzymes, a ferric-peroxo species has also been proposed as an active oxidant responsible for the cis-dihydroxylation of aromatic compounds catalyzed by Rieske dioxygenases. Very recently, the crystal structure of a ferric-peroxo intermediate has been obtained in naphthalene dioxygenase, in which the peroxo ligand is bound to the mononuclear iron in a side-on fashion. In biomimetic studies, it has been well-documented that ferric-peroxo complexes are easily prepared by the deprotonation of their corresponding ferric-hydroperoxides upon addition of base (eqn. 1).

Although nonheme ferric-peroxo complexes bearing pentadentate N5 ligands have been well characterized with various spectroscopic techniques including UV-vis, EPR, mass, Mössbauer, resonance Raman, and X-ray absorption spectroscopy, the reactivity of nonheme ferric-peroxo complexes has been rarely investigated in oxidation reactions. In this communication, we report the generation and characterization of a mononuclear nonheme ferric-peroxo complex bearing a macrocyclic tetradentate N4 ligand, \([\text{TMC})\text{Fe}^{III}{\text{O}}_2]^+\) (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), and its reactivity in aldehyde deformylation. A catalytic aldehyde deformylation by a nonheme iron(II) complex, \([\text{Fe}^{II}(\text{TMC})]^2+\), and molecular oxygen (O₂) is reported as well.

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(L)\text{Fe}^{III}{\text{O}}_2 = \frac{\text{base acid}}{(L)\text{Fe}^{III}{\text{O}}_2} \quad (1)
\]

Addition of 10 equiv. H₂O₂ to a solution containing Fe(TMC)-(CF₃SO)₂ and 5 equiv. of triethylamine in CF₃CH₂OH at 0 °C afforded a blue intermediate 1 with a maximum absorption wavelength λ_max at 750 nm (ε 600 M⁻¹ cm⁻¹) (Fig. 1a). The electrospray ionization mass spectrum (ESI MS) of 1 exhibits a prominent ion peak at a mass-to-charge ratio (m/z) of 344.1 (Fig. 1b), whose mass and isotope distribution pattern correspond to [Fe(III)(TMC)(O₂)]⁺ (calculated m/z of 344.1) (Fig. 1b, inset). When the reaction was carried out with isotopically labeled H₂O₂ (90% O₁₈-enriched, 2% H₁₈O₂ in water), a mass peak corresponding to [Fe(III)(TMC)(1⁸O₂)]⁺ appeared at m/z of 348.1 (calculated

![Fig. 1](image-url)
the formation of ketone as a major product via C–C bond cleavage is similar to the reaction of cytochrome P450 progesterone 17α-hydroxylase-17,20-lyase (CYP 45017α), in which a ferric-peroxo porphyrin intermediate is proposed to attack the carbonyl group of progesterone which leads to the formation of androstenedione and acetate (eqn. 3). The pseudo-first-order rate constants increased proportionally with the 2-PPA concentration, leading us to determine a second-order rate constant to be 4.1(2) × 10^{-2} M^{-1} s^{-1} (Fig. 2b). By determining the first-order-rate constants for the deformylation of 2-PPA by I from 273 K to 293 K, we were able to calculate activation parameters of ΔH^0 = 13(1) kcal mol^{-1} and ΔS^0 = -24(2) cal mol^{-1} K^{-1} (Fig. 2c). It is worth noting that [(N4Py)Fe^{III}–O2]^{+} (N4Py = N,N-bis(2-pyridylmethyl)-N-bis(2-pyridyl)methylamine) also reacts with 2-PPA much faster than I at -30 °C, yielding acetophenone as a major product. Further, the nonheme ferric-peroxo complexes (i.e., I and [(N4Py)Fe^{III}–O2]^{+}) react with other electrophiles (e.g., benzoyl chloride and acetic anhydride) at a fast rate. It has been shown in iron porphyrin studies that the reactions of ferric-peroxo porphyrins with electrophiles generate high-valent iron(IV)-oxo porphyrin intermediates. Thus detailed investigations of the reactions of nonheme ferric-peroxo complexes with various electrophiles are underway in this laboratory.

We then investigated the source of the oxygen in the acetophenone product, by carrying out isotope labeling studies. We first confirmed that the oxygen of acetophenone does not exchange with H2^{16}O under our reaction conditions. When 1-^{16}O2, prepared by reacting [Fe(TMC)]^{2+} with H2^{16}O (90% ^{16}O-enriched, 2% H2^{18}O in water), was reacted with 2-PPA under ^{16}O2 atmosphere, we found that > 95% of oxygen in acetophenone was derived from the ^{18}O-labeled peroxo group (eqn. 4) (ESI†, Experimental Conditions). Similarly, the reaction of 1-^{16}O2, prepared by reacting [Fe(TMC)]^{2+} with H2^{16}O2 (2% H2^{18}O in water), with 2-PPA under ^{18}O atmosphere (90% ^{18}O-enriched) afforded an acetophenone product containing less than 3% ^{18}O. These results demonstrate unambiguously that the source of the oxygen in the acetophenone product is not the molecular oxygen but the peroxo group of I. Since it has been shown very recently that [Fe(TMC)]^{2+} binds and activates O2 in alcohol solvents, we attempted to generate I by reacting [Fe(TMC)]^{2+} with O2 in the presence of 5 equiv. triethylamine in (CH3)2CHOH and observed the formation of I (See ESI†, Fig. S1). Interestingly, when the deformylation of 2-PPA (100 equiv., 0.2 M) was carried out in the presence of
and [Fe(BPMEN)]$_2$ turnover number in 2 h). In the absence of the catalyst or base, only a small amount (< 3 TON) of acetoephonone was produced under identical conditions. Further, as we have reported previously that the O$_2$ activation depends on the structure of nonheme iron(II) complexes, the catalytic deformylation of 2-PPA by O$_2$ was not observed with other nonheme iron(II) complexes such as [Fe(TPA)]$_2$ and [Fe(BPMEN)]$_2$ in (CH$_3$)$_2$CHOH under O$_2$ atmosphere, we observed a catalytic deformylation of 2-PPA at 40 equiv. 2-PPA at ~30 °C (2 mM) with 2-PPA at ~30 °C. A study of the effect of the structure of nonheme ferric-peroxo complexes on the reactivity is currently underway in this laboratory.

In summary, we have reported the generation and characterization of a mononuclear nonheme ferric-peroxo complex bearing a tetradentate N$_4$ ligand. By using the in situ generated ferric-peroxo intermediate directly in aldehyde deformylation reactions, we have demonstrated that the nonheme ferric-peroxo complex is capable of conducting aldehyde deformylation. In addition, we have shown that the aldehyde deformylation depends on aldehyde substrates and the ligand structure of nonheme iron ferric-peroxo complexes. By carrying out isolate labeling studies, the source of the oxygen in the deformylated product was shown to be the peroxo group bound to iron. A catalytic aldehyde deformylation by a nonheme iron(II) complex and molecular oxygen has been demonstrated as well. Future studies will focus on attempts at understanding mechanisms of the aldehyde deformylation by nonheme ferric-peroxo complexes and comparing reactivities of ferric-peroxo complexes of heme and nonheme ligands. Finally, the present results raise the possibility that nonheme iron enzymes may participate in aldehyde deformylation reactions, although such enzymes/reactions have not been discovered in biological systems yet.

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Notes and references