Mononuclear nonheme ferric-peroxo complex in aldehyde deformylation†

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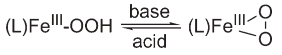
Received (in Cambridge, UK) 21st April 2005, Accepted 21st July 2005
First published as an Advance Article on the web 10th August 2005
DOI: 10.1039/b505562h

A mononuclear nonheme ferric-peroxo complex bearing a macrocyclic tetradentate N4 ligand, [(TMC)Fe^{III}–O$_2$]$^+$, was prepared and used in mechanistic studies of aldehyde deformylation; a catalytic aldehyde deformylation by a nonheme iron(II) complex, [Fe^{II}(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.[1,2] 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 progesterone to form androstenedione by progesterone 17α-hydroxylase-17,20-lyase.[1,3,4] Evidence for the ferric-peroxo species behaving as a nucleophile and attacking an aldehyde carbon has been obtained from mechanistic studies of the enzymes[3,4] and synthetic ferric-peroxo porphyrin complexes.[5–7]

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.[2b,8] 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.[9] 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).[10] 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,[10] 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, [(TMC)-Fe^{III}–O$_2$]$^+$ (**1**) (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, [Fe^{II}(TMC)]$^{2+}$, and molecular oxygen (O$_2$) is reported as well.



$$\mathrm{(L)Fe^{III}\text{-}OOH} \xrightleftharpoons[\text{acid}]{\text{base}} \mathrm{(L)Fe^{III}}\begin{smallmatrix}\mathrm{O}\\ |\\ \mathrm{O}\end{smallmatrix} \qquad (1)$$

Addition of 10 equiv. H$_2$O$_2$ to a solution containing Fe(TMC)-(CF$_3$SO$_3$)$_2$ and 5 equiv. of triethylamine in CF$_3$CH$_2$OH‡ 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)(O$_2$)]$^+$ (calculated *m*/*z* of 344.1) (Fig. 1b, inset). When the reaction was carried out with isotopically labeled H$_2{}^{18}$O$_2$ (90% ^{18}O-enriched, 2% H$_2{}^{18}$O$_2$ in water), a mass peak corresponding to [Fe(III)(TMC)(^{18}O$_2$)]$^+$ appeared at *m*/*z* of 348.1 (calculated

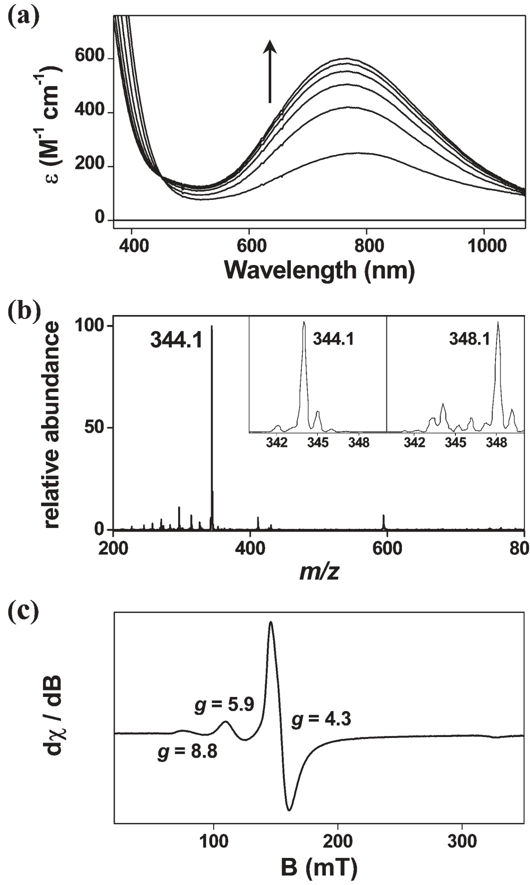


Fig. 1 (a) UV-vis spectral changes showing the formation of **1** upon addition of H$_2$O$_2$ (20 mM) to a solution containing [Fe^{II}(TMC)]$^{2+}$ (2 mM) and triethylamine (10 mM) in CF$_3$CH$_2$OH at 0 °C. (b) Electrospray ionization mass spectrum of **1**. Insets show observed isotope distribution patterns for [Fe(III)(TMC)(^{16}O$_2$)]$^+$ (left panel) and [Fe(III)(TMC)(^{18}O$_2$)]$^+$ (right panel). (c) EPR spectrum of **1**. Instrumental parameters: temperature, 4 K; microwaves, 9.05 GHz at 1 mW; modulation, 100 KHz.

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† Electronic supplementary information (ESI) available: experimental details and Figure S1. See http://dx.doi.org/10.1039/b505562h

m/*z* of 348.1) (Fig. 1b, inset). The X-band EPR spectrum of **1** exhibits an intense signal centered at $g = 4.3$ with two absorption-type features at $g \approx 8.8$ and 5.9 (Fig. 1c), typical of a high-spin ($S = 5/2$) Fe^{III} species. On comparison of the spectral features of **1** to those of the well-characterized nonheme ferric-peroxo complexes,[10] we conclude that a mononuclear ferric-peroxo complex, $[(TMC)Fe^{III}–O_2]^+$, was generated in the reaction of $[Fe^{II}(TMC)]^{2+}$ and H_2O_2 in the presence of base.

We then investigated the reactivity of **1** in aldehyde deformylation, with a precedent that the porphyrin analogue of **1** reacts with aldehydes to give the corresponding deformylated products.[1a,7] Upon addition of 60 equiv. 2-phenylpropionaldehyde (2-PPA)§ to the solution of **1** (2 mM) at 15 °C in CF_3CH_2OH, the intermediate reverted back to the starting iron complex, showing an isosbestic point at 450 nm (Fig. 2a). Pseudo-first-order fitting of the kinetic data allowed us to determine the k_{obs} value to be $4.6(3) \times 10^{-3}$ s^{-1} (Fig. 2a, inset), and product analysis of the reaction mixture with HPLC, LC-MS, GC, and GC-MS revealed that acetophenone was produced predominantly with the formation of formate (eqn. 2) (ESI†, Experimental Conditions).¶‖ It is of interest to note that 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 $450_{17\alpha}$), 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).[4] The pseudo-first-order rate constants increased proportionally with the 2-PPA concentration, leading us to determine a second-order rate constant to be $4.1(2) \times 10^{-2}$ M^{-1} s^{-1} (Fig. 2b). By determining the first-order-rate constants for the deformylation of 2-PPA by **1** from 273 K to 293 K, we were able to calculate activation parameters of $\Delta H^{\ddagger} = 13(1)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -24(2)$ cal mol^{-1} K^{-1} (Fig. 2c). It is worth noting that $[(N4Py)Fe^{III}–O_2]^+$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine)[10g] also reacts with 2-PPA much faster than **1** at −30 °C, yielding acetophenone as a major product.** Further, the nonheme ferric-peroxo complexes (*i.e.*, **1** and $[(N4Py)Fe^{III}–O_2]^+$) 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.[5] Thus detailed investigations of the reactions of nonheme ferric-peroxo complexes with various electrophiles are underway in this laboratory.[11]

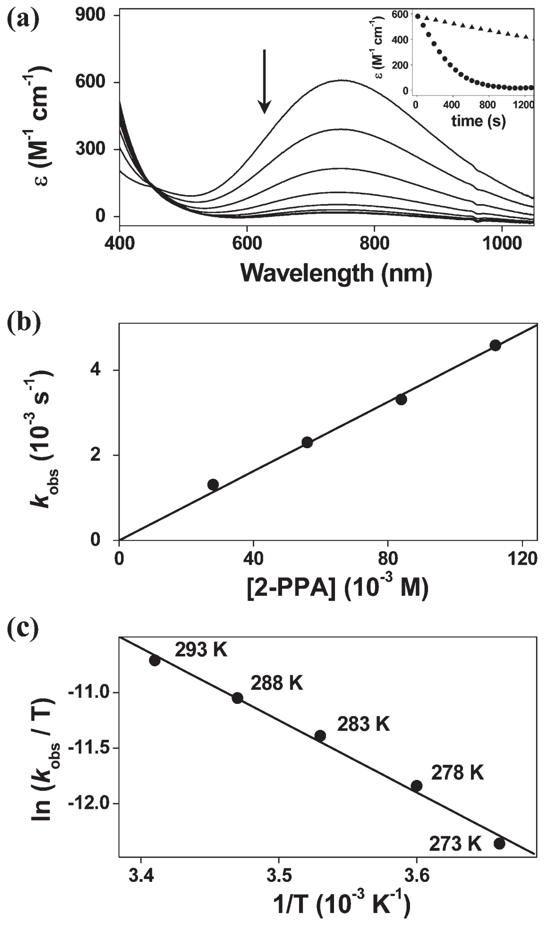
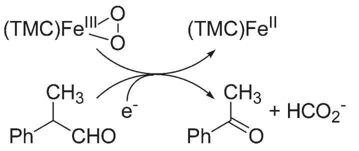
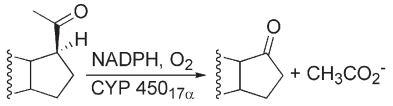


Fig. 2 Reactions of **1** with 2-phenylpropionaldehyde (2-PPA). (a) UV-vis spectral changes of **1** (2 mM) upon addition of 2-PPA (60 equiv., 120 mM) at 15 °C. Inset shows absorbance traces monitored at 750 nm (● for the reaction of **1** and ▲ for the natural decay). (b) Plot of k_{obs} against 2-PPA concentration to determine a second-order rate constant at 15 °C. (c) Plot of first-order rate constants against $1/T$ to determine activation parameters for the reaction of **1** (2 mM) and 2-PPA (60 equiv., 120 mM).

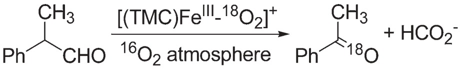


(2)



(3)

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 $H_2{}^{18}O$ under our reaction conditions. When **1**-$^{18}O_2$, prepared by reacting $[Fe(TMC)]^{2+}$ with $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 2% $H_2{}^{18}O_2$ in water), was reacted with 2-PPA under $^{16}O_2$ 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**-$^{16}O_2$, prepared by reacting $[Fe(TMC)]^{2+}$ with $H_2{}^{16}O_2$ (2% $H_2{}^{16}O_2$ in water), with 2-PPA under $^{18}O_2$ 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 **1**.[4]



$$PhCH(CH_3)CHO \xrightarrow[{}^{16}O_2\ \text{atmosphere}]{[(TMC)Fe^{III}-{}^{18}O_2]^+} PhC(CH_3)={}^{18}O + HCO_2^- \quad (4)$$

Since it has been shown very recently that $[Fe(TMC)]^{2+}$ binds and activates O_2 in alcohol solvents,[12] we attempted to generate **1** by reacting $[Fe(TMC)]^{2+}$ with O_2 in the presence of 5 equiv. triethylamine in $(CH_3)_2CHOH$ and observed the formation of **1** (See ESI†, Fig. S1). Interestingly, when the deformylation of 2-PPA (100 equiv., 0.2 M) was carried out in the presence of

$[\mathrm{Fe(TMC)}]^{2+}$ (2 mM) and triethylamine (5 equiv., 10 mM) at 25 °C in $\mathrm{(CH_3)_2CHOH}$ under O_2 atmosphere, we observed a catalytic conversion of the substrate to acetophenone and formate (20(2) turnover number in 2 h).¶ In the absence of the catalyst or base, only a small amount ($<$ 3 TON) of acetophenone 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,[12] the catalytic deformylation of 2-PPA by O_2 was not observed with other nonheme iron(II) complexes such as $[\mathrm{Fe(TPA)}]^{2+}$ (TPA = tris(2-pyridylmethyl)amine), $[\mathrm{Fe(N4Py)}]^{2+}$, and $[\mathrm{Fe(BPMEN)}]^{2+}$ (BPMEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane) in the presence of triethylamine under the conditions.

In summary, we have reported the generation and characterization of a mononuclear nonheme ferric-peroxo complex bearing a tetradentate N4 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 isotope 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.

This work was supported by the Ministry of Science and Technology of Korea through the Creative Research Initiative Program.

Notes and references

‡ **1** was formed in alcohol solvents such as $\mathrm{CH_3OH}$, $\mathrm{C_2H_5OH}$, *etc*; however, the formation and stability of **1** were different depending on the alcohols. Since **1** showed a high stability and better spectroscopic data in $\mathrm{CF_3CH_2OH}$, the characterization and kinetic studies of **1** were performed in $\mathrm{CF_3CH_2OH}$.

§ It is worth noting that the reaction of **1** with other aldehydes such as phenylacetaldehyde and 2-methyl-2-phenylpropionaldehyde was found to depend on the structure of the aldehydes. Although a similar observation was reported in ferric-peroxo porphyrin complex-mediated aldehyde deformylation reactions,[7] the dependence of the reactivity of **1** on the substrate structure is not clear at this moment and detailed investigations are underway in this laboratory.

¶ The formation of 2-phenylpropionic acid, which is a product in the oxidation of 2-phenylpropionaldehyde by oxoiron(IV) porphyrin π-cation radicals,[7] was not observed in this reaction. The formation of desaturation product (*i.e.*, styrene) was not detected either. Formate was produced in about an equimolar amount with respect to acetophenone.

‖ The deformylation of 2-PAA to acetophenone and formate involves four electrons, whereas three electrons are involved in the conversion of **1** to the corresponding iron(II) species. Although we do not know the source of the other electron at this moment, it may be suggested that one electron comes from triethylamine present in the reaction solution.

** The ferric-peroxo complex, $[\mathrm{(N4Py)Fe^{III}{-}O_2}]^+$, was prepared by a literature method.[10b,10g] The reaction of $[\mathrm{(N4Py)Fe^{III}{-}O_2}]^+$ (2 mM) with 40 equiv. 2-PPA at −30 °C completed within 1 min, whereas **1** did not react 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.

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