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Evidence for the participation of a high-valent iron–oxo species in stereospecific alkane hydroxylation by a non-heme iron catalyst

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The incorporation of ^{18}O from $H_2{}^{18}O$ into the product of stereospecific alkane hydroxylation by $[Fe^{II}(bpmen)(CH_3CN)_2](ClO_4)_2$–$H_2O_2$ provides the first strong evidence for the participation of a high-valent iron–oxo species in the mechanism of a non-heme iron catalyst.

The mechanisms for stereospecific hydrocarbon oxidation catalysed by iron-containing metalloenzymes have attracted significant interest in the chemical and biochemical communities.[1–3] Discrete high-valent iron-oxo species, formally Fe^V=O, have been proposed as oxidants in these reactions, *i.e.* a $[(Por\cdot)Fe^{IV}=O]^+$ species in alkane and alkene oxidation by cytochrome P450[1] and an $Fe^{IV}{}_2(\mu\text{-}O)_2$ intermediate in methane hydroxylation by methane monooxygenase.[4] In synthetic efforts to mimic these biological catalysts, both heme[5] and non-heme iron complexes[6,7] have been shown to be capable of catalysing alkane hydroxylation. Strong evidence has been obtained for the involvement of high-valent metal–oxo species on reactions involving some heme complexes and H_2O_2 from $H_2{}^{18}O$ exchange experiments,[8–11] but not for corresponding non-heme iron catalysts.[12,13] We have previously reported the first and thus far only example of stereospecific alkane hydroxylation by a non-heme iron catalyst, $[Fe^{II}(tpa)(CH_3CN)_2](ClO_4)_2$ **1** [tpa = tris(2-pyridylmethyl)amine, Fig. 1], in combination with H_2O_2.[7] Reported here are further studies on alkane hydroxylation by H_2O_2 catalysed by a related iron complex, $[Fe^{II}(bpmen)(CH_3CN)_2](ClO_4)_2$ **2** [bpmen = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethylene-1,2-diamine, Fig. 1], which exhibits higher catalytic activity. The incorporation of $H_2{}^{18}O$ into the oxidation product provides the first evidence that a non-heme iron catalyst can hydroxylate alkanes stereospecifically *via* a high-valent iron–oxo species.

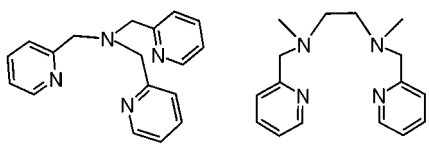


Fig. 1 Tetradentate ligands for non-heme Fe^{II} complexes **1** and **2**.

Complex **2** can be prepared from the reaction of equimolar amounts of $Fe^{II}(ClO_4)_2{\cdot}6H_2O$ and the ligand bpmen[14] in CH_3CN under Ar. Addition of diethyl ether into the CH_3CN solution gives a red solid, which can be recrystallised from CH_3CN–diethyl ether at 4 °C to afford red crystals suitable for crystallographic analysis (Fig. 2).† The crystal structure of **2** shows an iron(II) coordination sphere like that of **1**[15] with two solvent molecules in a *cis* geometry.

The alkane hydroxylation ability of **2** is superior to that of **1**. Under syringe pump conditions in CH_3CN solution in air,[7] 0.7 mM **2** catalyses the oxidation of cyclohexane with 10 equiv. H_2O_2 to afford 5.6(5) turnover (TN) of cyclohexanol and 0.7(2) TN of cyclohexanone within 30 min. The products account for 70% of the oxidant H_2O_2, which is much higher than the 40% conversion exhibited by **1**.[7] The high alcohol/ketone ratio obtained for **2** in air contrasts the much smaller ratios diagnostic of radical chain autoxidation found for other nonheme iron catalysts[6] and suggests the participation of a metal-based oxidant, as proposed in **1**–H_2O_2.[7]

Further mechanistic insight comes from ^{18}O-labeling experiments in the hydroxylation of cyclohexane.‡ With 10 equiv. H_2O_2 in the presence of 1000 equiv. $H_2{}^{18}O$, 18(3)% of the oxygen atom in the cyclohexanol product is ^{18}O-labeled. The complementary experiments with 10 equiv. $H_2{}^{18}O_2$ in the presence of 1000 equiv. H_2O show 84(4)% ^{18}O-labeled alcohol. These results demonstrate that O_2 is not involved in the reaction of **2**–H_2O_2. Furthermore, ^{18}O-incorporation can be significantly affected by the amount of $H_2{}^{18}O$ in the reaction solution. For example, with 200 equiv. $H_2{}^{18}O$, only 13(1)% of the cyclohexanol product is ^{18}O-labeled; and this value decreases further to 5.8(1)% in the presence of 50 equiv. $H_2{}^{18}O$. These observations show that the mechanism of alkane hydroxylation by **2**–H_2O_2 involves an oxidant capable of oxygen atom exchange with H_2O in competition with C–O bond formation.

The **2**–H_2O_2 combination is also capable of stereospecific alkane hydroxylation. The reaction of *cis*-1,2-dimethylcyclohexane with **2**–H_2O_2 affords 4.6(1) TN of *cis*-1,2-dimethylcyclohexanol and no isomeric *trans*-alcohol product. More interestingly, 26(1)% of the *cis*-alcohol product is ^{18}O-labeled when the reaction is carried out in the presence of 10 equiv. H_2O_2 and 1000 equiv. $H_2{}^{18}O$. Therefore, the oxidant responsible for stereospecific alkane hydroxylation can undergo oxygen-atom exchange with H_2O. Since the rate of epimerization of tertiary carbon radicals is quite fast (10^9 s^{-1}),[16] ^{18}O-exchange very likely happens prior to the interaction of the iron-based oxidant and the alkane C–H bond.

A mechanism for alkane hydroxylation by **2**–H_2O_2 combination is proposed based on the recent characterisation of Fe^{III}–OOH intermediates for several non-heme iron complexes

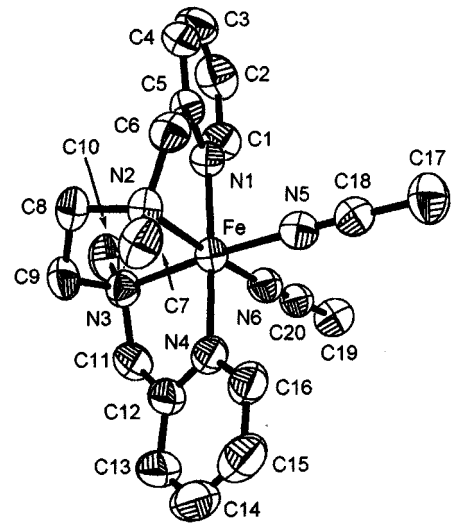
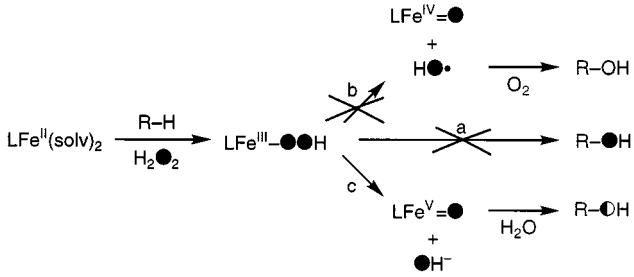


Fig. 2 Thermal ellipsoid plot of complex **2**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.



Scheme 1

(Scheme 1).[6j,7,17] Such an intermediate could attack the substrate directly [Scheme 1(a)] or undergo prior O–O bond scission. For the latter cases, homolysis of the O–O bond would afford Fe^{IV}=O and HO· [Scheme 1(b)], while heterolysis would give rise to Fe^{V}=O and HO^- [Scheme 1(c)]. The stereospecificity of *cis*-1,2-dimethylcyclohexane hydroxylation and lack of O_2 involvement in the reaction exclude the participation of hydroxyl radicals.[18] The observation of solvent exchange eliminates the possibility of direct attack of the Fe^{III}–OOH intermediate on the alkane substrate, since solvent exchange could not occur with such a species. The remaining mechanistic option is the heterolysis of the O–O bond to form a formally Fe^{V}=O species analogous to the $[(Por\cdot)Fe^{IV}=O]^+$ species observed for heme peroxidases and proposed for cytochrome P450.[1] Such a species would be capable of solvent exchange, provided its lifetime is long enough.[8–11, 19] Since solvent exchange is indeed observed for the stereospecific oxidation of *cis*-1,2-dimethylcyclohexane, a formally Fe^{V}=O intermediate must be involved in the **2**–H_2O_2 reaction. Complex **2** thus represents the first non-heme iron alkane hydroxylation catalyst for which evidence for a high-valent iron–oxo species has been obtained. Further studies into the nature of this species are in progress.

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Notes and references

† *Selected analytical data for* **2**. Elemental analysis. Calc. for $C_{20}H_{28}Cl_8FeN_6O_8$: C, 39.56; H, 4.65; N, 13.84; Cl, 11.68. Found: C, 39.41; H, 4.57; N, 13.76; Cl, 11.61%. X-Ray crystal data for $C_{20}H_{28}Cl_2FeN_6O_8$: M = 607.23, orthorhombic, space group $P2_12_12_1$, a = 9.984(2), b = 15.039(4), c = 17.653(2) Å, V = 2650.6(9) Å^3, T = 293(2) K, D_c = 1.522 g cm^{-1}, Z = 4, μ = 0.826 mm^{-1}, R [$I > 2\sigma(I)$] = 0.052 for 4642 independent reflections of the 5268 collected, R (all data) = 0.085. CCDC 182/1292. See http://www.rsc.org/suppdata/cc/1999/1375/ for crystallographic files in .cif format.

‡ $H_2{}^{18}O_2$ (ICON, 90%) or $H_2{}^{18}O$ (Isotec, 88.8% or ICON, 85 or 95%) was added to the reaction solutions in parallel experiments. Each product solution was treated with 0.1 mL 1-methylimidazole and 1 mL acetic anhydride to esterify the alcohol product (L. E. Elvebak, II, T. Schmitt and G. R. Gray, *Carbohydr. Res.*, 1993, **246**, 1). ^{18}O-incorporation was analysed by GC–CIMS (HP 5898, DB-5, and Finnigan MAT 95) with NH_3 as ionisation gas. Control experiments showed that cyclohexanol does not exchange its oxygen atom with H_2O under the experimental conditions.

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