

Stereospecific Alkane Hydroxylation with H₂O₂ Catalyzed by an Iron(II)–Tris(2-pyridylmethyl)amine Complex

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The stereospecific functionalization of aliphatic C–H bonds is an important goal for chemistry and biochemistry.¹ While such transformations can be carried out by organic peroxides in a stoichiometric fashion,² the prospect of using metal complexes and cheap and environmentally friendly oxidants (e.g., O₂, H₂O₂) to carry out such reactions catalytically has aroused considerable interest in these endeavors.^{3,4} The latter has been inspired by metalloenzymes such as cytochrome P450,⁵ which utilize a heme center for catalysis. Iron porphyrin complexes can be used as catalysts for stereospecific hydroxylation of hydrocarbons;⁶ however, the susceptibility of the porphyrin to oxidative self-degradation and the usual requirement for an expensive oxidant like PhIO have limited the utility of this approach.⁷ Our long-standing interest in oxygen activating nonheme iron enzymes such as methane monooxygenase⁸ has stimulated our efforts to use nonheme iron complexes to catalyze this chemistry.^{9,10} The combination of an iron complex with peroxides is often considered to afford Haber–Weiss chemistry,¹¹ generating hydroxyl (or alkoxy) radicals that initiate radical chain autoxidation reactions.^{12,13} In these reactions, alkanes typically afford alcohol (A) and ketone (K) products with an A/K ratio of about 1, while alkenes yield mostly allylic oxidation products. This pattern of reactivity does not appear to hold for the combination of [Fe(TPA)(CH₃CN)₂](ClO₄)₂ (**1**, TPA = tris(2-pyridylmethyl)amine) with H₂O₂.

Herein, we report the details of its reactivity and present evidence for an [Fe(TPA)(OOH)]²⁺ intermediate.

Complex **1** is a low-spin six-coordinate Fe(II) complex.¹⁴ Under the syringe pump conditions used for the hydroxylation of cyclohexane with [Fe₂O(TPA)₂(H₂O)₂]⁴⁺ (**2**) and ¹BuOOH,¹⁰ 0.7 mM **1** reacts with 10 equiv of H₂O₂ and 1000 equiv of cyclohexane in CH₃CN to afford 3.0 equiv of cyclohexanol and 0.7 equiv of cyclohexanone in the course of 15 min (Table 1); essentially the same results are obtained under Ar or in air. This reactivity is comparable to that of [Fe(TTP)Cl]/PhIO^{6c} (TTPH₂ = *meso*-tetrakis(*p*-tolyl)porphyrin) but superior to those of other nonheme iron catalysts with H₂O₂ as oxidant which afford lower oxidant-to-product conversions and smaller A/K ratios.^{15,16} Even more significant is the oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane to afford tertiary alcohol products with >99% retention of stereochemistry (Table 1). This high stereospecificity of hydroxylation is comparable to those found for [Fe-(porphyrin)Cl]/PhIO^{6b–d} and for stoichiometric organic peroxide oxidants such as perfluorodialkyldioxiranes, perfluorodialkylloxaziridines, and *p*-nitroperoxybenzoic acid,² but is not observed when hydroxyl radicals are involved.^{6c} To our knowledge, **1** is the first example of a nonheme iron catalyst/H₂O₂ combination capable of stereospecific alkane hydroxylation.¹⁷

Several lines of evidence suggest that the **1**/H₂O₂ combination generates an oxidant distinct from that typically associated with Haber–Weiss chemistry: (1) the fact that alcohol is the major oxidation product, (2) the insensitivity of the reaction to the presence of O₂, and (3) the stereospecificity of hydroxylation. Furthermore, the oxidant is capable of oxygen atom insertion into olefins, affording only epoxide products with complete retention of stereochemistry (Table 1). Lastly, the kinetic isotope effect for cyclohexanol formation is 3.5, a value indicative of an oxidant more selective than the hydroxyl radical (*k_H/k_D* = 1–2).¹⁸ These observations implicate a metal-based oxidant.

What is the nature of this iron oxidant? Among catalytic nonheme iron systems that utilize H₂O₂ as oxidant, iron(III)–peroxo species are often invoked as reaction intermediates, but in only two cases has some spectroscopic evidence for such species been reported.^{16b,c} With this system, we are able to trap a possible reaction intermediate (**3**) at –40 °C (70% yield) by treatment of **1** with 10 equiv of H₂O₂ in CH₃CN. Intermediate **3** exhibits UV–vis (*λ*_{max} = 538 nm, Figure 1a) and EPR properties (*S* = 1/2; *g* = 2.19, 2.15, and 1.97; Figure 1b), similar to those of previously reported for low-spin [Fe^{III}(TPA)(H₂O)(OO^tBu)]²⁺ derived from reaction of **1** or **2** with ¹BuOOH in CH₃CN at –40 °C.^{14,19} Electrospray ionization mass spectrometry of **3** shows prominent ion clusters at *m/z* 478, 461, and 445, which have mass values and isotope patterns consistent with

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(15) For comparison, we list the percent conversions of oxidant to alcohol, the A/K ratios, and reaction times for other nonheme iron catalyst/H₂O₂ systems reported thus far: Fe(ClO₄)₃, 25%, 2, 6 h;^{13a} Fe₂O(bpy)₂(O₂CCH₃)₂-Cl₂, 4%, 1, 6 h;^{13a} [Fe₂O(tmima)₂(O₂CCH₃)](ClO₄)₃, 4%, 1, 6 h;^{13a} [Fe₂O-(bpy)₂(H₂O)₂](ClO₄)₄, 12%, 1.5, 0.5 h;^{16a} [Fe(PMA)]²⁺, 5%, 1, 0.5 h;^{16b} [Fe(N₄Py)(CH₃CN)](ClO₄)₂, 13%, 2.6, 0.5 h.^{16c}

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Table 1. Stereospecific Hydrocarbon Oxidations by H₂O₂ Catalyzed by [Fe(TPA)(CH₃CN)₂]²⁺ (**1**)^a

substrate	product	turnover number ^b
cyclohexane	cyclohexanol	3.0
	cyclohexanone	0.7
	cyclohexene	0.1
<i>cis</i> -1,2-dimethylcyclohexane	<i>cis</i> -1,2-dimethylcyclohexanol	3.6
	2,3- and 3,4-dimethylcyclohexanol ^c	1.2
	1,2- and 1,6-dimethylcyclohexene	trace
<i>trans</i> -1,2-dimethylcyclohexane	<i>trans</i> -1,2-dimethylcyclohexanol	1.3
	2,3- and 3,4-dimethylcyclohexanol ^c	1.3
	1,2- and 1,6-dimethylcyclohexene	trace
1-hexene	1,2-epoxyhexane	2.1
<i>cis</i> -2-hexene	<i>cis</i> -2-hexene oxide	2.3
<i>trans</i> -2-hexene	<i>trans</i> -2-hexene oxide	2.2

^a Reaction conditions: 0.3 mL of a 70 mM H₂O₂ solution in CH₃CN was delivered by syringe pump over 15 min at room temperature to a stirred 2.7 mL CH₃CN solution containing 0.7 mM **1** and 700 mM substrate. All of the oxidant was consumed as indicated by iodometry. No products were observed in the absence of catalyst. ^b Moles of product/moles of catalyst. Products listed were identified based on GC and NMR analysis and comparisons with standards, and no other products were observed. ^c These were identified by comparison with commercially available mixtures of the isomeric secondary alcohols and not individually assigned.

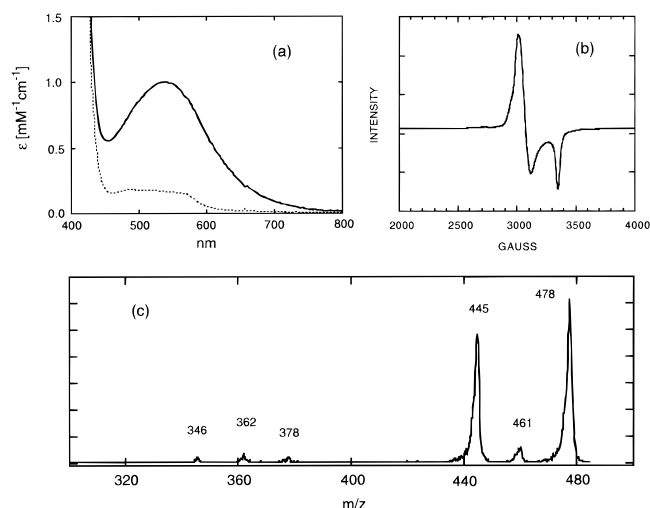


Figure 1. Spectroscopic properties of [Fe(TPA)(OOH)]²⁺ (**3**). (a) UV-vis spectrum in CH₃CN at -40 °C (solid line). For comparison, the spectrum of [Fe(TPA)(CH₃CN)₂]²⁺ (**1**) is shown in dashed lines. (b) EPR spectrum in CH₃CN at -40 °C. (c) Electrospray ionization mass spectrum.

the ions {[Fe(TPA)(OOH)](ClO₄)}⁺, {[Fe(TPA)(O)](ClO₄)}⁺, and {[Fe(TPA)](ClO₄)}⁺, respectively (Figure 1c). The latter two ions derive from the respective loss of HO• and HOO• fragments from {[Fe(TPA)(OOH)](ClO₄)}⁺. Taken together, the data indicate that intermediate **3** is best formulated as [Fe^{III}(TPA)(OOH)]²⁺.

At present we cannot establish the mechanism of oxidation, but it is clear that **1**/H₂O₂ behaves differently from 2/^tBuOOH. The latter in alkane hydroxylation reactions has been shown to generate a long-lived alkyl radical that can be trapped with O₂;¹⁰ in agreement, we have found that 2/^tBuOOH affords the two epimeric tertiary alcohol products in the hydroxylation of *cis*-

1,2-dimethylcyclohexane. Furthermore, unlike **1**/H₂O₂, 2/^tBuOOH cannot epoxidize olefins. The resemblance in reactivity of **1**/H₂O₂ to heme catalysts suggests that similar mechanisms may apply to both types of catalysts. The heme paradigm for alkane hydroxylation²⁰ involves hydrogen atom abstraction from substrate by a formally Fe^V=O species and rapid capture of the nascent alkyl radical by oxygen rebound; the high-valent iron-oxo species would also be responsible for oxygen atom insertion into olefins. Since the nonheme ligand environment of **1** may not support an Fe^V oxidation state, an alternative worth considering is a mechanism involving direct oxygen atom insertion by an (η²-peroxo)metal intermediate,²¹ as proposed for early transition metal peroxides that carry out stereospecific epoxidations.²² An [Fe(TPA)(η²-OOH)]²⁺ structure for **3** is consistent with the spectroscopic data obtained thus far and would account for its distinct reactivity from that of the related [Fe(TPA)(H₂O)(η¹-OO^tBu)]²⁺,^{10,20} but more work is needed to sort out these alternative mechanisms.

Irrespective of the structure of **3**, it is clear that **1** can catalyze stereospecific hydrocarbon oxidations with H₂O₂. Chiral groups may then be conveniently incorporated into the relatively simple TPA framework²³ to afford catalysts capable of enantiospecific alkane hydroxylation.

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