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Fe(TPA)-catalyzed alkane hydroxylation can be a metal-based oxidation

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Abstract

The hydroxylation of cyclohexane by t-butyl hydroperoxide using $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (**1**, TPA = tris(2-pyridylmethyl)amine) as the catalyst has been investigated with the use of a syringe pump to control the concentration of the alkyl hydroperoxide. Unlike an alkoxy radical-based radical chain autoxidation mechanism, the reaction observed produces only alcohol (no ketone) with a deuterium kinetic isotope effect of 10, similar to heme-catalyzed hydroxylations. An alkylperoxoiron(III) intermediate can be trapped at −40°C and characterized by a number of spectroscopic methods. A mechanistic scheme is proposed involving this intermediate which either serves as the precursor to the metal-based oxidant or oxidizes the substrate directly.

Keywords: Nonheme iron complexes; Oxygen activation; Alkylperoxide intermediates

Nonheme iron complexes have recently been investigated as catalysts for cyclohexane oxidation to model the reactivity of nonheme iron centers in enzymes such as methane monooxygenase [1–15]. A subset of these typically use a (μ-oxo)diiron(III) complex in concert with an alkyl hydroperoxide, usually t-butyl hydroperoxide, to afford good yields of cyclohexanol and cyclohexanone [8–14]. We have carried out a systematic investigation of Fe(TPA) [1] complexes and proposed the involvement of a metal-based oxidant, either a metal–peroxide intermediate or a high-valent iron–oxo species derived therefrom in the alkane oxidation reactions [11–14], i.e.,

$$R\text{–H} + (L\text{Fe}^{\text{III}} - \text{OO}R \text{ or } L\text{Fe}^{\text{V}}\text{=O}) \rightarrow R\cdot + L\text{Fe}^{\text{IV}}\text{–OH} \rightarrow R\text{–OH} + L\text{Fe}^{\text{III}} \quad (1)$$

in a mechanism somewhat analogous to that attributed to the heme center in cytochrome P450. Evidence to support this hypothesis included the interception of the oxidant by dimethyl sulfide producing dimethyl sulfoxide and, more importantly, the modulation of the selectivity of the catalyst by the metal ligands as indicated by deuterium isotope effects and adamantane 3°/2° ratios [11,12].

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[1] Abbreviations: CmOOH, cumene hydroperoxide; EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate; TMP, *meso*-tetramesitylporphinate dianion; TPA, tris(2-pyridylmethyl)amine; TPP, *meso*-tetraphenylporphinate dianion.

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Alternatively, the alkane oxidations may involve an alkoxy radical derived from the metal-catalyzed decomposition of the alkyl hydroperoxide, which can then initiate a radical chain autoxidation mechanism in the presence of oxygen. Arends et al. [15] in particular have favored the latter mechanism on the basis of three observations: (a) that the alcohol-to-ketone (A/K) ratios reported for the Fe(TPA) catalysts were typically 1:1 or favored ketone formation; (b) that a vigorous Ar purge significantly decreased the amount of oxidized products; and (c) that the use of 2-methyl-1-phenyl-2-propyl hydroperoxide in place of tBuOOH did not afford substrate oxidation because of the propensity of the corresponding alkoxy radical to undergo β-cleavage before being able to react with the substrate. The approximate 1:1 A/K ratio observed for these reactions suggested the involvement of alkylperoxy radicals which can disproportionate via Russell termination steps [16], such as

$$2C_6H_{11}OO\cdot \rightarrow C_6H_{11}OH + C_6H_{10}O + O_2 \quad (2)$$

$$C_6H_{11}OO\cdot + tBuOO\cdot \rightarrow C_6H_{10}O + tBuOH + O_2 \quad (3)$$

to yield ketone in amounts at least equal to those of alcohol. The alkylperoxy radicals could derive from a series of steps initiated by the Haber–Weiss decomposition of tBuOOH by the Fe(TPA) catalyst, i.e.,

$$Fe^{III}(TPA) + tBuOOH \rightarrow Fe^{II}(TPA) + tBuOO\cdot + H^+ \quad (4)$$

$$Fe^{II}(TPA) + tBuOOH \rightarrow Fe^{III}(TPA) + tBuO\cdot + OH^- \quad (5)$$

$$tBuO\cdot + tBuOOH \rightarrow tBuOH + tBuOO\cdot \quad (6)$$

$$2tBuOO\cdot \rightarrow 2tBuO\cdot + O_2 \quad (7)$$

$$tBuO\cdot + R\text{–}H \rightarrow tBuOH + R\cdot \quad (8)$$

$$R\cdot + O_2 \rightarrow ROO\cdot \quad (9)$$

Thus, the alcohol and ketone products formed by this mechanism would derive solely from an O_2-dependent reaction.

While the arguments put forth by Arends et al. [15] persuasively implicate a radical chain autoxidation mechanism, this mechanism does not satisfactorily rationalize the effect of dimethyl sulfide nor the ligand dependence of catalyst selectivity [11,12]. We have thus sought to find conditions under which the radical chain autoxidation mechanism may be suppressed. Since the source of O_2 in the radical chain autoxidation mechanism is the bimolecular decomposition of t-butylperoxy radical (Eq. (7)), the amount of O_2 evolved may be minimized by reducing the concentration of the t-butyl hydroperoxide precursor.

A typical catalytic reaction consisted of a mixture of the catalyst, $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (**1**), tBuOOH, and cyclohexane in a 1:150:1000 ratio in CH_3CN under Ar, and the alkyl hydroperoxide was consumed within 15 min. Usually the 150 eq. of tBuOOH were added all at once at the beginning of the reaction, so a significant amount of O_2 was evolved [11–14]. Under these conditions, **1** afforded 8 eq. cyclohexanol (A) and 16 eq. cyclohexanone (K) for an A/K ratio of 0.5 and a conversion efficiency of 16% from $ROOH$ (Table 1, run #1). In addition, 16 eq. cyclohexyl t-butyl peroxide were produced, presumably from a radical–radical combination reaction (Eq. (10)) or its equivalent.

$$R\cdot + tBuOO\cdot \rightarrow R\text{–}OOtBu \quad (10)$$

If the concentration of alkyl hydroperoxide was controlled by delivering the 150 eq. tBuOOH via syringe pump over the course of the reaction, the formation of alcohol was favored over ketone, making the A/K ratio 2 (Table 1, run #2). Further decreases of the concentration of tBuOOH reduced the yields of ketone and dialkyl peroxide significantly and increased the efficiency of conversion of tBuOOH to product alcohol dramatically (Fig. 1) [14]. With 10 eq. tBuOOH or less, *alcohol was the only product observed in the reaction!*

Table 1
Product distributions for the oxidation of cyclohexane by **1** [a]

Run	tBuOOH (eq.)	Syringe pumped [b]	*A*	*K*	*A*/*K*	% Conversion [c]	tBuOOCy
1	150	no [d]	8	16	0.5	16	16
2	150	yes	18	9	2.0	18	21
3	50	yes	10	1.0	10	22	5.5
4	20	yes	5.5	0.3	18	30	0.4
4a	20/air	yes	3.7	4.4	0.8	41	0.1
5	10	yes	4.0	–		40	–
5a	10/Me_2S [e]	yes	0.3	–		38 [e]	–
6	1	yes	0.55	–		55	–

[a] Values reported as mol product/mol catalyst. Reaction conditions: 0.7 mM complex, 0.7 M cyclohexane, 3 ml CH_3CN solvent, 25°C under argon. *A* = cyclohexanol, *K* = cyclohexanone and tBuOOCy = t-butylcyclohexyl peroxide.
[b] 0.3 ml of an appropriately diluted tBuOOH solution in CH_3CN was delivered by syringe pump over the time course of the reaction.
[c] % conversion of the initial ROOH.
[d] All 150 eq. tBuOOH added at once at the start of the reaction.
[e] 50 eq. of Me_2S added; 3.5 eq. Me_2SO formed in the reaction.

The diminishing amounts of ketone and dialkyl peroxide observed in the syringe pump experiments indicate that the radical chain autoxidation mechanism is becoming less favored under these conditions. Indeed when one of the syringe pump experiments was carried out in the presence of air, an *A*/*K* ratio close to unity was obtained instead (Table 1, run #4a). This result shows that alkyl radicals are formed in the reaction and that they can be trapped by O_2 if it were present. However, the predominant production of alcohol (*A*/*K* of 18) in the corresponding run #4 under Ar (Table 1, run #4) demonstrates that little or no O_2 is formed and trapped by the nascent alkyl radical under these conditions.

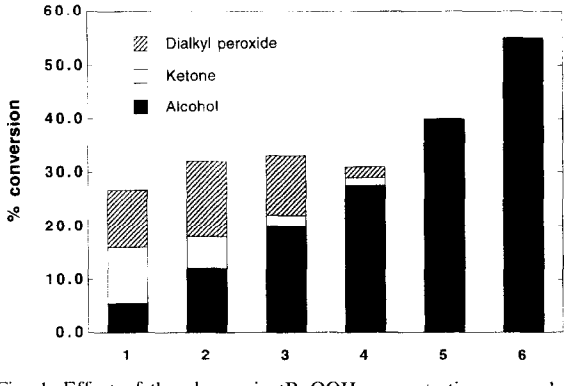


Fig. 1. Effect of the change in tBuOOH concentration on cyclohexane (0.7 M) oxidation by $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (0.7 mM) (**1**) and tBuOOH in CH_3CN at 25°C under Ar. The % conversion values plotted correspond to the run numbers listed in Table 1.

Further evidence against the radical chain autoxidation mechanism derives from kinetic isotope effect experiments [14]. In such a mechanism, the hydrogen abstraction agent is t-butoxy radical, which is typically associated with a k_H/k_D value of 4; we have confirmed this value for cyclohexane/cyclohexane-d_{12} as formed under our solvent conditions with di-t-butyl peroxalate as the tBuO· precursor (Table 2). Under the syringe pump conditions, the hydroxylation of cyclohexane/cyclohexane-d_{12} by **1**/10 eq. tBuOOH or CmOOH afforded a k_H/k_D value of 10, which is inconsistent with an alkoxy radical as the hydrogen abstraction. The similarity of this value to those (10–13) found for iron porphyrin catalysts (Table 2)

Table 2
Kinetic isotope effects on the oxidation of cyclohexane/cyclohexane-d_{12} (1/1) by various oxidants

Oxidant	k_H/k_D	Ref.
tBuO· [a]	3.9	[14]
1/tBuOOH (10 eq.) [b]	10	[14]
1/CmOOH (10 eq.) [b]	10	[14]
TPPFeCl/PhIO	13	[17]
TMPFeCl/NaOCl	10	[18]
$[Ru^V(EDTA)=O]^-$	11	[19]

[a] tBuO· radical generated from di-t-butyl peroxalate.
[b] 10 eq. ROOH delivered by syringe pump.

[17,18], which are believed to operate via a high-valent metal–oxo species [20–22], argues strongly for the involvement of a metal-based oxidant.

The notion of a metal-based oxidant was further supported by the observation that Me_2S can intercept the oxidizing species. The addition of 50 eq. Me_2S to the 10 eq. tBuOOH run (Table 1, run #5a) significantly diminished the yield of product alcohol, and Me_2SO was formed instead in an amount corresponding to that of alcohol that would have been formed in the absence of Me_2S. Such a conversion would be characteristic of a two-electron oxidant like a metal–oxo species, analogous to that implicated in heme-catalyzed oxidations [22]. However, stabilizing a formally Fe^V species may be rather difficult in a nonheme environment, so an alternative to consider may be an Fe^{III}–OO*R* species, which would contain the same number of oxidizing equivalents as the putative Fe^V=O species.

Recently, we have identified conditions under which such an alkylperoxoiron(III) intermediate can be trapped [23,24]. The reaction of **1** with tBuOOH in CH_3CN at −40°C afforded a transient blue intermediate **2** (λ_{max} = 598 nm, ϵ = 1500 M^{-1} cm^{-1}). Intermediate **2** has been formulated as $[Fe(TPA)(OOtBu)(H_2O)]^{2+}$ on the basis of its electrospray ionization mass spectra showing positive (Fig. 2a) and negative molecular ions with the correct mass and isotope distribution patterns, i.e., $\{[Fe(TPA)(OOtBu)(H_2O)](ClO_4)\}^+$ and $\{[Fe(TPA)(OOtBu)(H_2O)](ClO_4)_3\}^-$, respectively. The mononuclear nature of the blue species was corroborated by its EPR signal at g = 2.19, 2.14, and 1.98 (Fig. 2b), typical of a low-spin Fe^{III} center and with a signal intensity that corresponded to 80% of the iron in the sample. Evidence that the t-butylperoxy moiety remained intact in **2** was derived from the observation of resonance-enhanced vibrations at 490, 696, and 796 cm^{-1} (Fig. 2c), all of which were sensitive to the deuteration of

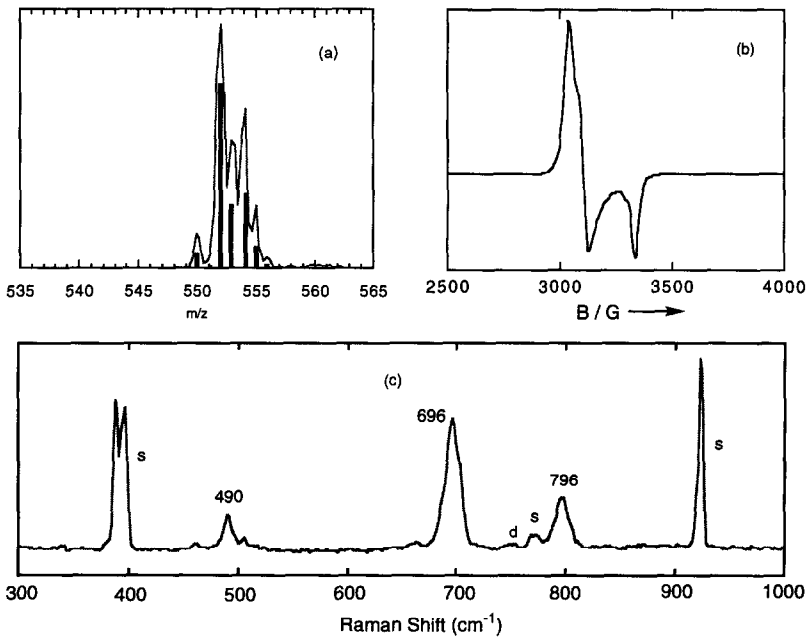
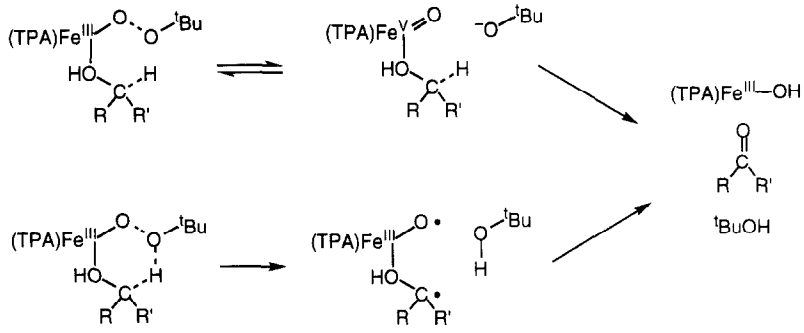


Fig. 2. Spectroscopic properties of $[Fe(TPA)(OOtBu)(H_2O)]^{2+}$ (**2**). (a) Positive ion electrospray ionization mass spectral data. Calculated isotope patterns are represented by the bars under the peak cluster. (b) EPR spectrum in CH_3CN at −40°C under Ar. (c) Resonance Raman spectrum in CH_3CN. Peaks labeled s and d derive from solvent and decomposed product, respectively.



Scheme 1.

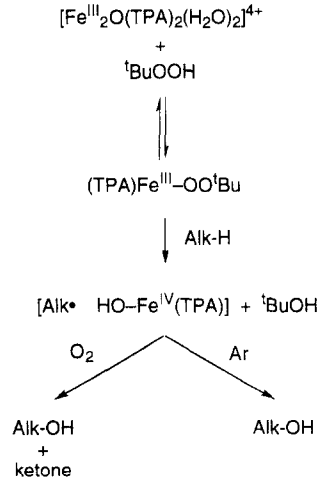
the alkyl group. Thus, dinuclear **1** is converted to mononuclear **2** upon treatment with tBuOOH, i.e.,

$$[Fe_2O(TPA)_2(H_2O)_2]^{4+} + 2tBuOOH \rightarrow 2[Fe(TPA)(OOtBu)(H_2O)]^{2+} + H_2O \quad (11)$$

The participation of **2** in the oxidation of alcohols was established by kinetic studies. We found that **2** decayed in a pseudo first order process in the presence of alcohols. The rate of decay of the blue chromophore was dependent on the concentration of alcohol but reached a maximum at high alcohol concentrations. This has been interpreted to indicate the presence of a prior equilibrium involving the binding of the alcohol to the metal center in **2**, presumably displacing the water ligand. Furthermore, the first order decay of **2** was significantly inhibited when benzyl alcohol-d_7 was used in place of benzyl alcohol ($k_H/k_D = 5$) in these studies. Since the decay process being observed is that of the alkylperoxoiron(III) species, this significant deuterium isotope effect on the decomposition of **2** implies one of two mechanisms. Either the O–O bond is reversibly cleaved, followed by rate-determining C–H bond cleavage by the high-valent iron–oxo species, or C–H bond breaking occurs as the alkylperoxo O–O bond is cleaved (Scheme 1). Because reversible cleavage of an O–O bond seems less likely, we currently favor the latter mechanism, which involves an attractive six-membered ring transition state.

However, the same mechanism cannot apply to alkane oxidation, since alkanes cannot coordinate to the iron(III) center. We are presently carrying out corresponding studies to determine whether **2** directly abstracts hydrogen from alkane as illustrated in Scheme 2 or first converts to a high valent iron–oxo species, which then cleaves the substrate C–H bond.

Once formed from the reaction of substrate with the metal-based oxidant, the substrate alkyl radical may be trapped by a metal hydroxide species to form the alcohol product analogous to the rebound step proposed for heme-catalyzed hydroxylations [25]. In the heme case, this rebound step [26–28] is known to be faster than the diffusion-controlled rate for trapping alkyl radicals with O_2 [29]. However, the fact that the syringe pump experiment for **1**/20 eq. tBuOOH when carried out in air (Table 1, run #4a)



Scheme 2.

afforded both alcohol and ketone with a ratio close to one showed that alkylperoxy radicals derived from substrate and O_2 were involved in that particular reaction. Thus, the so-called 'rebound' step in this nonheme system appears to be slower than O_2 trapping of the nascent alkyl radicals.

In summary, we have determined conditions under which the Fe(TPA)-catalyzed alkane hydroxylation is a metal-based oxidation, in which cyclohexane is converted to cyclohexanol alone with a deuterium kinetic isotope effect of 10. The metal-based oxidant in this scheme is an alkylperoxoiron(III) species, which can be trapped at -40°C and has been characterized by a number of spectroscopic techniques. Kinetic studies show that this intermediate can oxidize alcohols and suggest that O–O bond breaking is contemporaneous with the cleavage of the alcohol C–H bond. Whether this mechanistic notion can be extended to alkanes awaits further kinetic investigation.

1. Experimental procedure

1.1. Reactions

In a typical reaction, a 0.70 M solution of cyclohexane was reacted with 0.7–105 mM tBuOOH in acetonitrile in the presence of 0.70 mM catalyst at 25°C under 1 atm of oxygen-free argon. The reaction was quenched by addition of an equal volume of an aqueous 0.4 M Na_2SO_4 solution, followed by extraction with 3×2 ml samples of diethyl ether. The ether layers were combined and dried with anhydrous Na_2SO_4. Chlorobenzene was added at this point as an internal standard, and the mixture was analyzed by gas chromatography. Retention times for product peaks were compared directly to known standard compounds and confirmed by GC–MS. The syringe pump experiments were carried out in like manner using a Harvard Apparatus syringe pump. To a reaction solution was added 0.3 ml of 7–105 mM tBuOOH in acetonitrile by syringe pump over 15 min at 25°C. The reaction solution was stirred for an additional 5 min to ensure complete reaction.

1.2. Kinetics

The decrease of the 598 nm band of **2** was monitored on a Hewlett–Packard 8452A diode array spectrometer fitted for low-temperature measurements with a Dewar with quartz windows cooled by a Neslab Cryocool CC-100II immersion cooler.

1.3. Spectroscopic methods

Electrospray ionization mass spectra were acquired using a PE Sciex API III triple quadrupole mass spectrometer (Norwalk, CT). Samples in CH_3CN were infused into an Upchurch Scientific metal-free static mixing tee (Oak Harbor, WA) as described in Ref. [30], each delivering 20 μl min^{-1} of solution to the mixing tee. EPR spectra were obtained at liquid helium temperature on a Varian E-109 spectrometer equipped with a Oxford cryostat. Resonance Raman spectra were recorded on a Spex 1403 double monochromator interfaced with a Spex DM3000 data system using a Spectra Physics 2030-15 argon ion laser, and a 375B CW dye laser running Rhodamine 6G dye. Spectra were obtained at 77 K using a backscattering geometry, and $\lambda_{ex} =$ 599 nm. Samples were frozen onto a gold-plated copper cold finger in thermal contact with a Dewar containing liquid nitrogen [31]. Raman shifts were referenced to ν_1 of frozen CH_3CN at 922 cm^{-1}.

Acknowledgements

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