Fe(TPA)-Catalyzed Alkane Hydroxylation. Metal-Based Oxidation vs Radical Chain Autoxidation

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Abstract: Catalytic alkane functionalization by the Fe(TPA)/^{t}BuOOH system (with $[Fe(TPA)Cl_2]^+$ (**1**), $[Fe(TPA)Br_2]^+$ (**2**), and $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (**3**) as catalysts; TPA = tris(2-pyridylmethyl)amine) has been investigated in further detail to clarify whether the reaction mechanism involves a metal-based oxidation or a radical chain autoxidation. These two mechanisms can be distinguished by the nature of the products formed, their dependence on O_2 (determined from argon purge and $^{18}O_2$ labeling experiments), and the kinetic isotope effects associated with the products. The metal-based oxidation mechanism is analogous to heme-catalyzed hydroxylations and would be expected to produce mostly alcohol with a large kinetic isotope effect. The radical chain autoxidation mechanism entails the trapping of substrate alkyl radicals by O_2 to afford alkylperoxy radicals that decompose to alcohol and ketone products in a ratio 1:1 or smaller via Russell termination steps. Consistent with the latter mechanism, alcohol and ketone products were observed in a ratio of 1:1 or less, when catalysts **1**, **2**, or **3** were reacted with alkane and 150 equiv of ^{t}BuOOH; these product yields were diminished by argon purging, demonstrating the participation of O_2 in the reaction. However, when the **3**-catalyzed oxidation was carried out in the presence of a limited (<20 equiv) amount of ^{t}BuOOH or CmOOH, the sole product observed was alcohol; k_H/k_D values of 10 were observed, consistent with a metal-based oxidation. To reconcile these apparently conflicting results, a mechanistic scheme is proposed involving the formation of an alkylperoxyiron(III) intermediate which can oxidize either the substrate (metal-based oxidation) or excess ROOH (to generate alkylperoxy radicals that initiate a radical chain autoxidation process), the relative importance of the two mechanisms being determined by the concentration of ROOH.

There has been a significant amount of interest in the use of nonheme iron complexes as catalysts for alkane functionalization to model the reactivity of nonheme iron centers in enzymes such as methane monooxygenase.[1−4] The systems that provide the largest yields of products per unit time typically involve pyridine ligands; these include the "Gif" catalysts of Barton,[2] the $[Fe_2O(bpy)_4]^{4+}$/^{t}BuOOH[3] combination studied by Fontecave,[4] and the Fe(TPA)/^{t}BuOOH system we have investigated.[5] Based on a comparison of several Fe(TPA) catalysts, we have proposed that a metal-based oxidant, either a metal−peroxide intermediate or a high-valent iron−oxo species derived therefrom, must participate in the alkane functionalization reactions,[5] i.e.

$$R{-}H + (LFe^{III}{-}OOR \text{ or } LFe^{V}{=}O) \rightarrow R^{\bullet} + LFe^{IV}{-}OH \rightarrow R{-}OH + LFe^{III} \quad (1)$$

because dimethyl sulfide inhibited the formation of alcohol and ketone and, more importantly, the nature of the ligands on the catalyst affected the selectivity of the oxidant as indicated by the differing k_H/k_D values and adamantane 3°/2° product ratios of the various catalysts studied.[5]

However, this mechanism has recently been questioned by Arends et al.,[6] who favor ^{t}BuO$^{\bullet}$ radicals, and not a metal-based oxidant, as the sole agent for generating alkyl radicals in the Fe(TPA)/^{t}BuOOH system. Arends et al.[6] based their conclusion on three arguments: (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 observed for the $[Fe(TPA)Cl_2]^+$-catalyzed reaction; and (c) that the use of 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) in place of ^{t}BuOOH 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,[7] such as

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

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

to yield ketone in amounts at least equal to those of alcohol.

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(3) Abbreviations used: bpy, 2,2′-bipyridine; CmOOH, cumene hydroperoxide; EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate; F_{20}TPP, tetrakis(pentafluorophenyl)porphinate dianion; MPPH, 2-methyl-1-phenyl-2-propyl hydroperoxide; TMP, *meso*-tetramesitylporphinate dianion; TPA, tris(2-pyridylmethyl)amine; TPP, *meso*-tetraphenylporphinate dianion.

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Table 1. Comparison of Cycloalkane Product Yields for Catalysts **1**, **2**, and **3**

catalyst	conditions[a]	ROH[b]	ketone[b]	RX[b]	ROO^{t}Bu[b]
1[c]	Ar, 25 °C	0.5	2.9	0.7	6
1[c]	purge, 25 °C	0.2 (40%)	1.2 (41%)	0.7 (100%)	7 (117%)
1[c,d]	Ar, 25 °C	0.6	4.0	1.3	4.8
1[c,d]	purge, 25 °C	0.2 (34%)	2.3 (58%)	1.1 (85%)	5.8 (121%)
2[c]	Ar, 25 °C	0.6	5.5	0.8	7.5
2[c]	purge, 25 °C	0.3 (50%)	2.4 (44%)	1.0 (125%)	8 (107%)
3[e]	Ar, −20 °C	7.2	22		40
3[e]	purge, −20 °C	2.4 (33%)	6.6 (30%)		45 (112%)
3[e]	2× purge, −20 °C	2.1 (29%)	6.2 (28%)		47 (118%)
3[f]	Ar, 25 °C	6	11		8
3[f]	$^{16}O_2$, 25 °C	5	13		1
3[f,g]	$^{18}O_2$, 25 °C	6 [2.1]	13 [2.2]		2 [0]
3[f]	Ar, −20 °C	6	15		17
3[f]	$^{16}O_2$, −20 °C	6	20		4
3[f,g]	$^{18}O_2$, −20 °C	5 [2.9]	19 [13]		6 [0]

[a] Reaction conditions: 2 μmol of **1**, 2 μmol of **2** or 1 μmol of **3**, 1 mmol cyclooalkane, and 0.2 mmol of ^{t}BuOOH in 2 mL of CH_3CN under an atmosphere of argon or with an 80 mL/min Ar purge for 2 h (**1**), 0.5 h (**2**), and 10 min (**3**). Values reported as moles of product/moles of catalyst representing an average of 3 runs. [b] Numbers in parentheses reflect percent product retained under purge conditions relative to that without a purge; X = Cl (**1**) or X = Br (**2**). [c] Cyclooctane as substrate. [d] Values from ref 6. [e] Cycloheptane used as substrate because of its greater solubility in CH_3CN at −20 °C. [f] Cyclohexane as substrate. [g] Numbers in square brackets reflect the yields of ^{18}O-labeled products.

The alkylperoxy radicals could derive from a series of steps initiated by the Haber−Weiss decomposition of ^{t}BuOOH by the Fe(TPA) catalyst, i.e.

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

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

$${}^tBuO^{\bullet} + {}^tBuOOH \rightarrow {}^tBuOH + {}^tBuOO^{\bullet} \quad (6)$$

$$2{}^tBuOO^{\bullet} \rightarrow 2{}^tBuO^{\bullet} + O_2 \quad (7)$$

$${}^tBuO^{\bullet} + R{-}H \rightarrow {}^tBuOH + R^{\bullet} \quad (8)$$

$$R^{\bullet} + O_2 \rightarrow ROO^{\bullet} \quad (9)$$

Thus the alcohol and ketone products formed by this mechanism would derive solely from an O_2-dependent reaction. The involvement of O_2 has also been noted in other nonheme iron-catalyzed oxidations.[1b,d,2]

We have re-investigated the Fe(TPA)-catalyzed reactions (with $[Fe(TPA)Cl_2]^+$ (**1**), $[Fe(TPA)Br_2]^+$ (**2**), and $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (**3**) as catalysts) in light of the paper of Arends et al.[6] in order to resolve the two apparently conflicting mechanistic conclusions. We confirm that O_2 is a participant in the alkane hydroxylation process when a large excess (150 equiv) of ^{t}BuOOH is used. However, when the amount of ^{t}BuOOH or CmOOH is decreased to 10 equiv in the case of **3**, alcohol becomes the sole product of the reaction. Furthermore, the formation of alcohol is associated with a large kinetic isotope effect comparable to those associated with metal−oxo species.[8] These observations provide the basis for a new mechanistic scheme that incorporates both metal-based oxidation and radical chain autoxidation pathways.

Results and Discussion

Argon Purge and ^{18}O-Labeling Experiments. Three catalysts have been surveyed in this study: $[Fe(TPA)Cl_2]^+$ (**1**), $[Fe(TPA)Br_2]^+$ (**2**), and $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ (**3**). The 150 equiv of ^{t}BuOOH typically used in our catalytic oxidation experiments are completely decomposed by **1** in 2 h, by **2** in 0.5 h, and by **3** in 0.1 h. We have studied the reactions with **3** in detail because of the shorter reaction times involved. The differences in decomposition rates probably reflect the relative ease of ligand exchange and thus the accessibility of the peroxide to the iron coordination sphere. Complex **3** has aqua ligands which are more readily displaced than the halide ligands in **1** and **2**. Cyclooctane was used instead of cyclohexane in the ambient temperature argon purge experiments because of its lower volatility. For the purge experiments conducted at −20 °C, cycloheptane was used as substrate because of the poor solubility of cyclooctane in CH_3CN at that temperature.

The results of the argon purge experiments are summarized in Table 1. They show that product yields are significantly affected by an Ar purge. For **1**, the yields of alcohol and ketone decreased by 60% with the Ar purge, in agreement with the report of Arends et al.[6] For **2**, the yields of alcohol and ketone were cut in half. In the case of **3**, the argon purge at room temperature only decreased product yields by 10% (data not shown). However, O_2 evolution was clearly visible and much more vigorous with this catalyst, so the argon purge may not have been very effective. Cooling the reaction to −20 °C served to inhibit O_2 evolution significantly, and argon purging decreased the yields of alcohol and ketone by 70%. We thus agree with Arends et al.[6] that O_2 can be generated in the course of the catalytic reaction and that substrate alkyl radicals can be trapped by the O_2 evolved to form alkylperoxy species that decompose to the alcohol and ketone products observed via Russell termination reactions.[7]

The above conclusion was corroborated by carrying out reactions catalyzed by **3** in the presence of $^{18}O_2$. Thus the $^{18}O_2$ (>97% isotopic purity) added would be mixed with the $^{16}O_2$ generated in the course of the reaction (presumably by ^{t}BuOOH decomposition). The reaction solutions were initially prepared under argon and then pre-equilibrated with added $^{18}O_2$ (4.4 mmol, 100 mL at 1 atm) for 0.5 h before ^{t}BuOOH was introduced. The reaction with **3** was allowed to proceed for 0.5 h at 25 °C or 1.5 h at −20 °C, then the reaction products were analyzed by GC-MS to determine the extent of ^{18}O incorporation. No label was incorporated into the dialkyl peroxide and its yield decreased in the presence of O_2 (Table 1). However, both alcohol and ketone showed ^{18}O incorpora-

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Table 2. Product Distributions for the Oxidation of Cyclohexane[a]

catalyst	^{t}BuOOH(eq)	syringe pumped[b]	A	K	A/K	% conversion[c]	^{t}BuOOCy
1[d]	150	no[e]	2.8	3.9	0.7	4.5	3.9
	150	yes	1.1	2.4	0.5	2.3	3.6
2[d]	150	no[e]	2.4	4.6	0.5	4.7	3.2
	150	yes	0.8	1.6	0.5	1.6	3.2
3 3−1	150	no[e]	8	16	0.5	16	16
3−2	150	yes	18	9	2.0	18	21
3−3	50	yes	10	1.0	10	22	5.5
3−4	20	yes	5.5	0.3	18	30	0.4
3−5	20/air	yes	3.7	4.4	0.8	41	0.1
3−6	10	yes	4.0			40	
3−7	10/Me_2S[f]	yes	0.3			38[f]	
3−8	1	yes	0.55			55	
3−9	10 equiv CmOOH	yes	3.4			34	
3−10	10 equiv MPPH	yes	0			0	

[a] Values reported as moles of product/moles of catalyst. Reaction conditions: 0.7 mM complex, 0.7 M cyclohexane, 3 mL of CH_3CN solvent, 25 °C under argon. A = cyclohexanol, K = cyclohexanone, and ^{t}BuOOCy = *tert*-butylcyclohexyl peroxide. [b] 0.3 mL of an appropriately diluted ^{t}BuOOH solution in CH_3CN was delivered by syringe pump over the time course of the reaction (1 h for **1**, 0.5 h for **2**, 10 min for **3**). [c] Percent conversion of the initial ROOH. [d] 1 equiv of R−X was also produced in these reactions, consistent with our previous reports. [e] All 150 equiv of ^{t}BuOOH added at once at the start of the reaction. [f] 50 equiv of Me_2S added; 3.5 equiv of Me_2SO formed in the reaction.

tion. At 25 °C nearly equimolar amounts of alcohol (2.1 μmol out of a total of 6 μmol produced) and ketone (2.2 μmol out of 13 μmol) showed ^{18}O incorporation, showing that labeled products derived mostly from Russell termination reaction 2. At −20 °C, the amounts of ^{18}O incorporation increased for both alcohol (2.9 μmol out of 5 μmol) and ketone (13 μmol out of 19 μmol); labeled products represented 57% of the alcohol formed and 69% of the ketone. The observed ratio of labeled alcohol to labeled ketone shows that both Russell termination reactions (eqs 2 and 3) must operate at −20 °C. Thus O_2 can indeed trap alkyl radicals that are formed in the course of the reaction.

However, the results of both our Ar purge and ^{18}O labeling experiments also suggest that O_2 trapping is not necessarily the only means for incorporating oxygen into products. A significant fraction of the products was retained in the argon purge experiments. While this may be attributed to incomplete displacement of O_2 from the reaction solution, the amounts of residual alcohol and ketone varied with catalyst. For **1** a total of 2.8 μmol of alcohol and ketone was retained, for **2**, 5.4 μmol, and for **3**, 9 μmol (at −20 °C). If these products derived from residual O_2, it would imply that there was 2- to 3-fold more O_2 present in the cases of **2** and **3** with the same Ar purge rate, provided that the steady concentrations of alkyl radicals formed with each of the three catalysts were essentially the same. Even if the latter assumption did not hold, the observation that the amount of residual alcohol and ketone observed was not significantly altered by doubling the purge rate in the case of **3** suggests that the available O_2 in the solution had already been displaced. This notion is supported by a comparison of the yields of the alkyl *tert*-butyl peroxide, which derived from the trapping of the alkyl radical by ^{t}BuOO$^\bullet$ or its equivalent. The amount of the mixed dialkyl peroxide decreased dramatically when the reaction was carried out under O_2 (see Table 1), suggesting that O_2 trapping of the alkyl radicals competes with formation of the dialkyl peroxide. Since the yield of dialkyl peroxide increased by 10−20% under an Ar purge, little or no O_2 must remain in solution after the Ar purge. We also note that the $^{18}O_2$ labeling experiments conducted with **3** at −20 °C showed that a third of the alcohol and ketone products remained unlabeled, a value remarkably similar to the 30% residual alcohol and ketone retained in the Ar purge experiments. These observations suggest that these residual oxygenated products may derive from a mechanism that is independent of O_2.

Syringe Pump Experiments. To obtain further evidence for an O_2-independent mechanism, we sought to minimize the amount of O_2 that may be generated via the bimolecular decomposition of ^{t}BuOO$^\bullet$ radicals by decreasing the concentration of ^{t}BuOOH present in the catalytic system. A typical catalytic reaction we have studied consisted of a mixture of catalyst, ^{t}BuOOH, and substrate in a 1:150:1000 ratio in CH_3CN under Ar where the 150 equiv of ^{t}BuOOH were added all at once at the beginning of the reaction. Delivering the ^{t}BuOOH via syringe pump over the course of the reaction may significantly decrease the maximal concentration of ^{t}BuOO$^\bullet$ radicals at any given moment and thus diminish the amount of ketone formed from Russell termination reactions (eqs 2 ad 3). No dramatic change in the A/K ratio was observed when the ^{t}BuOOH was delivered by syringe pump for catalysts **1** and **2**. In fact, less than 10% of the ^{t}BuOOH added was converted into oxidized products, and not insignificant amounts of ^{t}BuOOH (10% for **1** and 20% for **2**) were found unreacted at the end of the syringe pumped reactions.

However, syringe pumping dramatically affected the product distribution of the reaction catalyzed by **3** (Table 2). With 150 equiv of ^{t}BuOOH added all at once (run no. 3−1), the A/K ratio was 0.5; syringe pumping favored the formation of alcohol, making the A/K ratio 2 (run no. 3−2). As the concentration of ^{t}BuOOH was decreased, the yields of ketone and dialkyl peroxide were significantly reduced; indeed at 10 equiv of ^{t}BuOOH or less, *alcohol was the only product observed in the reaction!* Furthermore, the efficiency of conversion of ^{t}BuOOH to product alcohol dramatically increased. With 150 equiv, 16−18% of the peroxide was converted into alcohol and ketone; this yield increased to 40% (run no. 3−6) and 55% (run no. 3−8) for the experiments with 10 and 1 equiv of ^{t}BuOOH, respectively. A similar result was obtained with 10 equiv of CmOOH (run no. 3−9). These results represent among the best conversion efficiencies of oxidant to alcohol in nonheme alkane oxidation systems.[1−4]

The absence of ketone in the 10 equiv of ^{t}BuOOH run showed that neither cyclohexyl hydroperoxide nor cyclohexylperoxy radical can be considered as precursors to the alcohol product. Cyclohexyl hydroperoxide, an intermediate found in "Gif" chemistry[2b] and the reactions of cyclohexane with some (μ-oxo)diiron(III) complexes and H_2O_2 in air,[1b] was converted mostly to cyclohexanone in the presence of these metal centers, as expected for the reaction of a secondary hydroperoxide with

Table 3. Kinetic Isotope Effects on the Oxidation of Cyclohexane/Cyclohexane-d_{12} (1/1) by Various Oxidants

		k_H/k_D				
catalyst	oxidant	A	K	A + K[a]	Cy-X[b]	references
	^{t}BuO$^\bullet$ [c]	3.9	4.3	4.2		this work
1	^{t}BuOOH (150 equiv)[d]	3.7	9.2	6	8	5b, 25
2	^{t}BuOOH (150 equiv)[d]	3.9	8.8	7	7	5b, 25
3	^{t}BuOOH (150 equiv)[d]	4.4	7.2	6		this work
3	^{t}BuOOH (10 equiv)[e]	10				this work
3	CmOOH (10 equiv)[e]	10				this work
TPPFeCl	PhlO	13				8a
TMPFeCl	NaOCl	10				8b
	$[Ru^V(EDTA)=O]^-$	11				16

[a] Values for alcohol and ketone have been considered together. A = cyclohexanol, K = cyclohexanone. [b] Cy-X = cyclohexyl halide. [c] ^{t}BuO$^\bullet$ radical generated from di-*tert*-butylperoxalate. [d] 150 equiv of ^{t}BuOOH added at once at the start of the reaction. [e] 10 equiv of ROOH delivered by syringe pump.

metal centers. Similarly, treatment of cyclohexyl hydroperoxide with **3** under the conditions of the experiment yielded an A/K ratio of 0.5. On the other hand, cyclohexylperoxy radical, an intermediate in radical autoxidation processes, would break down by Russell termination steps (eqs 2 and 3) to afford both alcohol and ketone with A/K ratios of ≤ 1. Indeed when the syringe pump experiment (run no. 3−5) was carried out in air, an A/K ratio close to unity was obtained. 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 no. 3−4 under Ar demonstrates that there is little or no O_2 that can be trapped by the nascent alkyl radical under these conditions.

There has been considerable discussion as to the nature of the hydrogen abstraction agent in this and other nonheme iron-catalyzed reactions.[5,6] The choices usually narrow down to two: an alkoxy radical or a metal-based oxidant. The alkoxy radical is favored by Arends et al.[6] for catalyst **1** ($[Fe(TPA)Cl_2]^+$). The alkoxy radical initiates a radical chain process that inevitably produces O_2, which should then lead to the production of both alcohol and ketone in a ratio ≤ 1. Hydrogen abstraction by ^{t}BuO$^\bullet$ is associated with a k_H/k_D value of 4 for cyclohexane/cyclohexane-d_{12} as formed under our solvent conditions with di-*tert*-butyl peroxyoxalate as the ^{t}BuO$^\bullet$ precursor (Table 3). In fact, the presence of O_2 was required in these experiments to obtain the oxygenated products; in the absence of O_2, only radical−radical coupling products were observed. Furthermore, we have found that the k_H/k_D value of 4 applied to the alcohol and ketone products considered separately or together, consistent with their formation via the decomposition of ROOOOR′ intermediates (eqs 2 and 3).

The alkoxy radical mechanism cannot be used to explain all our observations with catalyst **3**. The nearly exclusive production of alcohol in run nos. 3−4, 3−6, 3−8, and 3−9 (Table 2) cannot be rationalized by the Russell termination pathways associated with a radical chain mechanism and thus excludes the participation of O_2 in the formation of alcohol under these conditions. Furthermore, the k_H/k_D value of 10 obtained for cyclohexane/cyclohexane-d_{12} in the reactions with **3**/10 equiv of ^{t}BuOOH or CmOOH is comparable to values of 10−13 obtained for iron porphyrin catalysts[8] (Table 3), which are believed to operate via a high-valent metal−oxo species.[9] Additional support for a metal-based oxidant derives from the observation that Me_2S can intercept the Fe(TPA)-based oxidant. The addition of 50 equiv of Me_2S to the 10 equiv of ^{t}BuOOH run (run no. 3−7, Table 2) significantly diminished the yield of product alcohol and formed Me_2SO instead, the amount of Me_2SO produced replacing the amount of alcohol that would have been formed in the absence of Me_2S. Such a conversion would be characteristic of a two-electron oxidant such as a metal−peroxo or metal−oxo species, as noted previously in heme-catalyzed oxidations.[10] Taken together, our observations with **3** as catalyst support the notion that a metal-based oxidant can be responsible for the oxidation of cyclohexane to cyclohexanol.

Arends et al.[6] have proposed the use of 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) as a mechanistic probe for the participation of alkoxy radicals in these alkane functionalization reactions. While structurally similar to ^{t}BuOOH, MPPH undergoes a rapid β-cleavage ($k_\beta \sim 2.2 \times 10^8$ s^{-1})[6] upon formation of the corresponding alkoxy radical. Thus when **1** is treated with MPPH in the presence of alkane, only products derived from the benzyl radical were observed and no oxidation products of the alkane were detected. We have repeated the experiment with catalyst **3** (Table 2, run no. 3−10) and confirm the absence of oxidation products derived from the substrate alkane. These experiments demonstrate that MPPH readily decomposes to its alkoxy radical when it reacts with an Fe(TPA) center, as Arends et al. have concluded.[6] The alkoxy radical that is formed immediately affords benzyl radical which is incapable of abstracting hydrogen from cyclohexane. Based on the MPPH results, Arends et al. have proposed that ^{t}BuOOH similarly decomposes to its alkoxy radical when it reacts with an Fe(TPA) center. Since the *tert*-butoxy radical has a slower β cleavage rate ($k_\beta \sim 10^5$ s^{-1}),[6,11] it would have a sufficient lifetime to react with the alkane substrate. However, we have demonstrated above that cyclohexane hydroxylation by **3** in the presence of 10 equiv of ^{t}BuOOH or CmOOH ($k_\beta = 6.3 \times 10^5$ s^{-1} for cumyloxy radical)[12] is completely inconsistent with an alkoxy radical abstraction mechanism. Thus, it is not clear that MPPH is a competent substitute for ^{t}BuOOH. In support, olefin epoxidations catalyzed by [Fe(F_{20}TPP)Cl] were much less effective with MPPH (20% epoxide yield) than with ^{t}BuOOH (90% epoxide yield).[13]

Mechanistic Considerations. The results described above and in earlier papers[5a,b,6] indicate that the Fe(TPA)-catalyzed alkane functionalization reactions can be rather complex. Scheme 1 illustrates our current picture of this complexity and takes the effect of O_2 into consideration, a feature not included in our earlier schemes. While we had earlier noted the effects of O_2 on these reactions, Arends et al.[6] must be credited for providing the correct interpretation for these effects. In the present scheme, there are two principal competing mechanisms, a radical chain pathway (a) and a metal-based oxidation pathway (b). The radical chain pathway (a) affords the observed alcohol and ketone products via the trapping of substrate alkyl radicals by O_2 and subsequent decomposition of the alkylperoxy radical thus formed. It rationalizes the generation of O_2 in the course of the reaction, as evidenced by the argon purge results reported here and earlier by Arends et al.,[6] by the disproportionation of alkylperoxy radicals (eqs 2, 3, and 7). The metal-based oxidation pathway (b), on the other hand, rationalizes the role the metal ligands appear to play in modulating the selectivity

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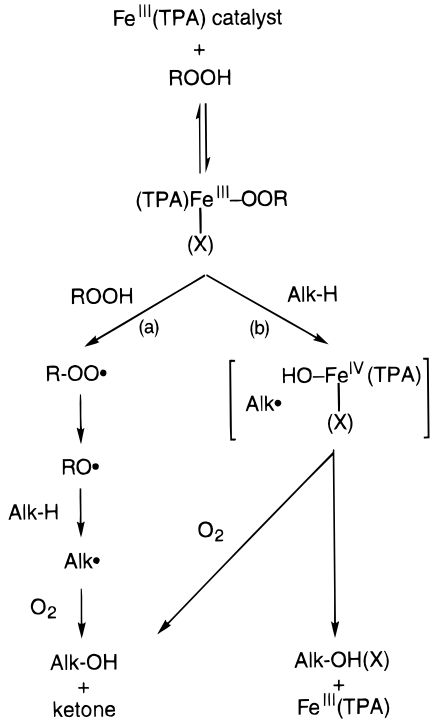
Scheme 1



of the alkane functionalization reaction and the inhibitory effect of Me_2S.[5] Like the mechanism proposed for heme catalysts, this pathway involves the initial formation of a metal−peroxo species,[14] which either abstracts hydrogen directly from the substrate alkane or does so via a high-valent metal−oxo species; an oxygen rebound step forms the C−O bond of the product alcohol.[15]

The observed A/K product ratios of ≤1 are, as pointed out recently by Arends et al.,[6] indicative of the participation of substrate alkylperoxy radicals. Such radicals may be obtained by the trapping of nascent substrate alkyl radicals by O_2 generated in the reaction mixture. At issue has been the nature of the hydrogen abstraction agent that generates the substrate alkyl radical. Either or both of these pathways (a and b) are capable of generating substrate alkyl radicals which are subsequently trapped by O_2; in the case of the metal-based oxidant, such O_2 trapping would imply that the rebound step is slower than the rate of O_2 trapping. However, since O_2 is generated by the disproportionation of *tert*-butylperoxy radicals, a second-order process, the amount of O_2 formed can be dramatically reduced by controlling the concentration of alkyl hydroperoxide. Thus when the alkyl hydroperoxide is dilute enough in the **3**-catalyzed reaction, *substrate alkane is converted to alcohol alone*, an outcome which cannot be rationalized by an alkoxy radical mechanism.

Insight into the nature of the hydrogen abstracting agent can also be gleaned from deuterium isotope effects on the alkane functionalization reaction. For comparison purposes, all alcohol and ketone are assumed to derive from the same initial hydrogen abstraction event. The k_H/k_D value for cyclohexane/cyclohexane-d_{12} oxidation by the *tert*-butoxy radical is 4, while that for **3**/10 equiv of ROOH (R = ^{t}Bu or Cm) is 10. This large difference strongly implies that the hydrogen abstraction agent in the latter reaction cannot be an alkoxy radical. Indeed the k_H/k_D value of 10 is comparable to those found for Fe(TPP)-Cl/PhIO and other metal−oxo oxidants[8,16] (Table 3) and strongly implies a metal-based oxidant analogous to the oxoiron(IV) porphyrin radical species generally accepted for heme-catalyzed hydroxylations.[9,14]

The differing behavior of catalysts **1** and **2**, on one hand, and **3**, on the other, can be rationalized by considering the initial step of the proposed oxidation mechanism. This step is an inner sphere ligand exchange reaction to form an alkylperoxoiron(III) complex, the rate of which is controlled by the lability of the metal ligand. Since **3** has terminal aqua ligands, ligand exchange can occur quite readily.[4] Furthermore, the oxo bridge can facilitate formation of an alkylperoxoiron(III) intermediate by acting as a convenient base to accept the proton(s) generated by this reaction. These factors shift the ligand exchange equilibrium to the right as shown below:

$$[Fe_2O(TPA)_2(H_2O)_2]^{4+}\ (\mathbf{3}) + 2ROOH \rightleftharpoons 2[Fe(TPA)OOR(H_2O)]^{2+} \quad (10)$$

We have observed this alkylperoxoiron(III) intermediate at −40 °C and found it to exhibit a characteristic blue color.[17] Indeed this intense blue color could be observed as drops of ^{t}BuOOH solution were introduced via syringe pump to the reaction mixture containing **3**. The fact that we can observe this intermediate implies that its rate of formation is significantly faster than its rate of decomposition. This intermediate oxidizes substrate either directly or indirectly via a high-valent iron−oxo species to afford alcohol with a k_H/k_D value 10, as observed in the **3**-catalyzed reactions with <20 equiv of ROOH.

As the amount of ROOH is increased, the excess ROOH, being more easily oxidized, competes with the alkane for the metal-based oxidant. This pathway (a) then generates alkylperoxy radicals which gives rise to products typical of radical chain autoxidation. The observation that the k_H/k_D value of 6 (A and K considered together) for the **3**/150 equiv of ^{t}BuOOH reaction is intermediate between those associated with the alkoxy radical and the metal-based oxidant suggests that hydrogen abstraction from alkane is carried out by both the metal-based oxidant and alkoxy radicals derived from the alkylperoxy radicals (Table 3). This conclusion is also supported by the significantly different k_H/k_D values obtained when alcohol and ketone are considered separately (Table 3), unlike in the pure *tert*-butoxy case where alcohol and ketone formation have essentially the same k_H/k_D value. The large k_H/k_D value for the ketone alone in the case of **3**/150 equiv of ^{t}BuOOH suggests that at least some of the ketone is derived from the oxidation of alcohol in a subsequent reaction; in this case, k_H/k_D values for the two consecutive C−H bond cleavage steps would be multiplicative. Such a mechanism wherein substrate and ROOH compete for the metal oxidant is analogous to that proposed by Traylor et al.[18] for the reactions of iron(III) porphyrins with alkyl hydroperoxides. We believe that this scheme may also apply to other Fe catalyst/ROOH reactions, as these reactions also exhibit intermediate k_H/k_D values.[1,4]

In the cases of **1** and **2**, a blue alkylperoxo intermediate is not observed upon addition of ROOH and the visible spectra

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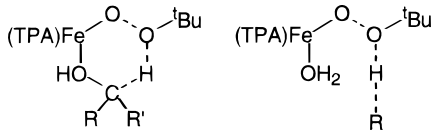
Chart 1



alcohol substrate alkane substrate

of the starting catalysts persist. These observations suggest that the ligand exchange equilibrium has shifted significantly to the left. The leftward shift can be rationalized by the fact that the negatively charged halide (X) would be more difficult to displace than the neutral aqua ligands on **3** and the displacement reaction would result in the formation of a strong acid HX,[14a] i.e.

$$[Fe(TPA)X_2]^+ (\mathbf{1} \text{ or } \mathbf{2}) + ROOH \rightleftharpoons [Fe(TPA)X(OOR)]^{2+} + HX \quad (11)$$

When formed, the alkylperoxoiron(III) intermediate reacts with substrate to form haloalkane product. As reported earlier,[5b] the addition of 1 equiv of ^{t}BuOOH affords haloalkane as the sole alkane-derived product in 70−80% yield, an excellent conversion efficiency. The k_H/k_D values associated with the formation of haloalkane by **1** and **2** (7 and 8, respectively) differ significantly from the value for ^{t}BuO$^\bullet$ abstraction (4), in agreement with the proposed metal-based oxidation. Furthermore, Me_2S has been shown to intercept the formation of haloalkane producing a stoichiometric amount of Me_2SO instead. This oxidative ligand transfer reaction is thus equivalent to the metal-based alkane hydroxylation associated with **3** at low ROOH concentrations.

As the amount of ^{t}BuOOH added is increased, the yield of haloalkane increases to a maximum value that is stoichiometric with catalyst.[5b] Alcohol and ketone are also produced. As in the case of **3**/150 equiv of ROOH, the k_H/k_D values for alcohol and ketone formation considered separately and together by **1** and **2** (Table 3) indicate the participation of both alkoxy radical and a metal-based oxidant in the hydrogen abstraction step. Thus, as with **3**, the excess ROOH present can compete with substrate for the oxidant and a radical chain autoxidation process is initiated. The involvement of these competing reactions reconciles the apparently conflicting observations reported by Arends et al.[5] and our group.[6]

The metal-based alkane hydroxylation we observe presumably results from the interaction of substrate with the alkylperoxoiron(III) intermediate or a high-valent iron−oxo species derived therefrom. Direct evidence for an alkylperoxo intermediate has been obtained when **3** and ^{t}BuOOH are reacted in the presence of alcohol substrate at −40 °C.[17a] In this study, the first-order decay of the visible absorption band assigned to the intermediate slowed down significantly when benzyl alcohol-d_7 was used in place of benzyl alcohol ($k_H/k_D = 5$). We proposed a mechanism involving the coordination of alcohol to the alkylperoxoiron(III) intermediate, formation of an attractive six-membered ring transition state, and its subsequent decomposition via contemporaneous O−O and C−H bond cleavage to afford the product aldehyde and ^{t}BuOH (Chart 1). However, the same mechanism cannot apply to alkane oxidation, since alkanes cannot coordinate to the iron(III) center. We are presently carrying out studies to determine whether the alkylperoxoiron(III) intermediate 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 metal oxidant, the substrate alkyl radical may be trapped by a metal hydroxide species to form the alcohol product in a rebound step analogous to that proposed for heme-catalyzed hydroxylations.[15] In the heme case, this rebound step[19] is known to be faster than the rate for trapping alkyl radicals with O_2 ($\sim 10^9$ s^{-1}).[20] However, the fact that the syringe pump experiment for **3**/20 equiv of ^{t}BuOOH when carried out in air (Table 2, run no. 3−5) afforded both alcohol and ketone with a ratio close to 1 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 the trapping of O_2 by the nascent alkyl radicals.

The notion of a slow "rebound step" is reminiscent of the chemistry of bleomycin, another nonheme iron oxidation catalyst. Bleomycin is an anti-tumor drug that has been shown to oxidize its DNA target via dioxygen-dependent and dioxygen-independent pathways.[21] The active form of the drug is "activated bleomycin", which has recently been demonstrated to be a hydroperoxoiron(III) species.[22] "Activated bleomycin" attacks the DNA ribose ring to generate a C-4′ radical. In the absence of O_2, the radical is converted to the C-4′−OH derivative which ring opens to the 4′-keto-1′-aldehyde. In the presence of O_2, the C-4′ peroxy radical is formed and the ribose ring is cleaved to afford the phosphoglycolate and base propenal products of bleomycin-catalyzed DNA degradation. Thus O_2 can compete with the metal center to trap the substrate radical in bleomycin chemistry as well.

In summary, we have formulated a unifying scheme that can explain the many observations associated with Fe(TPA)-catalyzed alkane hydroxylations.[5,6] At the heart of this scheme is a metal-based oxidant, probably an alkylperoxoiron(III) species, which is a two-electron oxidant (and thus can be intercepted by dialkyl sulfides) and whose oxidizing power can be modulated by the nature of the tripodal ligand. We have demonstrated that this metal-based oxidant is responsible for alkane hydroxylation at low ROOH concentration. With increasing ROOH concentration, ROOH competes with substrate for the metal-based oxidant and thereby initiates a radical chain process generating alkoxy radical and O_2. Substrate alkyl radicals generated by either the metal-based oxidant or the alkoxy radical can then be trapped by O_2 to afford the alcohol and ketone products observed at high ROOH concentrations. The complexity of this chemistry demonstrates the problems associated with developing biomimetic versions of enzyme-catalyzed oxidations, in particular, the competition of substrate and peroxide for the transient metal oxidant. To circumvent this problem, the enzyme active site enforces strict metal:substrate:oxidant stoichiometry. In our biomimetic system, we have resorted to using dilute solutions of alkyl hydroperoxide to minimize this competition and obtain efficient conversion of oxidant to hydroxylated product. However, new strategies will have to be developed to make such catalytic hydroxylation systems more practical.

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Experimental Section

Materials and Synthesis. All chemicals were of reagent grade unless otherwise noted. Acetonitrile for catalytic reactions (HPLC grade/glass distilled) was purchased from EM Science and used as received. Cyclohexane and Na_2SO_4 were obtained from Fisher, and all other reagents and organic products were purchased from Aldrich. *tert*-Butyl hydroperoxide (70% in H_2O) was purchased from Aldrich, WI. Cyclohexyl hydroperoxide[2b] and 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH)[6,23] were synthesized from corresponding alkyl bromides according to published procedures. The tripodal ligand, TPA·3HClO$_4$,[24] and its complexes, [Fe(TPA)Cl$_2$](ClO$_4$) (**1**),[5b] [Fe(TPA)-Br$_2$](ClO$_4$) (**2**),[5b] and [Fe$_2$(TPA)$_2$(O)(H$_2$O)$_2$](ClO$_4$)$_4$ (**3**),[17a] were synthesized according to published procedures. *Caution: The perchlorate salts are potentially explosive and should be handled with care.*

Instrumentation. Visible spectra were recorded on a Hewlett-Packard 8541A diode array spectrometer. Standard organic product analyses were performed using a Hewlett-Packard 5880A series gas chromatograph equipped with a flame-ionization detector. GC mass spectral measurements were obtained using a Hewlett-Packard GC equipped with a mass spectral detector. ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz. Chemical shifts (in ppm) were referenced to residual protic solvent peaks.

Reactions. In a typical reaction, a 0.70 M solution of cyclohexane was reacted with 0.7−105 mM ^{t}BuOOH 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 GC. 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 syringe pump.

For the Ar purge experiments, a three-flask system was used to minimize loss of volatile components and to recover them after escape from the reaction flask. Thus Ar was initially bubbled into a flask containing solvent, then through the reaction flask, and finally into a third flask cooled to −80 °C. At the end of the reaction period (2 h for **1**, 0.5 h for **2**, and 10 min for **3** at 25 °C; 1 h for **2** and **3** at −20 °C), the reaction solution was put on a silica gel column and extracted for organic products, which were then identified and quantified by GC.

The reactions under O_2 were carried out in 2 mL of CH_3CN with 2 mmol of **3** and 0.1 mL of cyclohexane which was first degassed by 3 freeze−thaw cycles and left under argon. The solution was then frozen with liquid nitrogen, and 100 mL (1 atm) of either $^{18}O_2$ or $^{16}O_2$ was condensed onto the frozen solution; upon warming, the solution was stirred for half an hour at the desired temperature before ^{t}BuOOH was added. Reaction times were 0.5 h at 25 °C and 1.5 h at −20 °C; as earlier described, the oxidation products were isolated by column chromatography and identified by GC-MS.

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