Alkane Functionalization at (μ-Oxo)diiron(III) Centers

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Abstract: The reactivity of (μ-oxo)diferric complexes with ^{t}BuOOH (TBHP) for the functionalization of alkanes in CH_3CN has been investigated as part of our efforts to model dinuclear sites in nonheme iron enzymes. $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**) (TPA = tris(2-pyridylmethyl)amine, OAc = acetate) is an efficient catalyst for cyclohexane oxidation, affording cyclohexanol (**A**, 9 equiv), cyclohexanone (**K**, 11 equiv), and (*tert*-butylperoxy)cyclohexane (**P**, 16 equiv) in 0.25 h at *ambient* temperature and pressure under an argon atmosphere. The catalyst is remarkably robust, as indicated by the ^{1}H NMR and UV–vis spectra of the reaction mixture during the catalytic reaction and by its ability to maintain its turnover efficiency with subsequent additions of oxidant. The catalytic mechanism for TBHP utilization was explored by observing the effects of varying the tripodal ligands on the (μ-oxo)(μ-carboxylato)diferric catalysts and varying the bridge on $Fe_2O(TPA)_2$ catalysts. The (**A** + **K**)/**P** ratio increased as the ligands became more electron donating. Solvent also played an important role in determining the partitioning of products between **A** + **K** and **P**, with benzonitrile favoring hydroxylated products at the expense of **P** and pyridine having the opposite effect. Most significantly, the addition of dimethyl sulfide (to trap two-electron oxidants) to this system completely suppressed the formation of **A** and **K** but did not affect the amount of **P** formed. These observations demonstrate that **A** and **K** must derive from an oxidant different from that responsible for **P** production. TBHP is thus decomposed by the catalyst via two mechanisms: a heterolytic process that affords a high-valent iron–oxo species responsible for **A** and **K** formation and a homolytic pathway that generates ^{t}BuO$^\bullet$ and ^{t}BuOO$^\bullet$ radicals that are responsible for the formation of **P**. It is proposed that the heterolytic mechanism is initiated by the dissociation of the bridging anion from one iron center to provide a site for coordinating the alkyl peroxide ion. Consistent with this notion, the hydrogen abstraction power of the oxidant, as indicated by isotope effects of cyclohexane hydroxylation, is modulated by the tripodal ligand but is independent of the bridging anion, although the affinity of the bridging anion for the (μ-oxo)diferric center plays a role in determining the efficiency of the catalyst in consuming the alkyl hydroperoxide.

The selective functionalization of alkanes has been a tantalizing challenge for chemists, since the great abundance of alkanes makes them the ideal feedstocks for many industrial syntheses.[1] However, the inertness of saturated hydrocarbons also makes them among the most difficult substrates to oxidize selectively. While commercial alkane oxidations require the application of high temperature or pressure,[2] nature has evolved a host of enzymes which carry out this task selectively, under extremely mild conditions.[3] Nonheme iron enzymes have emerged as a major subclass of this category;[4] in particular, methane monooxygenase (MMO), which catalyzes the conversion of methane to methanol, recently attracted a great deal of interest.[5] Spectroscopic studies indicate that the active site of MMO consists of a dinuclear iron center in a nonheme environment;[6] alkane hydroxylation can be effected by either treating the diferrous form with O_2[5] or treating the diferric form with H_2O_2.[7] On this basis, the catalytic mechanism has been proposed to involve the binding of dioxygen to the diferrous unit, forming a diferric peroxide intermediate, and its subsequent conversion to a high-valent ferryl species, which is responsible for the oxidation of substrate;[5] such a mechanism is analogous to that proposed for cytochrome P-450.[8]

Our interest in MMO and related dinuclear iron–oxo proteins has led us to explore suitable model compounds as catalysts for the oxidation of saturated hydrocarbons. While the number of relevant structural models dramatically increased in recent years,[9] functional models are fewer in number. Model systems that mimic some aspect of the hydroxylation chemistry of MMO include simple iron salts[10] or iron complexes[11] such as $[Fe(salen)]_2O$,[12] $Fe_2O(HB(pz)_3)_2(OAc)_2$,[13] $Fe(PA)_2$,[14] $Fe_3O(OAc)_6(py)_3$,[15] $Fe_2O(OAc)_2(bpy)_2Cl_2$,[16] and related manganese complexes.[17] These catalysts act in concert with O_2/electron donors or peroxides to

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(11) Abbreviations used: salen = *N*,*N*′-ethylenebis(salicylideneamine); HB(pz)$_3$ = hydrotris(pyrazolyl)borate; OAc = acetate; PA = picolinic acid; py = pyridine; bpy = bipyridine; TPA = tris(2-pyridylmethyl)amine; BPEA = *N*-(2-pyridylethyl)-*N*,*N*-bis(2-pyridylmethyl)amine; NTB = *N*,*N*,*N*-tris(2-benzimidazolylmethyl)amine; BPA = bis(2-pyridylmethyl)amine; OBz = benzoate.

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hydroxylate alkanes. However, save for studies on the iron catalysts collectively known as the "Gif" system,[18] little mechanistic insight has been gleaned from these studies. Progress toward this goal has in part been hampered by the difficulty in ascertaining the coordination environment of the metal catalyst and carrying out a systematic study to determine the effect of the ligands on the catalytic reaction. In addition, mechanistic studies of these reactions have been hindered by the low efficiency of alkane functionalization.

Recent work from our laboratory demonstrated the versatility of tripodal ligands for the synthesis of stable dinuclear iron complexes, affording a wealth of compounds which yield rich spectroscopic information on diiron centers.[19] We have carried out a systematic study of these dinuclear iron complexes with respect to their ability to catalyze alkane functionalization reactions in the presence of peroxides. During the course of these studies, we found that the complex $Fe_2(TPA)_2O(ClO_4)_4$ reacts stoichiometrically at −40 °C with H_2O_2 to give a high-valent oxoiron intermediate.[20] This intermediate is the first evidence for a high-valent species in a nonheme iron system and may shed light on the mechanism of MMO chemistry. This report details our investigation into the oxidation of cyclohexane by $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**)/TBHP, where cyclohexanol, cyclohexanone, and (*tert*-butylperoxy)cyclohexane are fomed rapidly in high yields, under ambient conditions. Special attention has been devoted to the mechanism of peroxide decomposition by diiron complexes in this study.

Experimental Section

Materials. 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. Methanol was dried and purified by distillation. Anhydrous *tert*-butyl hydroperoxide in toluene was prepared according to the procedure given by Sharpless,[21] carefully following the safety precautions outlined in these references. All hydroperoxide solutions were assayed by iodometric titration to determine active ROOH content. *tert*-Butyl cyclohexyl ether and (*tert*-butylperoxy)-cyclohexane were synthesized by following published preparations.[22] Cyclohexane and Na_2SO_4 were obtained from Fisher, and all other reagents and organic products were purchased from Aldrich. The tripodal ligands TPA·3$HClO_4$,[23] BPEA,[24] and NTB[25] were synthesized according to published procedures. The ligand BPA was purchased from the Nepara Co.

Instrumentation. Visible spectra were recorded on a Hewlett-Packard 8541A diode array spectrometer. Standard organic product analyses were performed using a Perkin-Elmer Sigma 3 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. ^1H NMR spectra were recorded on an IBM AC 300 spectrometer at 300 MHz. Chemical shifts (in ppm) were referenced to residual protic solvent peaks.

Syntheses. The complexes $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**),[19b] $[Fe_2(NTB)_2O(OAc)](ClO_4)_3$ (**4**),[26] $[Fe_2(HB(pz)_3)_2O(OAc)_2]$ (**5**),[27] $[Fe_2(TPA)_2O(OBz)](ClO_4)_3$ (**6**),[19b] $[Fe_2(TPA)_2O(O_2P(OPh)_2)](ClO_4)_3$ (**8**),[19b] $[Fe_2(TPA)_2O(CO_3)](ClO_4)_2$ (**9**),[19c] $[Fe_2(TPA)_2O(phthalate)](ClO_4)_2$ (**10**),[19c] and $[Fe_2(BPA)_2O(OBz)_2](ClO_4)_2$ (**3**)[19b] were synthesized as previously reported. The synthesis of $[Fe_2(TPA)_2O(O_2CC_6H_4\text{-}4\text{-}OCH_3)](ClO_4)_3$ (**7**) followed the procedure for **1** with 4-methoxybenzoic acid in place of acetic acid. The synthesis of $[Fe_2(BPEA)_2O(OAc)](ClO_4)_3$ (**2**) also followed the procedure for **1** with BPEA in place of TPA. The brown powder that precipitated from the reaction mixture was recrystallized overnight from CH_3CN/methyl acetate to afford a yield of 64%. Anal. Calcd for $C_{40}H_{43}Cl_3Fe_2N_8O_{15}$: C, 43.92; H, 3.96; N, 10.24. Found: C, 43.74; H, 4.00; N, 10.04. Complex **2** exhibits an electronic spectrum similar to that of **1**. λ_{max}, nm (ϵ, mM^{-1} cm^{-1}): 466 (1.2), 696 (0.16). NMR (δ, ppm; 300 MHz): 35, 32, 26, 22, 21 (broad, 8H, α-py or NCH_2); 16.4–14.1 (12H, β-py); 12.2 (3H, OAc); 8.5–6.0 (6H, γ-H); 0.0 (4H, NCH_2CH_2py).

Caution! Metal complexes with organic ligands and perchlorate anions are potentially explosive. Care should be exercised in handling these complexes, and they should only be prepared in small quantities.[28]

Catalytic Oxidation of Cyclohexane. In a typical reaction, a 0.77 M solution of cyclohexane was reacted with 0.01 M *tert*-butyl hydroperoxide (TBHP) in acetonitrile in the presence of 0.70 mM $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**) 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 three 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 those of injections of known standard compounds and initally confirmed by GC-MS. The reactions with other catalysts were carried out in the same manner, with the only variable being reaction time corresponding to the reactivity of the catalyst. Reactions with competitive substrates (Table I) were carried out in an analogous manner and entailed the addition of the competitive substrate prior to the addition of TBHP.

Results

Our efforts to model the reactivity of methane monooxygenase have centered on a catalytic system that consists of an Fe^{III}-(TPA) complex as catalyst and TBHP as oxidant with cyclohexane as substrate. We have communicated our observations on the reactivity of mononuclear $[Fe^{III}(TPA)X_2]^+$ complexes in functionalizing cyclohexane to **A**, **K**, **P**, and halocyclohexane.[29,30] In this paper, we focus on dinuclear complexes such as $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**). Complex **1** has been characterized crystallographically to have a (μ-oxo)(μ-carboxylato)diferric core. The TPA ligands that complete the coordination spheres of the two iron centers differ in their binding modes, with the tertiary amine on one iron center trans to the oxo bridge and one of the pendant pyridines on the other iron center trans to the oxo bridge. This unsymmetric arrangement is reflected in metal–ligand bond lengths and the spectroscopic properties of the complex.

Products of Alkane Oxidations. The results for a typical oxidation of cyclohexane catalyzed by $[Fe_2O(TPA)_2(OAc)](ClO_4)_3$ in acetonitrile are given in Table I. At ambient temperature and pressure and under an argon atmosphere, 0.7 mM catalyst reacted with 105 mM TBHP and 0.77 M cyclohexane

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Table I. Product Distributions for the Iron (0.7 mM) Catalyzed TBHP Oxidation of Cyclohexane (0.77 M) at 25 °C: Effect of Solvent or Traps

			products[a]				
catalyst	solvent	reacn time (h)	OH	O	OO^tBu	other products	(A + K)/P
1	CH_3CN	0.25	9	11	16		1.3
1	C_6H_5CN	0.5	7	9	6		2.7
1	C_5H_5N	1	3	7	32		0.3
1 (Ar purge)	CH_3CN	0.25	6	8	9		
6	CH_3CN	0.25	11	12	14		1.6
6 + $(CH_3)_2S$	CH_3CN	0.5	05	0.1	17		
6 + CH_2Br_2	CH_3CN	0.25	10	12	12	6[b]	
6 + R'OH	CH_3CN	0.25	10	14	18	2[c]	

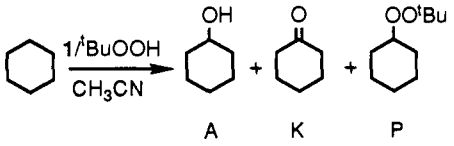
[a] Moles of product per mole of catalyst. [b] Bromocyclohexane formed as a result of the addition of 10% CH_2Br_2. [c] 4-Methylcyclohexanone formed as a result of the addition of 20 equiv of 4-methylcyclohexanol.

Table II. Product Distributions for the Iron (0.7 mM) Catalyzed TBHP Oxidation of Cyclohexane (0.77 M) in Acetonitrile under 1 atm of Argon at 25 °C: Effect of Ligand on the Reaction

		products[a]					
catalyst	reacn time (h)	OH	O	OO^tBu	(A + K)/P	TN/h[b]	k_H/k_D[c]
		A. Effect of the Terminal Ligand					
$[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**)	0.25	9	11	16	1.3	80	4.6
$[Fe_2(BPEA)_2O(OAc_2)](ClO_4)_3$ (**2**)	1	10	14	8	3	24	7.3
$[Fe_2(BPA)_2O(OBz)_2](ClO_4)_2$ (**3**)	16	15	13	10	2.8	1.8	6.1
$[Fe_2(NTB)_2OAc)](ClO_4)_3$ (**4**)	16	8	7	0.7	20	0.9	7.1
$[Fe_2(HB(pz)_3)_2O(OAc)_2]$ (**5**)	16	0	0	0		0	
		B. Effect of the Bridging Anion					
$[Fe_2(TPA)_2O(OBz)](ClO_4)_3$ (**6**)	0.25	11	12	14	1.6	92	4.4
$[Fe_2(TPA)_2O(O_2CC_6H_4\text{-}4\text{-}OCH_3)](ClO_4)_3$ (**7**)	1	11	13	18	1.3	24	4.9
$[Fe_2(TPA)_2O(O_2P(OPh)_2)](ClO_4)_3$ (**8**)	2	12	12	18	1.3	12	4.4
$[Fe_2(TPA)_2O(CO_3)](ClO_4)_2$ (**9**)	4	8	8	6	2.7	4	4.6
$[Fe_2(TPA)_2O(phthalate)](ClO_4)_2$ (**10**)	20	15	14	5	5.8	1.5	

[a] Moles of product per mole of catalyst. [b] TN = turnover number; calculated as moles of A + K per mole of catalyst per hour. [c] Values for alcohol formation with an estimated error of ±0.5.

with 0.25 h and afforded the functionalized alkane products shown as follows:



All of the TBHP was consumed within the 0.25-h reaction time and afforded the following product distribution: ^{t}BuOH (75%), ^{t}BuOOCy (11%), MeOH (10%),[31] and $^tBu_2O_2$ (<1%). The reaction mixtures were also analyzed for other specific cyclohexyl products, such as dicyclohexyl and *tert*-butyl cyclohexyl ether, but these were not observed. There was no change in the product distribution when workup of the reaction mixture was delayed for 3 h after TBHP was completely consumed. Since we know that the catalyst remains active even after TBHP is consumed (see Catalyst Stability), it is clear that **P** does not react with **1** within the time frame of these experiments. Furthermore, when the amount of unreacted substrate recovered was taken into account, all the reactions displayed complete mass balance, indicating that all major products derived from cyclohexane had been identified.

Catalyst Stability. The stability of **1** under the conditions of catalysis was investigated, and the complex was found to be unchanged at the end of the reaction. Complex **1** exhibits a characteristic ^{1}H NMR spectrum consisting of paramagnetically shifted resonances associated with the TPA and acetate ligand protons.[19] This spectrum obtained in a mixture of cyclohexane-d_{12}/CD_3CN remained unchanged after the addition of TBHP to the reaction mixture and after the oxidation reaction was completed. Similarly, the UV–vis spectrum of the reaction mixture was invariant during the catalytic process. Furthermore, the addition of a second aliquot of TBHP to the reaction mixture after 0.25 h of reaction doubled the yield of the reaction. Thus the catalytic activity of **1** appeared not to be diminished by multiple turnovers. These observations indicate that **1** is stable under these conditions and capable of sustaining very high turnover numbers.

Catalyst Ligand Effects. The various (μ-oxo)diferric complexes analogous to **1** are compared in Table IIA in terms of their catalytic properties and the products they form. The tripodal ligands are illustrated in Figure 1. It is clear that the coordination environment of the (μ-oxo)diferric center has a profound effect on its catalytic efficiency, strongly suggesting a role for the iron center in these reactions. Table IIA shows that the yields of **A** and **K** vary within a factor of 2 of each other, but the amount of time required for the reaction varies by almost 2 orders of magnitude. The data emphasize the high catalytic efficiency of the TPA complex. Replacing a pyridylmethyl arm with a pyridylethyl arm as in **2** increased the reaction time by a factor of 4. Removing a pendant pyridine from each tripod and replacing them with a bridging carboxylate to form a (μ-oxo)bis(μ-carboxylato)diferric complex (**3**) or substituting the pendant pyridines with benzimidazoles as in **4** increased the reaction times

(31) Under the conditions used for GC analysis of the product mixture acetone co-elutes with the solvent and thus was not quantitated.

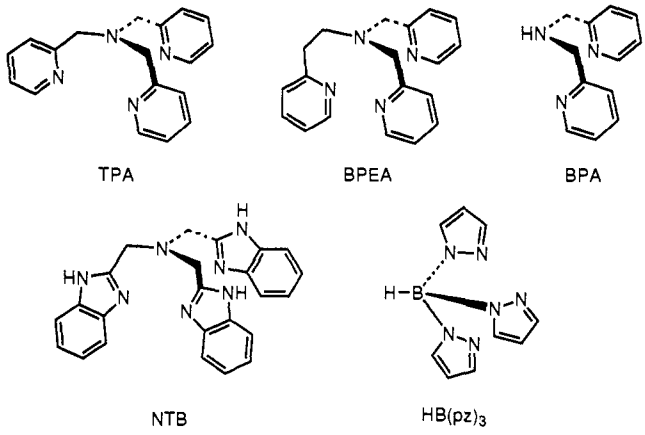


Figure 1. Tripodal ligands used in this study.

by almost 2 orders of magnitude. Interestingly, $[Fe_2\{HB(pz)_3\}_2O(OAc)_2]$, the prototype of models for diiron–oxo proteins, displayed no catalytic activity at all under these conditions.[32]

The availability of a number of (μ-oxo)diferric TPA complexes having different bridging groups prompted us to investigate the effect of the anionic bridging ligand on catalytic efficiency (Table IIB). With the exception of **7**, all the complexes in this group are crystallographically characterized. Complex **6** with a benzoate bridge displays a structure almost identical to that found for the acetate complex (**1**); not surprisingly, the catalytic activity of **6** was found to be very similar to that observed for **1**. The use of a more electron-donating benzoate (as in **7**) increased the reaction time by a factor of 4. The presence of a diphenyl phosphate bridge in place of benzoate (as in **8**) cut the catalytic efficiency yet further (a factor of 8), while the use of dianionic bridging groups such as carbonate (**9**) and phthalate (**10**) afforded the longest reaction times in this series, increasing by factors of 16 and 80 relative to that of **6**.

The product distribution also exhibited a dependence on the nature of the iron ligands. **1** and related TPA complexes such as **5**–**8** afforded an (A + K)/P ratio of ~1.4. However, complexes with more electron-donating ligands disfavored the formation of **P** relative to **A** and **K** (Table IIB). Complexes **2**, **3**, and **9** afforded (A + K)/P ratios of ca. 3, while the phthalate complex (**10**) gave a ratio of ca. 6. The NTB catalyst (**4**), although the least efficient of the group, suppressed the formation of the dialkyl peroxide almost completely. Furthermore, the (A + K)/P ratio was affected by the choice of solvent; in the case of **1**, benzonitrile shifted the balance of products in favor of hydroxylation with an (A + K)/P ratio of 2.7, while pyridine had the opposite effect, affording an (A + K)/P ratio of 0.3 (Table I). These results suggest the participation of different mechanisms in the formation of **A** + **K** and **P**.

Mechanistic Probes. The addition of competitive substrates or traps to the cyclohexane oxidation reactions provided insight into the mechanism of iron-catalyzed TBHP decomposition (Table I). Experiments using a 1/1 mixture of cyclohexane and cyclohexane-d_{12} as substrate afforded primary kinetic isotope effects for alcohol and dialkyl peroxide formation (Table II), indicating that C–H bond cleavage was an important component of the **A** and **P** formation mechanisms. Interestingly, the k_H/k_D value for dialkyl peroxide formation was 7.7 ± 0.5 for all catalysts, indicating that the C–H bond-breaking step for this product was independent of the metal complex used. On the other hand, the k_H/k_D value for alcohol formation was dependent on the nature of the tripodal ligand but largely independent of the bridging ligand in the TPA series.

(32) Though $[Fe_2\{HB(pz)_3\}_2O(OAc)_2]$ has been shown to give very limited catalytic activity for the oxidation of alkanes in the presence of Zn and HOAc (see ref 13), this complex yielded no organic products from the attempted oxidation of cyclohexane with TBHP (Table I).

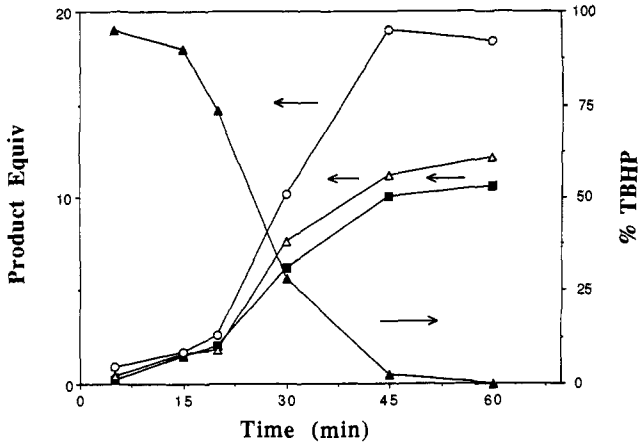


Figure 2. Time course for the (0.10 M) TBHP functionalization of (0.77 M) cyclohexane catalyzed by (0.7 mM) $[Fe_2(TPA)_2O(O_2CC_6H_4OMe)](ClO_4)_3$ (**7**) in acetonitrile at 25 °C under 1 atm of argon. Products: cyclohexanol (■), cyclohexanone (△), (*tert*-butylperoxy)cyclohexane (○), and the oxidant TBHP (▲). Product equiv = moles of product per mole of catalyst.

The presence of CH_2Br_2 (10% of sovlent by volume) in the reaction of **6**/TBHP/cyclohexane afforded 6 equiv of bromocyclohexane, suggesting the participation of cyclohexyl radicals in the reaction mechanism which were trapped by CH_2Br_2.[33] More interestingly, the addition of 50 equiv of $(CH_3)_2S$ to a typical **6**/TBHP/cyclohexane reaction dramatically diminished the production of **A** and **K**, without significantly affecting the formation of **P**.

The mechanism for ketone formation was explored. A perusal of Table I also shows that the **A**/**K** ratio hovers near 1 for all the catalysts. Fe(TPA)/TBHP systems have been shown to be capable of oxidizing **A** to **K**,[29] so **K** may be expected to derive from the oxidation of **A**. However, several lines of evidence suggested that the mechanism for ketone formation may be more complicated. A time course experiment was carried out for the oxidation of cyclohexane by **7**/TBHP in acetonitrile under conditions identical to those used for the reaction of **1** and the other dinuclear catalysts. Complex **7** was chosen for this study, because its longer reaction time (1 h) facilitated the construction of the time course plot. The plot (Figure 2) shows that all three cyclohexane-derived products appear to have very similar time courses; in particular, the appearance of **K** does not lag behind that of **A**. In a different experiment, cyclohexane was reacted with **6**/TBHP in the presence of 20 equiv of 4-methylcyclohexanol, the amount of 4-methylcyclohexanol added having been chosen to approximate the amount of **A** + **K** typically formed in the reaction (Table I). GC analysis showed that only 2 equiv of 4-methylcyclohexanol was oxidized to the corresponding ketone, and amounts of **A**, **K**, and **P** were not significantly affected. As a control, a 1/1 mixture of cyclohexanol and 4-methylcyclohexanol was oxidized by **6**/TBHP, and equal amounts of the corresponding ketones were produced. These results suggest that **K** is formed mainly by a mechanism not readily accessible to the added alcohol. Finally, running the **1**/TBHP reaction under an Ar purge affected the amounts of **A**, **K**, and **P** formed; the amounts of **A** and **K** diminished by 30%, while the amount of **P** was decreased by 45%. This observation suggests that O_2 plays some role in the formation of all the products observed.

Discussion

The last decade has been marked by the syntheses of a number of (μ-oxo)diferric complexes which model well the structural and spectroscopic properties of the metal sites in diiron–oxo proteins,[9] but few of these species display catalytic reactivity that mimic

(33) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6377–6380.

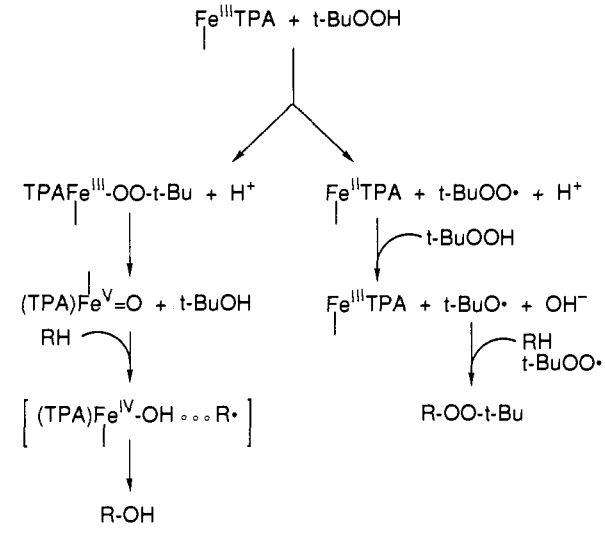
the alkane functionalization chemistry of methane monooxygenase. We have found that Fe(TPA) complexes serve as remarkable functional models, mimicking the oxidation reactions catalyzed by nonheme iron enzymes. $[Fe^{III}(TPA)(3,5\text{-di-}tert\text{-butylcatecholate})]^+$ reacts quantitatively with O_2 mimicking the oxidative cleavage chemistry of the intradiol cleaving catechol dioxygenases.[34] $[Fe^{II}(TPA)(benzoylformate)]^+$ serves as a model for the α-ketoacid-dependent iron hydroxylases and undergoes oxidative decarboxylation in the presence of O_2 to afford benzoic acid in quantitative yield.[35] $[Fe^{III}(TPA)X_2]^+$ complexes (X = Cl, Br, N_3) in concert with TBHP catalyze alkane hydroxylation[29] and effect stoichiometric alkane halogenation.[30] $Fe^{III}_2O(TPA)_2(ClO_4)_4$, upon reaction with hydrogen peroxide, affords a high-valent iron–oxo species[20] that is a putative intermediate in the reaction catalyzed by MMO.[5] We have therefore investigated the efficacy of $[Fe^{III}_2O(TPA)_2]^{4+}$ complexes to serve as catalysts for the peroxide-dependent oxidation of alkanes and the role the metal center plays in this reaction.

The present study represents thus far the most systematic investigation of an alkane functionalization system with respect to the metal center. Many of the complexes in the series (Table II) are structurally characterized; the ligand environments represented by the series modulate the electronic properties of the metal centers so that a range of reactivities is observed. Furthermore, protons on the tetradentate ligands in this study can be followed by NMR to allow the integrity of the catalyst to be monitored during turnover. Ease in handling and characterization make cyclohexane the test substrate of choice, enabling us to quantitate the amount of oxidized product and unreacted starting material. Indeed, complete mass balance of substrate is achieved in these reactions, accounting for all of the products of the oxidation reactions. The alkyl hydroperoxide TBHP has been chosen as oxidant to minimize the ambiguities associated with the various species that can be formed by O_2 and a reductant; the presence of the alkyl group greatly facilitates the task of determining the fate of the decomposed peroxide.

In using an organic ligand for an alkane hydroxylation catalyst, it is essential that the stability of the catalyst be determined, since the potential for ligand degradation under conditions necessary for alkane oxidation is high. Many metalloporphyrin catalysts are prone to ligand decomposition under oxidizing conditions, often limiting the effectiveness of these systems in catalytic reactions.[36] However, the stability of the TPA-based catalysts is remarkably high. In the **1**/TBHP system, introduction of a second aliquot of TBHP after the initial aliquot has been consumed doubles the yield of oxidized products and affords a similar product distribution. Furthermore, monitoring the catalyst by ^1H NMR and UV–vis spectroscopy shows that the ligand is unchanged by catalysis and the complex remains intact under the normal conditions of excess substrate. **1** is capable of high turnover numbers, generating as much as 80 equiv of **A** and **K** in 1 h, which is almost 2 orders of magnitude more efficient than $[Fe_2O(bpy)_2(OAc)_2Cl_2]$ in the TBHP-dependent functionalization of cyclohexane.[16a] Our observations demonstrate the utility of TPA as a ligand, affording a catalyst sufficiently reactive to promote rapid reaction but also sufficiently robust to support high turnover numbers.

Varying the tripodal ligand and the bridging anion on the catalyst produces a large change in the efficiency of TBHP decomposition and formation of functionalized cyclohexane (Table II). Among tripodal ligands, TPA affords the most effective oxidation catalysts of the carboxylate-bridged complexes in Table II, **1** and **6** being 2 orders of magnitude more efficient than **3** and **4**. In the TPA series, bridging monoanions give rise to shorter reaction times than bridging dianions. These observations support a role for the metal centers in these reactions.

Scheme I



Three products derived from cyclohexane oxidation are found in these reactions: cyclohexanol (**A**), cyclohexanone (**K**), and (*tert*-butylperoxy)cyclohexane (**P**). All three products form concurrently, as illustrated in the time course of this reaction (Figure 2). **P** appears to be stable under the experimental conditions used here; the ratio and amounts of **A**, **K**, and **P** measured after the TBHP was completely consumed did not change when a typical reaction mixture was allowed to stand for an extended period of time in the presence of catalyst. Since **1** has been shown to be active at the end of the reaction, this demonstrates that it does not react with **P** under these conditions.

The observed products do not appear to result from a common mechanism. The product distribution was altered by changes in solvent and catalyst (Tables I and II), with less polar solvents and electron-donating ligands disfavoring the production of **P**. Remarkably, Me_2S added to the **1**/TBHP reaction suppresses the formation of **A** and **K** but does not affect the amount of **P** formed. This observation indicates that Me_2S can intercept the reactive species responsible for the formation of **A** and **K** but not of **P**. In a study of heme-catalyzed decomposition of alkyl hydroperoxides, Labeque and Marnett demonstrated the participation of dual mechanisms by showing that *p*-methoxythioanisole did not affect transformations resulting from peroxide homolysis but inhibited reactions resulting from peroxide heterolysis presumably by trapping the resultant high-valent iron–oxo species $[(TPP^{\cdot})Fe^{IV}{=}O]^+$.[37] Similarly, Kochi et al. found that the TBHP oxidation of cyclohexene catalyzed by [Mn(salen)]$^+$ afforded the corresponding epoxide (via peroxide heterolysis and a Mn^V–oxo species) and 3-(*tert*-butylperoxy)cyclohexene (via peroxide homolysis).[38]

By analogy to these reactions, we propose the following two competing mechanisms for alkyl hydroperoxide decomposition: a peroxide heterolysis mechanism forming a high-valent iron–oxo species that converts alkane to alcohol analogous to pathways associated with cytochrome P450 and synthetic heme hydroxylation chemistry[8] and a peroxide homolysis mechanism[39] that affords RO· and ROO· radicals to produce dialkyl peroxide (Scheme I).

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(39) (a) Kharasch, M. S.; Sosnovsky, G. *Tetrahedron* **1958**, *3*, 105. (b) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72. (c) Saussine, L.; Brazi, E.; Robine, A.; Mimoun, H.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1985**, *107*, 3534–3540.

Table III. Comparisons of Structural Properties of the Fe(TPA) Catalysts[a] and Their Reactivities

catalyst	∠Fe–O–Fe (deg)	$Fe–O_{bridging\ anion}$ (Å)	TN/h
$[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (**1**)	129.7(3)	1.984(5) 2.046(5)	80
$[Fe_2(TPA)_2O(OBz)](ClO_4)_3$ (**6**)	129.2(2)	1.972(6) 2.038(6)	92
$[Fe_2(TPA)_2O(O_2P(OPh)_2)](ClO_4)_3$ (**8**)	138.1(2)	1.963(3) 2.045(3)	12
$[Fe_2(TPA)_2O(CO_3)](ClO_4)_2$ (**9**)	125.4(3)	1.911(6) 1.953(6)	4
$[Fe_2(TPA)_2O(phthalate)](ClO_4)_2$ (**10**)	143.4(3)	1.924(5) 1.956(5)	1.5

[a] Derived from ref 19b,c.

Reactions 1–3 have been proposed previously to rationalize the introduction of the ROO–functionality into hydrocarbons by metal complexes.[39] The notion that the hydrogen abstraction

$$^tBuO^\cdot + RH \rightarrow {}^tBuOH + R^\cdot \quad (1)$$

$$^tBuO^\cdot + {}^tBuOOH \rightarrow {}^tBuOH + {}^tBuOO^\cdot \quad (2)$$

$$^tBuOO^\cdot + R^\cdot \rightarrow {}^tBuOOR \quad (3)$$

agent is the $^tBuO^\cdot$ radical, and not the metal center, is consistent with the independence of the primary kinetic isotope effect of dialkyl peroxide formation from the nature of the metal complex. As previously noted by Labeque and Marnett,[37] such a species would not react with Me_2S, thus rationalizing the ineffectiveness of Me_2S to inhibit the formation of **P**. The $^tBuO^\cdot$ and $^tBuOO^\cdot$ radicals responsible for the formation of **P** may be formed by a Haber–Weiss mechanism (reactions 4 and 5).[40] The fact that

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

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

electron-donating ligands on the catalyst retard the formation of dialkyl peroxide is consistent with the involvement of this mechanism. Such ligands shift the redox potential of the catalysts to more negative values,[42] and they would disfavor the initial step of the Haber–Weiss mechanism and slow down the initiation of the chain reaction.

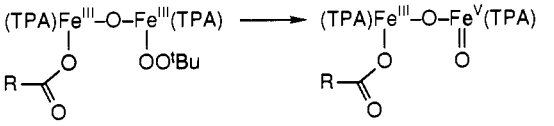
The observation that argon purging decreases the amount of **P** by almost 50% indicates that O_2 is formed in the catalytic system during the reaction and plays a significant role in the formation of **P**. O_2 may be formed by the decomposition of $^tBuOOOO^tBu$ derived from the dimerization of $^tBuOO^\cdot$ radicals[43] and may participate in **P** formation according to reactions 6 and 7.

$$R^\cdot + O_2 \rightarrow ROO^\cdot \quad (6)$$

$$^tBuOO^\cdot + ROO^\cdot \rightarrow {}^tBuOOR + O_2 \quad (7)$$

The observation that Me_2S essentially eliminates the production of **A** and **K** strongly implicates peroxide heterolysis as the pathway responsible for their formation. By analogy to the mechanism proposed for iron porphyrin-mediated alkane hydroxylations,[8] peroxide heterolysis produces a high-valent iron–oxo species which reacts with the alkane. The iron–oxo species abstracts hydrogen from substrate, generating an alkyl radical and an iron hydroxide

Scheme II



in a solvent cage; the cage then collapses to form a alcohol by an oxygen-rebound mechanism (Scheme I). The notion that alcohol formation (unlike **P** formation) is a metal-centered process is supported by the observation that the k_H/k_D values for alcohol formation depend on the nature of the tripodal ligand (Table IIA).

For these (μ-oxo)diferric catalysts, the peroxide heterolysis reaction must be initiated by generating an open site on one of the coordinatively saturated iron centers. This would be most readily achieved by the dissociation of the bidentate anion bridge from one iron center. Since no spectral changes are observed for the (μ-oxo)diferric center during catalysis, this dissociation may represent the rate-determining step in generating the hydroxylating agent. Indeed, the order of reactivity for the TPA catalysts can be rationalized by the relative affinities of the bridging anion for the metal center. The dianionic carbonate- and phthalate-bridged complexes have average Fe–O bonds that are 0.06–0.07 Å shorter than those of their monoanionic counterparts[19b,c] and are the least effective catalysts (Table III). Furthermore, the introduction of a para methoxy group on the benzoate bridge, resulting in a more basic carboxylate and presumably a slightly stronger $Fe–O_{carboxylate}$ bond, slows the reaction time by a factor of 4 (**6** vs **7**). The Fe–O–Fe angle may play a secondary role in the dissociation of the bridge, as complexes with carboxylate bridges are more efficient at alkane functionalization than catalysts with similarly charged bridges but larger Fe–O–Fe angles,[19b,c] i.e. **6** vs **8** and **9** vs **10** (Table III). Diferric complexes with unsupported oxo bridges typically have Fe–O–Fe angles of 150° or greater,[44] thereby enhancing $Fe–O_{oxo}$ π bonding.[45] Carboxylate bridges restrict this angle to values under 130°;[19b] the relief of this constraint on the Fe–O–Fe unit may promote the breaking of the carboxylate bridge to initiate catalysis.

The dissociation of the bridge allows the coordination of the alkyl peroxide ion and its subsequent heterolysis, as shown in Scheme II. The oxidizing iron center would thus be insulated from the electronic effects of the bridging anion. Consistent with Scheme II, the isotope effect for alcohol formation in the TPA series (Table IIB) is independent of the bridge. Either species in Scheme II may be intercepted by Me_2S, but the heterolysis of the bound peroxide is likely to involve the high-valent iron–oxo species as a transition state or an intermediate.

The hydrogen-abstracting power of the Fe^{III}—OOR or the formally Fe^V=O species is clearly modulated by the nature of the tripodal ligand (Table IIA), with TPA engendering the most powerful (and least selective) oxidant by virtue of having the

(40) The possibility that $^tBuOO^\cdot$ radicals can be produced by the reaction of the high-valent iron–oxo species with free TBHP as proposed by Traylor[41] can be excluded, because such a mechanism would be affected by Me_2S.

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smallest k_H/k_D values (~4.6). The more electron-donating environments found in **3** and **4** clearly mitigate the oxidizing power of the reactive species ($k_H/k_D \sim 6$–7), as may by expected for the stabilization of a high-valent species. Similar selectivity trends are observed for the stoichiometric halogenation of alkanes by TBHP using mononuclear [Fe(tripodal ligand)X_2]$^+$ complexes,[46] wherein a related [Fe(TPA)O(X)]$^{2+}$ species is suggested in the oxidative ligand-transfer reaction to alkane. For comparison, the oxidation of cyclohexane to cyclohexanol by Fe$(NO_3)_3$/TBHP[10d] or Fe(picolinate)$_2$/TBHP[14a] has a k_H/k_D value of ~8, while that by Fe(TPP)Cl/PhIO has a k_H/k_D value of 13.[47]

The notion of a high-valent iron–oxo species in a nonheme environment derived from peroxide heterolysis is supported by our recent spectroscopic characterization of a transient species minimally formulated as [Fe(TPA)O]$^{3+}$, resulting from the reaction of [Fe_2O(TPA)$_2$]$(ClO_4)_4$ with H_2O_2 in acetonitrile.[20] This species is stable at –40 °C for 2 h and capable of oxo transfer. At present we cannot directly determine whether an analogous species participates in the catalytic hydroxylation reaction or whether such a species is mononuclear or dinuclear (as shown in Scheme II), since no intermediates have been observed in this reaction. We do not understand the factors that allow the [Fe(TPA)O]$^{3+}$ intermediate to be stabilized and thus be observed under these conditions. The absence of an analogous species in the catalytic hydroxylation reactions described in this paper does not discount its participation, since its lifetime could be too short to permit detection. (Indeed there is as yet no direct spectroscopic evidence for the participation of a high-valent iron–oxo species in the cytochrome P450 reaction, though such a species enjoys wide acceptance as a plausible intermediate.[48]) A significantly shorter lifetime for an iron–oxo species derived from 1/TBHP would be consistent with the high catalytic efficiency of 1/TBHP versus the longer lifetime associated with the intermediate formed from [Fe_2O(TPA)$_2$]$(ClO_4)_4/H_2O_2$, which is a substantially poorer alkane functionalization catalyst.[20]

The mechanism of ketone formation is somewhat more complex. We have demonstrated that our catalyst systems were capable of oxidizing **A** to **K**. However, there is no obvious lag phase for **K** formation, suggesting that the oxidation of **A** to **K** is faster than that of cyclohexane to **A**. Moreover, the oxidation of 4-methylcyclohexanol in the presence of cyclohexane is not very effective, despite the fact that cyclohexanol and 4-methylcyclohexanol are converted to their respective ketones equally efficiently in competitive oxidation experiments. These observations suggest that exogenous alcohol may not penetrate the solvent cage (also noted by Labeque and Marnett[37]) and that there is a direct pathway to **K** without going through free **A**. One possible mechanism is that **A** is oxidized to **K** by a second equivalent of TBHP before **A** is able to escape the solvent cage. Such a possibility has also been raised by Nam and Valentine[15b] to rationalize the appearance of ketone in their studies.

Another possible mechanism is the interception of the nascent alkyl radical by O_2, forming cyclohexyl hydroperoxide, which decomposes to **K**. Recently, cyclohexyl hydroperoxide (CyOOH) was identified to be an intermediate in the oxidation of cyclohexane by the "Gif" system[49] and by $Fe_2O(OAc)_2(bpy)_2Cl_2/H_2O_2$ under aerobic conditions.[16b] Metal-catalyzed decomposition of CyOOH would then result in the formation of **A** and **K**. Indeed, when run under an Ar purge, both $Fe_2O(OAc)_2(bpy)_2Cl_2/H_2O_2$[16b] and Fe$(NO_3)_3$/TBHP[10d] systems are completely ineffective in forming alcohol and ketone from the substrate alkane, indicating that O_2 is absolutely essential for the formation of these products. In contrast, the argon purge experiments on the 1/TBHP catalyst system demonstrate that only 30% of the **A** and **K** produced are eliminated by argon purging and presumably derive from CyOOH. In order to be consistent with the inhibition effect of Me_2S, the CyOOH that gives rise to **A** and **K** must derive solely from the cyclohexyl radical generated by the Fe^{III}—OOR or Fe^{V}=O species in the radical cage, and not from the cyclohexyl radical formed by $^tBuO^\bullet$. Since argon purging can completely prevent dioxygen trapping of the nascent alkyl radicals formed by $Fe_2O(OAc)_2(bpy)_2Cl_2/H_2O_2$[16b] and Fe$(NO_3)_3$/TBHP,[10d] the 70% of **A** and **K** that remain with argon purging in the 1/TBHP system must derive from a different mechanism, perhaps oxygen rebound as proposed in Scheme I.

In summary, the (μ-oxo)diferric TPA complexes are the most efficient and robust nonheme iron catalysts for alkane functionalization with TBHP, converting cyclohexane into alcohol, ketone, and dialkyl peroxide products under very mild conditions. Because the nature of the tripodal ligand modulates the oxidizing power of the active species, the metal center must be directly involved in abstracting hydrogen from substrate to form alcohol.

Acknowledgment. This work was supported by funds from the National Institutes of Health (Grant No. GM-38767) and the Amoco Corp. R.A.L. acknowledges an NIH National Research Service Award (GM-13343).

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