[Fe^{III}(PMA)]$^{2+}$: A Mononuclear Non-Heme Iron Complex That Catalyzes Alkane Oxidation

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The iron(III) complex [Fe^{III}(PMA)](ClO$_4$)$_2$ (**3**) of a designed ligand PMAH (**1**; H is a dissociable amide H), which mimics the metal-binding domain of the antitumor antibiotic bleomycin, promotes alkane oxidation in conjunction with TBHP or H_2O_2. In anhydrous acetonitrile, reaction of **3** + TBHP with cyclohexane affords high yields of cyclohexanol and cyclohexanone (1:1 ratio, 1700% yield on the basis of catalyst concentration) along with the mixed peroxide ^{t}Bu−OO−Cy. The presence of water lowers the yields of oxidized products. Product ratios obtained in oxidations of adamantane and 3-methylpentane with **3** + TBHP confirm that reaction occurs at more-substituted carbon centers. No oxidation of an aromatic C−H bond is observed with **3** + TBHP. EPR spectra at low temperatures indicate that the low-spin Fe(III)−peroxo intermediate [(PMA)Fe^{III}−O−OR]$^+$ (R = H, ^{t}Bu) is formed in the reaction mixture. Since the PMA$^-$ ligand framework is incapable of stabilizing the high-valent iron center and oxidation of both cyclohexene and norbornene with **3** + TBHP yields only the allylic oxidation products and the *exo*-epoxide, respectively, involvement of a perferryl [(PMA)Fe^{V}=O]$^{2+}$ intermediate in the oxidation reactions appears unlikely. Product distributions of the oxidation reactions strongly suggest that homolysis of the O−O bond in [(PMA)Fe^{III}−O−O^{t}Bu]$^+$ occurs in the reaction mixtures. Abstraction of an H atom from cyclohexane by ^{t}BuO$^\bullet$, a product of the homolytic cleavage of the O−O bond in [(PMA)Fe^{III}−O−O^{t}Bu]$^+$, results in the production of the cyclohexyl radical. A k_H/k_D value of 6.5 ± 0.5 for the cyclohexane oxidation by the **3** + TBHP system indicates that C−H bond cleavage is an important step in the overall oxidation mechanism. Reaction of the cyclohexyl radical with O_2 (generated in reactions of ^{t}BuO$^\bullet$ and ^{t}BuOO$^\bullet$) produces CyOO$^\bullet$ in the reaction mixture, which undergoes a Russell-type termination to afford cyclohexanol and cyclohexanone in a 1:1 ratio. Combination of ^{t}BuOO$^\bullet$ and the cyclohexyl radical results in the formation of the mixed peroxide ^{t}Bu−OO−Cy. The second product from the homolytic cleavage of the O−O bond in [(PMA)-Fe^{III}−O−O^{t}Bu]$^+$, namely [(PMA)Fe^{III}−O$^\bullet$]$^+$, also takes part in the catalytic process by abstracting an H atom from TBHP and generating ^{t}BuOO$^\bullet$, a species that provides both O_2 and ^{t}BuO$^\bullet$ in the reaction mixture. Since catalysis is noted only in the presence of iron complexes that give rise to the [(ligand)$_n$Fe^{III}−O−OR]$^+$ intermediates (EPR results) and the yields of the oxidation products vary depending on the nature of the ligands in the starting iron complexes, it is evident that the iron complexes do take part in the oxidation reactions. Results of the present work also suggest that low-spin Fe(III) peroxides are viable intermediates in peroxide-mediated alkane oxidations by certain non-heme iron complexes.

Introduction

Our current understanding of the mechanism(s) of alkane functionalization, especially the C−H → C−OH transformation, is advanced for cases involving heme (iron−porphyrin) as the catalyst, and the hypothesis is that such reactions proceed via hypervalent iron−oxo (ferryl (Fe^{IV}=O) or perferryl (Fe^{V}=O)) intermediates.[1] Such intermediates have been proposed for the reactions of the monooxygenase enzyme cytochrome P-450. The situation is however, less clear in the case of the non-porphyrin systems.[2] For example, methane monooxygenase (MMO), which catalyzes the oxidation of methane by dioxygen to methanol, contains a binuclear non-heme iron active site.[3,4] Not much is known about the chemical nature of the active intermediate or intermediates that react with the organic substrates in these non-porphyrin systems. While investigators have speculated that the mechanism(s) could be similar to those of the heme-containing systems, it is difficult to imagine that an Fe^{V}=O (or Fe^{IV}=O) intermediate is involved without the porphyrin prosthetic group; the ligand environments of these systems are not expected to be capable of stabilizing such a high oxidation state of iron. However, in recent accounts, two groups (Lipscomb and co-workers;[4a] Lippard and co-workers[3b]) have demonstrated the existence of an intermediate Q in the MMO catalytic cycle which appears to contain iron centers with oxidation state higher than +3 although the possibility of electron loss from a ligand at the active site of the enzyme (and not from the iron atoms) has not been ruled out.[3b] Also, Que and co-workers recently reported a mixed-valence bis(μ-oxo) low-spin (S = $^1/_2$) Fe^{III}−low-spin (S = 1) Fe^{IV} species [Fe$_2$(O)$_2$(5-Me-TPA)$_2$](ClO$_4$)$_3$ (5-Me-TPA = tris((5-methyl-2-

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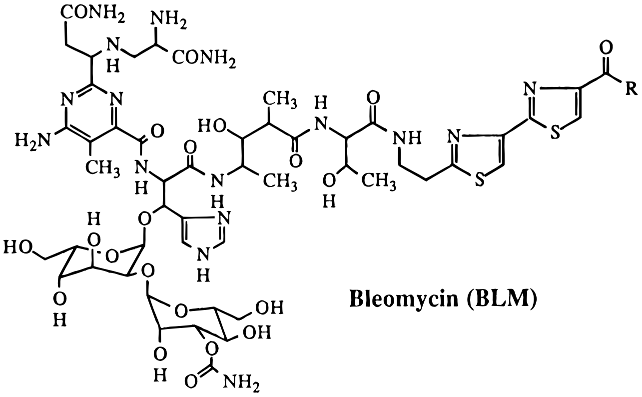
pyridyl)methyl)amine) which is claimed to be the "first example of how a high-valent state can be attained in a non-heme environment".[5] The assignment of Fe^{IV} in this intermediate however awaits further analyses of the magnetic[5] and Mössbauer data.[3b]

The recent interest in the chemistry of MMO has led to the exploration of suitable model complexes of iron as catalysts for oxidation of saturated hydrocarbons.[6] Model systems that mimic some aspects of the hydroxylation chemistry include simple iron salts[7,8] as well as iron complexes[9] such as $[Fe(salen)]_2O$,[10] $[Fe_2O(HB(pz)_3)_2(OAc)_2]$,[11] $[Fe_3O(OAc)_6(py)_3]$,[12] $[Fe_2OL_4(H_2O)_n](ClO_4)_m$ (L = bpy, substituted bpy, phen),[13] $[Fe_2O(OAc)_2(bpy)_2Cl_2]$,[14ab] $[Fe_2O(H_2O)_2(tmima)_2](ClO_4)_4$,[14b,c] and $[Fe(PA)_2]$.[15] These catalysts act in concert with O_2/electron donors or peroxides to hydroxylate alkanes. Recently, Que and co-workers reported results of their systematic studies on functionalization of alkanes with (μ-oxo)diferric complexes using *tert*-butyl hydroperoxide (^{t}BuOOH, TBHP).[16] $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (TPA = tris(2-pyridylmethyl)amine) was shown to be a robust and moderately efficient catalyst for cyclohexane oxidation, affording cyclohexanol, cyclohexanone, and (*tert*-butylperoxy)cyclohexane in relative amounts. Biomimetic oxidation of alcohols in aqueous solution by (μ-oxo)-diferric complexes of TPA (and related ligands) have also been reported by Fish and co-workers.[17] In recent accounts, Barton and co-workers compared the mechanism of the Gif-type chemistry with the MMO chemistry and proposed a μ-oxo−Fe(III) dimeric species as the catalyst[7,18] although, in the earlier papers, a trimeric complex was assumed to be the catalyst[12] and a mononuclear Fe−picolinato complex was also isolated from the reaction mixture.[18c] Clearly, the nature of the iron-containing catalyst(s) in these systems remains elusive at this time.



Bleomycin (BLM)

The iron complexes of the antitumor antibiotic bleomycin (BLM)[19] deserve special attention in this context. Fe-BLMs inflict strand breaks in DNA under aerobic conditions. An oxygenated Fe-BLM, often referred to as "activated bleomycin", is believed to be responsible for the oxidative damage of DNA. Activated bleomycin initiates DNA cleavage via *H atom abstraction* at the C4′ of the deoxyribose moieties of pyrimidine nucleotides adjacent to the guanines.[19c] In line with the oxidizing nature of activated bleomycin, Fe-BLMs also catalyze stereoselective oxo transfer to a wide range of olefinic substrates such as *cis*-stilbene with various oxygen sources like iodosylbenzene (PhIO), H_2O_2, alkyl peroxide, and O_2.[20] This property of Fe-BLMs is unique because it is the first example of a *mononuclear* non-heme system capable of oxygen activation.

As part of our research efforts toward elucidation of the structures and functions of the metallobleomycins, we recently reported the spectral characteristics of the Fe(II) and Fe(III) complexes of a designed ligand PMAH (**1**; H is the dissociable amide H) that mimics the entire metal-binding locus of BLM.[21] In both $[Fe^{II}(PMA)]^+$ (**2**) and $[Fe^{III}(PMA)]^{2+}$ (**3**), the iron is coordinated to five nitrogen donor atoms located in the primary and secondary amines, pyrimidine and imidazole rings, and the

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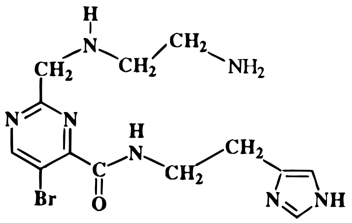
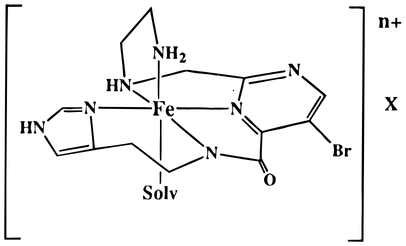
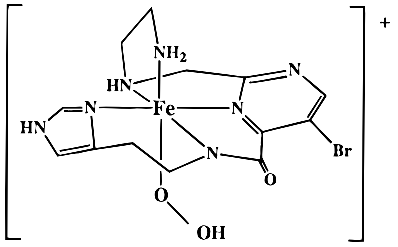


PMAH (**1**)



[Fe^{II}(PMA)]$^+$, X = Cl (**2**)
[Fe^{III}(PMA)]$^{2+}$, X = (ClO$_4$)$_2$ (**3**)



[(PMA)Fe^{III}-O-OH]$^+$ (**4**)

deprotonated amide moiety. Oxygenation of **2** as well as reaction of **3** with H_2O_2 affords the low-spin Fe(III)−hydroperoxo complex [(PMA)Fe^{III}−O−OH]$^+$ (**4**), which exhibits an EPR spectrum (g = 2.27, 2.18, 1.93; signal I hereafter) that is identical to that of activated bleomycin. This along with other chemical evidence[21] confirms that activated bleomycin is a low-spin Fe(III)−peroxide complex of BLM. Recently, Sam and co-workers utilized electrospray mass spectrometry to demonstrate that activated bleomycin is a ferric peroxide complex.[22] Results of X-ray absorption spectroscopy by Solomon and co-workers also confirm the Fe(III)−peroxo formulation of activated bleomycin.[23]

[(PMA)Fe^{III}−O−OH]$^+$ (**4**) is a very strong oxidant. In methanolic solution, it rapidly produces the $^{\bullet}CH_2OH$ radical (detected by spin trapping; A^H = 22.7 G, A^N = 16 G[24]) via H atom abstraction. This radical in turn gives rise to formaldehyde and the $^{\bullet}OOCH_2OH$ radical (g = 2.22, 2.05) in the reaction mixture within minutes. In addition, **4** promotes (a) rapid DNA cleavage via damage to sugar moieties and formation of base propenals and (b) stereoselective oxo transfer to olefinic substrates.[21] This unusually strong oxidizing nature of **4** and the recent report of a mononuclear Fe(III)−alkylperoxy intermediate in peroxide-mediated oxidation of hydrocarbons by Menage and co-workers[13a,b] prompted us to look into the possibility of alkane oxidation by **3** in conjunction with ROOH (R = H, ^{t}Bu). Reported in this account are the results of alkane functionalization by the Fe(III) complex **3** with TBHP and H_2O_2 as the oxidant. **3** gives rise to signal I with both oxidants (vide infra). Several substrates including cyclohexane, adamantane, and 3-methylpentane have been used in this study.

Experimental Section

Materials. All chemicals were of reagent grade unless otherwise noted. The solvents were purified by standard procedures. The batch of 90% TBHP (Aldrich) was further dried over anhydrous $MgSO_4$. [Fe^{III}(PMA)](ClO$_4$)$_2$ (**3**), *tert*-butyl cyclohexyl peroxide,[25] and 4,4′,6,6′-tetra-*tert*-butyl-*o*,*o*′-biphenol[26] were synthesized by following published procedures.

Instrumentation. Standard organic product analyses were performed on a Hewlett-Packard GC 5890 Series II Plus equipped with a flame-ionization detector and a Heliflex AT-1701 (30 m × 0.25 mm o.d.; film thickness 0.25 μm) capillary column (Alltech). Absorption spectra were obtained with a Perkin-Elmer Lambda 9 spectrophotometer. The EPR spectra at X-band frequencies were recorded on a Bruker ESP-300 spectrometer.

Oxidation of Hydrocarbon Substrates. All manipulations were performed at 25 °C and under dioxygen-free N_2 atmosphere such as in a glovebox or a Schlenk line. In a typical reaction, 7.35 mmol of substrate (350 equiv)[27] was reacted with 2.10 mmol of dry TBHP (100 equiv) in acetonitrile (total volume 3 mL) in the presence of 0.021 mmol of [Fe^{III}(PMA)](ClO$_4$)$_2$ at 25 °C under dry N_2 atmosphere. After 30 min of reaction, the mixture was filtered through a 0.45 μm Acrodisc Nylon filter. A known amount of toluene or mesitylene (internal standard) was added to the filtrate, and the mixture was analyzed by GC. Retention times for product peaks were compared directly with those of known standard compounds. The yields were calculated using proper correction factors. When adamantane or 3-methylpentane was used as the substrate, the reaction mixture also contained 30% benzene for solubility reasons. The time course of the cyclohexane oxidation was determined by employing conditions similar to those of the substrate oxidation; aliquots of the reaction mixture were taken out periodically and filtered through 0.45 μm Acrodisc Nylon filters, and the mixtures were analyzed immediately by GC.

Results and Discussion

In acetonitrile, **3** promotes facile oxidation of cyclohexane with TBHP or H_2O_2 as the O source (Table 1). Both cyclohexanol and cyclohexanone are formed in moderate-to-high yields (ratio 1:1) within 30 min. With H_2O_2, the yields are lower due to the presence of water (we used 50% H_2O_2) in the reaction mixture. Considerably lower yields are also noted when wet TBHP (with 5−10% water) is used. The oxidation reactions are clean, and all the products are identifiable (Supporting Information). In Table 1, the percent yields are reported on the basis of the concentration of the catalyst (**3**). When the same yields are expressed in terms of turnover numbers (TN, calculated as moles of products per mole of catalyst per hour), the TN values clearly indicate that the iron complex does participate in multiple cycles of reactions before decomposition. For example, under typical reaction conditions, TN for the cyclohexane oxidation by **3** is 80. If the reaction mixture contains limited amount of TBHP (2 equiv), one recovers ~98% of the catalyst (as judged by the electronic absorption spectrum of **3**) at the end of the oxidation reaction. Further addition of TBHP to the reaction mixture initiates more oxidation, and more products are obtained. We monitored the time course of the oxidation of cyclohexane by **3** and TBHP.

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Table 1. Product Distributions for Cyclohexane Oxidation Catalyzed by Iron Complexes in Conjunction with Various Oxidants[a]

catalyst	oxidant	solvent system	% yields of products[b]			other products
			cyclohexanol	cyclohexanone	^{t}BuOOCy	
$[Fe^{III}(PMA)]^{2+}$	TBHP	MeCN/no H_2O	1750	1700	530	
$[Fe^{III}(PMA)]^{2+}$	TBHP	MeCN/100 μL of H_2O	1170	1250	250	
$[Fe^{III}(PMA)]^{2+}$	TBHP	MeCN/200 μL of H_2O	920	840	160	
$[Fe^{III}(PMA)]^{2+}$	TBHP	MeCN/500 μL of CCl_4	600	760	120	1300[c]
$[Fe^{III}(PMA)]^{2+}$	50% H_2O_2	MeCN	460	520		
$[Fe^{III}(PMA)]^{2+}$	PhIO	MeCN[d]	nd	nd		
$[Fe^{III}(PMC)]^{2+}$	TBHP	MeCN/no H_2O	1000	900	290	

[a] Reactions were performed under dry N_2 atmosphere. Catalyst:oxidant:substrate ratio = 1:100:350 mol equiv. [b] Percent yields based on catalyst concentration. Turnover numbers for each reaction (moles of products per mole of catalyst per hour) could be obtained by dividing the sum of the yields of all products by 50. [c] Chlorocyclohexane formed as a result of the addition of 30% CCl_4. [d] The reaction mixture also contained a small amount of MeOH.

Table 2. Product Distributions for the Various Oxidation Reactions Catalyzed by $[Fe^{III}(PMA)](ClO_4)_2$ (**3**) in MeCN[a]

substrate	oxidant	products (% yield)[b]	
heptane	TBHP	1-heptanal (200) 4-heptanol (160)	2-heptanol (260)
adamantane	TBHP	1-adamantanol (600) 2-adamantanone (185)	2-adamantanol (105)
3-methylpentane	TBHP	3-methyl-3-pentanol (305)	3-methyl-2-pentanone (140)
3-methylpentane	30% H_2O_2	3-methyl-3-pentanol (40)	3-methyl-2-pentanone (30)[c]
toluene	TBHP	benzaldehyde (1040)	
benzyl alcohol	TBHP	benzaldehyde (9040)	
benzene	TBHP	phenol (nd)[d]	
benzene	50% H_2O_2	phenol (200)	
cyclohexene	TBHP	epoxycyclohexane (nd) 2-cyclohexen-1-one (490)	2-cyclohexen-1-ol (310)
cyclohexene	50% H_2O_2	epoxycyclohexane (140) 2-cyclohexen-1-one (180)	2-cyclohexen-1-ol (120)
cyclohexene	90% TBHP	epoxycyclohexane (140) 2-cyclohexen-1-one (720)	2-cyclohexen-1-ol (230)
cis-stilbene	TBHP	*cis*-stilbene oxide (trace) benzaldehyde (2100)	*trans*-stilbene oxide (870) deoxybenzoin (95)
norbornene	TBHP	*exo*-1,2-epoxynorbornane (940) *endo*-1,2-epoxynorbornane (nd)	

[a] For reaction conditions, see Experimental Section. [b] Percent yields based on $[Fe^{III}(PMA)](ClO_4)_2$ concentration. [c] A small amount of phenol is also produced from oxidation of the cosolvent (benzene). [d] nd = not detected.

The amounts of cyclohexane and TBHP decrease rapidly with time (Figure 1). Formation of both cyclohexanol and cyclohexanone increases and reaches the maximum values around 30 min (the other major product is ^{t}Bu−OO−Cy; yield ~500%). No product is obtained when **3** is excluded from the reaction mixture; i.e., **3** is absolutely required for the oxidation reaction. Time course measurements on individual products indicate that the alcohol and the ketone are produced simultaneously; i.e., cyclohexanone is not a product of alcohol oxidation.[28]

As seen in Table 2, oxidation of adamantane by **3** + TBHP affords adamantan-1-ol as the major product along with moderate amounts of the 2-ol and the 2-one (normalized C^3:C^2 ratio = 6). When the substrate is the branched alkane 3-methylpentane, one obtains 3-methyl-3-pentanol as the major oxidation product. Oxidation of heptane produces 2- and 4-heptanols along with 1-heptanal in a 2:1 ratio. It thus appears that, with these substrates, the more-substituted carbon centers are preferentially oxidized. Use of H_2O_2 in place of TBHP also results in oxidation at the more-substituted carbons, albeit in lower yields and different ratios. It is interesting to note that **3** + TBHP does not promote oxidation of benzene; no phenol is detected under our reaction conditions. Also in line with this, one obtains benzaldehyde as the exclusive product when toluene is used as the substrate (Table 2).

In a previous account, we reported that **3** in conjunction with PhIO as the oxygen surrogate reacts with cyclohexene in aqueous acetonitrile to produce epoxycyclohexane as the predominant product.[21] In contrast, **3** + TBHP exclusively affords 2-cyclohexen-1-ol and 2-cyclohexen-1-one under the present reaction conditions (Table 2). It is important to note that the allylic oxidation products are obtained with TBHP in a medium which contains very little water whereas, in a medium containing ~30% water, the PhIO-mediated reaction gives rise to epoxide as the major product. It thus appears that formation of the epoxide is favored in the presence of water. Indeed, oxidation of cyclohexene by **3** + aqueous TBHP or H_2O_2 affords

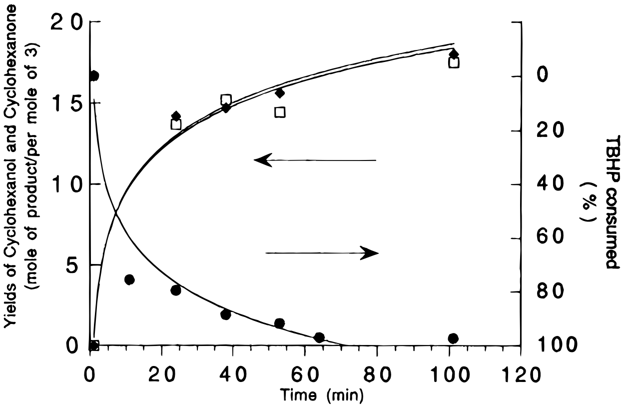

Figure 1. Time course for cyclohexane functionalization and TBHP consumption (for reaction conditions, see text) promoted by **3** in anhydrous acetonitrile at 25 °C under N_2 atmosphere. Products: cyclohexanol (◆), cyclohexanone (□), and the oxidant TBHP (●).

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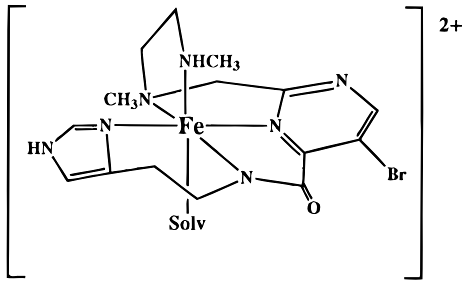
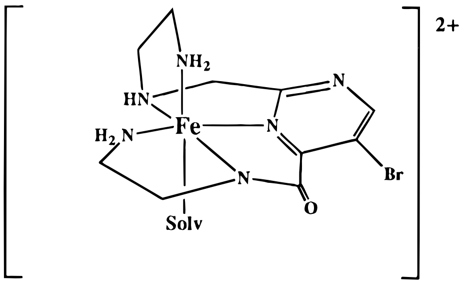
[28] Interestingly, when cyclohexanol is used as the substrate, the **3** + TBHP mixture converts it into cyclohexanone.

moderate amounts of epoxycyclohexane along with the allylic oxidation products (Table 2).

Results included in Tables 1 and 2 demonstrate that **3** promotes facile oxidation of both cyclic and acyclic alkanes with TBHP or H_2O_2 in acetonitrile solutions. Since catalysis occurs only in presence of **3**, it is evident that at least one key intermediate comprises the [(PMA)Fe] moiety.[29] The EPR spectra of mixtures of **3** and TBHP and of **3** and H_2O_2 in acetonitrile/DMSO glass (Figure 2, panels a and b, respectively) establish that the low-spin $[(PMA)Fe^{III}{-}O{-}OR]^+$ (R = H, ^{t}Bu) intermediate is formed in significant yield upon addition of TBHP or H_2O_2 to a solution of **3** in acetonitrile. The intensity of the EPR signal (signal I) diminishes rapidly with addition of the substrate. Formation of this Fe(III)−peroxo species is crucial for the oxidation reaction to proceed. This is shown by the use of the Fe(III) complexes of two other structural derivatives of PMAH, namely PMCH[30] and PMDH.[31] The Fe(III) complex of PMCH, $[Fe^{III}(PMC)]^{2+}$, gives rise to signal I with TBHP and H_2O_2 while $[Fe^{III}(PMD)]^{2+}$ does not. The inability to form the Fe(III)−peroxo species from $[Fe^{III}(PMD)]^{2+}$ stems from the absence of the strong-field imidazole donor in the basal plane of iron.[31] In line with our hypothesis, oxidation of cyclohexane proceeds smoothly with $[Fe^{III}(PMC)]^{2+}$ (Table 1) while $[Fe^{III}(PMD)]^{2+}$ does not afford any oxidation product(s). These observations strongly suggest that the low-spin $[(PMA)Fe^{III}{-}O{-}OR]^+$ (R = H, ^{t}Bu) species is a key intermediate in the oxidation of hydrocarbons by **3** and TBHP or H_2O_2. A similar low-spin $[(bpy)_2(PhCH_2OH)Fe^{III}{-}O{-}O^tBu]^{2+}$ (g = 2.17, 2.11, 1.97) intermediate has been implicated in the oxidation of benzyl alcohol by $[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4$ and TBHP.[13a] Very recently, Que and co-workers also characterized two such low-spin intermediates, namely $[(TPA)Fe^{III}{-}O{-}O^tBu]^{2+}$ (g = 2.19, 2.14, 1.98)[16c] and $[(N4Py)Fe^{III}{-}O{-}OH]^{2+}$ (g = 2.17, 2.12, 1.98),[32] that promote oxidation of aliphatic C−H bonds.



$[Fe^{III}(PMC)]^{2+}$



$[Fe^{III}(PMD)]^{2+}$

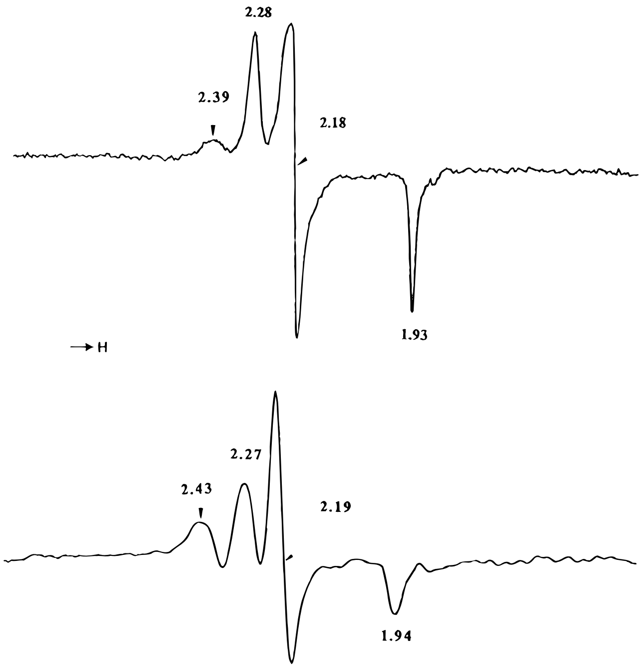


Figure 2. X-Band EPR spectra of $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ (top) and $[(PMA)Fe^{III}{-}O{-}OH]^+$ (bottom) in acetonitrile/DMSO (7:3) glass (100 K). The samples were rapidly frozen following addtion of 1 equiv of the peroxides to cold solutions of **3**. Selected g values are indicated. The small peak around g = 2.4 is due to the remaining $[Fe^{III}(PMA)]^{2+}$ in the reaction mixture. The low-spin Fe(III) peroxides are reactive species; although detectable at low temperatures, they rapidly decompose at room temperature, as evidenced by the disappearance of the EPR signals. Spectrometer settings: microwave frequency, 9.43 GHz; microwave power, 12 mW; modulation frequency, 100 kHz; modulation amplitude, 2 G.

That the low-spin $[(PMA)Fe^{III}{-}O{-}OR]^+$ species plays a crucial role is further indicated by the effect of water on the yields of the oxidized products. As mentioned above, considerably low yields of the oxidized products are obtained when (a) aqueous H_2O_2 or TBHP is used and (b) the reaction medium contains water. Results of EPR experiments demonstrate that the intensity of signal I is rapidly diminished when small amounts (<5%) of water are added to the sample containing **3** + TBHP in acetonitrile.[33] For the same reason, the intensity of signal I exhibited by **3** + H_2O_2 (sample containing a few microliters of water) is always weak in comparison to the one exhibited by **3** + TBHP (Figure 2). This correlation between destruction of the low-spin $[(PMA)Fe^{III}{-}O{-}OR]^+$ species and the lower yields of the oxidized products in media containing water indicates definite involvement of the Fe(III)−peroxo species in alkane oxidation.

Changes in reaction conditions and use of competitive substrates in the cyclohexane oxidation reactions have provided insight into the mechanism of the oxidation by **3** + TBHP. We have determined the primary kinetic isotope effect (KIE = k_H/k_D) for the formation of cyclohexanol at 298 K by using a 1:1 mixture of cyclohexane and cyclohexane-d_{12} as the substrate. The k_H/k_D value of 6.5 ± 0.5 for the formation of cyclohexanol by **3** + TBHP is low compared to the k_H/k_D value of 13 noted

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[29] Under similar reaction conditions, simple iron salts like $Fe(ClO_4)_3{\cdot}xH_2O$ afford very low yields of cyclohexanol and cyclohexanone.

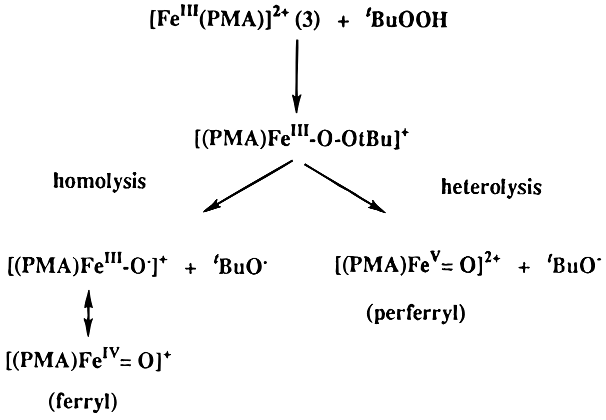
[30] Guajardo, R. J.; Tan, J. D.; Mascharak, P. K. *Inorg. Chem.* **1994**, *33*, 2838.

[31] For more discussion, see: Guajardo, R. J.; Chavez, F.; Farinas, E. T.; Mascharak, P. K. *J. Am. Chem. Soc.* **1995**, *117*, 3883.

[32] Lubben, M.; Meetsma, A.; Wilkinson, E. C.; Feringa, B.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1512.

[33] Our preliminary EPR data indicate that, in the presence of water, $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ generates a new low-spin Fe(III) species that does not promote alkane oxidation. Thus the *presence of water lowers the effective concentration of* $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ and hence the yields of cyclohexanol and cyclohexanone.

Scheme 1



for oxidation of cyclohexane by [Fe(TPP)]Cl and PhIO.[1d] A k_H/k_D value of 2.5 has been reported for the oxidation of cyclohexane by the Gif ^{IV} system.[12b] Our value (6.5 ± 0.5) however agrees well with the theoretical value of 6.5 calculated at 298 K for systems in which the C−H bond stretching in the transition state is rate limiting.[34] This suggests that the C−H bond cleavage is an important step in the overall oxidation mechanism.

Several species in the reaction mixture could be responsible for the C−H bond cleavage of cyclohexane (and other hydrocarbons). By analogy to the heme chemistry, one can propose homolysis of the O−O bond in the $[(PMA)Fe^{III}-O-O^{t}Bu]^{+}$ intermediate, a process that gives rise to ^{t}BuO$^{\bullet}$ (Scheme 1) and promotes alkane oxidation via ^{t}BuO$^{\bullet}$-mediated H atom abstraction.[35] One can also propose heterolytic scission of the O−O bond in the same intermediate and involve the hypervalent iron−oxo perferryl (Fe^{V}=O) species in the H atom abstraction process.[36] The notion of a perferryl species in a non-heme environment like $[(PMA)Fe^{V}=O]^{2+}$ is however equivocal on the ground of poor stabilization of the high oxidation state of iron by the PMA^{-} ligand framework.[37] Also, convincing spectroscopic or structural evidence in favor of any perferryl species is still missing although perferryl intermediates have been invoked in alkane oxidations by non-heme iron-containing enzymes[2,4] and model complexes.[6,16b,d]

The products of oxidation of cyclohexene and norbornene by the **3** + TBHP system clearly indicate that no perferryl intermediate is involved in the oxidation reactions. No epoxide is detected in the products of oxidation of cyclohexene by **3** + TBHP (Table 2), and epoxidation of norbornene by **3** in conjunction with TBHP exclusively affords the *exo* epoxide (Table 2). It is now established that perferryl intermediates epoxidize alkenes quite efficiently.[38] Also, systems that are known to involve perferryl intermediates give rise to *endo* epoxides in addition to the exo products.[36b,38] Since no endo epoxide is formed in the oxidation reaction, it is quite unlikely that a perferryl intermediate is responsible for the epoxide formation.

The failure to observe epoxidation of alkenes by the **3** + TBHP system has prompted us to investigate the possibility of ^{t}BuO$^{\bullet}$-initiated alkane oxidation following homolysis of the O−O bond in the $[(PMA)Fe^{III}-O-O^{t}Bu]^{+}$ intermediate. The first hint of radical(s) in the reaction mixture came from the observation that when 2,4-di-*tert*-butylphenol was used as the substrate, a high yield of 4,4′,6,6′-tetra-*tert*-butyl-*o,o*′-biphenol was obtained. In solution, genuine ^{t}BuO$^{\bullet}$ radical regioselectively abstracts a hydrogen atom to give a ratio of 44:10:1 per hydrogen for the tertiary/secondary/primary positions of alkanes while the same ratio for the $^{\bullet}$OH radical is 10:5.5:1.[39] Since the products of the oxidations by **3** + TBHP exhibit similar trends of more reactivity at the more-substituted carbon atoms (Table 2), it appears that the ^{t}BuO$^{\bullet}$ radical could be directly responsible for the abstraction of hydrogen atoms of the C−H groups. Indeed, the "radical strength" (a thermodynamic parameter for the formation of ^{t}BuOH from the ^{t}BuO$^{\bullet}$ radical) of the ^{t}BuO$^{\bullet}$ radical of 97 kcal/mol[40] is sufficient to an abstract H atom from C−H bonds of higher molecular weight (>C4) alkanes including cyclohexane (95 kcal/mol).[41] The radical strength of the ^{t}BuO$^{\bullet}$ radical is however not sufficient for H atom abstraction from benzene (bond energy = 1111 kcal/mol), and quite expectedly, we observe no oxidation of benzene by the **3** + TBHP system. Scaiano and co-workers have demonstrated that ^{t}BuO$^{\bullet}$, generated by photolysis, abstracts hydrogen only from the methyl group of toluene.[42] This is expected on the basis of the C−H bond energy for the methyl group of toluene (88 kcal/mol).[40] In the present study, we also observe exclusive formation of benzaldehyde (and no cresols) when toluene is oxidized by **3** + TBHP.[43]

Several other observations support the presence of the ^{t}BuO$^{\bullet}$ radical in hydrocarbon oxidations by **3** + TBHP. In each case, the oxidation products contain acetone and methanol which are products of decomposition of the ^{t}BuO$^{\bullet}$ radical.[44] Formation of the mixed peroxide *tert*-butyl cyclohexyl peroxide (^{t}Bu−OO−Cy, Table 1) is further strong evidence in favor of the intermediacy of the ^{t}BuO$^{\bullet}$ radical. This species arises from condensation of the cyclohexyl and ^{t}BuOO$^{\bullet}$ radicals (reaction 3) in the reaction mixture.[16d,45,46] That ^{t}BuOO$^{\bullet}$ radicals are present in our reaction mixtures is indicated by the facile formation of *trans*-stilbene oxide when *cis*-stilbene is oxidized by the **3** + TBHP system (Table 2).[36,47]

The rates of reactions of ^{t}BuO$^{\bullet}$ with TBHP (8.7×10^{6} M^{-1} s^{-1}) and with C−H groups of hydrocarbons (1.6×10^{6} and 5.7×10^{6} M^{-1} s^{-1} for cyclohexane and cyclohexene, respectively) are comparable.[35a,c] Consequently, concentrations of the ^{t}BuOO$^{\bullet}$ radical in the reaction mixtures under study are always significant. Although the radical strength of ^{t}BuOO$^{\bullet}$ (83 kcal/

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(34) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1987; pp 233−235.

(35) (a) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929. (b) Almarsson, O.; Bruice, T. C. *J. Am. Chem. Soc.* **1995**, *117*, 4533 and references cited therein. (c) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.

(36) (a) Traylor, T. G.; Kim, C.; Richards, J. L.; Xu, F.; Perrin, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 3468. (b) Traylor, T. G.; Fann, W.-P.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1989**, *111*, 8009.

(37) The deprotonated amido group of the PMA^{-} ligand cannot stabilize the Fe(V) center since the ligand contains H atoms on adjacent carbon atoms. The amide group in such cases is known to undergo reductive elimination to form imine and in the process causes reduction of the iron center. For more discussion, see: Collins, T. J. *Acc. Chem. Res.* **1994**, *27*, 279.

(38) Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115*, 2775.

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(40) Barton, D. H. R.; Sawyer, D. T. In *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum Press: New York, 1993; p 4.

(41) *Handbook of Chemistry and Physics*, 67th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987; pp F178−179.

(42) Paul, H.; Small, R. D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4520.

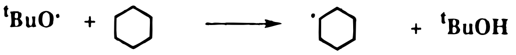
(43) Ready oxidation of benzyl alcohol to benzaldehyde under our reaction conditions does not allow us to detect benzyl alcohol in such reactions.

(44) Bruice, T. C. *Acc. Chem. Res.* **1991**, *24*, 243.

(45) Saussine, L.; Brazi, E.; Robine, A.; Mimoun, H.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1985**, *107*, 3534.

(46) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72.

(47) Labeque, R.; Marnett, L. J. *J. Am. Chem. Soc.* **1989**, *111*, 6621.

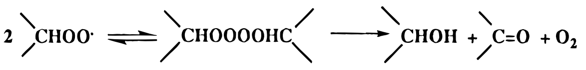

(1)

$$^{t}\mathrm{BuO^{\bullet}} + \mathrm{H\text{-}O\text{-}O\text{-}^{t}Bu} \longrightarrow {}^{t}\mathrm{BuOO^{\bullet}} + {}^{t}\mathrm{BuOH} \quad (2)$$


(3)

mol) is not strong enough to abstract an H atom from cyclohexane,[40] it readily provides the $^{t}\mathrm{BuO^{\bullet}}$ radical via the disproportionation reaction (6) and eventually facilitates the formation of the cyclohexyl radical in the reaction mixture.

It is important to note that oxidation of cyclohexane by **3** + TBHP results in an approximately 1:1 ratio of cyclohexanol and cyclohexanone (Table 1, Figure 1). The roughly equal yields of alcohol and ketone are symptomatic of a Russell-type termination of two secondary peroxyl radicals (reaction 4).[48] Even though we performed the oxidation reactions under


(4)

anaerobic conditions, reactions of the $^{t}\mathrm{BuOO^{\bullet}}$ radical (eqs 5−7) do produce O_2 in the reaction mixture.[25,35] That the cyclohexyl

$$^{t}\mathrm{BuO^{\cdot}} + {}^{t}\mathrm{BuOO^{\cdot}} \longrightarrow {}^{t}\mathrm{BuOO^{t}Bu} + 1/2\ \mathrm{O_2} \quad (5)$$

$$^{t}\mathrm{BuOO^{\cdot}} \longrightarrow {}^{t}\mathrm{BuO^{\cdot}} + 1/2\ \mathrm{O_2} \quad (6)$$

$$2\,{}^{t}\mathrm{BuOO^{\cdot}} \longrightarrow {}^{t}\mathrm{BuOOOO^{t}Bu} \longrightarrow {}^{t}\mathrm{BuOOO^{t}Bu} + 1/2\ \mathrm{O_2} \quad (7)$$

radical is present in the reaction mixture containing **3**, TBHP, and cyclohexane is readily confirmed by the detection of chlorocyclohexane (1300%, Table 1) when the reaction medium contains 25% CCl_4.[49,50] Combination of the cyclohexyl radical (produced in reaction 1) with O_2 therefore generates the peroxy radical $\mathrm{CyOO^{\bullet}}$, which then undergoes a Russel-type termination to afford cyclohexanol and cyclohexanone in a 1:1 ratio as products of cyclohexane oxidation in the present case. Thus the cyclohexyl radical affords (a) cyclohexanol and cyclohexanone via a Russell-type radical-termination reaction (reaction 4) and (b) $^{t}\mathrm{Bu{-}OO{-}Cy}$ via combination with $^{t}\mathrm{BuOO^{\bullet}}$ (reaction 3). A very similar situation has been noted in alkane oxidation by $\mathrm{[Fe^{III}Cl_2(TPA)]BF_4}$ in acetonitrile medium.[52] Reactions 5−7 also account for the more-than-stoichiometric consumption of TBHP observed in the oxidation of cyclohexane by the **3** + TBHP system (Figure 1). In order to further check the the role of O_2 generated from $^{t}\mathrm{BuOO^{\bullet}}$, we have performed the oxidation of cyclohexane by the **3** + TBHP system at 0 °C with and without continuous deoxygenation via passage of N_2. When the reaction mixture is continuously deoxygenated by passage of N_2, the yields of cyclohexanol and cyclohexanone drop drastically (to 20% of the yields of the control experiment) while the yield of the mixed peroxide increases to some extent. This observation strongly suggests that alcohol and the ketone are formed via reaction 4.

That the $^{t}\mathrm{BuO^{\bullet}}$ radical, a product of homolysis of the O−O bond of the $\mathrm{[(PMA)Fe^{III}{-}O{-}O^{t}Bu]^{+}}$ intermediate, is the key species in the H-abstraction step is further confirmed by the use of the mechanistic probe 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH).[52] When cyclohexane is oxidized by **3** + MPPH under the same experimental conditions (**3**:MPPH: cyclohexane = 1:100:350), only small amounts (∼50% each) of cyclohexanol and cyclohexanone are detected while the products of the β-scission of the $\mathrm{PhCH_2CMe_2O^{\bullet}}$ radical, namely benzyl alcohol, benzaldehyde, and bibenzyl, are obtained in 1400%, 1500%, and 150% yields, respectively. This result clearly demonstrates that when MPPH is used as the oxidant, (a) homolysis of the O−O bond in the $\mathrm{[(PMA)Fe^{III}{-}O{-}OMe_2CCH_2Ph]^{+}}$ intermediate produces the $\mathrm{PhCH_2CMe_2O^{\bullet}}$ radical in the reaction mixture and (b) the rapid rate of the β-scission reaction of the $\mathrm{PhCH_2CMe_2O^{\bullet}}$ radical ($\mathrm{PhCH_2CMe_2O^{\bullet}} \rightarrow \mathrm{PhCH_2^{\bullet}} + \mathrm{Me_2CO}$, $k \sim 2.2 \times 10^{8}\ \mathrm{s^{-1}}$) severely inhibits H-abstraction from cyclohexane.

The role of the iron-containing species produced in the homolytic pathway (Scheme 1), namely $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ (or $\mathrm{[(PMA)Fe^{IV}{=}O]^{+}}$), must be considered at this point. Catalytic oxidation of the substrates requires (a) multiple regeneration of **3** or derivative(s) therefrom, such as $\mathrm{[(PMA)Fe^{III}{-}X]^{n+}}$, and (b) repeated formation of $\mathrm{[(PMA)Fe^{III}{-}O{-}O^{t}Bu]^{+}}$. Since the $\mathrm{PMA^{-}}$ ligand framework does not provide stabilization to hypervalent iron centers,[37] we propose that, following homolysis of the O−O bond in $\mathrm{[(PMA)Fe^{III}{-}O{-}O^{t}Bu]^{+}}$, the iron-containing species exists mainly in the $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ form (and not as the ferryl species $\mathrm{[(PMA)Fe^{IV}{=}O]^{+}}$). Similar $\mathrm{Fe^{III}{-}O^{\bullet}}$ formalism has been proposed for the iron sites in MMO by Lippard and co-workers.[3b] The overall yields of the oxidation reactions in the present work (Table 1) and the rapid consumption of TBHP at early stages of the oxidation of cyclohexane (Figure 1) indicate that this high-energy radical-type $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ intermediate is capable of H atom abstraction from TBHP (reaction 8).[53]

$$\mathrm{[(PMA)Fe^{III}\text{-}O^{\cdot}]^{+}} + \mathrm{TBHP} \longrightarrow \mathrm{[(PMA)Fe^{III}\text{-}OH]^{+}} + {}^{t}\mathrm{BuOO^{\cdot}} \quad (8)$$

$$\mathrm{[(PMA)Fe^{III}\text{-}OH]^{+}} + \mathrm{TBHP} \longrightarrow \mathrm{[(PMA)Fe^{III}\text{-}O\text{-}O^{t}Bu]^{+}} + \mathrm{H_2O} \quad (9)$$

Abstraction of an H atom from TBHP by $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ produces $\mathrm{[(PMA)Fe^{III}{-}OH]^{+}}$ (reaction 8), which in the presence of excess TBHP is rapidly converted into $\mathrm{[(PMA)Fe^{III}{-}O{-}O^{t}Bu]^{+}}$ (reaction 9) and enters into the next catalytic cycle. The 1 equiv of water produced at the end of the catalytic cycle is at least partly responsible for the slow degradation of the catalyst in the present case. Thus, $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ takes an *indirect* role in the overall alkane oxidation process by providing additional $^{t}\mathrm{BuOO^{\bullet}}$ radicals in the reaction mixture (reaction 8).[54] As discussed above, the $^{t}\mathrm{BuOO^{\bullet}}$ radicals introduce $^{t}\mathrm{BuO^{\bullet}}$ radicals (which in turn produce cyclohexyl radicals; reaction 1) and O_2 in the reaction mixture and promote formation of cyclohexanol

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(48) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 3871.

(49) Since CCl_4 traps a significant fraction of the cyclohexyl radicals, oxidations in an acetonitrile/CCl_4 medium always afford much lower yields of the three oxidation products (Table 1).

(50) Trapping of the cyclohexyl radical by halocarbons has been noted in cyclohexane oxidation by (a) Gif catalysts,[12] (b) metalloporphyrins,[51] and (c) non-heme iron complexes.[16]

(51) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375.

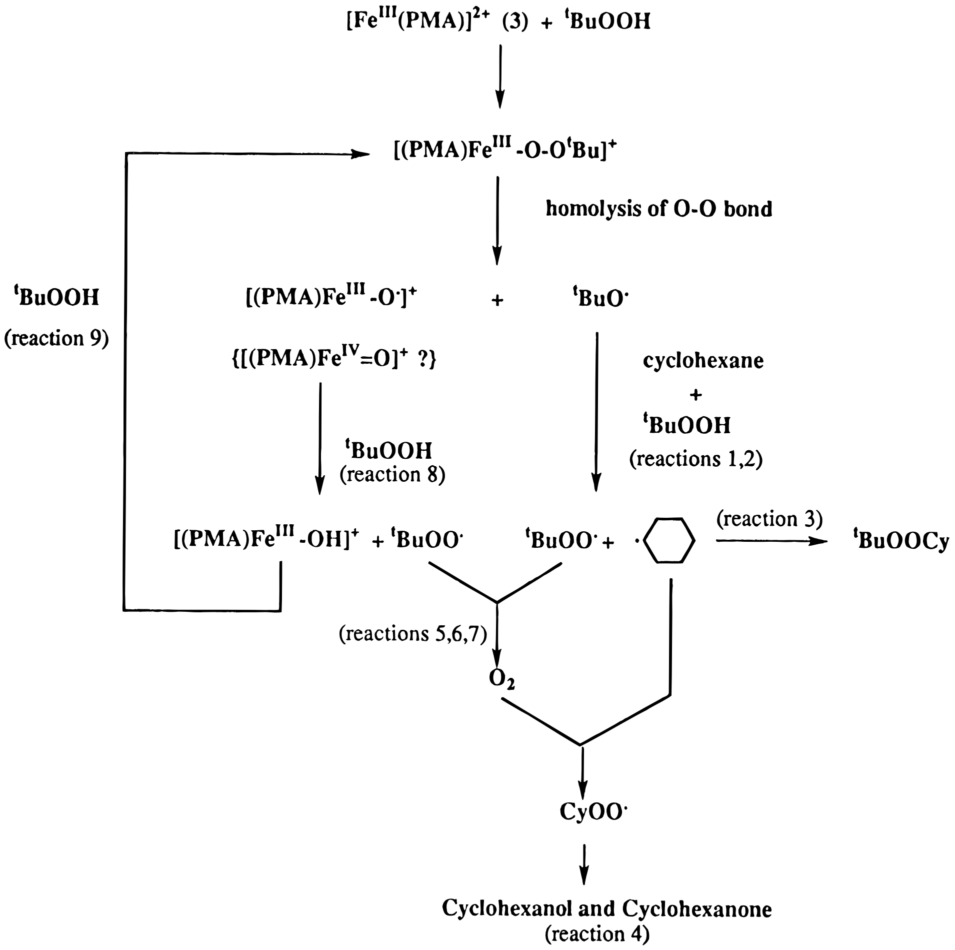
(52) Arends, I. W. C. E.; Ingold, K. U.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 4710.

(53) The reported radical strengths of TBHP and hypervalent iron−oxo species [40] support this hypothesis. Ferryl species like $\mathrm{[(porphyrinato)Fe^{IV}{=}O]}$ are inert toward hydrocarbon oxidation.[36] Thus it seems unlikely that the radical-type $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ intermediate will be a sufficiently strong oxidant to abstract an H atom from cyclohexane.

(54) A reviewer has suggested that some other more selective oxidant may be involved in addition to the $^{t}\mathrm{BuO^{\bullet}}$ radical since the k_H/K_D value of 6.5 for **3** + TBHP and the adamantane C^3:C^2 ratio of 6 are both significantly larger than those attributed to the $^{t}\mathrm{BuO^{\bullet}}$ radical (k_H/K_D is ∼4 for the $^{t}\mathrm{BuO^{\bullet}}$ radical[16b]). While it is tempting to assign the $\mathrm{[(PMA)Fe^{III}{-}O^{\bullet}]^{+}}$ species as this more selective oxidant, we do not believe that the present data provide any hint in this direction. Since k_H/K_D values vary widely depending on the nature of the ligands in the cases of both non-heme iron complexes ($k_H/K_D \approx 4-10$)[16d] and heme complexes ($k_H/K_D \approx 3-13$),[55] a value of 6.5 hardly tells us anything about the nature of the oxidant.

(55) Sorokin, A.; Robert, A.; Meunier, B. *J. Am. Chem. Soc.* **1993**, *115*, 7293.

Scheme 2



and cyclohexanone. Also, $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O{-}O^{t}Bu}]^{+}$ produced in reaction 9 replenishes the reaction mixture with fresh $^{t}\mathrm{BuO}^{\bullet}$ and $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O^{\bullet}}]^{+}$ to continue the oxidation reaction after termination reactions (3)−(5) have occurred.

The catalytic cycle (Scheme 2) therefore involves the following steps: (a) formation of the $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O{-}O^{t}Bu}]^{+}$ intermediate upon addition of TBHP to **3** in anhydrous acetonitrile; (b) homolysis of the O−O bond to form two oxidizing species $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O^{\bullet}}]^{+}$ and $^{t}\mathrm{BuO}^{\bullet}$; (c) $^{t}\mathrm{BuO}^{\bullet}$ radical initiated reactions following H atom abstraction from cyclohexane and TBHP ($[(\mathrm{PMA})\mathrm{Fe^{III}{-}O^{\bullet}}]^{+}$ also promoting H atom abstraction from TBHP); (d) formation of cyclohexanol and cyclohexanone via the Russell-type radical-termination reaction 4 and the mixed peroxide via reaction 3; and (e) regeneration of $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O{-}O^{t}Bu}]^{+}$ in reaction between $[(\mathrm{PMA})\mathrm{Fe^{III}{-}OH}]^{+}$ and TBHP. *We emphasize that Scheme 2 is a plausible mechanism that is supported by a variety of results described in the preceding sections.*

Close scrutiny of Table 2 reveals that the presence of water in the reaction mixture alters the product distributions to a significant extent. For example, the reaction of cyclohexene with **3** + dry TBHP affords only the allylic oxidation products and no epoxide, while use of aqueous TBHP results in the formation of a considerable amount of epoxide in addition to the allylic oxidation products. We suggest that this change arises from modulations of the effective concentrations and reactivities of the $^{t}\mathrm{BuO}^{\bullet}$ and $^{t}\mathrm{BuOO}^{\bullet}$ radicals in the reaction mixtures. It is known that, between the two radicals, $^{t}\mathrm{BuOO}^{\bullet}$ is more resonance-stabilized and comparatively unreactive.[56] The change in the distribution of the oxidized products of cyclohexene indicates that, in anhydrous media, the products are derived mostly from the reactions of the $^{t}\mathrm{BuO}^{\bullet}$ radical while, in presence of water, one also detects the product derived from the $^{t}\mathrm{BuOO}^{\bullet}$ radical, namely the epoxide.[38] Epoxide formation is also observed when H_2O_2 (30% or 50% aqueous solution) is used. We suspect that the $^{\bullet}\mathrm{OOH}$ radical is responsible for epoxidation in such cases. A small amount of the $^{\bullet}\mathrm{OH}$ radical is also expected from $^{\bullet}\mathrm{OOH}$,[57] and indeed one observes a moderate extent of oxidation of benzene to phenol by the **3** + H_2O_2 system. The $^{\bullet}\mathrm{OH}$ radical has sufficient radical strength to oxidize benzene (111 kcal mol^{-1}).[40] The $^{t}\mathrm{BuOO}^{\bullet}$ radical, on the other hand, is incapable of such a transformation, and hence no oxidation of benzene is noted with TBHP (with or without water). Collectively, these results indicate that alkane oxidations by **3** + TBHP and **3** + H_2O_2 follow the same mechanism (Scheme 2) although the product distributions vary because of the stabilities of the incipient radicals (and other species) in media containing different amounts of water. At this time, we are actively trying to establish the quantitative role of water in these reactions.

Several factors appear to facilitate homolysis of the O−O bond in $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O{-}O^{t}Bu}]^{+}$ in the present study. We anticipate that the most important one is the failure of the PMA^{-} ligand framework to stabilize an Fe(V) center in a $[(\mathrm{PMA})\mathrm{Fe^{V}{=}O}]^{2+}$ intermediate. The nature of the solvent and H-bonding are also two key factors. In aprotic media, absence of H-bonding between $[(\mathrm{PMA})\mathrm{Fe^{III}{-}O{-}O^{t}Bu}]^{+}$ and the solvent

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(56) Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1.

(57) Cohen, G. In *Handbook of Methods for Oxygen Radical Research*; Greenwald, R. A., Ed.; CRC Press: Boca Raton, FL,1985; p 55.

molecule(s) renders heterolysis of the O−O bond quite difficult, since negative charge develops on the leaving O.[58] In addition, H-bonding between TBHP and solvent modulates the rate of reaction 2 and the extent of reaction between ^{t}BuO$^\bullet$ and cyclohexane.[35c] That the nature of the solvent critically affects the mode of the O−O bond cleavage (homolysis vs heterolysis) in $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ is evident by the observation that different products and product ratios are obtained when cyclohexene is oxidized by the **3** + TBHP system in anhydrous and aqueous acetonitrile (Table 2). Collectively, results of this work indicate that, in anhydrous acetonitrile, homolysis of the O−O bond of the $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ intermediate is preferred over heterolysis.

In a recent account, Que and co-workers reported that, in the oxidation of cyclohexane by $[Fe_2(TPA)_2O(OAc)](ClO_4)_3$ (and related catalysts) + TBHP, the presence of Me_2S in the reaction medium dramatically diminishes the production of cyclohexanol and cyclohexanone without significantly affecting the formation of the mixed peroxide ^{t}Bu−OO−Cy.[16d] This result was interpreted by Que and co-workers as the key evidence in favor of a hypervalent iron−oxo intermediate being responsible for alkane oxidation. The conclusion that Me_2S does intercept only the hypervalent iron−oxo intermediate (the result being Me_2SO) and not radicals like ^{t}BuO$^\bullet$ and ^{t}BuOO$^\bullet$ is however quite surprising, since in our control experiments we find that Me_2S intercepts many oxidizing species. For example, Me_2S is readily oxidized to Me_2SO by a mixture of PhIO and TBHP (no iron catalyst) in which ^{t}BuO$^\bullet$ and ^{t}BuOO$^\bullet$ radicals are the active intermediates.[25] We therefore believe that inhibition of oxidation by Me_2S cannot be considered as evidence in favor of a hypervalent iron−oxo intermediate only. In line with this statement, we notice that, in case of cyclohexane oxidation by **3** + TBHP, increasing amounts of Me_2S in the reaction mixture inhibit productions of all three products in a linear fashion.

We have compared, under our experimental conditions, the efficiencies of cyclohexane oxidation by **3** and by $[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4$ in conjunction with TBHP. In both cases, a low-spin $[(ligand)_nFe^{III}{-}O{-}O^tBu]^+$ intermediate was detected at low temperature by EPR spectroscopy. The two oxidizing systems afford similar products although the overall yields are lower in the case of $[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4$ (450% cyclohexanol, 550% cyclohexanone, and 150% ^{t}Bu−OO−Cy). Such differences in yields clearly indicate that the nature of the ligand in the $[(ligand)_nFe^{III}{-}O{-}O^tBu]^+$ intermediate affects the overall reactivity of the Fe(III)−peroxo species and, in particular, the rate of the O−O bond cleavage. This in turn confirms the involvement of the iron-containing species in the process of catalysis. Que and co-workers have also noted that, in cyclohexane oxidation by (μ-oxo)diferric complexes of tripodal ligands and TBHP, the coordination environment has a profound effect on the efficiency of the iron-containing catalysts.[16d]

In summary, $[Fe^{III}(PMA)](ClO_4)_2$ (**3**) is an efficient non-heme iron catalyst for alkane functionalization with TBHP that operates at room temperatue. A low-spin $[(PMA)Fe^{III}{-}O{-}O^tBu]^+$ intermediate has been spectroscopically identified in the reaction mixture at low temperatures. On the basis of the results reported in this account and others,[13,16] we propose that low-spin Fe(III) peroxides are viable intermediates in the oxidation of hydrocarbons by selected non-heme iron complexes in conjunction with ROOH in aprotic media. Further studies toward elucidation of the role of such intermediates in alkane oxidation are in progress in this laboratory.

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Supporting Information Available: Gas chromatogram of the reaction mixture (solvent: acetonitrile) containing cyclohexane + **3** + TBHP after 30 min (Figure S1) (1 page). Ordering information is given on any current masthead page.

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(58) Wu, Y.-D.; Houk, K. N.; Valentine, J. S.; Nam, W. *Inorg. Chem.* **1992**, *31*, 719.