A Putative Monooxygenase Mimic Which Functions via Well-Disguised Free Radical Chemistry[1]

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Abstract: The hydroxylation of cycloalkanes at 25 °C by the syringe pump addition of *tert*-alkyl hydroperoxides (10 and 1 equiv based on catalyst) to deoxygenated acetonitrile containing cycloalkanes (0.64 M) and 0.61 mM of the catalyst, $[Fe^{III}_2O(TPA)_2(H_2O)_2]^{4+}$, is demonstrated to be a reaction which involves freely diffusing cycloalkyl radicals, i.e., *free* alkyl radicals.

In recent years there have been many attempts to mimic the chemistry of monooxygenases such as cytochrome P450 and methane monooxygenase which can oxidize saturated hydrocarbons by processes which do not involve *free* (i.e., freely diffusing) radicals.[3] Following the lead provided by these enzymes, (ferric) iron has generally been chosen as the

$$RH + O_2 \xrightarrow[+2H^+ + 2e^-]{\text{enzyme}} ROH + H_2O \quad (1)$$

catalytically active metal and two-electron-reduced oxygen, in the form of H_2O_2 or *tert*-butyl hydroperoxide (TBHP), has been utilized (to avoid the requirement for a sacrificial reductant). However, Fe^{III}/TBHP systems may not undergo the desired *heterolysis* to give a high-valent iron−oxo species (formally Fe^{V}═O) as is believed to occur when monooxygenases react with hydroperoxides. Instead, a *homolysis* may occur to form

$$Fe^{III} + Me_3COOH \xrightarrow{\text{het}} Fe^{V}{=}O + Me_3COH \quad (2)$$

free tert-butoxyl radicals which then dominate the subsequent chemistry (see Scheme 1).

Scheme 1

$$Me_3COOH + (XFe^{III}) \rightleftarrows Me_3COO(Fe^{III}) + XH \quad (3)$$

$$Me_3COO(Fe^{III}) \rightarrow Me_3CO^{\bullet} + O{=}(Fe^{IV}) \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} HO{-}(Fe^{IV}) \quad (4)$$

$$Me_3COOH + O{=}(Fe^{IV}) \rightarrow Me_3COO^{\bullet} + HO{-}(Fe^{III}) \quad (5)$$

$$Me_3CO^{\bullet} + Me_3COOH \rightarrow Me_3COH + Me_3COO^{\bullet} \quad (6)$$

$$2Me_3COO^{\bullet} \rightarrow 2Me_3CO^{\bullet} + O_2 \quad (7)$$

$$Me_3CO^{\bullet} + c\text{-}C_nH_{2n} \rightarrow Me_3COH + c\text{-}C_nH^{\bullet}_{2n-1} \quad (8)$$

$$c\text{-}C_nH^{\bullet}_{2n-1} + O_2 \rightarrow c\text{-}C_nH_{2n-1}OO^{\bullet} \quad (9)$$

$$2\ c\text{-}C_nH_{2n-1}OO^{\bullet} \rightarrow \mathbf{c\text{-}C_nH_{2n-1}OH} + \mathbf{c\text{-}C_nH_{2n-2}{=}O} + O_2 \quad (10)$$

$$c\text{-}C_nH^{\bullet}_{2n-1}\ (c\text{-}C_nH_{2n-1}OO^{\bullet}) + Me_3COO^{\bullet} \rightarrow \mathbf{c\text{-}C_nH_{2n-1}OOCMe_2}\ (+O_2) \quad (11)$$

The oxidation of an alkane to a mixture of alcohol, ketone, and the mixed peroxide (shown in bold face in the scheme) is a very clear indication that *free*-radical chemistry has occurred. Unfortunately, this signature has all too frequently been ignored.

2-Methyl-1-phenyl-2-propyl hydroperoxide (MPPH) is a probe capable of distinguishing between *free* alkoxyl radical chemistry and *radical-free* (enzyme mimetic) chemistry in iron/*tert*-alkyl hydroperoxide/hydrocarbon oxidation systems.[4] This probe relies on the fact that if the corresponding *tert*-alkoxyl radical were formed and diffused from its site of formation into the bulk solution it would undergo far too rapid a β-scission ($k_\beta \sim 2 \times 10^8\ s^{-1}$) for it to abstract a hydrogen atom from a

$$PhCH_2CMe_2OOH \rightarrow PhCH_2CMe_2O^{\bullet} \xrightarrow{k_\beta} PhCH_2^{\bullet} + Me_2CO \quad (12)$$
(MPPH)

saturated hydrocarbon, i.e., the equivalent of reaction 8 cannot occur. MPPH has been employed at the NRC in Ottawa to demonstrate that cycloalkane oxidations using TBHP and two tris(2-pyridinylmethyl)amine (TPA) complexes,[5] $[Fe^{III}Cl_2(TPA)]^+$ and $[Fe^{III}_2O(OAc)(TPA)_2]^{3+}$, and a Fe^{III} picolinate/pyridine complex[6] all occurred via straighforward free radical

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chemistry.[4,7−9] This work led to both implicit[10] and explicit[11] suggestions that MPPH is not "a competent substitute" for TBHP (apparently because it is particularly subject to, and hence, induces *free* radical chemistry). However, MPPH has very recently been demonstrated to be a competent substitute for TBHP in hydrocarbon oxidations which are *genuine* two electron processes.[12]

The question as to whether or not simple (i.e., nonenzyme) Fe^{III}/*tert*-alkyl hydroperoxide systems oxidize alkanes via freely diffusing alkoxyl radicals or via a metal-based intermediate was reopened in 1996 with work on a new iron TPA catalyst, $[Fe^{III}_2O(TPA)_2(H_2O)_2]^{4+}$ (**1**).[11] When 10 equiv (based on **1**) of TBHP was added continuously by syringe pump to cyclohexane in acetonitrile at 25 °C under argon, *cyclohexanol was the only product*.[11] This was an exciting result because *cyclohexanol would also be the sole product expected from a genuine monooxygenase mimic*. On the other hand, the syringe pump addition of 10 equiv of MPPH gave no cyclohexane oxidation products.[11,13] To some of us this implied that the **1**/TBHP couple, like other Fe^{III}(TPA)/TBHP couples,[4,8,9] oxidized alkanes by a *free*-radical mechanism, i.e., via freely diffusing *tert*-butoxyl radicals. Thus, iron/alkyl hydroperoxide chemistry was faced with an intriguing mechanistic conundrum: does catalyst **1** do radical-free or free-radical chemistry?

Results

The experimental conditions and results with 10 equiv of TBHP and 10 equiv of MPPH[14] are given in Table 1 together with the original results.[11] With cyclohexane and syringe pump addition of 10 equiv of TBHP directly into the solution containing the other reagents, *only* alcohol (4.0 equiv) was observed originally (entry 2).[11] The present results (entry 1) using the same experimental procedure, i.e., syringe needle below the surface of the solution containing the other reagents combined with vigorous stirring, essentially confirm the earlier report although slightly less alcohol was obtained. However, a small amount of the mixed peroxide was also detected, which is a sign that free-radical chemistry may be occurring. Interestingly, when the TBHP solution was added dropwise at the same rate (by holding the needle from the syringe pump over the solution), the mixed peroxide became the *major* product (entry 3), and when the TBHP was added "all at once", the mixed peroxide became the only product (entry 4). Similar results and product yields were obtained using cyclooctane as substrate (entries 5−7). When cyclohexane was oxidized with 1 equiv of TBHP added by syringe pump, *only* cyclohexanol was observed originally (0.55 equiv)[11] and in the present work (0.43 and 0.35 equiv). Finally, and in agreement with the earlier report (entry 9),[11] the **1**/10 equiv of MPPH catalyst system gave no cycloalkane oxidation products. However, products were detected and they were clearly derived from benzyl radicals (entries 8, 10, and 11), the main product under syringe pump conditions being benzyl alcohol (3.0 equiv, entry 8). Interestingly, the **1**/1 equiv of MPPH catalyst system gave only bibenzyl (0.1 and 0.15 equiv, i.e., 0.2 and 0.3 equiv of benzyl radicals) and no benzyl alcohol. We attribute the difference in product type between the 1 equiv of TBHP and 1 equiv of MPPH experiments to the lower reactivity of the resonance-stabilized benzyl radicals.

Table 1. Product Yields (in equiv, Based on Catalyst)[a] after 10 min Oxidation of Cycloalkanes (0.64 M) by *tert*-Alkyl Hydroperoxides (6.1 mM) Catalyzed by $[Fe^{III}_2O(TPA)_2(H_2O)_2]^{4+}$ (**1**, 0.61 mM) at 25 °C in Acetonitrile Prepurged with Argon[a]

TBHP

entry	alkane	syringe pumped	$C_nH_{2n-1}OH$	$C_nH_{2n-2}O$	$C_nH_{2n-1}OO$-CMe_3
1	c-C_6H_{12}	yes	2.6; 3.6	0; 0	0.3; 0.5
2	c-C_6H_{12}[b]	yes	4.0	0	0
3	c-C_6H_{12}	drop[c]	0.5; 0.9	0; 0	1.0; 1.8
4	c-C_6H_{12}	no	0; 0	0; 0	2.1; 2.3
5	c-C_8H_{16}	yes[d]	2.4; 2.8	0; 0	tr; tr
6	c-C_8H_{16}	drop[c]	0.9; 0.9	0.4; tr	0.2; tr
7	c-C_8H_{16}	no	1.1; 0.8	1.0; 0.8	1.4; 0.9

MPPH

entry	alkane	syringe pumped	$PhCH_2OH$	$(PhCH_2)_2$	$PhCH_2OO$-CMe_2CH_2Ph
8	c-C_8H_{16}[e]	yes	3.0; 3.0	tr; tr	0; 0
9	c-C_6H_{12}[b]	yes	not reported		
10	c-C_8H_{16}[e]	drop[c]	0.9; 0.6	tr; 0	0.2; 0.2
11	c-C_8H_{16}[e]	no	1.0; 0.9	tr; tr	0.2; tr

[a] Reactions were carried out under argon. Yields are from duplicate runs with the first number referring to the same reaction; tr = trace, too small to quantify. All analyses were by GC-FID. [b] From ref 11. [c] Dropwise addition of TBHP. [d] Cyclooctene (0.1 equiv) was also formed in both runs. [e] There were no cyclooctane-derived products and no benzaldehyde.

To distinguish *unequivocally* between *free*-radical and radical-*free* processes, the following critical experiments were designed and the reactions were carried out under (otherwise) normal conditions, viz., 0.64 M cycloalkane(s) and 0.61 mM **1** in acetonitrile preflushed with argon. The TBHP (6.1 mM, 10 equiv in argon-flushed acetonitrile) was added by syringe pump directly into the stirred solution over the 10 min course of a reaction which was run at 25 °C under argon.

1. Addition of a *low* concentration of CCl_3Br (30.5 mM) to a cyclohexane oxidation gave **only** cyclohexyl bromide (3.4 and 3.6 equiv in duplicate runs). A similar experiment with cyclooctane gave **only** cyclooctyl bromide (2.5 and 2.9 equiv). (Control experiments carried out in the absence of TBHP gave no cycloalkyl bromides.) Dropwise addition of the TBHP to a cyclohexane oxidation carried out in the presence of 30.5 mM CCl_3Br also gave only cyclohexyl bromide (3.9 and 4.1 equiv). Even if the trapping of alkyl radicals by CCl_3Br is diffusion-controlled, the time scale for bromine atom transfer is about 2 orders of magnitude slower than the time scale for the reaction of a caged radical pair. Thus CCl_3Br cannot capture cycloalkyl radicals while they are still in the solvent cage in which they were formed. This result demonstrates that the overall process yields freely diffusing cycloalkyl radicals *exclusively*.

$$\text{c-}C_nH^{\bullet}_{2n-1} + CCl_3Br \rightarrow \text{c-}C_nH_{2n-1}Br + {}^{\bullet}CCl_3 \quad (13)$$

2. In duplicate competitive oxidations with [c-C_8H_{16}] = [c-C_6H_{12}] = 0.32 M in the presence of 30.5 mM CCl_3Br, only

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(13) The presence or absence of the products expected from any benzyl radicals produced via reaction 12 was not remarked upon.[11]
(14) Use of 140 equiv of TBHP gave the usual *free*-radical-derived products (alcohol, ketone, mixed peroxide plus traces of olefin); similarly 140 equiv of MPPH gave the usual benzyl radical-derived products (benzyl alcohol, benzaldehyde, bibenzyl, and mixed peroxide): see Supporting Information. Cyclooctane was used in all the MPPH experiments because it is more reactive than cyclohexane.[7−9]

Table 2. Product Ratios from Competitive Oxidation of Cycloalkanes (0.32 + 0.32 M) by **1** (0.61 mM) and *tert*-Butyl Hydroperoxide (6.1 mM) under Argon or Di-*tert*-butyl Hyponitrite (BONNOB) under Vacuum in Acetonitrile at 25 °C[a]

entry	competition	conditions	products	ratio
1	c-C_8H_{16}/c-C_6H_{12}	**1** + TBHP + CCl_3Br	c-$C_8H_{15}Br$/c-$C_6H_{11}Br$	2.0_5:1[b,c]
2	c-C_8H_{16}/c-C_6H_{12}	BONNOB + CCl_3Br	c-$C_8H_{15}Br$/c-$C_6H_{11}Br$	2.2:1[d]
3	c-C_8H_{16}/c-C_6H_{12}	**1** + TBHP	c-$C_8H_{15}OX$/c-$C_6H_{11}OX$[e]	2.0_5:1[b]
4	c-C_6H_{12}/c-C_6D_{12}	**1** + TBHP + CCl_3Br	c-$C_6H_{11}Br$/c-$C_6D_{11}Br$	4.3_5:1[b,f]
5	c-C_6H_{12}/c-C_6D_{12}	BONNOB + CCl_3Br	c-$C_6H_{11}Br$/c-$C_6D_{11}Br$	4.9:1[d]
6	c-C_6H_{12}/c-C_6D_{12}	**1** + TBHP	c-$C_6H_{11}OX$/c-$C_6D_{11}OX$[e]	4.5:1[b,g]
7	c-C_6H_{12}/c-C_6D_{12}	**1** + TBHP	c-$C_6H_{11}OX$/c-$C_6D_{11}OX$[e]	6.5_5:1[b,h]
8	c-C_6H_{12}/c-C_6D_{12}	**1** + TBHP	c-$C_6H_{11}OH$/c-$C_6D_{11}OH$	6.3_1:1[b,i,j]
9	c-C_6H_{12}/c-C_6D_{12}	**1** + TBHP	c-$C_6H_{11}OH$/c-$C_6D_{11}OH$	5.7_1:1[b,k,l]

[a] TBHP in argon-purged acetonitrile was added via syringe pump over the 10 min course of the reaction to a stirred argon-purged acetonitrile solution of the reagents. BONNOB was added all-at-once, and the reagents were degassed by the freeze−pump−thaw method, following which they were sealed under vacuum and the reactions were allowed to proceed for 5 days. All analyses were by GC-FID except for the extra data given in the footnotes. [b] Duplicate runs. [c] Dropwise addition of TBHP gave a mean ratio of 2.0:1. [d] Single run. [e] Mainly X = H plus traces of X = Me_3CO. [f] Dropwise addition of TBHP gave a mean ratio of 4.7:1. [g] Dropwise addition of TBHP gave a mean ratio of 6.0:1. [h] GC−MS/SIM mean ratio for alcohols only = 6.0. [i] Using catalyst prepared at the University of Minnesota. [j] GC−MS/SIM mean ratio = 5.7. [k] Competitive oxidation of c-C_6H_{12} and c-C_6D_{12} in a 1:5 molar ratio. [l] GC−MS/SIM mean ratio = 6.5.

the two cycloalkyl bromides were produced (total 4.1 and 3.6 equiv) with [c-$C_8H_{15}Br$]/[c-$C_6H_{11}Br$] = 1.9 and 2.2 (Table 2, entry 1). Triplicate analogous competitive experiments with dropwise addition of the TBHP gave only the two bromides (total yields 3.9−5.6 equiv) with [c-$C_8H_{15}Br$]/[c-$C_6H_{11}Br$] = 1.8, 2.1, and 2.1. All of these values are consistent with the independently measured rate constant ratio of 2.2:1.0 for hydrogen atom abstraction from c-C_8H_{16} and c-C_6H_{12} by authentic *tert*-butoxyl radicals (Table 2, entry 2).[15]

3. Duplicate analogous competitive experiments in the absence of CCl_3Br gave $\sum$c-C_8H_{16} oxidation products = 1.6_4 and 2.3_5 equiv and $\sum$c-C_6H_{12} oxidation products = 0.7_8 and 1.1_9 equiv. These data yield C_8/C_6 reactivity ratios of 2.1 and 2.0 (Table 2, entry 3). These values are in satisfactory agreement with the reactivity ratio of 2.2 obtained with authentic *tert*-butoxyl radicals (Table 2, entry 2)**.**

4. The magnitude of the c-C_6H_{12}/c-C_6D_{12} deuterium kinetic isotope effect (DKIE) in Fe^{III}(TPA)/TBHP oxidations has been employed as a probe of reaction mechanism.[5c,d,11] In duplicate competitive oxidations with [c-C_6H_{12}] = [c-C_6D_{12}] = 0.32 M in the presence of 30.5 mM CCl_3Br only, the two bromides were formed (total 4.5 and 3.4 equiv) and the calculated DKIE's were 4.3 and 4.4 (Table 2, entry 4). Dropwise addition of the TBHP gave, in duplicate experiments, total bromide yields of 2.8 and 2.3 equiv and DKIE's of 4.6 and 4.8. The independently measured DKIE using authentic *tert*-butoxyl radicals was 4.9 (Table 2, entry 5).[16]

5. Duplicate analogous competitive experiments in the absence of CCl_3Br gave ($\sum$c-C_6H_{12} oxidation products)/($\sum$c-C_6D_{12} oxidation products) = 4.9_5 and 4.0_5 (Table 2, entry 6). Duplicate runs with dropwise addition of the TBHP gave ratios of 5.6_5 and 6.3_3. These DKIE's (overall mean 5.2_5) are in excellent agreement with the (expected) DKIE of 4.9 for authentic *tert*-butoxyl radicals (Table 2, entry 5), but they are considerably smaller than the DKIE of ~10 originally reported[11] although the product yields are similar. Additional duplicate sets of experiments were performed using both a sample of catalyst **1** prepared at the NRC in Ottawa (Table 2, entry 7) and a sample of **1** prepared in Minnesota (Table 2, entry 8). Analyses by GC-FID of all four samples gave ($\sum$c-C_6H_{12} oxidation products)/($\sum$c-C_6D_{12} oxidation products) values of 4.9 and 8.2 (NRC's catalyst) and 6.4 and 6.2 (Minnesota's catalyst), overall mean 6.4_3. To reduce the rather large errors associated with the GC-FID. analyses of the small yields of the deuterated products the samples were also analyzed by GC−MS. operated in the single ion monitoring (GC−MS/SIM.) mode for *m*/*z* 82 and 92, i.e., the dehydration products of the nondeuterated and the deuterated alcohols. After a correction for the deuterium isotope effect of the dehydration (1.25), the DKIE values for alcohol formation were calculated to be 5.0 and 6.9 (NRC's catalyst) and 6.2 and 5.1 (Minnesota's catalyst), overall mean 5.8.

6. The relatively small yield of the deuterated alcohol makes the measurement of the c-$C_6H_{11}OH$/c-$C_6D_{11}OH$ ratio rather imprecise by any method; we therefore carried out a competitive oxidation of c-C_6D_{12} and c-C_6H_{12} in a 5:1 ratio. If the correct DKIE is around 5 this should yield GC peaks for the deuterated and nondeuterated alcohols of similar size which will reduce the errors arising from the measurement of small peak areas relative to much larger peak areas (as in the 1:1 c-C_6H_{12}/c-C_6D_{12} oxidations). GC-FID and GC−MS/SIM analyses of duplicate experiments gave peaks of similar size. The calculated DKIE values for alcohol formation by GC-FID were 5.5 and 5.9 (Table 2, entry 9), and by GC−MS/SIM, 6.4 and 6.6, overall mean 6.1.

7. With cyclohexene (0.68 M) as the substrate, the syringe pump addition of 10 equiv of TBHP gave **no** cyclohexene oxide. This result stands in sharp contrast to genuine two-electron-oxidation catalysts which readily epoxidize cyclohexene using TBHP in acetonitrile at 25 °C.[12] The failure of other Fe^{III}(TPA) catalysts to epoxidize cyclohexene has been observed previously.[5c]

Mechanistic Considerations

We have demonstrated that the addition, even by syringe pump, of 10 equiv of a *tert*-alkyl hydroperoxide to **1** in acetonitrile at 25 °C generates the corresponding freely diffusing *tert*-alkoxyl radical which is the agent responsible for product formation. In the case of MPPH these products are derived from the benzyl radical formed in reaction 12. With 10 equiv of TBHP, all that remains to be explained is why different mixtures of products are obtained by syringe pump and by dropwise or all-in-at-once addition of the hydroperoxide and why none of these product slates resembles those found with 140 equiv of TBHP (see Supporting Information).

The explanation is simple once it is recognized that there is virtually no oxygen present at the beginning of an experiment and, furthermore, that very little oxygen will be formed (reaction

(15) Determined in a competitive experiment carried out in the presence of CCl_3Br by measuring, the relative yields of c-$C_8H_{15}Br$ and c-$C_6H_{11}Br$ formed in degassed acetonitrile using *tert*-butoxyl radicals generated over 5 days at 25 °C by the thermal decomposition of di-*tert*-butyl hyponitrite.

(16) A competitive experiment carried out over 5 days in the presence of CCl_3Br in degassed acetonitrile using di-*tert*-butyl hyponitrite at 25 °C as the *tert*-butoxyl source and measurement of the relative yields of c-C_6H_{11}-Br and c-$C_6D_{11}Br$ gave a DKIE = 4.9. Absolute rate measurements by laser flash photolysis using the cumyloxyl radical gave a DKIE = 5.1.

7, Scheme 1) as the reaction progresses (see Scheme 2). With syringe pump addition the TBHP concentration will always be very low. As a consequence, the formation of *tert*-butylperoxyl radicals via reactions 5 or 6 will be less important than for 10 equiv of TBHP added all-at-once and very much less important than for 140 equiv of TBHP (whether added by syringe pump or all-at-once). With reaction 9 "shut down" the cycloalkyl radicals are forced to react with the most available reagent.[17] For the all-at-once procedure this will be the *tert*-butylperoxyl radicals and, hence, the mixed peroxide (reaction 11′)[18] will be the major (c-C_8H_{16}) or sole (c-C_6H_{12}) product. Even for the dropwise addition of TBHP by syringe pump there is a reduction in the yield of alcohol and an enhancement in the yield of mixed peroxide (and for cyclooctane, ketone) relative to the normal syringe pump addition (see Table 1). For dropwise addition, it is clear that relatively high local concentrations of TBHP and *tert*-butylperoxyl radicals are present. In the virtual absence of oxygen and *tert*-butylperoxyl radicals the *only* available trap for the cycloalkyl radicals is the original catalyst, **1**, and its likely products, viz., HO−(Fe^{IV}) and HO−(Fe^{III}) formed in reactions 4 and 5, respectively. A simple HO-ligand transfer with one of these three iron species might yield alcohol (which is by far the major product under syringe pump conditions for both cycloalkanes). To check on the possibility of a direct reaction of cyclohexyl radicals with **1**, these radicals were generated by the thermal decomposition of (c-$C_6H_{11}CO_2)_2$ in degassed acetonitrile at 25 °C in the presence of **1**. No cyclohexanol could be detected. We suggest, therefore, that the most likely trap for the cycloalkyl radicals is HO−(Fe^{IV}) (see reaction 14, Scheme 2).

Scheme 2

$$Me_3COO(Fe^{III}) \rightarrow Me_3CO^{\bullet} + O{=}(Fe^{IV}) \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} HO{-}(Fe^{IV}) \quad (4)$$

$$Me_3COOH + O{=}(Fe^{IV}) \rightsquigarrow Me_3COO^{\bullet} + HO{-}(Fe^{III}) \quad (5)$$

$$Me_3CO^{\bullet} + Me_3COOH \rightsquigarrow Me_3COH + Me_3COO^{\bullet} \quad (6)$$

$$Me_3CO^{\bullet} + \text{c-}C_nH_{2n} \rightarrow Me_3COH + \text{c-}C_nH^{\bullet}_{2n-1} \quad (8)$$

$$\text{c-}C_nH^{\bullet}_{2n-1} + Me_3COO^{\bullet} \rightarrow \textbf{c-}\mathbf{C_nH_{2n-1}OOCMe_3} \quad (11')$$

$$\text{c-}C_nH^{\bullet}_{2n-1} + HO{-}(Fe^{IV}) \rightarrow \textbf{c-}\mathbf{C_nH_{2n-1}OH} + (Fe^{III}) \quad (14)$$

The "hydroxyl" oxygen atom in TBHP appeared to be the most likely source of the oxygen atom in the cycloalkanols produced under syringe pump conditions with 10 equiv (or less) of TBHP. This was confirmed by oxidizing cyclooctane in acetonitrile under argon using **1** and 10 equiv of $(CH_3)_3CO$-^{18}OH (96% ^{18}O) added by syringe pump. The incorporation of ^{18}O into the cyclooctanol was 93%. A control experiment using cyclooctane, **1**, and 10 equiv of unlabeled TBHP added by syringe pump to the acetonitrile solution containing 100 mM $H_2{}^{18}O$ gave cyclooctanol with no ^{18}O incorporation. It is clear that the C−O bond-forming step must be significantly faster than solvent water exchange with the HO-(Fe^{IV}) species.

Conclusion

We believe that the present results prove beyond any reasonable doubt that alkane oxidations catalyzed by **1** and small quantities of TBHP involve freely diffusing radicals even when the hydroperoxide is added by syringe pump. It must, however, be admitted that *the radical nature of these reactions was extremely well disguised.* Thus the conundrum presented by the apparently contradictory results originally reported[11] and herein confirmed when using **1** and adding TBHP or MPPH by syringe pump is resolved. To our knowledge, no simple (i.e., nonenzyme) complex of Fe^{III} has been described which *really* can use *tert*-alkyl hydroperoxides to mimic the monooxygenase-catalyzed oxidation of alkanes. We hope that any future claim for such an important scientific breakthrough will have been subjected to *all* of the tests described herein and in earlier publications.[4,7−9]

Experimental Section

Materials. $[Fe^{III}_2O(TPA)_2(H_2O)_2]^{4+}$ (**1**),[19] di-*tert*-butyl hyponitrite (BONNOB),[20] 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH),[21] and dicyclohexylformyl peroxide[22] (**1**H NMR (200 MHz, $CDCl_3$): δ 1.10−1.55 (12 H, m), δ 1.60−2.05 (8H, m), and δ 1.25 (2H, m)**)** were all prepared according to referenced literature procedures. *tert*-Butyl hydroperoxide (90% Aldrich) was extracted into ether and dried with sodium sulfate, and the solvent was removed and the pure, dried material made up to the required concentration in acetonitrile (Omnisolve), which itself was distilled prior to use. The $(CH_3)_3CO^{18}OH$ was synthesized by Dr. E. H. Appelman.[23] All other chemicals were commercially available and used as received.

Instrumentation. UV−visible spectra were recorded on a Varian Cary 3 spectrophotometer. ^{1}H NMR were recorded on a Bruker AM200 spectrometer. GC analyses were performed on a Hewlett-Packard 5890 gas chromatograph using a HP methyl silicone Ultra 1 column. Data analyses were performed using a Hewlett-Packard chemstation. GC−MS analyses were carried out on a Hewlett-Packard 5890 gas chromatograph connected to a 5970 series mass selective detector operated in the single ion monitoring mode. Liquid chromatography was performed on a HP 1090 liquid chromatograph equipped with a reverse phase ODS Hypersil column using a water/methanol solvent system. Syringe pump additions were achieved using a Sage instruments 341A syringe pump.

Cycloalkane Oxidations. Cyclooctane oxidations by **1** with Me_3-COOH and MPPH were performed by adding the cyclooctane to a solution of the catalyst in acetonitrile and deoxygenating the solution by purging the solution with oxygen-free argon for 10 min. In the case of the cyclohexanes, a known volume of the deoxygenated cycloalkane was added to the deoxygenated catalyst solution. A known volume of deoxygenated oxidant solution was then added all at once to start the reaction or delivered via syringe pump over the course of the reaction (10 min). The reaction product mixtures were quenched with excess triphenylphosphine to reduce all unreacted hydroperoxides to the corresponding alcohols. 1,4-Dibromobenzene was then added as an internal standard, and either the solution was combined with an equal volume of aqueous sodium sulfate, followed by extraction into diethyl ether and injection of the ethereal solution onto the GC column, or the acetonitrile solutions were analyzed directly by GC. Both methods gave similar results. Response factors for the GC-FID and the GC−MS single ion monitoring (*m/z* 82 and 92) analyses were calculated using authentic samples of the alcohols. Injection of a 1:1 ratio of c-$C_6H_{11}OH$:c-$C_6D_{11}OH$ gave 1:1 ratio of peak areas in the GC-FID but gave a 1.25:1 ratio in the GC−MS/SIM mode. The results from the GC−MS/SIM analyses were adjusted to account for the DKIE of the dehydration. For experiments involving CCl_3Br, a known volume of the oxygen-free trapping agent was added prior to the addition of the oxidant. For the reactions involving the thermal decomposition of

(17) Indeed, when a **1**/20 equiv of TBHP syringe pump experiment was performed under air without prior deoxygenation of the solvent the "usual" free-radical-derived product slate was obtained.[11]

(18) This cross-radical−radical reaction is strongly favored by the Ingold−Fischer "persistent radical effect".[9]

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BONNOB or the diacyl peroxide, all of the reagents were mixed together and then degassed by performing four freeze−pump−thaw cycles. The samples were then sealed and left at room temperature for 5 days, after which they were subjected to the usual workup procedures.

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Supporting Information Available: Four tables giving the complete product analyses for 82 individual experiments with 140, 10, or 1 equiv of hydroperoxide (6 pages). See any current masthead page for ordering and Internet access instructions.

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