

A Mechanistic Probe for Oxygen Activation by Metal Complexes and Hydroperoxides and Its Application to Alkane Functionalization by [Fe^{III}Cl₂tris(2-pyridinylmethyl)amine]⁺BF₄⁻

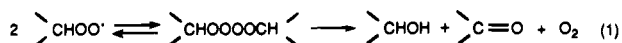
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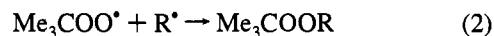
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The selective oxidation and functionalization of alkanes under mild conditions is an exciting scientific and economic goal.³ Although much of the research has focused on oxidations catalyzed by metalloporphyrins (putative cytochrome P450 mimics), there is a growing interest in catalysis by other types of metal complexes. Notably, Que and co-workers⁴ have characterized some non-heme iron catalysts with tripodal tris-(pyridinylmethyl)amine (TPA) ligands, [Fe^{III}X₂(TPA)]⁺ and have employed these complexes together with *tert*-butyl hydroperoxide to oxidize cyclohexane and adamantane in acetonitrile at room temperature. Thus, with an excess of hydroperoxide, cyclohexane was found to yield cyclohexanol, cyclohexanone, and cyclohexyl *tert*-butyl peroxide in a roughly 1:1:1 ratio in more than stoichiometric quantities based on catalyst plus, for X = Cl, cyclohexyl chloride in a roughly stoichiometric amount.

Our attention was drawn by the roughly equal yields of alcohol and ketone since this is symptomatic of a Russell-type termination of two secondary peroxy radicals,^{5,6} eq 1. However,

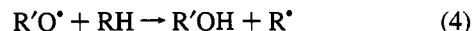


Que *et al.*⁴ proposed instead that a high-valent iron-oxo species (formally Fe^V=O) abstracted hydrogen from cyclohexane and that chloride and alcohol were formed by a Groves-type⁷ chlorine and oxygen rebound mechanism in the solvent cage, i.e., ligand transfer. A specific mechanism for ketone formation was not given. In contrast, the mixed peroxide was attributed to two radical-radical reactions, eqs 2 and 3.⁸ In the present

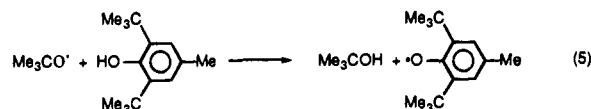


Communication, we provide evidence that [Fe^{III}Cl₂(TPA)]⁺·BF₄⁻/alkyl hydroperoxide (R'OOH) systems probably oxidize

alkanes via alkoxy radicals, eq 4, rather than via the postulated high-valent iron-oxo species,^{4c}



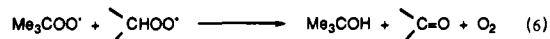
One of the major reasons for Que concluding that reaction 4 was unimportant was that the addition of 15 mM 2,6-di-*tert*-butyl-4-methylphenol (BHT)—a well-known oxyl radical trap—to a typical oxidation experiment (0.7 mM catalyst, 0.77 M cyclohexane, 3.5 mM Me₃COOH) did not change the yield of haloalkane (which remained stoichiometric with respect to catalyst). However, this argument is invalid because in acetonitrile the rate constant for reaction 5 is 2.0 × 10⁷ M⁻¹ s⁻¹ at 295 K,¹⁰ whereas the rate constant for reaction 4 with RH = cyclohexane is 1.2 × 10⁶ M⁻¹ s⁻¹.¹¹ In view of the relative



concentrations of BHT and *c*-C₆H₁₂, it is clear that H atom abstraction from the cyclohexane is ~3 times as rapid as that from the BHT. Thus, 15 mM BHT in acetonitrile can have only a minor effect on R[•] production.

We attempted to reproduce Que's results using the [Fe^{III}Cl₂(TPA)]⁺·BF₄⁻ complex¹² with vigorous bubbling of the reaction mixture with argon (rather than merely carrying out the reaction under Ar, as done by Que).^{4a-c} Vigorous bubbling with Ar ensures that much of the oxygen produced during the Me₃CO[•] radical-induced chain decomposition of Me₃COOH¹³ will be expelled from the reactant solution. However, cyclohexane proved too volatile to be studied under these conditions, so cyclooctane was used instead. Our results are summarized in Table 1 (top).

In contrast to Que's findings for cyclohexane oxidation,^{4a-c} only traces of alcohol are formed under continuous deoxygenation conditions, and the yields of ketone are low. That the alcohol is too unreactive to be the source of the ketone was demonstrated by the addition of cyclohexanol (see experiments 5 and 6; cf. also ref 4d). Thus, it appears probable that essentially all of the alcohol and most of the ketone observed by Que were formed via reaction 1, which is suppressed by continuous, vigorous deoxygenation. We attribute our small yields of ketone and alcohol to traces of oxygen, with the excess of ketone over alcohol being due to the cross-reaction, eq 6.¹⁴



With vigorous deoxygenation, the chloroalkane is formed in a roughly stoichiometric amount, presumably via chlorine atom

(1) Issued as NRCC No. 37315.

(2) Visiting Scientist.

(3) Reviews: (a) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401–1449. (b) Drago, R. S. *Coord. Chem. Rev.* **1992**, *117*, 185–213. (c) Feig, A. L.; Lippard, S. J. *Chem. Rev.* **1994**, *94*, 759–805. Monographs: (d) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981. (e) *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley: New York, 1989. (f) *The Activation of Dioxigen and Homogeneous Catalytic Oxidation*; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum: New York, 1993.

(4) (a) Leising, R. A.; Norman, R. E.; Que, L., Jr. *Inorg. Chem.* **1990**, *29*, 2553–2555. (b) Leising, R. A.; Zang, Y.; Que, L., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8555–8557. (c) Kojima, T.; Leising, R. A.; Yan, S.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 11328–11335. (d) For related work with (μ-oxo)diiron(III) complexes, see: Leising, R. A.; Kim, J.; Pérez, M. A.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 9524–9530.

(5) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 3871–3877.

(6) Tetroxides are short-lived intermediates in the bimolecular self-reactions of alkylperoxy radicals at ambient temperatures. See, e.g.: Bartlett, P. D.; Günther, P. *J. Am. Chem. Soc.* **1966**, *88*, 3288–3294. Bartlett, P. D.; Guaraldi, G. *J. Am. Chem. Soc.* **1967**, *89*, 4799–4801.

(7) Groves, J. T.; McCluskey, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154–160.

(8) The formation of mixed peroxides during the oxy functionalization of hydrocarbons using metal ions and alkyl hydroperoxides is more commonly assumed to involve ligand transfer, e.g., R[•] + Fe^{III}OOCMe₃ → ROOCMe₃ + Fe^{II}, a class of reactions first suggested by Kochi.^{3d,9}

(9) Kochi, J. K. *Tetrahedron* **1962**, *18*, 483–497. Kochi, J. K.; Mains, H. E. *J. Org. Chem.* **1965**, *30*, 1862–1872. Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 11.

(10) Measured by monitoring the growth of phenoxyl following laser flash photolysis (LFP) of Me₃COOCMe₃ and the phenol in CH₃CN.

(11) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Luszyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466–470. We assume that Me₃CO[•] and PhCMe₂O[•] abstract hydrogen from cyclohexane at essentially the same rate.

(12) Synthesized according to ref 4c as the BF₄⁻ salt.

(13) Hiatt, R.; Clipsham, J.; Visser, T. *Can. J. Chem.* **1964**, *42*, 2754–2757. Factor, A.; Russell, C. A.; Traylor, T. G. *J. Am. Chem. Soc.* **1965**, *87*, 3692–3706. Thomas, J. R. *J. Am. Chem. Soc.* **1965**, *87*, 3935–3940. Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 3797–3801.

(14) The ketone can, at most, be formed only in part from the mixed peroxide since this compound is relatively stable under our conditions; see experiment 7.¹⁵

Table 1. Products Identified after 2 h of Oxidation of Cyclooctane (0.64 M) by Me₃COOH (Top) and MPPH (Bottom) and [Fe^{III}Cl₂(TPA)]⁺ (0.61 mM) in Acetonitrile at 25 °C with Vigorous Purging by Argon^a

expt	Me ₃ COOH	C ₈ H ₁₅ Cl	C ₈ H ₁₅ OH	C ₈ H ₁₄ =O	C ₈ H ₁₅ OOCMe ₃
1	1	0.84			0.07
2	14	0.91	< 0.01	0.09	0.30
3	114	0.86	0.07	1.2	4.3
4 ^b	140	1.1	0.2	2.3	5.8
5 ^c	140	1.1	0.1	3.0	7.4
6 ^d	140	1.2	0.2	2.1	6.4
7 ^e	(140) ^f	1.3	0.43	1.5	(10.2) ^g
8 ^h	140	nd ⁱ	0.48	3.8	0.20
9 ^j	140	<0.1	0.16	3.0	0.10

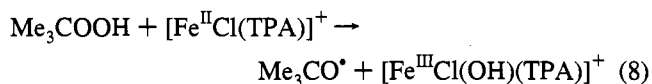
expt	MPPH	PhCH ₂ Cl	PhCH ₂ OH	PhCHO	PhCH ₂ OO-CMe ₂ CH ₂ Ph	(PhCH ₂) ₂
A ^k	140	0.47	4.7	6.9	29	5.0
B	140	0.61	0.80	3.0	5.9	2.3
C	140	0.59	< 0.20	2.7	10	2.8

^a Unless otherwise noted. Product yields and quantities of hydroperoxide employed are given in equivalents relative to catalyst. Conversion of 140 equiv of hydroperoxide to products was quite low in 2 h. ^b In an identical experiment (except that the reaction was carried out under argon after an argon purge of the solvents (i.e., Que conditions)), the products were C₈H₁₅Cl, 1.3; C₈H₁₅OH, 0.59; C₈H₁₄=O, 4.0; and C₈H₁₅OOCMe₃, 4.8. ^c With 2.1 equiv of c-C₆H₁₁OH added, recovered c-C₆H₁₁OH, 2.2 equiv; c-C₆H₁₀=O, <0.1 equiv. ^d With 109 equiv of c-C₆H₁₁OH added, recovered c-C₆H₁₁OH, >100 equiv; c-C₆H₁₀=O, 5 equiv. ^e With 10.9 equiv of c-C₈H₁₅OOCMe₃. ^f *n*-BuOOH used instead of *t*-BuOOH. ^g Recovered, i.e., not more than 0.5 equiv consumed. There was also 0.21 equiv of c-C₈H₁₅OO(CH₂)₃CH₃ produced. ^h Solution presaturated with O₂. ⁱ Not detected. ^j Solution presaturated with ¹⁸O₂. ^k Not vigorously purged with Ar.

abstraction (ligand transfer) from the catalyst by freely diffusing cyclooctyl radicals, eq 7. Such reactions are known to be fast.^{3a,9}



Presaturation of the solution with oxygen or air dramatically reduces the yield of chloride and peroxide (experiment 8). Even after 24 h, the chloride yield was still well below stoichiometric. This we attribute to the very effective trapping of R* by O₂ and a consequent failure to produce much [Fe^{II}Cl(TPA)]⁺, which is expected to react more rapidly with Me₃COOH to generate radicals, eq 8, than [Fe^{III}Cl₂(TPA)]⁺.

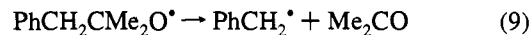


Presaturation with ¹⁸O₂ (experiment 9) gave ketone containing 79% ¹⁸O. Although the low yield of alcohol precluded measurement of its ¹⁸O content, the result with the ketone confirms that dioxygen is an important¹⁵ source of oxygen in at least one product and may even be the sole source. The variations in product yields between experiments 8 and 9 are fairly typical of the results we have obtained in apparently similar experiments. These variations are to be expected since, in radical reactions, small changes in rates of initiation and/or adventitious termination by impurities can have quite large effects on product yields.

The facts outlined above implied that it was the *tert*-butoxyl radical rather than a high-valent iron-oxo species which abstracted hydrogen from the alkane. As a critical, though nonrigorous, test for such a mechanism, we devised a mechanistic probe: 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH).¹⁶ This is expected to give the same chemistry as *tert*-

(15) A similar conclusion has been drawn for the reaction catalyzed by a (μ-oxo)Fe^{III}₂ complex.^{4d}

butyl hydroperoxide if iron-oxo species are kinetically competent intermediates. However, if alkoxy radicals are involved, there will be essentially no alcohol and little ketone because the extremely rapid ($k \sim 2.2 \times 10^8 \text{ s}^{-1}$)¹⁹ β-scission, eq 9, will almost totally inhibit hydrogen abstraction from the alkane.²²



Under typical experimental conditions, *except* for the replacement of Me₃COOH by MPPH ([Fe^{III}Cl₂(TPA)]⁺, 0.64 mM, MPPH, 90 mM (140 equiv), and c-C₈H₁₆, 670 mM in CH₃CN at room temperature), the yields of cyclooctyl chloride, cyclooctanol, cyclooctanone, and the cyclooctyl *tert*-alkyl peroxide were below our limits for their detection. The products which were formed are listed in Table 1 (bottom). Obviously, the role played by the cyclooctyl radical with Me₃COOH as oxidizer is taken up by the benzyl radical when MPPH is used as the oxidizer. This radical is presumably produced in reaction 12. The lower reactivity of the benzyl radical relative to the cyclooctyl radical accounts for the lower yield of chloride and the formation of dibenzyl.

We conclude that [Fe^{III}Cl₂(TPA)]⁺ probably oxidizes alkanes via Fenton-type chemistry, with alkoxy radicals responsible for hydrogen atom abstraction from the alkane rather than a high-valent iron-oxo species. Similar conclusions have recently been drawn by others²³ about the nature of the oxidizing agent in Barton's Gif-type systems for alkane oxidation^{24,25} and for other alkane oxidation systems more reminiscent of Que chemistry.²⁶ We suggest that each claim for alkyl hydroperoxide-derived high-valent metal-oxo species as oxidizing agents should at least be checked using MPPH as a mechanistic probe.

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(16) Synthesized from 2-methyl-1-phenyl-2-propyl bromide (itself prepared from the corresponding alcohol with concentrated HBr (aqueous) and LiBr¹⁷ using silver trifluoroacetate and dry H₂O₂¹⁸ and purified by flash chromatography over silica. Synthesis via the "classical" alcohol/H₂O₂ route gave only low yields of MPPH at room temperature but quite acceptable yields (60%) at 40 °C.

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(19) Based on the ratio of the rate constants for H atom abstraction from cyclopentane, k_H , to β-scission, k_9 , using PhCH₂CMe₂O* radicals generated from the hyponitrite at 40 °C, viz., ²⁰ $k_H/k_9 = 0.004$, and an LFP measured value for $k_H = 8.8 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for H atom abstraction from cyclopentane by Me₃CO* radicals at room temperature.²¹ A 266 nm LFP experiment with MPPH in CH₃CN showed "instantaneous" formation of the benzyl radical, which confirms that reaction 9 is very fast, i.e., $k_9 \geq 2 \times 10^7 \text{ s}^{-1}$.

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(24) See, e.g.: Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504–512. Barton, D. H. R.; Wang, T.-L. *Tetrahedron* **1994**, *50*, 1011–1032. Barton, D. H. R.; Hill, D. R. *Tetrahedron Lett.* **1994**, *35*, 1431–1434. Barton, D. H. R.; Bèvière, S. D.; Hill, D. R. *Tetrahedron* **1994**, *50*, 2665–2670. Bardin, C.; Barton, D. H. R.; Hu, B.; Rojas-Wahl, R.; Taylor, D. K. *Tetrahedron* **1994**, *35*, 5805–5808.

(25) These conclusions have been, in part, refuted. See, e.g.: Barton, D. H. R.; Chavasiri, W.; Hill, D. R.; Hu, B. *New J. Chem.* **1994**, *18*, 611–620. Barton, D. H. R. Private communication.

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