# Oxygen activation by metal complexes and alkyl hydroperoxides. Applications of mechanistic probes to explore the role of alkoxyl radicals in alkane functionalization†

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**The mechanism of the oxidation of cycloalkanes by tertiary alkyl hydroperoxides catalysed by iron(III) dichlorotris(2-pyridylmethyl)amine $[Fe^{III}Cl_2(TPA)]^+$ and by the acetate bridged (μ-oxo) di-iron complex $[Fe_2^{III}(TPA)_2O(OAc)]^{3+}$ has been investigated. Product studies do not support oxidation *via* a high valent iron–oxo intermediate (formally $Fe^V{=}O$), but are consistent with a mechanism involving hydrogen atom abstraction from the alkane by alkoxyl radicals derived from the hydroperoxide. In the presence of a large excess of *tert*-butyl hydroperoxide, the oxidation of cyclohexane yields cyclohexanone, cyclohexanol and *tert*-butylcyclohexyl peroxide in more than stoichiometric amounts and, in the case of the mono-iron catalyst, one equivalent of cyclohexyl chloride. Replacement of $Me_3COOH$ by hydroperoxides, which could yield *tert*-alkoxyl radicals having much shorter lifetimes than the *tert*-butoxyl radical prevents oxidation of the cycloalkane. The products obtained with these hydroperoxide mechanistic probes are those derived from the fast unimolecular reactions (generally β-scissions) of the corresponding alkoxyl radicals. The inapplicability of dimethyl sulfide as a mechanistically diagnostic trap for the putative $Fe^V{=}O$ intermediate and the value of di-*tert*-butyl hyponitrite as a non-iron-based source of *tert*-butoxyl radicals are discussed.**

The selective oxidation and functionalization of alkanes under ambient conditions is an exciting scientific and worthwhile economic goal.[1] The aim of most research in this area has been to duplicate the behaviour of the monooxygenases, *i.e.* to mimic enzymes which use dioxygen to functionalize saturated hydrocarbons [reaction (1)]. The best known of these enzymes are the

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

cytochrome P450s[2] and the methane monooxygenases[3] which, in the resting state, contain an iron(III) protoporphyrin IX and a (μ-oxo) di-iron complex, respectively. Attempts to model the chemistry of these enzymes have therefore generally involved the specific synthesis of relatively simple mono- and di-iron complexes.[4]

The iron(III) protoporphyrin IX cofactor is present in a number of peroxidases[5] and in catalase[6] as well as in cytochrome P450. The active species in all these enzymes is an oxo-iron(IV) porphyrin π-radical cation (called Compound I in the peroxidase catalytic cycle) which is two oxidation equivalents above the resting-state of the enzyme. This oxo-iron(IV) intermediate is capable of oxidizing organic substrates either by oxygen-atom transfer [reaction (2)] or by electron-transfer depending

$$RH + (Fe^{IV}{=}O)^{\cdot +} \longrightarrow ROH + (Fe^{III}) \qquad (2)$$

on the nature of the ligand environment surrounding the active site (*i.e.* the structure and conformation of the protein) and the nature of the substrate. Compound I is generated in catalase and the peroxidases by the reaction of the resting-state of the enzyme with hydrogen peroxide or, in the case of some peroxidases, an organic hydroperoxide. In cytochrome P450 the active $(Fe^{IV}{=}O)^{\cdot +}$ intermediate is formed by initial reduction of the resting enzyme to the Fe(II) state, rapid reaction with dioxygen and the addition of a second electron and two protons. The formation of the highly reactive oxidant in what appears to be an initial reduction reaction is driven by the formation of water. The activation of dioxygen by some synthetic porphyrins[7] and also by some natural (*e.g.* bleomycin) and synthetic (*e.g.* PMAH)[8] non-heme iron complexes appears to be mechanistically similar to the activation by P450. However, in much of the research on synthetic metalloporphyrins the oxo-iron(IV) porphyrin π-radical cation has been generated by direct oxidation using sacrificial oxygen atom donors (*e.g.* iodosylbenzene). Nevertheless, these activated species are able to mimic P450 chemistry, including alkane hydroxylation and alkene epoxidation.[7] Alkyl hydroperoxides also have been used to generate high valent iron porphyrin species,[7,9] although in this case it appears that the initial step involves the homolytic scission of the O–O bond with formation of an $(Fe^{IV}{=}O)$ species [*i.e.* one oxidation state below the oxo-iron(IV) porphyrin π-radical cation] and an alkoxyl radical.[7,9,10]

The field of metal catalysed oxidations has been expanded in recent years by several groups who have investigated the oxidation of substrates such as cyclohexane and adamantane by non-heme iron complexes activated with alkyl hydroperoxides. Notably, Que and co-workers[11] have characterized a number of iron complexes containing the tetradentate, tripodal tris(pyridylmethyl)amine (TPA) ligands. Both mono-iron(III) complexes, *e.g.*[11a–c] $[Fe^{III}Cl_2(TPA)]^+$, and (μ-oxo) di-iron(III) complexes, *e.g.*[11d] $[Fe_2^{III}(TPA)_2O(OAc)]^{3+}$ react with an excess of *tert*-butyl hydroperoxide and an excess of cyclohexane in acetonitrile at room temperature to give cyclohexanol, cyclohexanone and cyclohexyl *tert*-butyl peroxide in a roughly 1 : 1 : 1 ratio in more than stoichiometric quantities based on catalyst plus, for the mono-iron complex, cyclohexyl chloride in a roughly stoichiometric amount. It was proposed that the

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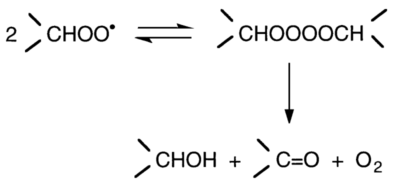
reaction of the catalyst with the hydroperoxide led to the formation of a high valent iron-oxo species (formally $Fe^{V}$=O) which abstracted a hydrogen atom from the cyclohexane. The chloride and alcohol were suggested to form by a Groves-type[12] chlorine atom and hydroxyl group rebound mechanism in the solvent cage, *i.e.* by ligand transfer. A specific mechanism for ketone formation was not given.[11f]

The formation of roughly equal amounts of alcohol and ketone under the conditions originally reported by Que *et al.* caught our attention since such equality is suggestive of a Russell-type bimolecular self-reaction of secondary alkylperoxyl radicals[13] occurring *via* an intermediate short-lived tetraoxide,[14] [reaction (3)]. This raised the possibility that the reactions yielding the principal cyclohexane-derived products, *viz.* alcohol, ketone, mixed peroxide and chloride, more probably involved free radicals, *i.e.* radicals able to diffuse through the solution, rather than the caged radical pairs which had been proposed.[11] We envisaged a set of free radical reactions which could readily account for the cyclohexane-derived products. A very simplified set of reactions is shown in Scheme 1 for a catalyst which can yield cyclohexyl chloride (*i.e.* $[Fe^{III}Cl_2(TPA)]^+$) with the four products of interest indicated in bold typeface. This Scheme will be further elaborated as this paper progresses.



(3)

**Formation of *tert*-butoxyl radicals**

$$Me_3COOH \xrightarrow{catalyst} Me_3CO^{\bullet} \qquad (4)$$

$$2Me_3COO^{\bullet} \longrightarrow 2Me_3CO^{\bullet} + O_2 \qquad (5)$$

**Destruction of *tert*-butoxyl radicals**

$$Me_3CO^{\bullet} + Me_3COOH \longrightarrow Me_3COH + Me_3COO^{\bullet} \qquad (6)$$

$$Me_3CO^{\bullet} + c\text{-}C_6H_{12} \longrightarrow Me_3COH + c\text{-}C_6H_{11}^{\bullet} \qquad (7)$$

**Formation of cyclohexane-derived products**

$$c\text{-}C_6H_{11}^{\bullet} + O_2 \longrightarrow c\text{-}C_6H_{11}OO^{\bullet} \qquad (8)$$

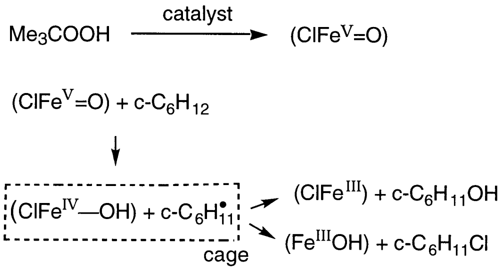
$$2\ c\text{-}C_6H_{11}OO^{\bullet} \longrightarrow \mathbf{c\text{-}C_6H_{11}OH} + \mathbf{c\text{-}C_6H_{10}O} + O_2 \qquad (9)$$

$$c\text{-}C_6H_{11}OO^{\bullet} + Me_3COO^{\bullet} \longrightarrow \mathbf{c\text{-}C_6H_{11}OOCMe_3} + O_2 \qquad (10)$$

$$c\text{-}C_6H_{11}^{\bullet} \xrightarrow{catalyst} \mathbf{c\text{-}C_6H_{11}Cl} \qquad (11)$$

**Scheme 1**

The essential feature of Scheme 1 is the formation of free *tert*-butoxyl radicals which are responsible for the formation of free cyclohexyl radicals and oxygen and hence for the four cyclohexane-derived products. This contrasts with the proposed high valent iron-oxo species as the reagent which abstracts a hydrogen atom from cyclohexane and yields cyclohexanol and cyclohexyl chloride by in-cage processes [reactions (12) and (13)]. As a critical, though non-rigorous method for distinguishing between the *tert*-alkoxyl radical mechanism shown in Scheme 1 and the high valent iron-oxo mechanism we devised a mechanistic probe: 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH).[15] This would be expected to give the same chemistry as *tert*-butyl hydroperoxide if iron-oxo species were kinetically competent intermediates. However, if alkoxyl radicals were involved there would be essentially no alcohol or



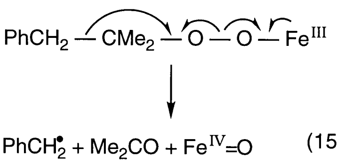
(12)

(13*a*)

(13*b*)

ketone because the extremely rapid ($k_{14}$ ~2.2 × $10^8\ s^{-1}$)[16] β-scission [reaction (14)] should almost totally inhibit hydrogen atom abstraction from the alkane. As we have described in a preliminary communication[19] benzyl radical products were formed and, more importantly, no cycloalkane oxidation products were observed when MPPH was used with the $[Fe^{III}Cl_2(TPA)]^+$ catalyst. Thus, we concluded that the chemistry of this catalyst and *tert*-butyl hydroperoxide is most simply described in terms of Scheme 1. However, an unequivocal conclusion in favour of Scheme 1 cannot be drawn because of the possibility (remote in our eyes) that the critical $Fe^{III}$–MPPH product undergoes a concerted fragmentation [reaction (15)] and in so doing imposes benzyl radical chemistry on the system.[20]

$$PhCH_2CMe_2O^{\bullet} \longrightarrow PhCH_2^{\bullet} + Me_2CO \qquad (14)$$



(15)

In the present work, we elaborate on our earlier report on $[Fe^{III}Cl_2(TPA)]^+$ and the MPPH probe. We also use this probe with the (μ-oxo) di-iron catalyst, $[Fe_2^{III}(TPA)_2O(OAc)]^{3+}$. Two other hydroperoxide mechanistic probes which address the potential concern that MPPH might have a predilection towards radical chemistry have been characterized and used with both catalysts. In addition, the change in products which occurs upon the addition of dimethyl sulfide to the two catalyst–*tert*-butyl hydroperoxide systems has been explored since these changes have been used to argue in favour of the chemically active species being a high valent iron-oxo species. All of our results are consistent with the free radical mechanism shown in a simplified form in Scheme 1 and do not support alternative non-free radical schemes.

## Results

Products have been reported for the cyclohexane–*tert*-butyl hydroperoxide reaction catalysed by three $[Fe^{III}X_2(TPA)]^+$ complexes (X = Cl, Br and $N_3$) and by four other mono-iron complexes,[11a–c] by six $[Fe_2^{III}(TPA)_2O(Y)]^{3+}$ complexes [Y = OAc, OBz, 4-$CH_3OC_6H_4CO_2$, $(PhO)_2PO_2$, $CO_3$ and phthalate][11d] and by four other (μ-oxo) di-iron complexes.[11d] We have examined one mono- and one di-iron TPA complex, *viz.* $[Fe^{III}Cl_2(TPA)]^+$ and $[Fe_2^{III}(TPA)_2O(OAc)]^{3+}$, and hence our conclusions do not necessarily apply to all of the catalysts reported by Que.[11f] However, there is a general similarity in all of the results (with active catalysts in the absence of additives such as $Me_2S$) in that with a large excess of *tert*-butyl hydroperoxide, cyclohexanol, cyclohexanone and cyclohexyl *tert*-butyl hydroperoxide are always formed and, moreover, are generally formed in comparable amounts. In retrospect this is not at all surprising since in this paper we will demonstrate that with the two catalysts we have employed, the oxidation of cycloalkanes involves free radicals and dioxygen. It is well known that metal-catalysed

**Table 1** Products identified after 2 h of oxidation of cyclohexane (0.64 M) by $Me_3COOH$ (85.4 mM) and $[Fe^{III}Cl_2(TPA)]BF_4$ (0.61 mM) or $[Fe^{III}Cl_2(TPA)]ClO_4$ (0.61 mM) in acetonitrile at 25 °C[a]

| Entry no. | Conditions[b] (catalyst) | RCl | ROH | $R_{-H}O$ | $ROOCMe_3$ | Σ Prod[c] |
|---|---|---|---|---|---|---|
| 1 | Ar ($Fe^{III}$, $BF_4$) | 1.1; 0.5 | 8.3; 8.7 | 5.1; 6.3 | 1.3; 1.0 | 15.8; 16.5 |
| 2 | Ar[d] ($Fe^{III}$, $ClO_4$) | 1 | 15 | 12 | 8 | 36 |
| 3 | Ar ($Fe^{III}$, $ClO_4$) | 1.0; 0.8 | 1.4; 1.1 | 4.6; 4.4 | 6.1; 5.6 | 13.1; 11.9 |
| 4 | Air ($Fe^{III}$, $ClO_4$) | 0[e]; 0[e] | 0[e]; 0[e] | 0[e]; 0[e] | 0[e]; 0[e] | 0; 0 |

[a] Product yields are given in equivalents relative to catalyst. The results of duplicate runs by the same experimentalist are given with a semi-colon between the data, the first number in each column corresponds to the first run. [b] Ar = under argon (Que conditions); Air = not purged and run under air. [c] Total yield of cycloalkane derived products, *i.e.* Σ [chloride (RCl) + alcohol (ROH) + ketone ($R_{-H}O$) + mixed peroxide ($ROOCMe_3$)]. [d] With 0.70 mM $[Fe^{III}Cl_2(TPA)](ClO_4)$, 0.77 M cyclohexane, 0.10 M $Me_3COOH$. Data are from ref. 11*a*. [e] Not detected.

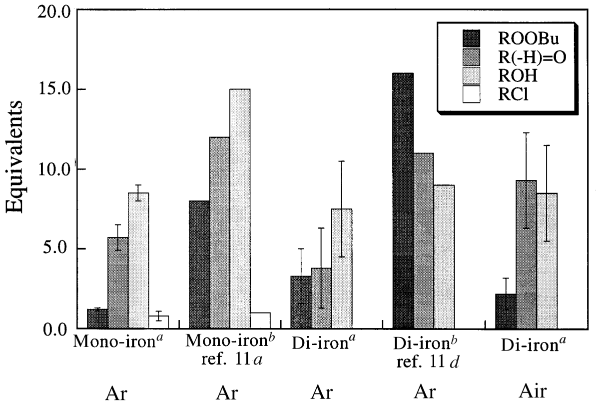


**Fig. 1** Products (equivs. based on catalyst) identified after 2 h of oxidation of cyclohexane (0.64 M) by $Me_3COOH$ (85.4 mM) and $[Fe^{III}Cl_2(TPA)]^+$ or $[Fe_2^{III}O(OAc)(TPA)_2]^{3+}$ (0.61 mM) in acetonitrile at 25 °C. Ar = under an atmosphere of argon; Air = under an atmosphere of air. [a] The results are averages of at least duplicate experiments. [b] With 0.77 M cyclohexane, 0.10 M $Me_3COOH$ and 0.70 mM catalyst.

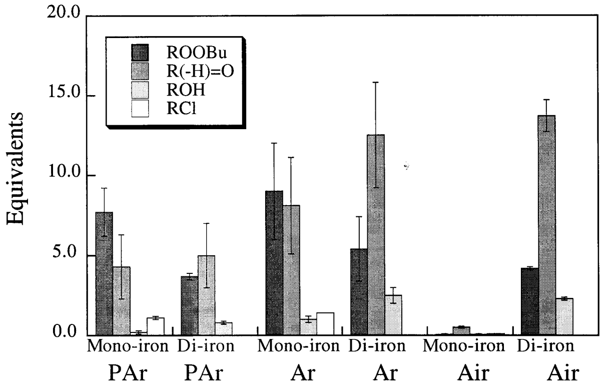


**Fig. 2** Products (equivs. based on catalyst) identified after 2 h of oxidation of cyclooctane (0.64 M) by $Me_3COOH$ (85.4 mM) and $[Fe^{III}Cl_2(TPA)]^+$ or $[Fe_2^{III}O(OAc)(TPA)_2]^{3+}$ (0.61 mM) in acetonitrile at 25 °C. The results are averages of duplicate experiments. PAr = continuously purged with argon; Ar = under an atmosphere of argon; Air = under an atmosphere of air.

autoxidations are rather irreproducible because of variable initiation rates[21] (often leading to autocatalysis or autoinhibition). Indeed, we find that the results obtained with the two catalysts we employed are so similar in terms of cycloalkane oxidation products *etc.*, that we will present the results for the mono- and di-iron complexes together for each aspect of our studies.

### Reactions of $[Fe^{III}Cl_2(TPA)]^+$ and $[Fe_2^{III}(TPA)_2O(OAc)]^{3+}$ with *tert*-butyl hydroperoxide under argon

In initial experiments, an attempt was made to reproduce results reported[11a] with the mono-iron complex, $[Fe^{III}Cl_2(TPA)](ClO_4)$ (0.70 mM), cyclohexane (0.77 M) and *tert*-butyl hydroperoxide (0.1 M, 143 equiv. based on catalyst) at 25 °C under an atmosphere of argon with product analysis after 2 h. However, because we considered it possible that the perchlorate anion acted as an oxidizing agent we used the tetrafluoroborate salt, $[Fe^{III}Cl_2(TPA)](BF_4)$, in our first experiments. The results of duplicate runs with this catalyst are given in Table 1 (entry 1). The absence of perfect reproducibility between our duplicate runs (carried out by the same experimentalist) is both noticeable and quite typical of free radical reactions. It serves further to indicate the dangers of drawing conclusions from relatively minor differences in product yields and product ratios. The literature result with $[Fe^{III}Cl_2(TPA)](ClO_4)$ as catalyst[11a] is also shown in Table 1 (entry 2). The agreement between the results of entries 1 and 2 is reasonable (in our opinion), but in the hope that it might be improved we carried out the same experiments using $[Fe^{III}Cl_2(TPA)](ClO_4)$ as the catalyst (entry 3). While there was a significant change in the product profile with perchlorate as the counter ion *versus* the tetrafluoroborate, the agreement with the literature data was not improved. Indeed, our own work shows very much better agreement between pairs of experiments carried out with exactly the same catalyst preparation as between experiments using different salts of $[Fe^{III}Cl_2(TPA)]^+$ and hence between different catalyst preparations. On the whole, we consider the results given in entries 1–3 to be in reasonable agreement. These results together with results obtained using the (μ-oxo) di-iron catalyst for the oxidation of cyclohexane under the same experimental conditions are represented graphically in Fig. 1 and are available in tabular form as Supplementary Material.¶ The agreement between duplicate experiments with the di-iron catalyst was also not particularly good and again serves to emphasize that mechanistic conclusions should only be drawn from the overall product profiles.

We considered that one reason for the variable yields of the products might be the oxygen concentration in the solutions since this would undoubtedly affect the product outcome if free radicals were responsible for the chemistry. Oxygen would be formed *via* reactions (5), (9) and (10) (Scheme 1)[22] and hence its concentration would not be constant during the reaction. We therefore attempted to repeat these experiments with continuous and vigorous bubbling of argon through the reaction mixture. However, cyclohexane proved too volatile to be studied under these conditions, so cyclooctane was used instead.

The results of duplicate experiments with cyclooctane and $[Fe^{III}Cl_2(TPA)](BF_4)$ or $[Fe_2^{III}(TPA)_2O(OAc)](BF_4)_3$ as catalyst under argon are summarized in Fig. 2. Once again, we find that the product profiles obtained with the perchlorate catalyst differ appreciably from those with the tetrafluoroborate catalyst (data available as Supplementary Material). Indeed, the change of catalyst caused just as large a change in the product profile as did the change from carrying out the reaction under an atmosphere of argon to carrying it out with continuous purging with argon (Fig. 2). The variations in product profiles are more

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¶ Supplementary material (SUPPL. NO. 57194, 10 pp.) has been deposited at the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, Issue 1, 1997.

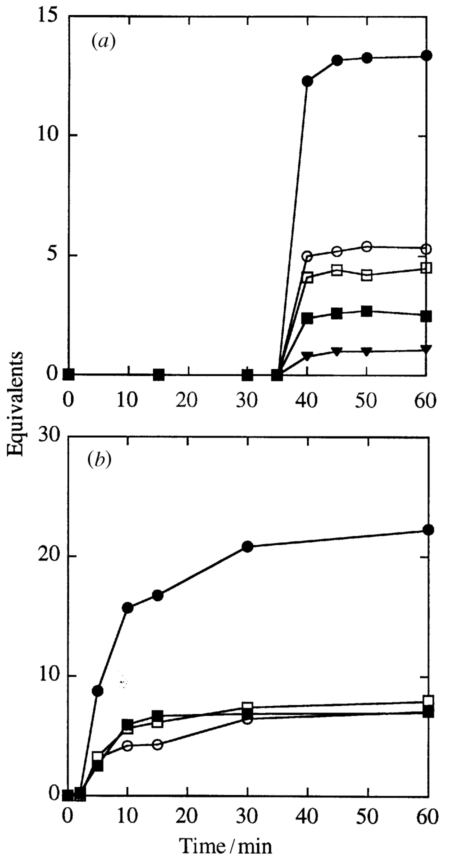


**Fig. 3** Oxidation of cyclohexane by (*a*) $[Fe^{III}Cl_2(TPA)]^+$ and (*b*) $[Fe^{III}_2O(OAc)(TPA)_2]^{3+}$ in acetonitrile at 25 °C under an atmosphere of argon: (●) total products; (○) cyclohexyl *tert*-butyl peroxide; (□) cyclohexanol; (■) cyclohexanone; (▼) cyclohexyl chloride

probably a result of differences in trace impurities from one catalyst preparation to the next than to any intrinsic reactivities of the counter ions.

It is interesting to note that considerably less alcohol is produced from cyclooctane than from cyclohexane under comparable experimental conditions (*cf.* Figs. 1 and 2). Experiments with cyclohexanol and cyclooctanol in the presence of either catalyst but in the absence of hydroperoxide showed that neither catalyst oxidized the alcohol to the corresponding ketone under normal experimental conditions. The much lower yield of cyclooctanol compared with cyclohexanol indicates that the two cycloalkylperoxyl and/or cycloalkoxyl radicals undergo somewhat different chemistries. While it would be interesting to discover exactly why cyclohexane and cyclooctane gave such different alcohol : ketone[24] ratios such a study was considered to be beyond the scope of the present investigation. However, we did demonstrate that this phenomenon is not due to iron-mediated reactions since the much lower alcohol : ketone ratio for cyclooctane relative to cyclohexane was also observed when *tert*-butoxyl radicals were generated in iron catalyst-free mixtures of the cycloalkanes and *tert*-butyl hydroperoxide in acetonitrile (*vide infra*).

### Time dependence of product profiles

An examination of the product yields as a function of time under standard conditions {$[Fe^{III}Cl_2(TPA)](ClO_4)$, 0.61 mM; cycloalkane, 0.64 M; $Me_3COOH$, 85.4 mM in dry acetonitrile under argon at room temperature} over a 1 h period show that these reactions have a very distinct induction period, following which the majority of the products are formed extremely rapidly [Figs. 3(*a*) and 4(*a*)]. These results led us to hypothesize that the reaction of the carbon-centred cycloalkyl radical with the $(Fe^{III})$ catalyst to produce $(Fe^{II})$ and the cycloalkyl chloride [reaction (16)] must play a vital role in the overall chemistry.

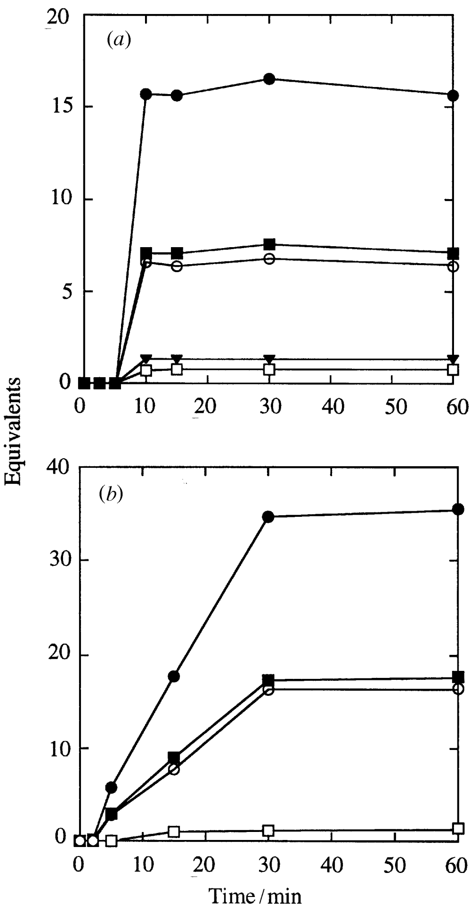


**Fig. 4** Oxidation of cyclooctane by (*a*) $[Fe^{III}Cl_2(TPA)]^+$ and (*b*) $[Fe^{III}_2O(OAc)(TPA)_2]^{3+}$ in acetonitrile at 25 °C under an atmosphere of argon: (●) total products; (■) cyclooctyl *tert*-butyl peroxide; (□) cyclooctanol; (○) cyclooctanone; (▼) cyclooctyl chloride

$$c\text{-}C_nH^{\bullet}_{2n-1} + Cl(Fe^{III}) \longrightarrow c\text{-}C_nH_{2n-1}Cl + (Fe^{II}) \quad (16)$$

The reduced catalyst $(Fe^{II})$ is expected to be much more reactive than the $(Fe^{III})$ catalyst towards *tert*-butyl hydroperoxide, reacting in a 'Fenton-type' manner,[25] [reaction (17)]. Thus, the

$$Me_3COOH + (Fe^{II}) \longrightarrow Me_3CO^{\bullet} + (Fe^{III}) + OH^- \quad (17)$$

formation of $(Fe^{II})$ would lead to a 'burst' of radicals which will quickly end the induction period and yield the cycloalkane oxidation products.

It will be obvious that the foregoing concepts have, as a necessary corollary, the consequence that dioxygen should prolong the induction period since alkylperoxyl radical formation *via* reaction (8) (Scheme 1) will compete with reaction (16). The inhibitory effect of dioxygen is very apparent when the mono-iron catalysed reactions are carried out under air (Table 1, entry 4 *versus* entry 3 and Fig. 2). Indeed, the longer induction period found with cyclohexane compared with cyclooctane [Fig. 3(*a*) *vs.* 4(*a*)] can simply be attributed to the difficulty of deoxygenating the cyclohexane-containing system under a stream of argon because of the volatility of this hydrocarbon. Certainly, in a competitive experiment with the two hydrocarbons, the $C_6$- and $C_8$-products were formed at the same time (see Supplementary Material). The last experiment is particularly interesting because the $C_8$-product : $C_6$-product ratio (found to be 2.4 : 1) is consistent with the ratio of the absolute rate constants for hydrogen atom abstraction from cyclooctane[26] and cyclohexane[27] by *tert*-alkoxyl radicals, *viz.* $k_{(RO^{\bullet}+C_8H_{16})} : k_{(RO^{\bullet}+C_6H_{12})} =$

$2.7 \times 10^6$ M$^{-1}$ s$^{-1}$ : $1.2 \times 10^6$ M$^{-1}$ s$^{-1}$ = 2.3 : 1.0. A better proof of the role played by *tert*-butoxyl radicals in the *tert*-butyl hydroperoxide modulated reactions would be difficult to imagine.

The (μ-oxo) di-iron catalyst gave a very much shorter induction period than the mono-iron catalyst [Figs. 3(*b*) and 4(*b*)].[28] This suggested that dioxygen would not be nearly such a good inhibitor for the (μ-oxo) $Fe_2^{III}$-catalysed reactions and this was readily shown to be the case. Thus, carrying out the reactions under air or argon gave essentially the same product yields and profiles (Figs. 1 and 2).

## Mechanistic considerations

Que and co-workers based their mechanistic conclusions in favour of the cycloalkane oxidations involving reactive, high valent iron-oxo[11a–d] or iron alkyl peroxide[11e,f] species largely on the results they obtained with two additives, 2,6-di-*tert*-butyl-4-methylphenol (BHT) and dimethyl sulfide, together with c-$C_6H_{12}$ : c-$C_6D_{12}$ product-based substrate deuterium isotope effects. In a pair of fairly typical experiments employing [Fe$^{III}$(TPA)Br$_2$](ClO$_4$) at 3.0 mM, cyclohexane at 1.15 M and Me$_3$COOH at 15.0 mM and with a 30 min reaction time, 1 equiv. of cyclohexyl bromide was formed in the absence of BHT and in the presence of 15 mM BHT.[11b] This result was used to argue against the presence of free radicals in the reaction and was said to exclude the possibility that peroxide homolysis occurred to generate alkoxyl radicals which then abstract hydrogen from the substrate.[11c] The truth is that BHT is a very ineffective scavenger of carbon-centred radicals, but is moderately active in scavenging oxygen-centred radicals. As we pointed out in our preliminary communication,[19] the rate constant for the reaction of the *tert*-butoxyl radical with BHT at 295 K is $2.0 \times 10^7$ M$^{-1}$ s$^{-1}$ in acetonitrile,[29] whereas the rate constant for the reaction of the *tert*-butoxyl radical with cyclohexane is $1.2 \times 10^6$ M$^{-1}$ s$^{-1}$.[27,30] In view of the relative concentrations of BHT and cyclohexane, hydrogen atom abstraction from the cyclohexane will be *ca.* 4 times as rapid as from BHT. Thus, 15 mM BHT in acetonitrile can have only a minor effect on any production of cyclohexyl radicals *via tert*-butoxyl radicals.

The formation of high valent iron-oxo species, Fe$^V$=O, *via* a heterolytic scission of the O–O bond in an Fe$^{III}$-hydroperoxide complex [reaction (18)] rather than, or as well as, *via* a homolytic

$$\mathrm{Fe^{III} + ROOH \xrightarrow{het} Fe^{V}{=}O + ROH} \qquad (18)$$

scission to form an Fe$^{IV}$=O species and an alkoxyl radical [reaction (19)] has been probed with sulfides on various

$$\mathrm{Fe^{III} + ROOH \xrightarrow{hom} Fe^{IV}{=}O + RO^{\bullet} + H^{+}} \qquad (19)$$

occasions. The basic idea is that the very strong oxidant Fe$^V$=O will be diverted from whatever its normal fate might be and will instead oxidize the sulfide to a sulfoxide [reaction (20)]. This

$$\mathrm{Fe^{V}{=}O + R'SR'' \longrightarrow Fe^{III} + R'S(O)R''} \qquad (20)$$

approach was used by Labeque and Marnett[31] to show that in the reaction between a secondary hydroperoxide and an iron porphyrin–imidazole complex the homolytic and heterolytic pathways for hydroperoxide scission occurred competitively. Thus, epoxidation of (*Z*)-stilbene produced approximately equal yields of (*Z*)- and (*E*)-stilbene oxide. The formation of both epoxides was inhibited by BHT, but *p*-methoxythioanisole selectively inhibited the formation of (*Z*)-stilbene oxide. Heterolysis [reaction (18)] yields Fe$^V$=O which epoxidizes (*Z*)-stilbene stereospecifically to the (*Z*)-epoxide, a reaction which is prevented by the sulfide [reaction (20)]. Homolysis [reaction (19)] yields Fe$^{IV}$=O and an RO$^\bullet$ radical which then reacts with ROOH to form the peroxyl radical, ROO$^\bullet$, and it is this radical which is responsible for the formation of the (*E*)-epoxide.

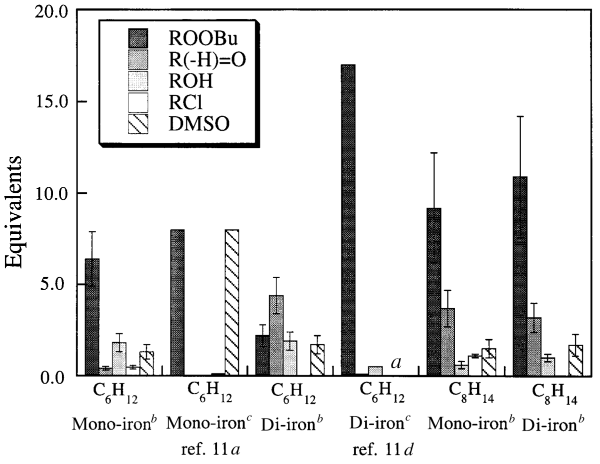


**Fig. 5** Products (equivs. based on catalyst) identified after 2 h of oxidation of cyclooctane (0.64 M) by Me$_3$COOH (85.4 mM) and [Fe$^{III}$Cl$_2$(TPA)]$^+$ or [Fe$_2^{III}$O(OAc)(TPA)$_2$]$^{3+}$ (0.61 mM) in the presence of 100 equivs. of demethyl sulfide in acetonitrile at 25 °C under an atmosphere of argon. [a] DMSO yield not given. [b] The results are averages of duplicate experiments. [c] With 0.77 M cyclohexane, 0.10 M Me$_3$COOH and 0.70 mM catalyst.

Que used dimethyl sulfide to modulate cyclohexane–Me$_3$COOH reactions catalysed by a mono-iron[11a,c] and a di-iron[11d] complex. For example, two runs were carried out with [Fe$^{III}$(TPA)Br$_2$](ClO$_4$) and cyclohexane. In one run with 3 mM complex and 1.15 M cyclohexane, 1 equiv. (based on catalyst) of Me$_3$COOH and 100 equivs. of Me$_2$S was reported to yield 1 equiv. of dimethyl sulfoxide only.[11c] In the other run with 0.70 mM complex and 0.77 M cyclohexane, 143 equiv. of Me$_3$COOH (0.1 M) and a 7 : 1 mole ratio of cyclohexane to Me$_2$S was reported to yield (in equiv.) 0.1 bromide, 0 alcohol, 0 ketone, 8 cyclohexyl *tert*-butyl peroxide and 8 DMSO.[11a] In our hands, DMSO was a relatively minor product produced in somewhat more than stoichiometric quantities. The main effect of added Me$_2$S was to decrease the total yield of cycloalkane derived products and to change the product profiles to favour, generally, the mixed peroxide at the expense of alcohol and ketone (compare Fig. 5 with Figs. 1 and 2).

One possible reason for differences between our own experimental results and those reported by Que and co-workers[11a–d] was the absence or presence of water. Our reactions were performed under anhydrous conditions whereas a 70% aqueous solution of Me$_3$COOH was used in the earlier work.[11a–d] We therefore carried out experiments involving the addition of small amounts of water under otherwise standard reaction conditions. The addition of either 20 or 50 μl of water to the cyclooctane–[Fe$^{III}$Cl$_2$(TPA)](ClO$_4$)–Me$_3$COOH system had very little effect on the overall reaction products and the addition of 50 μl of water to the cyclooctane–[Fe$_2^{III}$(TPA)$_2$-O(OAc)](ClO$_4$)$_3$–Me$_3$COOH system also produced only a minimal change in the oxidation product profile (see Supplementary Material).

Before completing this section we will return briefly to the mechanism(s) of formation of the mixed peroxide in these systems. In the early stages of the reaction this peroxide is formed by coupling of cycloalkyl and *tert*-butylperoxyl radicals (*vide supra*). Later in the reaction we anticipated that the mixed peroxide would be formed by reaction of cycloalkylperoxyl and *tert*-butylperoxyl radicals [reaction (10)]. The occurrence of reaction (10) was readily demonstrated using cyclooctane (0.64 M), Me$_3$COOH (85.4 mM) and [Fe$^{III}$Cl$_2$(TPA)]$^+$ (0.61 mM) in CH$_3$CN which had been pre-saturated with $^{18}O_2$ (see Supplementary Material). After 2 h at 25 °C an LC–MS analysis of the products showed that 76% of the mixed peroxide (total yield, 0.10 equiv.) contained one atom of $^{18}$O, *i.e.* reactions (8′) and (10′) had occurred.[32]

$$\text{c-C}_8\text{H}_{15}^{\bullet} + {}^{18}\text{O–}{}^{18}\text{O} \longrightarrow \text{c-C}_8\text{H}_{15}\text{–}{}^{18}\text{O–}{}^{18}\text{O}^{\bullet} \quad (8')$$

$$\text{c-C}_8\text{H}_{15}\text{–}{}^{18}\text{O–}{}^{18}\text{O}^{\bullet} + \text{Me}_3\text{C–}{}^{16}\text{O–}{}^{16}\text{O}^{\bullet} \longrightarrow \text{c-C}_8\text{H}_{15}\text{–}{}^{18}\text{O–}{}^{16}\text{O–CMe}_3 + {}^{16}\text{O–}{}^{18}\text{O} \quad (10')$$

These results (and results described in the following section) lead us to question the long-prevailing general view that the formation of mixed peroxides in reactions involving a metal catalyst, *tert*-butyl hydroperoxide and a hydrocarbon must proceed *via* ligand exchange on the metal (*vide infra*).

### Reaction of the cycloalkanes with *tert*-butyl hydroperoxide initiated by the thermal decomposition of di-*tert*-butyl hyponitrite in the absence of iron catalysts

Our conclusion that the $\text{Fe}^{\text{III}}$(TPA) and (probably) the $\text{Fe}_2^{\text{III}}(\text{TPA})_2$ catalysts were functioning simply (and solely) to produce *tert*-butoxyl radicals from the hydroperoxide necessarily demands that reaction will occur in the absence of an iron catalyst provided another source of *tert*-butoxyl radicals is presented to the reactants. Di-*tert*-butyl hyponitrite (BONNOB) provides a safe and convenient source of *tert*-butoxyl radicals at temperatures slightly above ambient (reaction 21).[33] Reactions

$$\text{Me}_3\text{CON=NOCMe}_3 \longrightarrow 2\ \text{Me}_3\text{CO}^{\bullet} + \text{N}_2 \quad (21)$$

were carried out in acetonitrile under an atmosphere of argon at 34 °C with analyses after 3 days (*ca.* 2.5 half-lives of BONNOB).[33] The product yields were rather low but the same three oxygen-containing products were formed, *viz.* alcohol, ketone and mixed peroxide and there is nothing 'unusual' about the product profile, *e.g.* under the same experimental conditions the alcohol : ketone ratio is considerably greater for cyclohexane than for cyclooctane (see Fig. 6). Furthermore, the addition of dimethyl sulfide had only a minor effect on the yield of mixed peroxide, slightly lowered the overall yield of alcohol and ketone and led to the formation of significant amounts of DMSO. Thus, an iron catalyst is not required for the formation of DMSO from $\text{Me}_2\text{S}$ in the presence of $\text{Me}_3\text{COOH}$, all that is required is a source of *tert*-butoxyl radicals.

A very important point to note about Fig. 6 is that the mixed peroxides are formed in substantial yields. Since this occurs in the absence of a transition metal, it is clear that the formation of mixed peroxides ($\text{ROOCMe}_3$) in the presence of a transition metal, RH and $\text{Me}_3\text{COOH}$ does not necessarily involve ligand transfer of the alkylperoxyl moiety from the iron catalyst to the carbon-centred radical [reaction (22)]. Such a

$$\text{R}^{\bullet} + \text{Fe}^{\text{III}}\text{OOCMe}_3 \longrightarrow \text{ROOCMe}_3 + \text{Fe}^{\text{II}} \quad (22)$$

process was first proposed by Kochi[34,35] as an essential step in Kharasch and Fono's[36] syntheses of mixed peroxides in the copper-catalysed, radical chain reactions of *tert*-butyl hydroperoxide with alkenes, alkyl aromatics and other compounds containing activated C–H bonds [*e.g.* reaction (23)]. These reactions can also be catalysed by cobalt and manganese.[36]

$$\text{R}^{\bullet} + \text{Cu}^{\text{II}}\text{OOCMe}_3 \longrightarrow \text{ROOCMe}_3 + \text{Cu}^{\text{I}} \quad (23)$$

Furthermore, cumene hydroperoxide can be used in place of $\text{Me}_3\text{COOH}$.[36] It has also been suggested recently that mixed peroxides, $\text{ROOCMe}_3$, are formed by reaction (22)[37,38] and *via* an analogous reaction with manganese.[38a] However, as early as 1950 Kharasch *et al.*[39] demonstrated that *tert*-butyl-α-cumyl peroxide could be obtained in good yields in the absence of metal ions when acetyl peroxide (a source of methyl radicals) was decomposed in cumene containing *tert*-butyl hydroperoxide.

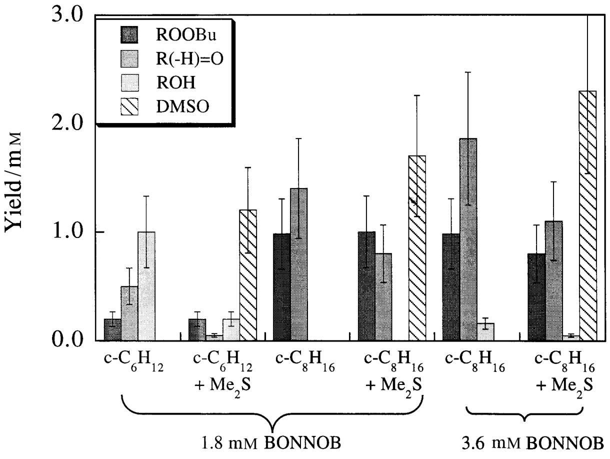
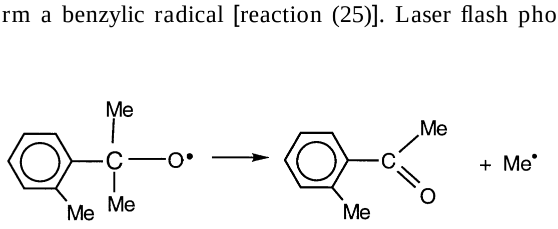


**Fig. 6** Products identified after 3 days of oxidation of cyclohexane or cyclooctane (0.64 M) by $\text{Me}_3\text{COOH}$ (85.4 mM) initiated by BONNOB in the absence and presence of $\text{Me}_2\text{S}$ (61 mM) in acetonitrile under argon at 34 °C. The results are averages of duplicate experiments.

### Reactions of $[\text{Fe}^{\text{III}}\text{Cl}_2(\text{TPA})]^+\ \text{BF}_4^-$ and $[\text{Fe}_2^{\text{III}}(\text{TPA})_2\text{O(OAc)}]^{3+}(\text{BF}_4^-)_3$ with selected *tert*-alkyl hydroperoxides as mechanistic probes

As was mentioned in the Introduction, we originally[19] used 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH) and the mono-iron catalyst as a critical probe to distinguish between the *tert*-alkoxyl radical mechanism and the proposed high valent iron–oxo mechanism.[11a–d] The alkoxyl radical derived from this hydroperoxide, *viz.* $\text{PhCH}_2\text{CMe}_2\text{O}^{\bullet}$, undergoes extremely rapid β-scission [reaction (14)] and so this alkoxyl radical is too short-lived to abstract hydrogen from the cycloalkane. As we expected, and have already reported,[19] the combination cyclooctane–(MPPH)–$[\text{Fe}^{\text{III}}\text{Cl}_2(\text{TPA})]^+$ gave no cyclooctane oxidation products but only the products expected from the benzyl radical formed *via* the β-scission of $\text{PhCH}_2\text{CMe}_2\text{O}^{\bullet}$, *viz.* $\text{PhCH}_2\text{Cl}$, $\text{PhCH}_2\text{OH}$, PhCHO, $\text{PhCH}_2\text{OOCMe}_2\text{CH}_2\text{Ph}$ and $(\text{PhCH}_2)_2$ (Table 2). Using the di-iron catalyst and MPPH also gave only benzyl radical products and no cyclooctane oxidation products (Table 2). These last results should put to rest any lingering doubts regarding the mechanism of the reaction catalysed by $[\text{Fe}_2^{\text{III}}(\text{TPA})_2\text{O(OAc)}]^{3+}$.

Although we consider the data in Table 2 to provide unequivocal evidence for the alkoxyl radical mechanism there have been suggestions that MPPH represents a 'special case' (*i.e.* it is predisposed to homolytic chemistry, see Introduction). We therefore decided to use two other *tert*-alkyl hydroperoxides which could not conceivably be consigned to the MPPH special case category. The first of these was *o*-methyl cumene hydroperoxide (*o*-MCH).[40] The alkoxyl radical derived from this hydroperoxide would be expected to be short-lived relative to *tert*-butoxyl because of a more rapid β-scission [reaction (24)] and because of an intramolecular hydrogen atom abstraction to form a benzylic radical [reaction (25)]. Laser flash photolysis


(24)

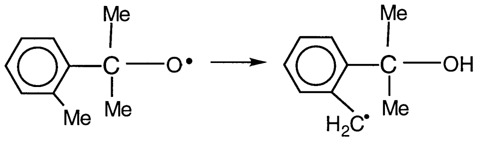

(25)

**Table 2** Products identified after 2 h of oxidation of cyclooctane (0.64 M) by MPPH (85.4 mM) and $[Fe^{III}Cl_2(TPA)]BF_4$ (0.61 mM) or $[Fe_2^{III}(TPA)_2O(OAc)](BF_4)_3$ (0.61 mM) in acetonitrile at 25 °C[a]

| Conditions[b] (catalyst) | $PhCH_2Cl$ | $PhCH_2OH$ | PhCHO | $PhCH_2OOCMe_2CH_2Ph$ | $(PhCH_2)_2$ | Σ Prod |
|---|---|---|---|---|---|---|
| Ar ($Fe^{III}$) | 0.35 | 2.2 | 5.8 | 10.1 | 1.0 | 19.5 |
| Ar ($Fe^{III}$) | 0.47 | 4.7 | 6.9 | 2.9 | 5.0 | 20.0 |
| PAr ($Fe^{III}$) | 0.31 | 5.4 | 5.8 | 4.4 | <0.2 | ~16 |
| PAr ($Fe^{III}$) | 0.61 | 0.8 | 3.0 | 5.9 | 2.3 | 12.6 |
| Ar ($Fe_2^{III}$) | — | 3.3 | 5.4 | 2.3 | 4.1 | 15.1 |
| PAr ($Fe_2^{III}$) | — | 4.5 | 4.9 | 6.1 | 1.2 | 16.7 |

[a] Product yields are given in equivalents relative to catalyst. [b] Ar = under argon (Que conditions); PAr = pre-purged with argon and run under continuous argon purging.

**Table 3** Products identified after 2 h of oxidation of cyclooctane (0.64 M) by *o*-MCH (85.4 mM) and $[Fe^{III}Cl_2(TPA)]BF_4$ (0.61 mM) or $[Fe_2^{III}(TPA)_2O(OAc)](BF_4)_3$ (0.61 mM) in acetonitrile at 25 °C[a]

| Conditions[b] (catalyst) | *o*-$MeC_6H_4COMe$ | *o*-$ClCH_2$-$C_6H_4CMe_2OH$ | *o*-$HOCH_2$-$C_6H_4CMe_2OH$ | *o*-O=CH-$C_6H_4CMe_2OH$ | *o*-$MeC_6H_4CMe_2OO$-$CH_2C_6H_4CMe_2OH$ | Σ Prod |
|---|---|---|---|---|---|---|
| Ar ($Fe^{III}$) | 4.2 | <0.1 | 0.14 | 0.36 | 1.21 | ~5.9 |
| PAr ($Fe^{III}$) | 2.5 | 0.16 | 0.29 | 0.52 | 0.87 | 4.3 |
| Ar ($Fe_2^{III}$) | 3.3 | — | <0.1 | 0.28 | 0.26 | ~3.8 |
| PAr ($Fe_2^{III}$) | 2.8 | — | 1.0 | 1.0 | 0.24 | 5.0 |

[a] Product yields are given in equivalents relative to catalyst. [b] See footnote *b* in Table 2.

(266 nm) of *o*-MCH in deoxygenated $CH_3CN$ at room temperature generated the expected[41] transient absorption in the visible ($\lambda_{max} = 490$ nm) for an alkyl substituted cumyloxyl radical. This absorption decayed with first order kinetics, $k_{24} + k_{25} = 2.5 \times 10^6\ s^{-1}$, with the concurrent growth of a new absorption at 320 nm. This new absorption can be assigned to the benzylic radical formed in reaction (25) on the basis of previous spectroscopic studies of benzylic radicals and the fact that it is not observed in oxygen-saturated $CH_3CN$. It is, perhaps, worth noting that reaction (25) is not particularly fast, presumably because this intramolecular reaction involves cleavage of the C–H bond in the plane of the aromatic ring and thus little or no benzylic stabilization can be developed in the transition state.

The new hydroperoxide mechanistic probe, *o*-MCH, behaved just as we expected with both the mono- and di-iron catalysts. That is, no cyclooctane oxidation products could be detected. The major products were *o*-methyl acetophenone [reaction (24)] and the expected products arising from the benzyl radical formed in reaction (25) *viz*. chloride, alcohol, aldehyde and the mixed peroxide, see Table 3.

Our success with *o*-MCH prompted us to see just how long the alkoxyl radical lifetime could be made and still show competition between its unimolecular decay reaction(s) and hydrogen atom abstraction from cyclooctane under normal experimental conditions. To this end, we examined the products formed using cumene hydroperoxide (CH) and the mono- and di-iron catalysts. The cumyloxyl radical undergoes β-scission [reaction (26)] with a rate constant of $k_{26} = 6.3 \times 10^5\ s^{-1}$ in acetonitrile at 30 °C.[27]

$$PhCMe_2O^{\bullet} \longrightarrow PhCOMe + Me^{\bullet} \qquad (26)$$

With cumene hydroperoxide and the mono-iron and di-iron catalysts acetophenone is formed [reaction (26)] in a yield roughly comparable to the yield of the products derived from cyclooctane *via* reaction (27), see Table 4. This result is consistent with the expected fate of the cumyloxyl radical under normal conditions, *viz.*, $k_{26}$ ($= 6.3 \times 10^5\ s^{-1}$) ≈ $k_{27}$ [$c$-$C_8H_{16}$] ($= 2.7 \times 10^6\ M^{-1}\ s^{-1} \times 0.64\ M = 1.7 \times 10^6\ s^{-1}$).[26]

$$PhCMe_2O^{\bullet} + c\text{-}C_8H_{16} \longrightarrow PhCMe_2OH + c\text{-}C_8H_{15}^{\bullet} \qquad (27)$$

## Discussion

### The effect of dimethyl sulfide

The product yields and profiles found by Que and co-workers in the experiments in which dimethyl sulfide was added led them to conclude that the species responsible for peroxide formation was not the same as the species responsible for alcohol and ketone formation.[11a,c,d] By analogy with the work of Labeque and Marnett[31] (*vide supra*) it was concluded that the mixed peroxide was formed in a radical–radical reaction, [reaction (10) or (28)] because radicals ‘would not react with $Me_2S$’.[11d]

$$c\text{-}C_6H_{11}OO^{\bullet} + Me_3COO^{\bullet} \longrightarrow c\text{-}C_6H_{11}OOCMe_3 + O_2 \qquad (10)$$

$$c\text{-}C_6H_{11}^{\bullet} + Me_3COO^{\bullet} \longrightarrow c\text{-}C_6H_{11}OOCMe_3 \qquad (28)$$

The alcohol was assumed to be formed from an $Fe^V$=O species *via* a Groves-type of oxygen-rebound mechanism since the active reagent would be destroyed by $Me_2S$ [reaction (20)]. The mechanism of ketone formation was undefined, but it was demonstrated that it was not produced to any significant extent by the further oxidation of ‘free’ alcohol, a result we have fully confirmed.

There is an alternative explanation for the effect of $Me_2S$. It occurred to us that the $Me_2S$ might simply function as an inhibitor of the mono- and di-iron catalysed decompositions of *tert*-butyl hydroperoxide to form *tert*-butoxyl radicals because it coordinated to the iron in these catalysts. That there is at least a weak interaction was demonstrated by showing that the UV–VIS spectra of the catalysts changed upon addition of $Me_2S$. If reaction (4) was inhibited then fewer *tert*-butoxyl radicals would be formed and not only would the overall product yield be reduced (as we observe) but, more importantly, the different distribution of products found in the presence of $Me_2S$ can readily be explained. This explanation becomes clearer once it is recognized that under the standard experimental conditions originally chosen (and hence used also by us), the *tert*-butoxyl radicals generated in reaction (4) partition almost exactly equally between hydrogen atom abstraction from cyclohexane [reaction (7)] and hydrogen atom abstraction from *tert*-butyl hydroperoxide [reaction (6)]. That is, in acetonitrile at ambient temperatures $k_7\ [C_6H_{12}] = 1.2 \times 10^6\ M^{-1}\ s^{-1}$[27,30] $\times 0.77\ M = 9.2 \times 10^5\ s^{-1}$ and $k_6\ [Me_3COOH] = 8.7 \times 10^6\ M^{-1}\ s^{-1}$[30,42] $\times 0.1\ M = 8.7 \times 10^5\ s^{-1}$. Thus, cyclohexyl and *tert*-butylperoxyl

**Table 4** Products identified after 2 h of oxidation of cyclooctane (0.64 M) by CH (85.4 M) and $[\text{Fe}^{\text{III}}\text{Cl}_2(\text{TPA})]\text{BF}_4$ (0.61 mM) or $[\text{Fe}_2^{\text{III}}\text{-}(\text{TPA})_2\text{O}(\text{OAc})](\text{BF}_4)_3$ (0.61 mM) in acetonitrile at 25 °C[a]

| Conditions[b] (catalyst) | PhCOMe | $\text{C}_8\text{H}_{15}\text{Cl}$ | $\text{C}_8\text{H}_{15}\text{OH}$ | $\text{C}_8\text{H}_{14}\text{O}$ | $\text{C}_8\text{H}_{15}\text{OOCMe}_2\text{Ph}$ | Σ Prod |
|---|---|---|---|---|---|---|
| Ar ($\text{Fe}^{\text{III}}$) | 7.4 | 2.3 | 4.1 | 4.0 | 9.5 | 27.3 |
| PAr ($\text{Fe}^{\text{III}}$) | 5.8 | 1.4 | 1.4 | 4.4 | 8.9 | 21.9 |
| Ar ($\text{Fe}_2^{\text{III}}$) | 2.3 | — | 0.2 | 0.6 | 10.7 | 13.8 |
| PAr ($\text{Fe}_2^{\text{III}}$) | 4.6 | — | 0.9 | 1.2 | 9.2 | 15.9 |

[a] Product yields are given in equivalents relative to catalyst. [b] See footnote *b* in Table 2.

radicals are formed (fortuitously) at essentially equal rates. The bimolecular self-reaction of cyclohexyl radicals [reaction (29)]

$$2\,\text{c-C}_6\text{H}_{11}^{\bullet} \longrightarrow (\text{c-C}_6\text{H}_{11})_2 + (\text{c-C}_6\text{H}_{12} + \text{c-C}_6\text{H}_{10}) \qquad (29)$$

occurs at, or close to, the diffusion-controlled limit (*e.g.* $2k_{29}^{295\,\text{K}} \approx 2.4 \times 10^9\ \text{M}^{-1}\ \text{s}^{-1}$ in cyclohexane),[43] whereas the bimolecular self-reaction of *tert*-butylperoxyl radicals [reactions (5) and (30)] is an extremely slow radical–radical reaction

$$2\,\text{Me}_3\text{COO}^{\bullet} \longrightarrow \text{Me}_3\text{COOCMe}_3 + \text{O}_2 \qquad (30)$$

(*e.g.* $2k_5^{303\,\text{K}} \approx 4 \times 10^3\ \text{M}^{-1}\ \text{s}^{-1}$ and $2k_{30}^{303\,\text{K}} \approx 4 \times 10^2\ \text{M}^{-1}\ \text{s}^{-1}$ in cumene[44a] and $\text{CCl}_4$[23d,44b]). In those chemical circumstances in which two radicals are generated at equal rates and one of these radicals is transient (*i.e.* undergoes a fast bimolecular self-reaction)[45] and the other is persistent (*i.e.* undergoes a slow bimolecular self-reaction)[45] the Ingold–Fischer 'Persistent Radical Effect'[46] dominates product formation and the major product(s) will be formed in the cross-reaction between the transient and persistent radicals. That is, in the present case, the *tert*-butylperoxyl radicals build up rapidly to a relatively high steady-state concentration and trap most of the cyclohexyl radicals that are generated, *i.e.* reaction (28) dominates product formation. Of course, eventually sufficient oxygen has been produced *via* the bimolecular self-reactions of *tert*-butylperoxyl radicals [reactions (5) and (30)] that trapping of cyclohexyl radicals by oxygen [reaction (8)] becomes competitive and eventually dominates their trapping by *tert*-butylperoxyl radicals. As indicated in Scheme 1, this does not mean that cyclohexyl *tert*-butyl peroxide formation would necessarily cease since some could be and is formed *via* the cross-peroxyl radical reaction [reaction (10), *vide supra*]. However, what it does mean is that an increasing fraction of the cyclohexyl radicals generated will go on to yield alcohol and ketone[49] [reaction (9)] and, in the case of the mono-iron catalyst, chloride [reaction (11) or (16)]. These ideas were tested by carrying out reactions with reduced quantities of $\text{Me}_3\text{COOH}$ and also by adding the $\text{Me}_3\text{COOH}$ slowly to the other reactants *via* a syringe pump so as to reduce the amount of dioxygen generated during the reaction. Using the mono-iron catalyst, the only products observed with 10 and 1 equiv. of $\text{Me}_3\text{COOH}$ were the mixed peroxide and chloride, while experiments with the di-iron catalyst and a slow addition of 140 equiv. of $\text{Me}_3\text{COOH}$ clearly showed a higher ratio of mixed peroxide to alcohol plus ketone compared with the normal 'all in at once' procedure (see Supplementary Material). Thus, we conclude that the effect of dimethyl sulfide on these iron–$\text{Me}_3\text{COOH}$-catalysed reactions is simply to reduce the activity of the iron catalyst (*i.e.* the rate of initiation) and hence reduce the overall product yield at a fixed time relative to the yield at the same time in the absence of $\text{Me}_2\text{S}$. There is no experimental justification for more complex explanations. Furthermore, there is a literature precedent for the conversion of sulfides to sulfoxides in the presence of $\text{Me}_3\text{COOH}$ under free radical conditions.[50]

## Mechanistic conclusions

Our results demonstrate conclusively that at least the majority (and possibly all) of the products formed under standard Que conditions, *viz.* cycloalkane : hydroperoxide : mono- or di-iron catalyst at *ca.* 1000 : 140 : 1 (equiv.) in dry acetonitrile at room temperature, derive from the alkoxyl radical formed from the hydroperoxide. It is worth noting at this point that we have reached exactly the same conclusion in recent studies of a branch of D. H. R. Barton's 'Gif chemistry'.[4,51] The system we investigated (christened $\text{GoAgg}^{\text{V}}$) involved the oxidation of cycloalkanes (0.142 M) in pyridine–acetic acid (10 : 1, v/v) by $\text{Fe}^{\text{III}}$ nitrate (0.0142 M), *tert*-butyl hydroperoxide (0.284 M) and picolinic acid (0.0426 M).[52] These oxidations had also been supposed to proceed by a high valent iron-oxo intermediate.[4,52] However, when we replaced the $\text{Me}_3\text{COOH}$ by MPPH, or *o*-MCH or CH it was obvious that the reaction actually involved alkoxyl radicals derived from the *tert*-alkyl hydroperoxides.[51]

In iron-TPA chemistry, four main arguments have been used in favour of alkane oxidation occurring *via* a high-valent iron-oxo species,[11a–d] *viz.* (*i*) the lack of effect of BHT on the products, (*ii*) the effect of $\text{Me}_2\text{S}$ on the products, (*iii*) the fact that the precise product profile differs from catalyst to catalyst, and (*iv*) $\text{c-C}_6\text{H}_{12}/\text{c-C}_6\text{D}_{12}$ deuterium kinetic isotope effects based on identified products are $> 5$. We have demonstrated that argument (*i*) is invalid because the concentration of BHT employed was insufficient for it to have any effect on the products (*vide supra* and ref. 19). In the present work we have demonstrated that argument (*ii*) is invalid because the $\text{Me}_2\text{S}$ appears to do nothing more than reduce the rate of the overall reaction and this change in rate is generally sufficient to change the product profile measured after a fixed reaction time. (Specifically, the major initial product would appear to be the mixed peroxide which is formed *via* reaction (28) as a consequence of the Ingold–Fischer 'Persistent Radical Effect.[46]) Our results also show that argument (*iii*) is not very persuasive. That is, even when duplicate experiments were carried out by the same investigator at the same time and with the same batch of catalyst, our product profiles measured after a fixed time interval varied quite substantially and this variation became even more substantial when different batches of (nominally) the same catalyst were employed. This is a well known characteristic of autocatalytic free radical reactions and it indicates nothing more than that apparently identical initial experimental conditions are never truly identical. Thus, the fact that different iron–TPA complexes appear to have (at least, initially) slightly different catalytic activities should not be taken as evidence that alkane oxidation occurs *via* slightly different high valent iron-oxo species.[53] Finally, mechanistic conclusions derived from isotope effects based on identified products rely on the assumption that all products in the reaction have been identified and that a specific product (*e.g.* alcohol) accurately reflects the relative rates of hydrogen and deuterium atom abstraction from $\text{C}_6\text{H}_{12}$ and $\text{C}_6\text{D}_{12}$.

None of the foregoing is intended to imply that high valent iron-oxo species and alkylperoxyiron(III) species are not formed in any of these systems.[55] Indeed, a *tert*-butylperoxyiron(III) intermediate has been generated from $\text{Fe}_2^{\text{III}}(\text{TPA})_2\text{O}(\text{H}_2\text{O})_2]^{4+}$[11e,f] and *tert*-butyl hydroperoxide at −40 °C.[60c] However, we maintain that under the standard conditions originally chosen by Que and used by us, the observed products can be properly accounted for in terms of the chemistries undergone by alkoxyl radicals produced by the normal metal-catalysed decomposition of the *tert*-alkyl hydroperoxides. This applies to our three probe hydroperoxides, MPPH, *o*-MCH and CH, and also to *tert*-butyl hydroperoxide as we demonstrated with our no iron, BONNOB-initiated reactions. We tentatively suggest that the initiation of iron–TPA chemistry involves the formation of an alkylperoxyiron(III) species which slowly undergoes homolytic scission of the O–O bond [reaction (19)]. However, the high valent iron(IV)-oxo species which is formed in reaction (19) is not kinetically competitive with the chemistry induced by the simultaneously formed alkoxyl radical. That is, the iron(IV)-oxo species does not form identifiable oxidation products in significant yields. We further suggest that the principal fate of the iron(IV)-oxo species is oxidation of the alkyl hydroperoxide to form peroxyl radicals and return the catalyst to its original iron(III) state [reaction (31)]. In this connection, we note that not only will reaction (31) be *ca.* 10 kcal mol$^{-1}$[||] more exothermic than the putative reaction (32) but also, hydrogen atom

$$\mathrm{Fe^{IV}{=}O + ROOH \longrightarrow Fe^{III}{-}OH + ROO^{\bullet}} \qquad (31)$$

$$\mathrm{Fe^{IV}{=}O + c\text{-}C_{\mathit{n}}H_{2\mathit{n}} \longrightarrow Fe^{III}{-}OH + c\text{-}C_{\mathit{n}}H_{2\mathit{n}-1}^{\bullet}} \qquad (32)$$

abstraction by oxygen-centred reactive intermediates is a great deal more facile from an O–H group than from a C–H group for compounds having equal O–H and C–H bond strengths.[68] Furthermore, oxo-iron(IV) porphyrins, generated from the iron(III) porphyrin and $Me_3COOH$, can abstract phenolic hydrogen atoms, but are unable to oxidize unactivated alkanes.[69]

## Conclusions

The present paper provides additional support for a perceptive and italicized sentence in Meunier's comprehensive review of catalysis by metalloporphyrins, *viz.*,[7] '*All these data strongly suggest that many hydroxylation reactions with alkyl hydroperoxides in the presence of transition-metal complexes are not due to a metal-centred active species, but to a free-radical process initiated by RO$^{\bullet}$*'. We urge all investigators who would like to claim that *tert*-butyl hydroperoxide-derived high-valent metal-oxo species are the effective oxidizing agents in their systems to check that the mechanistic probe hydroperoxides we have described yield the same results as *tert*-butyl hydroperoxide before they draw any mechanistic conclusions.

## Experimental

### Materials

$[Fe^{III}Cl_2(TPA)]^{+}$[11c] and $[Fe^{III}_2(TPA)_2O(OAc)]^{3+}$[70] (both as the tetrafluoroborate and perchlorate salts), di-*tert*-butyl hyponitrite (BONNOB),[71] 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH),[72] *o*-methylcumyl hydroperoxide (*o*-MCH)[39] and the mixed peroxides[73] were all prepared according to the referenced literature procedures. All other chemicals were commercially available and were used as received with three exceptions. $Me_3COOH$ (90%; Aldrich) was extracted into diethyl ether and dried with sodium sulfate. Acetonitrile (Omnisolve) was distilled prior to use. Dicumyl peroxide (Aldrich) was recrystallised from methanol. $^{18}O_2$ was obtained by electrolysing $H_2{}^{18}O$ (97.1%; Merck, Sharp and Dohme Isotopes) with 0.2 M $Na^{18}OH$ as the electrolyte (made by dissolving Na metal in $H_2{}^{18}O$). The U-tube in which the electrolysis was carried out was cooled to 0 °C and the exit gas outlet cooled with dry ice to prevent water vapour from entering the reaction mixture.

### Instrumentation

UV–VIS spectra were recorded on a Varian Cary 3 spectrophotometer. $^1H$ NMR spectra were recorded on a Bruker AM200 spectrometer. GC analyses were performed on a Hewlett Packard 5890 gas chromatograph using an HP methyl silicone column. The data analyses were performed using a Hewlett Packard chemstation. For GC–MS an HP 5790 GC attached to a 5970 A Series mass selective detector was employed. Liquid chromatography was carried out on an HP 1090 liquid chromatograph equipped with a reverse phase ODS Hypersil column using a methanol–water solvent system. LC–MS analyses were performed on an HP 5980 A GC/1090 HPLC MS operated in the thermospray mode. Syringe pump experiments were accomplished using a Sage Instruments 341A syringe pump. The laser flash photolysis apparatus has been described in detail elsewhere.[74]

### Cycloalkane oxidations

In a typical cyclooctane reaction, the hydrocarbon was added to a solution of the catalyst in acetonitrile, and this solution was then purged with Argon for 10 min. In the case of cyclohexane, a known volume of deoxygenated cyclohexane was added to a prepurged acetonitrile solution of the catalyst. The reaction was started by addition of the hydroperoxide. In experiments involving dimethyl sulfide, a known volume of $Me_2S$ was added to the catalyst–cycloalkane solution prior to the addition of the hydroperoxide. For the reaction under $^{18}O_2$, the reaction mixture was purged with $^{18}O_2$ at a rate of 1.2 ml min$^{-1}$ for 20 min prior to, and 5 min following, the addition of $Me_3COOH$. Reactions were generally stopped by quenching with an equal volume of aqueous $Na_2SO_4$ (0.1 M). The resultant solutions were extracted with diethyl ether, the internal standard was added, the ether was dried with anhydrous $Na_2SO_4$, and the products were then analysed by GC and GC–MS. In the experiments involving dimethyl sulfide a different procedure was followed. The reactions were quenched by the addition of excess triphenylphosphine which rapidly and quantitatively converts all the remaining *tert*-butyl hydroperoxide to the corresponding alcohol. This was followed by direct analysis by GC and GC–MS. For the experiments in which MPPH, *o*-MCH and CH replaced $Me_3COOH$ the ethereal solution was divided into two with one part being analysed by LC and LC–MS for the mixed peroxides (authentic standards were used for the MPPH and CH reactions). $Ph_3P$ was added to the remaining part (to convert hydroperoxide to alcohol) and this was followed by GC and GC–MS analysis. For the BONNOB initiated reactions the experimental conditions and work-up procedure were kept the same as above except that the reaction vessel was kept at 34 °C in a thermostatted water bath for the duration of the experiment (3 days).

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[||] 1 cal = 4.184 J.

2 *Cytochrome P-450*: *Structure*, *Mechanism and Biochemistry*, ed. P. R. Ortiz de Montellano, Plenum Press, New York, 1986.

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12 J. T. Groves, G. A. McClusky, R. E. White and M. J. Coon, *Biochem. Biophys. Res. Commun.*, 1978, **81**, 154.

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14 See, *e.g.* P. D. Bartlett and G. Guaraldi, *J. Am. Chem. Soc.*, 1967, **89**, 4799.

15 10-Hydroperoxyoctadeca-8,12-dienoic acid has previously been employed as a mechanistic probe in systems of biochemical interest.[10a,e,f]

16 Based on the ratio of the rate constants for H-atom abstraction from cyclopentane, $k_H$, to β-scission, $k_{14}$, using $PhCH_2CMe_2O^{\bullet}$ radicals generated from the hyponitrite at 40 °C, *viz.*,[17] $k_H/k_{14} = 0.004\ \text{M}^{-1}$ 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 $Me_3CO^{\bullet}$ radicals at room temperature.[18] A 266 nm LFP experiment with MPPH in $CH_3CN$ showed 'instantaneous' formation of the benzyl radical, which confirms that reaction (14) is very fast, *i.e.* $k_{14} \geq 2 \times 10^7\ \text{s}^{-1}$.

17 C. Walling and J. A. McGuiness, *J. Am. Chem. Soc.*, 1969, **91**, 2053.

18 H. Paul, R. D. Small, Jr., and J. C. Scaiano, *J. Am. Chem. Soc.*, 1978, **100**, 4520.

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20 We thank Professor D. H. R. Barton for this suggestion.

21 We consider it extremely probable that variable initiation rates are a feature of the different catalysts employed by Que and co-workers[11] and that this factor is, at least in part, responsible for the (rather minor) differences in product ratios found after reaction for specific lengths of time with different catalysts.

22 The initial sole source of $O_2$ is, of course, the $Me_3CO^{\bullet}$ radical-induced chain decomposition of $Me_3COOH$.[23]

23 (*a*) R. Hiatt, J. Clipsham and T. Visser, *Can. J. Chem.*, 1964, **42**, 2754; (*b*) A. Factor, C. A. Russell and T. G. Traylor, *J. Am. Chem. Soc.*, 1965, **87**, 3692; (*c*) J. R. Thomas, *J. Am. Chem. Soc.*, 1965, **87**, 3935; (*d*) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, 1969, **47**, 3797.

24 Professor Cheves Walling has suggested to us that another potential source of ketone is the reaction of the secondary hydroperoxide (formed in the exchange reaction: c-$C_nH_{2n-1}OO^{\bullet} + Me_3COOH \longleftarrow$ c-$C_nH_{2n-1}OOH + Me_3COO^{\bullet}$) with the iron(III) catalyst to form an alkylperoxyl iron(III) complex which decomposes to yield ketone: c-$C_nH_{2n-1}OO(Fe^{III}) \longrightarrow$ c-$C_nH_{2n-2}O + HO(Fe^{III})$. Analogous reactions had previously been suggested for secondary alkyl peroxy-iron(III) porphyrin complexes, see: R. D. Arasingham, A. L. Balch, C. R. Cornman and L. Latos-Grazynski, *J. Am. Chem. Soc.*, 1989, **111**, 4357.

25 C. Walling, *Acc. Chem. Res.*, 1975, **8**, 125.

26 See ref. 22, in ref. 19.

27 D. V. Avila, C. E. Brown, K. U. Ingold and J. Lusztyk, *J. Am. Chem. Soc.*, 1993, **115**, 466.

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29 Measured (by Dr P. Mulder) by monitoring the growth of phenoxyl radical following laser flash photolysis of $Me_3COOCMe_3$ and BHT in MeCN.

30 We assume that $Me_3CO^{\bullet}$ and $PhCMe_2O^{\bullet}$ abstract hydrogen from cyclohexane at essentially the same rate.

31 R. Labeque and L. J. Marnett, *J. Am. Chem. Soc.*, 1989, **111**, 6621.

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33 H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 1966, 6163.

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35 (*a*) J. K. Kochi, *Tetrahedron*, 1962, **18**, 483; (*b*) J. K. Kochi and H. E. Mains, *J. Org. Chem.*, 1965, **30**, 1862. In much later work, Kochi apparently abandoned the idea that mixed peroxides were formed *via* ligand transfer and favoured, instead, $R^{\bullet} + Me_3COO^{\bullet}$ coupling, *cf*. reaction (28), *vide infra*, see: K. Srinavasan, S. Perrier and J. K. Kochi, *J. Mol. Catal.*, 1986, **38**, 297.

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38 (*a*) F. Minisci, F. Fontana, S. Areneo, F. Recupero, S. Banfi and S. Quici, *J. Am. Chem. Soc.*, 1995, **117**, 226. This paper provides some very interesting new insights into the Kharasch[36] synthesis of mixed peroxides; (*b*) F. Minisci, F. Fontana, S. Araneo and F. Recupero, *J. Chem. Soc., Chem. Commun.*, 1994, 1823; (*c*) F. Minisci, F. Fontana, S. Araneo, F. Recupero and L. Zhao, *Synlett*, 1996, **2**, 119.

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50 L. Bateman and K. R. Hargrave, *Proc. R. Soc. London, A*, 1954, **224**, 399.

51 D. W. Snelgrove, P. A. MacFaul, K. U. Ingold and D. D. M. Wayner, *Tetrahedron Lett.*, 1996, **37**, 823.

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