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Kharasch and Metalloporphyrin Catalysis in the Functionalization of Alkanes, Alkenes, and Alkylbenzenes by t-BuOOH. Free Radical Mechanisms, Solvent Effect, and Relationship with the Gif Reaction[†]

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Abstract: New results for the oxidation of alkanes, alkenes, and alkylbenzenes by t-BuOOH according to the Kharasch reaction and Mn(III)− and Fe(III)−porphyrin catalysis are reported. Chemical and kinetic evidence show the role of t-BuO$^{\bullet}$ and t-BuOO$^{\bullet}$ radicals in these oxidations and the strict relationship with the Gif reaction, for which recently a free-radical mechanism has been emphasized in contrast with the Barton interpretation. A key step appears to be the hydrogen abstraction from t-BuOOH by t-BuO$^{\bullet}$, very fast in nonbasic solvents, but inhibited by solvents which form hydrogen bonds with t-BuOOH. As a consequence, the generally accepted Kochi mechanism of the Kharasch reaction must be modified, and the similar mechanistic features of the three types of catalysis (Kharasch, metalloporphyrins, and Gif) are discussed.

Introduction

The metalloporphyrins play an important role among the metal complexes utilized as catalysts in the oxidation of organic compounds, as they can be considered good models of heme-containing enzymes, which are able to catalyze various oxidation reactions. This research field, inspired by studies on the activity of cytochrome P-450, was opened with the purpose of mimicking the enzyme-mediated reactions, to realize processes having the so-called "biomimetic flavor"; for the reactivity of the porphyrinic systems several mechanisms have been suggested, which are often contrasting and remain speculative.[1] Particularly for the oxidation of alkanes, the possibility of two alternatives has been debated: either the insertion of Fe═O and Mn═O complexes on the C−H bonds, with the intermediate formation of metal−carbon bonds, similar to the mechanism suggested by Barton for the Gif reaction,[2] or free-radical mechanisms. The most recent interpretation of the latter, generally referred to as "oxygen rebound", involves hydrogen abstraction from the alkane by a Fe(V)═O complex, followed by rapid transfer of OH$^{\bullet}$ to the resulting alkyl radical. A very high "oxygen rebound" rate constant ($k \sim 10^{10}$ s^{-1}) has been evaluated[3] for cytochrome P-450, but more traditional free-radical reactions could be involved with synthetic metalloporphyrins, even if in a number of cases the mechanism would appear to be similar to that of natural systems.[1]

In this paper we report new synthetic developments and chemical and kinetic evidences showing the involvement of t-BuO$^{\bullet}$ and t-BuOO$^{\bullet}$ radicals in the oxidation of alkanes, alkenes, and alkylbenzenes catalyzed by Fe(III)− or Mn(III)−porphyrins by t-BuOOH. Results indicate a strict relationship of these oxidations with the Gif reaction,[2] for which a free-radical mechanism has been recently suggested by us[4] in contrast with the Barton interpretation. Moreover, we show that the classical Kharasch synthesis of mixed peroxides,[5] catalyzed by transition metal salts, also has a close resemblance with both Gif and metalloporphyrin catalysis and its mechanism, suggested by Kochi[6] and generally accepted, must be modified in view of the new results and the solvent effect reported in this paper.

Results and Discussion

Kharasch Synthesis. The stoichiometry of the Kharasch reaction[5] is shown by eq 1, which is identical to that obtained by us[4c] under Gif conditions.

$$\mathrm{RH + 2R'OOH \xrightarrow{M^{n+}} ROOR' + R'OH + H_2O} \qquad (1)$$

The mechanism suggested by Kochi[6] for M = Cu involves the redox chain of Scheme 1.

Scheme 1

$$\mathrm{Cu(II)OH + R'OOH \rightarrow Cu(II)OOR' + H_2O}$$

$$\mathrm{Cu(I) + R'OOH \rightarrow Cu(II)OH + R'O^{\bullet}}$$

$$\mathrm{R'O^{\bullet} + HR \rightarrow R'OH \rightarrow R^{\bullet}}$$

$$\mathrm{R^{\bullet} + Cu(II)OOR' \rightarrow ROOR' + Cu(I)}$$

[†] Dedicated to Prof. Fernando Montanari on the occasion of his 70th birthday.

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Table 1. Relative Rates for the Kharasch Reaction

$$\mathrm{RH\ (R'H) + 2t\text{-}BuOOH \rightarrow ROOBu\text{-}t\ (R'OOBu\text{-}t) + t\text{-}BuOH + H_2O}$$

RH (mmol)	R′H (mmol)	ROOBu-t (%)	R′OOBu-t (%)	RH/R′H
toluene (1)	cyclohexane[a] (1)	>99	<1	>100
cumene (1)	cyclohexane[a] (1)	>99	<1	>100
cyclohexene (1)	cyclohexane[a] (10)	>99	<1	>100
cumene (1)	toluene (1)	88.2	11.8	7.5
cumene (1)	toluene (2)	78.5	21.5	7.3
cumene (1)	toluene (5)	58.2	41.8	7.0
cyclohexene (1)	cumene (1)	68.4	32.6	2.1
cyclohexene (1)	cumene (2)	57.5	42.5	2.7
p-cymene[b] (1)	toluene (5)	54.5	39.5	9.1[b]

[a] Traces (<1%) of cyclohexanol, cyclohexanone, and cyclohexyl *tert*-butyl peroxide are formed. [b] 7% of i-$\mathrm{PrC_6H_4CH_2OOBu}$-t is also formed, in addition to 54.5% of $\mathrm{MeC_6H_4CMe_2OOBu}$-t.

A similar mechanism has been suggested by us [4c] for the Gif reaction in contrast with the Barton interpretation,[7] which does not involve free radicals.

The facts, however, that the Kharasch reaction occurs with C−H bonds activated by enthalpic effects (allylic, benzilic, α-cyano, and α-keto C−H bonds) and/or polar effects (α-amino and α-oxy C−H bonds), while the Gif reaction also takes place with unactivated alkanes, caused us to wonder about the nature of the actual hydrogen abstracting species, particularly when taking into account the high reactivity and selectivity of t-BuO$^\bullet$ radical in hydrogen abstraction ($k = 2.3 \times 10^5$, 8.7×10^5, and 5.7×10^6 $\mathrm{M^{-1}\ s^{-1}}$ at 22 °C respectively for toluene, cumene, and cyclohexene and 1.6×10^6 $\mathrm{M^{-1}\ s^{-1}}$ at 27 °C for cyclohexane).[8] Toluene and cumene appear to be less reactive than cyclohexane in spite of the lower energies of the C−H bonds, implying a prevalence of the polar effect over the enthalpic effect. The selectivity of oxidation observed in the Gif reaction[4] is in good agreement with these rate constants. We have, however, observed that cyclohexane is hardly reactive in the Kharasch reaction. Competitive reactions of cyclohexane with toluene and cumene by t-BuOOH lead to the substantial peroxidation of the alkylbenzenes with only traces of oxidation products of cyclohexane (<1% cyclohexanol, cyclohexanone, and cyclohexyl *tert*-butyl peroxide). Similarly, cyclohexene is 3−4 times more reactive than cyclohexane towards t-BuO$^\bullet$ radical;[8] again, we have observed that these relative rates are followed by the Gif reaction,[4] while competitive kinetics have shown that cyclohexene is >100 times more reactive than cyclohexane in the Kharasch reaction. Competitions between toluene and cyclohexene, toluene and cumene, toluene and *p*-cymene, and cyclohexene and cumene show a reactivity sequence cyclohexene > cumene > toluene, while the tertiary benzylic hydrogen in *p*-cymene is somewhat more reactive than the corresponding one in cumene (Table 1); this selectivity, too, is higher than that expected from the t-BuO$^\bullet$ radical as the hydrogen abstracting species; similarly, the regioselectivity with *p*-cymene is higher than that expected from the t-BuO$^\bullet$ radical.

All these results clearly suggest that the Gif and Kharasch reactions, apparently identical (the same stoichiometry, shown by eq 1, and the same suggested mechanism, Scheme 1), are actually quite different for what concerns the selectivities; above all, t-BuO$^\bullet$ radical cannot be the hydrogen abstracting species in the Kharasch reaction according to the Kochi mechanism (Scheme 1), but a species much more sensitive to the energy of C−H bonds must be involved.

Table 2. Reaction of Styrene and α-Methylstyrene with t-BuOOH in the Kharasch Process[9]

alkene	solvent	**5** (%)	**6** (%)	**7** (%)	**8** (%)	**9** (%)
α-methylstyrene	benzene	85.3	9.9	3.9		0.9
α-methylstyrene	none	53.3	12.4	8.2	traces	26.1
α-methylstyrene	pyridine (1 mmol)	28.1	7.2	22.5		42.2
α-methylstyrene	pyridine (5 mmol)	20.1	21.9		4.8	53.2
α-methylstyrene	pyridine (3 mL) + AcOH (0.3 mL)			5.1	11.7	83.2
α-methylstyrene	t-BuOH	51.2	10.2	0.7	24.1	13.8
α-methylstyrene[b]	t-BuOH	64.3	9.1	0.5	21.5	4.6
α-methylstyrene	t-BuOH (10 mL) + pyridine (2 mL)	7.3	4.1		39.5	49.1
α-methylstyrene[c]	benzene	90.2	9.8			

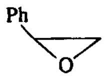
alkene	solvent	**1** (%)	**2** (%)	**3** (%)	**4** (%)
styrene	benzene	68.5	8.9	21.4	1.2

[a] 80−90% yields based on the reacted alkene; 30−40% conversion of alkene based on t-BuOOH. [b] In refluxing t-BuOH. [c] AIBN was utilized in the absence of metal salt; 15% conversion of α-methylstyrene, based on t-BuOOH.

A further evidence of this difference comes from the behavior of adamantane in the Gif and Kharasch oxidation; the Gif oxidation by t-BuOOH gives an overall ratio of attack $C^3/C^2 = 0.9$, considering all the reaction products (1- and 2-adamantanol, adamantanone, and adamantylpyridines), which induced Barton to exclude the involvement of free radicals in the oxidation,[2] while the Kharasch reaction gives a C^3/C^2 ratio of 3.7 (1- and 2-adamantanol, adamantanone, and 1-adamantyl-*tert*-butyl hydroperoxide), as indicated in the Experimental Section. Again the chlorination of adamantane by t-BuOCl, in which t-BuO$^\bullet$ radical is mainly the hydrogen abstracting species, gives a C^3/C^2 ratio = 0.9, supporting the free-radical mechanism of Scheme 1 for the Gif reaction, but not for the Kharasch reaction.

The paradox is that what appeared to be a generally accepted mechanism (the Kochi mechanism of the Kharasch reaction) is not consistent with these results, whereas the Gif reaction, for which a great effort has been done to show its nonradical nature, fits very well in a free-radical mechanism similar to that of Scheme 1.

In order to identify the hydrogen abstracting radical species in the Kharasch reaction, we have investigated the behavior of styrene and α-methylstyrene with t-BuOOH: compounds **1−9** are formed.



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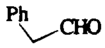

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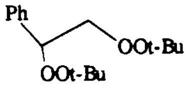

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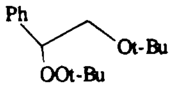

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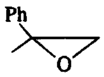

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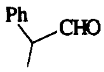

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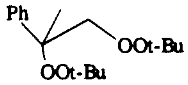

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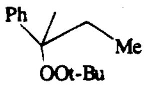

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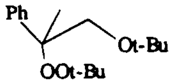

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The ratios among compounds **1−4**, as well as **5−9**, are strictly dependent on the solvent utilized; a careful investigation has been carried out with α-methylstyrene (Table 2). In the absence of solvent (Kharasch procedure) products **5−9** are all formed,

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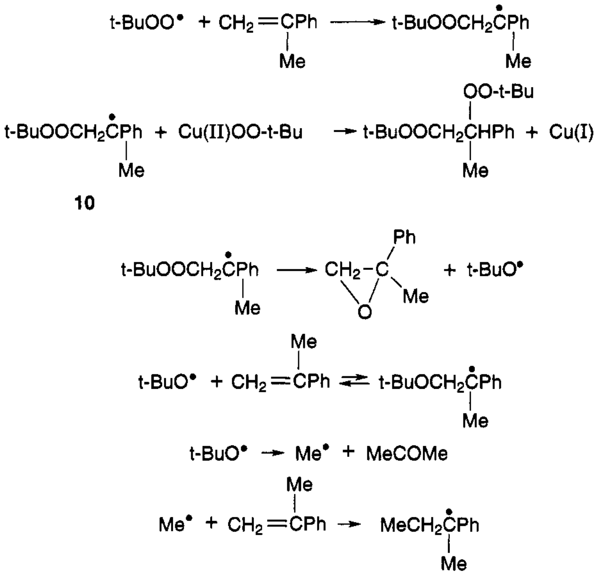
with a predominance of **5** and **6**, but with significant amounts of **9**; if pyridine is added to the reaction mixture, **9** becomes the main reaction product, as we had already observed in the Gif reaction. In benzene solution **5** is practically the only reaction product, with just traces of **6**–**9**, and the reaction is useful for the synthesis of the epoxide. In t-BuOH solution at 60 °C the amounts of **8** and **9** increase, while in refluxing t-BuOH **8** further increases, but **9** decreases.

The formation of **3** and **7** suggests that t-BuOO˙ radical is an intermediate of the reaction (eqs 2 and 3). The formation of products **1**–**9** is explained by reactions 2–7. **1** and **5** would be generated by the fission of the radical adduct **10** (eq 4). The aldehydes **2** and **6** would be formed by the known rearrangement of the corresponding epoxides, and **4** and **9** would be generated by addition of t-BuO˙ radical to the alkene (eq 5), followed by ligand-transfer oxidation as in eq 3.



$$\text{t-BuOO}^\bullet + \text{CH}_2{=}\underset{\text{Me}}{\text{CPh}} \longrightarrow \text{t-BuOOCH}_2\underset{\text{Me}}{\overset{\bullet}{\text{C}}}\text{Ph} \qquad (2)$$

$$\text{t-BuOOCH}_2\underset{\text{Me}}{\overset{\bullet}{\text{C}}}\text{Ph} + \text{Cu(II)OO-t-Bu} \longrightarrow \text{t-BuOOCH}_2\underset{\text{Me}}{\overset{\text{OO-t-Bu}}{\text{C}}}\text{HPh} + \text{Cu(I)} \qquad (3)$$

10

$$\text{t-BuOOCH}_2\underset{\text{Me}}{\overset{\bullet}{\text{C}}}\text{Ph} \longrightarrow \text{CH}_2\text{–C(Ph)(Me)–O (epoxide)} + \text{t-BuO}^\bullet \qquad (4)$$

$$\text{t-BuO}^\bullet + \text{CH}_2{=}\overset{\text{Me}}{\text{C}}\text{Ph} \rightleftharpoons \text{t-BuOCH}_2\underset{\text{Me}}{\overset{\bullet}{\text{C}}}\text{Ph} \qquad (5)$$

$$\text{t-BuO}^\bullet \longrightarrow \text{Me}^\bullet + \text{MeCOMe} \qquad (6)$$

$$\text{Me}^\bullet + \text{CH}_2{=}\overset{\text{Me}}{\text{C}}\text{Ph} \longrightarrow \text{MeCH}_2\underset{\text{Me}}{\overset{\bullet}{\text{C}}}\text{Ph} \qquad (7)$$

A reasonable explanation for the formation of **8** is provided by the β-scission of t-BuO˙ (eq 6), followed by addition of the methyl radical to the double bond (eq 7) and by ligand-transfer oxidation of the radical adduct, as in eq 3.

Now the question arises about how t-BuOO˙ is formed; in principle, it could be generated by the oxidation of t-BuOOH by Cu(II) salt (eq 8) or by hydrogen abstraction by t-BuO˙ radical (eq 9).

$$\text{t-BuOOH} + \text{Cu(II)} \rightarrow \text{t-BuOO}^\bullet + \text{H}^+ + \text{Cu(I)} \qquad (8)$$

$$\text{t-BuO}^\bullet + \text{HOOR} \rightarrow \text{t-BuOH} + {}^\bullet\text{OOR}$$
$$k = 2.5 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1} \text{ at } 22\ ^\circ\text{C} \qquad (9)$$

Reaction 9 appears to be very fast,[9] namely 2–3 orders of magnitude faster than either hydrogen abstraction from C–H bonds[8] or addition to conjugated double bonds,[10] even if the evaluation of the rate constant has been based on just one t-BuOOH concentration, due to the experimental difficulties of the used methodology.[9]

This high rate constant, however, should have as a consequence that the redox decomposition of t-BuOOH by metal salts should rarely involve the reaction of t-BuO˙ radical with C–H or double bonds. This is clearly not the general case: for example, it is not applicable to the Gif reaction[4] and to many other reaction systems involving monoelectronic reduction of hydroperoxides.[11]

Our interpretation is that *the high rate constant of eq 9 only occurs in diluted solution in nonbasic solvents*, which are not able to form hydrogen bonds with the hydroperoxide. *When the hydroperoxide forms hydrogen bonds with the solvent or with other compounds present in reaction medium* (the hydroperoxide can also form hydrogen bonds with itself if its concentration is high enough) *the rate constant would decrease*, allowing the reaction of t-BuO˙ with C–H or double bonds to compete or prevail over reaction 9, depending on the strength of the hydrogen bond.

This interpretation explains all the facts reported above, first of all the substantial difference between the Gif and Kharasch syntheses of mixed peroxides from alkylbenzenes, cyclohexane, and cyclohexene, which are characterized by the same stoichiometry. In the Gif reaction, the strong hydrogen bonds formed by t-BuOOH with pyridine, used as solvent, (evaluated at 8 kcal/mol),[12] greatly lowers the rate constant of eq 9, so that the selectivity is due to the hydrogen abstraction by t-BuO˙ radical from the C–H bonds; this latter reaction has a low selectivity, in agreement with the absolute rate constants of hydrogen abstraction by t-BuO˙ radical. In the Kharasch reaction, characterized by nonbasic solvent, reaction 9 prevails and the hydrogen abstraction from C–H bonds would mainly take place by t-BuOO˙ radical, which is much less reactive and much more selective; thus, the rate constants for hydrogen abstraction by t-BuOO˙ radical have been evaluated[13] as 2.6×10^{-4}, 1.7×10^{-2}, 1.6×10^{-1}, and 3.7×10^{-1} $\text{M}^{-1}\ \text{s}^{-1}$ at 30 °C, respectively, for cyclohexane, toluene, cumene, and cyclohexene; i.e., cyclohexane is more reactive than toluene toward t-BuO˙ radical for polar reasons, while it is 100 times less reactive than toluene toward t-BuOO˙ radical, which is more sensitive to the strength of the C–H bonds.

This interpretation explains even better the behavior of the oxidation of styrenes, which in the Gif reaction mainly gives **4**, **8**, and **9**, generated from eqs 5, 6, and 7, whereas in the Kharasch reaction the products arising from eq 2 are by far prevailing and the addition of pyridine to the reaction medium shifts the composition toward the compound formed from the radical produced via eq 5.

Further support of this interpretation comes from the results in the Kharasch oxidation of α-methylstyrene in t-BuOH solution; the hydrogen bonds formed by this solvent with t-BuOOH are weaker than those formed by pyridine, but the effect is qualitatively similar, with a considerable increase of the amounts of **8** and **9**; if pyridine is added to the solution this trend is further enhanced. Moreover, at higher temperature in t-BuOH solution, the amount of **8** increases, while that of **9** decreases; this occurs, in our opinion, because eq 5 is likely to be reversible and unfavored at higher temperatures, which increase instead the importance of eq 6, also favored by a solvent effect in protic medium.[14] The corresponding reaction (addition of t-BuO˙ radical to the double bond) on styrene is irreversible, so that no methyl derivative is detected with this latter substrate.

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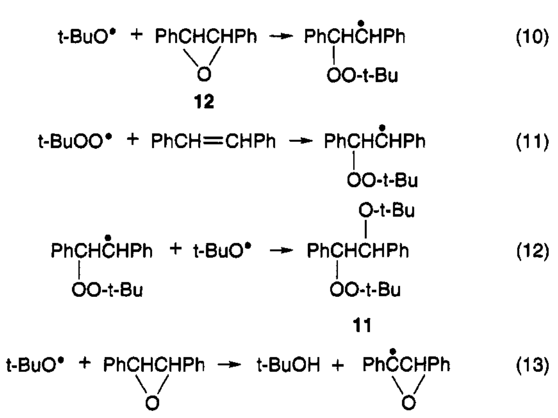
In order to obtain evidence that the epoxide **5** can be formed according to eq 4, the reaction with α-methylstyrene and t-BuOOH was carried out in benzene solution in the absence of metal complexes and in the presence of AIBN: the epoxide **5** is practically the only reaction product, together with small amounts of the aldehyde **6** and without significant amounts of the compounds **7**–**9**, because reaction 9 is prevailing and reactions 3, 5, and 6 are not possible. In this case the epoxide is formed by a free-radical chain involving eqs 2, 4, and 9 and initiated by AIBN.

All these facts and interpretations indicate that the Kochi mechanism for the Kharasch synthesis of mixed peroxides (Scheme 1) must be modified by taking into account eq 9, as the reaction is generally carried out in media in which t-BuOOH does not form hydrogen bonds, apart those with itself, so that the reaction products and the selectivities must be ascribed to the reaction of t-BuOO$^\bullet$ radical with the various substrates and only to a minor extent to the reaction of t-BuO$^\bullet$ radical.

Actually, Kochi did take into consideration the possibility that t-BuOO$^\bullet$ radicals could be involved in the Kharasch synthesis, but he rejected it because, in attempts to trap the peroxy radical by butadiene, he obtained the addition of t-BuO$^\bullet$ radical to the alkene; now we explain those results considering that the reaction was carried out in solvents (methanol, acetic acid) which form hydrogen bonds with t-BuOOH.

Oxidations Catalyzed by Mn(III)– and Fe(III)–Metalloporphyrins. Recently, Bruice and He[15] have reported the formation of **11** as a side product in the oxidation of *cis*-stilbene by t-BuOOH, catalyzed by P-Fe(III)(Cl) (P = porphyrin), mainly leading to the epoxide **12**.

Compound **11** is quite similar to **4** and **9**, obtained in the Gif and Kharasch oxidations of styrenes by t-BuOOH. The suggested[15] mechanism for the formation of **11** (eqs 10–12)



appeared to us at once extremely unlikely, for two reasons: (i) t-BuO$^\bullet$ radical is much too reactive a species[8] to reach a stationary concentration sufficient for a cross-coupling with carbon-centered radicals; (ii) t-BuO$^\bullet$ radical reacts with epoxides by hydrogen abstraction (eq 13) and not by addition to the epoxide ring.

Table 3. Reaction of Styrene and α-Methylstyrene with t-BuOOH, Catalyzed by Metalloporphyrines[a]

alkene	catalyst	pyridine[b] (mmol)	**3** (%)	**4** (%)
styrene	Mn(III)TDClPP-OAc	0.3	87.2	12.8
styrene	Mn(III)TDClPP-OAc	3	81.5	18.5
styrene	Mn(III)TDClPP-OAc	30	72.2	27.8
styrene	Mn(III)TDClPP-OAc	60	56.5	43.5
styrene	Mn(III)TDClPP-OAc	75	41.2	58.8
styrene	Fe(III)TDClPP-OAc	3	82.1	17.9

alkene	catalyst	pyridine (mmol)	**5** (%)	**6** (%)	**7** (%)	**8** (%)	**9** (%)
α-methyl styrene	Fe(III)TDClPP-OAc	3	23.2	3.8	49.6	1.7	21.7
α-methyl styrene	Mn(III)TDClPP-OAc	3	25.1	4.0	47.7	1.6	21.6

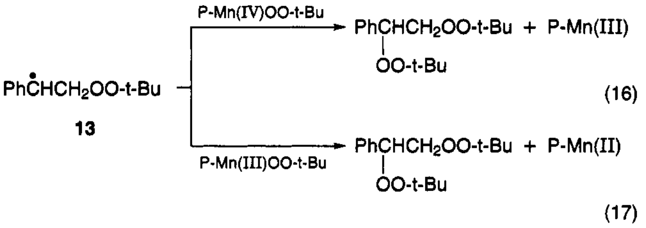
[a] 80–90% yields based on the reacted alkene; 25–30% conversion of alkene, based on t-BuOOH. [b] 10 mL of CH_2Cl_2 as solvent.

Thus, we have investigated the oxidation of styrene and α-methylstyrene by t-BuOOH, catalyzed by Mn(III)–tetra(2,6-dichlorophenyl)porphyrin acetate (TDClPP-OAc) and by Fe(III)TDClPP-OAc. The reaction with styrene is clean, and **3** and **4** are the significant reaction products, **3** being largely prevalent over **4** in CH_2Cl_2 solution. With α-methylstyrene considerable amounts of **5** and **6** are formed, in addition to **7**–**9** (Table 3). We explain the formation of **3**, **4**, **7**, and **9** by the redox oxidation of the metalloporphyrin by t-BuOOH (eqs 14 and 15).

$$\text{P-Mn(III)OAc} + \text{t-BuOOH} \rightarrow \text{P-Mn(III)OO-t-Bu} + \text{AcOH} \tag{14}$$

$$\text{P-Mn(III)OO-t-Bu} \rightarrow [\text{P-Mn(III)O}^\bullet \leftrightarrow \text{P-Mn(IV)=O}] + {}^\bullet\text{O-t-Bu} \tag{15}$$

The fastest reaction of t-BuO$^\bullet$ radical in CH_2Cl_2 solution is given by eq 9, with formation of t-BuOO$^\bullet$, which adds to styrenes (eq 2) giving the benzylic radical; this latter is then oxidized through a ligand-transfer process by the metalloporphyrin (eqs 16 and 17).



The ligand-transfer oxidation could take place either by P-Mn(IV) or by P-Mn(III); the Kharasch reaction has shown that Mn(III) salts are able to transfer a peroxy group to a carbon-centered radical, while Mn(II) salts are known to decompose t-BuOOH giving t-BuO$^\bullet$ radical (eq 18).

$$\text{P-Mn(II)} + \text{t-BuOOH} \rightarrow \text{P-Mn(III)} + \text{t-BuO}^\bullet + \text{OH}^- \tag{18}$$

Presently, we have no direct evidence about the redox chains P-Mn(II)/P-Mn(III) (eqs 17 and 18) or P-Mn(III)/P-Mn(IV) (eqs 15 and 16). The fact that the epoxide, formed according to eq 4 and always present in the Kharasch reaction, is not formed in the metalloporphyrin-catalyzed reaction of styrene suggests that either the redox chain of eqs 15 and 16 is involved or the Mn(III)–porphyrin complex is more effective in transferring a peroxy group to carbon-centered radicals than are the simple Mn salts utilized in the Kharasch reaction. Also in this case, as in the Kharasch reaction, reaction 4 is more effective with α-methylstyrene than with styrene (Tables 2 and 3).

To a minor extent t-BuO$^\bullet$ radical adds to styrenes leading, by the same mechanism, to compounds **4** and **9**, similar to the product **11**, obtained by Bruice and He from *cis*-stilbene. We

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[15] He, G.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 2747.

Table 4. Oxidation of Cumene and Adamantane by t-BuOOH, Catalyzed by Metalloporphyrins

		reaction products		
substrate	catalyst	cumyl alcohol (%)	cumyl *tert*-butyl peroxide	convn[a] (%)
cumene	Fe(III)TDClPP-OAc	89.9	10.2	27
cumene	Mn(III)TDClPP-OAc	86.2	13.8	31
cumene (1) + cyclohexane (1)[b]	Mn(III)TDClPP-OAc	87.4	12.6	29

		reaction products			
substrate	catalyst	1-adamantanol (%)	2-adamantanol (%)	adamantanone (%)	convn[a] (%)
adamantane[c]	Mn(III)TDClPP-OAc	72	12	8	8
adamantane[c]	Fe(III)TDClPP-OAc	71	13	10	9

[a] Based on t-BuOOH. [b] No oxidation products of cyclohexane were formed. [c] Small amounts (2–5%) of adamantyl *tert*-butyl peroxide was formed.

Table 5. Halogenation of Alkanes by $CBrCl_3$[a]

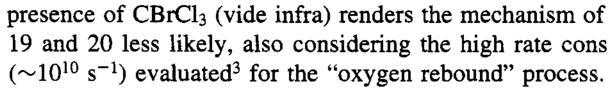
alkane	catalyst	**16** (%)	**17** (%)	**18** (%)	C^3_{ad}/C^2_{ad}	C^2_{ad}/C^2_{alk}	C^3_{ad}/C^3_{alk}	**17/16**
adamantane[b]	benzoyl peroxide	5	85	10	27			17
adamantane[b]	Fe(III)TDClPP-OAc	3.6	61.4	35.0	5.6			17.1
adamantane[b]	Mn(III)TDClPP-OAc	3.8	66.6	29.6	7.1			17.5
adamantane + cyclohexane	Mn(III)TDClPP-OAc	4.1	68.1	27.8	7.8	1.5		16.6
adamantane + *n*-hexane	Mn(III)TDClPP-OAc	3.9	65.5	30.6	6.8	2.1		15.8
adamantane + 2,3-dimethylbutane	Mn(III)TDClPP-OAc	3.8	64.2	32.2	6.9		3.4	16.9

[a] Yields based on the reacted alkane >90%; conversions of alkanes based on t-BuOOH 25–30%. [b] Reference 17.

believe that also the formation of **11** should be explained by reactions such as 5, 16, or 17.

To verify, also for the case of metalloporphyrin catalysis, our interpretation about the importance of hydrogen bonding and solvent effects, we have investigated the reaction of styrene in CH_2Cl_2 solution with increasing amounts of pyridine. The results (Table 3) fully support our hypotheses also in this case: as the concentration of pyridine increases, the reactivity of styrene shifts from t-BuOO$^\cdot$ to t-BuO$^\cdot$ addition, by increasing the formation of **4** to the detriment of **3**. The oxidation of cumene by t-BuOOH, catalyzed by Fe(III)– or Mn(III)–porphyrin, mainly leads to cumyl alcohol (**14**) and to *tert*-butyl cumyl peroxide (**15**) as side product (Table 4); we have verified that the cumyl alcohol is not formed from the mixed peroxide under the same reaction conditions. The mechanism of the formation of the mixed peroxide appears to be similar to the one discussed above for the Kharasch reaction, i.e., hydrogen abstraction from cumene by t-BuOO$^\cdot$, followed by the ligand-transfer of the peroxy group (eq 16 or 17) to the cumyl radical. Competition between cumene and cyclohexane leads to the exclusive oxidation of cumene, suggesting that t-BuO$^\cdot$ radical is not involved in hydrogen abstraction from C–H, but that it follows eq 9. A possible explanation for the formation of cumyl alcohol is provided by the "oxygen rebound mechanism" (eqs 19 and 20).

$$\text{P-Fe(III)OO-t-Bu} \rightarrow \text{P-Fe(V)=O} + {}^{-}\text{O-t-Bu} \qquad (19)$$

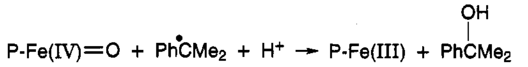


$$\text{P-Fe(V)=O} + \text{PhCHMe}_2 \rightarrow \text{P-Fe(IV)OH} + \text{Ph}\dot{\text{C}}\text{Me}_2 \rightarrow \text{P-Fe(III)} + \text{Ph}\overset{\text{OH}}{\overset{|}{\text{C}}}\text{Me}_2 \qquad (20)$$

However, the above-discussed behavior of styrenes and the halogenation of alkanes under the same conditions in the presence of $CBrCl_3$ (vide infra) renders the mechanism of eqs 19 and 20 less likely, also considering the high rate constant ($\sim10^{10}$ s^{-1}) evaluated[3] for the "oxygen rebound" process.

An alternative explanation involves reactions such as 15 and 9, followed by hydrogen abstraction from cumene (eq 21) and oxidation of the cumyl radical by P-Fe(IV)=O (eq 22), which would compete with ligand-transfer oxidations such as those of eqs 16 or 17.

$$\text{t-BuOO}^\bullet + \text{PhCHMe}_2 \rightarrow \text{t-BuOOH} + \text{Ph}\dot{\text{C}}\text{Me}_2 \qquad (21)$$



$$\text{P-Fe(IV)=O} + \text{Ph}\dot{\text{C}}\text{Me}_2 + \text{H}^+ \rightarrow \text{P-Fe(III)} + \text{Ph}\overset{\text{OH}}{\overset{|}{\text{C}}}\text{Me}_2 \qquad (22)$$

Equation 22 should be particularly sensitive to polar effects, which explains the different reactivity of radical **13**, less nucleophilic for the presence of a β-oxygen atom and cumyl radical toward reactions 16 (or 17) and 22.

We have also investigated the oxidation of adamantane by t-BuOOH, catalyzed by metalloporphyrins; the conversion is low (8% based on t-BuOOH), and the main reaction products are 1-adamantanol (72%), 2-adamantanol (12%), adamantanone (8%), and traces of adamantyl-*tert*-butylperoxide. The C^3/C^2 ratio (3.6) of the oxidation products is quite close to that obtained in the oxidation of adamantane by the Kharasch reaction (3.7) and different from the ratio (0.9) obtained either by Gif reaction or by chlorination by t-BuOCl. These results further support the hypothesis that also in this oxidation t-BuOO$^\cdot$ is the hydrogen abstracting species.

The free-radical character of alkane oxidation by t-BuOOH with metalloporphyrin catalysis is strongly supported by the behavior of the reaction with $CBrCl_3$: in the case of adamantane the formation of oxygenated products is suppressed and 1-chloro- (**16**), 1-bromo- (**17**), and 2-bromoadamantane (**18**) are formed (Table 5). Two aspects are relevant as for what concerns the regioselectivity: the behavior of the adamantyl radical is very peculiar in chlorine and bromine abstraction from $CBrCl_3$, as it is quite different from that of simple secondary and tertiary alkyl and cycloalkyl radicals: these latter selectively abstract bromine atom from $CBrCl_3$; the behavior of 2-adamantyl radical is quite similar in that only bromine atom abstraction occurs, whereas Rüchardt[16] and Tabushi[17] have shown that with 1-adamantyl radical chlorine abstraction competes with bromine

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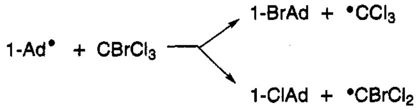
(16) Rüchardt, C.; Herwig, K.; Eichler, S. *Tetrahedron Lett.* **1969**, 421.
(17) Tabushi, I.; Aoyama, Y.; Kojo, S.; Hamuro, S, Yoshida, Z. *J. Am. Chem. Soc.* **1972**, *94*, 1177.

abstraction. Moreover, the ratio between 1-chloro- and 1-bromoadamantane (1:17), obtained by metalloporphyrin catalysis, is identical to that reported by Tabushi[17] for the classical free-radical halogenation by $CBrCl_3$ (eq 23), which supports the free-radical character of the reaction.



$$1\text{-}Ad^{\bullet} + CBrCl_3 \longrightarrow \begin{cases} 1\text{-}BrAd + {}^{\bullet}CCl_3 \\ 1\text{-}ClAd + {}^{\bullet}CBrCl_2 \end{cases} \qquad (23)$$

The regioselectivity in the halogenation of secondary and tertiary C−H bonds of adamantane, catalyzed by metalloporphyrins, is, however, considerably different from that of the classical free-radical halogenation[17] by $CBrCl_3$, in which the free-radical chain of eqs 23 and 24 occurs.

$$^{\bullet}CCl_3 + H\text{-}Ad \rightarrow CHCl_3 + Ad^{\bullet} \qquad (24)$$

We believe that the behavior observed under metalloporphyrin catalysis is due to a superimposition of several radical and redox chains, because reaction 24 is slow and reversible (the reversal of eq 24 is a key step of the free-radical addition of $CHCl_3$ to alkenes) and the kinetic length of the chain (eqs 23 and 24) is small, so that oxygen-centered radicals, generated in eqs 9 and 15, can contribute to determine the selectivity in hydrogen abstraction (eq 25). Thus, the C^2/C^3 and intermolecular selectivities (Table 5) would be rather complex.

$$AdH + {}^{\bullet}OX \rightarrow Ad^{\bullet} + HOX \qquad (25)$$

$$XO^{\bullet} = t\text{-}BuO^{\bullet},\ tBuOO^{\bullet},\ P\text{-}Mn(III)O^{\bullet}$$

Conclusions

The oxidations by t-BuOOH catalyzed by Kharasch, metalloporphyrins, and Gif systems would have, as common features, the formation of t-BuO$^{\bullet}$ radical, carbon-centered radicals, and ligand transfer of a peroxy group to these latter. The specificity of the Gif reaction would be related to a solvent effect: the use of pyridine as solvent would inhibit reaction 9 by forming strong hydrogen bonds with t-BuOOH, increase the electron availability of the Fe(III) salt by coordination, making its oxidation by t-BuOOH easier, and catalyze the decomposition of secondary hydroperoxides or mixed peroxides to carbonyl compounds[4]. Differences among the three catalytic systems, apart from the solvent effect, are related to the different reactivity of the metal salt complexes toward carbon-centered radicals.

Experimental Section

General Procedures and Materials. All the reagents were commercial products (Aldrich, Fluka), utilized without further purification; two metalloporphyrins were utilized: Mn(III)−tetra(2,6-dichlorophenyl)porphyrin acetate (Mn(III)TDClPP-OAc) and Fe(III)−tetra(2,6-dichlorophenyl)porphyrin acetate (Fe(III)TDClPP-OAc); they were prepared according to procedures previously[18] reported.

GC analyses were performed on a Dani 8610 gas chromatograph equipped with an OV101 capillary column, a PTV injector and a flame ionization detector. NMR spectra were recorded on a Bruker AC 250 MHz spectrometer; MS spectra were obtained on a Hitachi RMU-60 instrument.

General Procedure for the Competitive Kharasch Reactions of Cyclohexene, Cyclohexane, and Alkylbenzenes. The Kharasch procedure[5] in the absence of solvents was utilized: a mixture of 10 mmol of the two substrates, in the ratios reported in Table 1, t-BuOOH (1 mmol) and $Cu(OAc)_2$ (20 mg), was heated at 70 °C for 18 h under N_2. Ten mL of ethyl acetate was then added, and the solution was filtered and analyzed by GLC, using biphenyl as internal standard. All the mixed peroxides (benzyl-*tert*-butyl, cumyl-*tert*-butyl, cyclohexenyl-*tert*-butyl, *p*-$MeC_6H_4CMe_2OOBu$-t and *p*-i-$PrC_6H_4CH_2OOBu$-t) were prepared according to the Kharasch procedure with the single substrates; the pure peroxides were obtained by chromatographic separation on alumina, using petroleum ether as the eluent, and utilized to determine the gaschromatographic response of the standard. The results are reported in Table 1.

Oxidation of Adamantane by Kharasch Reaction with t-BuOOH. A mixture of 5 mmol of adamantane, 1 mmol of t-BuOOH, 10 mL of benzenes and 10 mg of $Cu(OAc)_2$ was heated at 68 °C for 15 h under N_2. The copper salt was collected on a filter, and the solution was analyzed by GLC by using biphenyl as internal standard; 37% conversion of adamantane, based on t-BuOOH, was obtained with formation of 4 compounds: 1-adamantanol (72.8%), 2-adamantanol (8.6%), adamantanone (12.6%), and adamantyl-*tert*-butyl peroxide (7.2%); the reaction products were identified by comparison with authentic samples.

Chlorination of Adamantane by t-BuOCl. A solution of 4 mmol of adamantane and 1 mmol of t-BuOCl in 10 mL of CH_2Cl_2 was irradiated at 254 nm for 4 h under N_2. The solution was analyzed by GLC using biphenyl as internal standard. 1-Chloro- and 2-chloroadamantane are the only reaction products; they were identified by comparison with commercial products; yields based on reacted adamantane are > 90% (47.7% of 1-chloro- and 52.3% of 2-chloroadamantane).

Oxidation of Styrene and α-Methylstyrene by Kharasch Reaction with t-BuOOH. (A) A mixture of styrene or α-methylstyrene (1 mmol), t-BuOOH (1 mmol), benzene (10 mL), and $Cu(OAc)_2$ (10 mg) was heated at 60 °C for 18 h under N_2. The copper salt was collected on a filter, and the solution was analyzed by GLC using biphenyl as internal standard.

(B) A mixture of α-methylstyrene (10 mmol), t-BuOOH (5 mmol), $Cu(OAc)_2$ (20 mg), and increasing amounts of pyridine, as reported in Table 2, was heated at 60 °C for 18 h under N_2. Ten mL of ethyl acetate was added, and the solution was filtered and analyzed by GLC.

(C) The reaction was carried out as in B in t-BuOH as solvent (10 mL): (i) at 60 °C, (ii) at refluxing temperature, (iii) in the presence of pyridine (2 mL).

Compounds **1** and **2**, **5** and **6** were identified by comparison with commercial products. Compounds **3**, **4**, **7**, **8**, and **9** were isolated as liquids by chromatographic separation on silica, using ethyl acetate/hexane (5:95) as the eluent, and characterized by NMR spectra.

3: NMR ($CDCl_3$) δ 1.22 (s 9H, t-BuOO), 1.24 (s 9H, t-BuOO), 4.15 (m 2H, CH_2O), 5.21 (m 1H, −CHO), 7.0−7.4 (m 5H, Ph).

4: NMR ($CDCl_3$) δ 1.13 (s 9H, t-BuO), 1.22 (s 9H, t-BuOO), 3.76 (m 2H, CH_2O), 5.01 (m 1H, −CHO), 7.0−7.4 (m 5H, Ph).

7: NMR ($CDCl_3$) δ 1.23 (s 9H, t-BuOO), 1.25 (s 9H, t-BuOO), 1.61 (s 3H, CH_3), 3.79 (m 2H, CH_2O), 5.21 (m 1H, −CHO), 7.1−7.4 (m 5H, Ph).

8: NMR ($CDCl_3$) δ 0.8 (t 3H, CH_3CH_2), 1.22 (s 9H, t-BuOO), 1.58 (s 3H, CH_3), 1.85 (q 2H, CH_2CH_3), 7.2−7.4 (m 5H, Ph).

9: NMR ($CDCl_3$) δ 1.15 (s 9H, t-BuO), 1.24 (s 9H, t-BuOO), 1.57 (s 3H, CH_3), 3.74 (m 2H, CH_2O), 7.0−7.4 (m 5H, Ph).

The results are reported in Table 2.

Oxidation of α-Methylstyrene by t-BuOOH, Initiated by AIBN. A solution of α-methylstyrene (2 mmol), t-BuOOH (2 mmol), and AIBN in 20 mL of benzene was refluxed for 4 h. The solution was directly analyzed by GLC, using biphenyl as internal standard. Conversion 15%; yields 87% of **5** and 6% of **7**, based on the converted alkene. **5** and **7** were identified by comparison with authentic samples.

Oxidation of Styrene and α-Methylstyrene by t-BuOOH, Catalyzed by Metalloporphyrins. General Procedure. A solution of the alkene (20 mmol), t-BuOOH (10 mmol), and Mn(III)- or Fe(III)-TDClPP-OAc (0.01 mmol) and the amounts of pyridine reported in Table 3, dissolved in 10 mL of CH_2Cl_2, was stirred under N_2 for 30 min at 0 °C and then for 30 min at 25 °C. The isolation, identification, and analysis of compounds **3**−**9** has been carried out as above described for the results reported in Table 3.

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[18] (a) Banfi, S.; Maiocchi, A.; Montanari, F.; Quici, S. *Gazz. Chim. Ital.* **1990**, *120*, 123. (b) Quici, S.; Banfi, S., Pozzi, G. *Ibid.* **1993**, *123*, 597. (c) Banfi, S.; Maiocchi, A.; Maggi, A.; Montanari, F.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1794.

Oxidation of Adamantane and Cumene by t-BuOOH, Catalyzed by Metalloporphyrins. A solution of adamantane or cumene (10 mmol), t-BuOOH (5 mmol), pyridine (1.5 mmol), and Mn(III)- or Fe(III)TDClPP-OAc (0.01 mmol) in 5 mL of CH_2Cl_2, was stirred under N_2 for 30 min at 0 °C and then for 30 min at 25 °C. The solution was directly analyzed by GLC using biphenyl as internal standard. Cumyl alcohol, cumyl *tert*-butyl peroxide, 1- and 2-adamantanol, and adamantanone were identified by comparison with authentic samples. Small amounts of 1-adamantyl *tert*-butyl peroxide (2−5%) were isolated by column chromatography on silica, using hexane/ethyl acetate (95:5) as the eluent; the NMR spectrum ($CDCl_3$) shows 9H at 1.22 δ (s, t-BuOO) and 15 H (m, 1.5−1.8 δ) of the adamantyl group. The results are reported in Table 4.

Halogenation of Alkanes by $CBrCl_3$ and t-BuOOH, Catalyzed by Metalloporphyrins. A solution of adamantane (5 mmol), $CBrCl_3$ (5 mmol), t-BuOOH (5 mmol), metalloporphyrin (0.01 mmol), and pyridine (3 mmol) in 6 mL of CH_2Cl_2 was stirred under N_2 for 30 min at 0 °C and then for 30 min at 25 °C. The solution was directly analyzed by GLC using biphenyl as internal standard. 1-chloro-, 1-bromo-, and 2-bromoadamantane were identified by comparison with authentic samples. The competitive halogenations were carried out by the same procedure, using 5 mmol of adamantane and 5 mmol of cyclohexane, *n*-hexane, or 2,3-dimethylbutane per mol of t-BuOOH; 2- and 3-bromohexane were not separated, but evaluated together in GLC. The results are reported in Table 5.