Radical versus "Oxenoid" Oxygen Insertion Mechanism in the Oxidation of Alkanes and Alcohols by Aromatic Peracids. New Synthetic Developments

Anna Bravo, Hans-René Bjorsvik, Francesca Fontana, Francesco Minisci,* and Anna Serri

Dipartimento di Chimica del Politecnico, via Mancinelli 7, I-20131 Milano, Italy

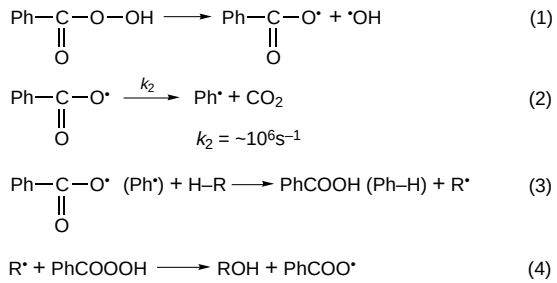
Received July 19, 1996[⊗]

Evidences concerning a novel free-radical mechanism for the oxidation of alkanes by aromatic peracids are reported. The mechanism involves hydrogen abstraction from the OH group of peracids by an aroyloxyl radical; the acylperoxyl radical thus generated is responsible for the selective oxidation. The reaction is affected by the presence of oxygen and it is inhibited by TEMPO and by solvents forming hydrogen bonds with peracids. A more simple and effective synthetic procedure has been developed, on the basis of the autoxidation of aliphatic and aromatic aldehydes in the presence of alkanes. It is also shown that the previously reported inertness of alcohols toward peracids must be ascribed to solvent effects, due to the formation of hydrogen bonds; in suitable solvents alcohol oxidation smoothly occurs.

An "oxenoid" oxygen insertion mechanism has been suggested to explain unusual selectivities in the oxidation of unactivated C−H bonds by a variety of oxidants and catalytic systems (dioxiranes,[1] perfluorooxaziridines,[2] Gif systems,[3] cytochrome P450,[4] metalloporphyrins, and other metal salt complexes[5]), sometimes characterized by enzyme-like specificity.

We and other research groups have recently reported evidences suggesting that oxidations by Gif systems,[6−8] dioxiranes[9,10] and metalloporphyrin catalysis[11,12] can be explained by radical mechanisms. This dualism (oxenoid oxygen insertion versus radical mechanism) is quite general. Aromatic peracids represent another class of oxidants, characterized by high selectivity in the oxidation of nonactivated C−H bonds, for which both mechanisms have been proposed.

The suggested radical mechanism[13] involves a chain process initiated by the homolysis of the peroxidic bond (eq 1), with propagation steps characterized by hydrogen abstraction from unactivated C−H bonds and induced decomposition of the peracid by alkyl radical (eqs 2−4).



This mechanism, however, is not consistent with the selectivity of the process. Aryl radicals can be ruled out as hydrogen-abstracting species as the oxidation has been successfully carried out in benzene as solvent: it is known[14] that the addition rate of phenyl radical to benzene ($\sim 10^6$ M^{-1} s^{-1}) is at least of the same order of magnitude as the rate of hydrogen abstraction from unactivated C−H bonds (10^5-10^6 M^{-1} s^{-1}). Moreover, the regio- and chemoselectivity of hydrogen abstraction by phenyl radical is rather low,[14] while this oxidation is highly selective.

In spite of the clearly incongruous rate constants reported in a recent book on free radicals[15] (1.4×10^6 M^{-1} s^{-1} at 22 °C and 2.5×10^3 M^{-1} s^{-1} at 25 °C for hydrogen abstraction by benzoyloxyl radicals respectively from cyclohexane and THF), very reliable absolute rate constants have been reported by the research groups of Ingold[16] and Tokumaru,[17] who have clearly shown that hydrogen abstraction from alkanes by aroyloxyl radicals can compete with decarboxylation, which is subject to dramatic solvent effects and also to substituent effects.[16]

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) Adam, W.; Hadjiarapoglou, L. P. *Top. Curr. Chem.* **1993**, *49*, 2227 and references therein.

(2) Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511.

(3) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. Barton, D. H. R.; Hill, D. R. *Tetrahedron Lett.* **1994**, *35*, 1431.

(4) *Cytochrome P450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986.

(5) *Metallo-porphyrin catalyzed oxidation*; Montanari, F.; Casella, L., Eds.; Kluwer Academic Publishers: Dordrecht, 1994. Kaufman, M. D.; Grieco, P. A.; Bougie, D. W. *J. Am. Chem. Soc.* **1993**, *115*, 11648; Nomura, K.; Vemura, S. *J. Chem. Soc., Chem. Commun.* **1994**, 129.

(6) Minisci, F.; Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427. Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *J. Chem. Soc., Chem. Commun.* **1994**, 823. Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.* **1994**, *35*, 3759. Minisci, F.; Fontana, F.; Bravo, A.; Yan, Y. M. *Gazz. Chim. Ital.*, **1996**, *126*, 85. D. H. R. Barton does not consider anymore "Gif chemistry" the oxidations by GoAgg[IV] and GoAgg[V] systems: *Synlett*, in press.

(7) Snelgrove, D. W.; MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M. *Tetrahedron Lett.* **1996**, *37*, 823.

(8) Newcomb, M.; Simakov, P. A.; Park, S. *Tetrahedron Lett.* **1996**, *37*, 819.

(9) Minisci, F.; Zhao, L.; Fontana, F.; Bravo, A. *Tetrahedron Lett.* **1995**, *36*, 1697, 1895. Bravo, A.; Fontana, F.; Fronza, G.; Mele, A.; Minisci, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1573. Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Serri, A. *Tetrahedron Lett.* **1995**, *36*, 6945.

(10) Vanni, R.; Garden, S. J.; Banks, J. T.; Ingold, K. U. *Tetrahedron Lett.* **1995**, *36*, 7999.

(11) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.

(12) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.

(13) (a) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995; p 217. (b) Tokumaru, K.; Simamura, O. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1678.

(14) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589. Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.

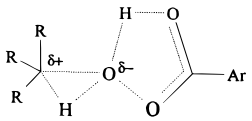
(15) Reference 13a, p 290.

(16) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.***1987**, *109*, 897; **1988**, *110*, 2877, 2886.

(17) Misawa, H.; Sawabe, K.; Takahara, S.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* **1988**, 355.

S0022-3263(96)01366-7 CCC: $12.00

Scheme 1



However, the observed selectivity for hydrogen abstraction (5.3×10^5 and 7.3×10^5 M^{-1} s^{-1} at 24 °C in CCl_4 respectively for cyclohexane and THF),[16] is very low and it is not consistent with the high regio- and chemoselectivity observed in the oxidation by aromatic peracids. Moreover, eq 4 does not satisfactorily explain the observed stereoselectivity. The high degree of configurational retention in the oxidation of epimeric cycloalkanes has in facts led other authors[18] to exclude a radical mechanism and to suggest an oxenoid oxygen insertion mechanism based on a cyclic transition state with some charge separation, as first proposed by Bartlett[19] (Scheme 1).

A quite similar transition state has been suggested in alkane oxidation by dioxiranes; LFER studies with both oxidants (dioxirane and peracids) would indicate that these hydroxylations occur in a concerted electrophilic process (Scheme 1).[20] A very recent evolution of the "concerted oxenoid mechanism of insertion" by dioxiranes has been reported[21] according to Scheme 2.

Though a concerted insertion mechanism by definition does not involve intermediates, the radical pair depicted in Scheme 2 is considered *not distinct*. This lack of *distinction* would prevent the coupling of the "singlet" radical pair in the cage and would lead to a hydroxyl transfer and to a not better defined "radical leakage".

We now report evidences concerning a novel free-radical mechanism, different from the one described by eqs 1−4, for the oxidation of alkanes and alcohols by peracids, and new synthetic developments arising as direct consequence of this interpretation.

Results

We have investigated the oxidation of adamantane, cyclohexane, cyclohexanol, cyclopentanol, 1-heptanol, 2-heptanol, and benzyl alcohol at different temperatures in several solvents by *m*-chloroperbenzoic acid (*m*-CPBA) or by aldehydes and molecular oxygen.

Oxidation of Adamantane. Adamantane has been oxidized by *m*-CPBA in several solvents at temperatures ranging between 18 and 65 °C in an atmosphere of air, oxygen, or argon. In CH_2Cl_2, $ClCH_2CH_2Cl$ (DCE), and benzene solutions two main reaction products are formed from adamantane, with high regioselectivity: 1-hydroxyadamantane (**1**) and 1-adamantyl-*m*-chlorobenzoate (**2**); minor amounts of 2-hydroxyadamantane (**3**) and traces of adamantanone (**4**) are also formed. In methylene chloride or DCE solution under an argon atmosphere, chlorobenzene (**5**) is a significant reaction product at 18 °C and its amount increases with temperature. At 18 °C under oxygen atmosphere **5** is practically absent. *No chlorobenzene is formed under an argon atmosphere, but in the absence of adamantane.* When benzene is utilized as solvent no chlorobenzene is formed, but *m*-chlorobiphenyl (**6**) is an important byproduct; also in this case, the presence of oxygen inhibits the formation of **6**.

In $CHCl_3$ solution the results are similar to those obtained in CH_2Cl_2 and DCE (compounds **1**−**5** are formed), with the difference that a considerable amount of 1-chloroadamantane is also formed.

By using a more effective chlorine-transfer solvent, such as CCl_4, chlorination of adamantane with low selectivity (mono- and dichloro derivatives) is by far prevailing, while *m*-dichlorobenzene and hexachloroethane were identified as byproducts.

A still more effective halogen-transfer reagent, such as $CBrCl_3$, is effective also at low concentrations, and the ratio between oxidation and halogenation products is strictly related to $CBrCl_3$ concentration. Bromoadamantanes are prevailing, but 1-chloroadamantane is a significant byproduct. The oxidation is substantially inhibited by the use of *t*-BuOH as solvent or in the presence of TEMPO in DCE solution. The presence of cyclohexanone also inhibits adamantane oxidation. The results are reported in Table 1.

The effect of the solvent on the rate of adamantane oxidation by *m*-CPBA is shown in Table 2: the reaction is slower in benzene than in DCE, and it is practically inhibited in *t*-BuOH solution. The results of the oxidation of adamantane by aldehydes (butanal, benzaldehyde, and *m*-chlorobenzaldehyde) and oxygen are reported in Table 3. The reaction was carried out at 70 °C in the absence of initiator and at 40 °C in the presence of $(t\text{-BuOOCO})_2$ as initiator. In the presence of an excess of cyclohexanone, the reaction is not inhibited; 1-hydroxyadamantane and 1-adamantyl esters similar to **2** are the main reaction products.

Oxidation of Cyclohexane. Cyclohexanol, cyclohexanone, and caprolactone are the reaction products of cyclohexane oxidation in DCE or CH_2Cl_2 by *m*-CPBA. Chlorobenzene (**5**) is a significant byproduct of the reaction; *t*-BuOH again inhibits the reaction. In CCl_4 solution chlorination of cyclohexane exclusively takes place and *m*-dichlorobenzene and hexachloroethane are significant reaction products. Bromocyclohexane is the reaction product in DCE solution in the presence of $CBrCl_3$, and *m*-chlorobromobenzene is a byproduct. The results are reported in Table 4. In a competitive experiment, adamantane was >50 times more reactive than cyclohexane.

Oxidation of Alcohols. Cyclohexanol and cyclopentanol are oxidized by *m*-CPBA respectively to caprolactone and valerolactone in all the solvents investigated (CH_2Cl_2, DCE, $CHCl_3$, CCl_4, benzene); *t*-BuOH, when used as solvent, inhibits the oxidation of both alcohols. Chlorobenzene is a byproduct in all the reactions but the ones carried out in benzene or CCl_4 solution, in which m-dichlorobenzene is the byproduct. The oxidation of 1-heptanol gives heptanoic acid as the main reaction product and heptanal and hexyl formate as minor products. Similarly, benzyl alcohol mainly gives benzoic acid, with minor amounts of benzaldehyde; 2-heptanol is oxidized to hexyl acetate, 2-heptanone, and methyl hexanoate. The results are reported in Table 5. The effect of the solvent on the oxidation rate of cyclohexanol by *m*-CPBA is reported in Table 6. The reaction is slower in benzene than in CH_2Cl_2, and it is substantially inhibited in *t*-BuOH.

The oxidation of cyclohexanol has also been carried out under autoxidation conditions of butanal: cyclohexanone and caprolactone are the main reaction products (Table

(18) Schneider, H. J.; Müller, W. *J. Org. Chem.* **1985**, *50*, 4609. Tori, M.; Matsuda, R.; Asakawa, Y. *Tetrahedron Lett.* **1985**, *26*, 227.
(19) Bartlett, P. D. *Rec. Chim. Progr.* **1950**, *11*, 47.
(20) Murray, R. W.; Gu, H. *J. Org. Chem.* **1995**, *60*, 5673.
(21) Curci, R., Dinoi, A.; Fusco, C.; Lillo, M. A. *Tetrahedron Lett.* **1996**, *37*, 249.

Scheme 2

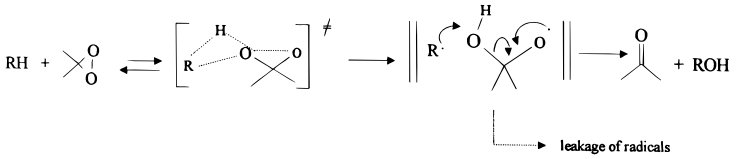


Table 1. Oxidation of Adamantane by *m*-CPBA[a]

entry	solvent	conversion, %[b]	*T*, (°C)	reaction time, h	**1**, %[c]	**2**, %[c]	**3**, %[c]	mono- and dihaloadamantanes[c]	**5**, %[d]
1	DCE[e]	30.2	18	100	70.1	19.3	1.6		18.1
2	DCE[f]	29.4	18	100	77.2	11.4	1.3		
3	DCE[g]	44.1	65	24	68.0	10.5	2.0		24.9
4	CH_2Cl_2[e]	32.1	20	100	72.2	16.3	1.1		16.6
5	CH_2Cl_2[f]	31.3	20	100	74.2	15.4	1.3		
6	CH_2Cl_2[g]	15.3	40	24	66.5	10.4	1.9		31.3
7	$CHCl_3$[g]	49.9	60	24	39.4	3.5	1.2	18.1 (1-chloro)	9.5
8	CCl_4[g]	~99	65	24	~1.0			88.2	
9	benzene[h]	9.4	18	96	75.2	18.3	0.8		
10	benzene[i]	11.4	18	96	74.5	17.6	0.9		
11	benzene[l]	21.0	65	24	84.6	10.8	2.4		
12	DCE[g] ($CBrCl_3$, 0.25 mmol)	73.3	65	24	25.1	4.8	0.8	53.3	
13	DCE[g] ($CBrCl_3$, 0.5 mmol)	74.9	65	24	7.3	1.2	0.3	77.2	
14	DCE[g] ($CBrCl_3$, 1 mmol)	95.4	65	24				85.1	
15	CH_2Cl_2[g] (TEMPO 0.5 mmol)	3.1	40	24	traces				
16	*t*-BuOH[g]	4.2	40	24	traces				
17	DCE[m] (cyclohexanone 3 mmol)		65	24					

DCE = 1,2-dichloroethane. [a] 1 mmol of adamantane, 1 mmol of *m*-CPBA in 5 mL solvent. [b] Conversion of adamantane. [c] Yields based on converted adamantane. [d] Yields based on *m*-CPBA. [e] Argon atmosphere. [f] Oxygen atmosphere. [g] Air atmosphere. [h] Argon atmosphere, 5% of **6** based on *m*-CPBA is formed. [i] Oxygen atmosphere, no **6** is formed. [l] Air atmosphere, 18% of **6**, based on *m*-CPBA, is formed. [m] Caprolactone is the only reaction product.

Table 2. Solvent Effect on the Rate of Oxidation of Adamantane by *m*-CPBA (20° C)[a]

reaction time, h	conversion, %[b]		
	DCE	benzene	*t*-BuOH
4	5.1	2.7	
12	9.4	3.9	
24	13.3	5.3	
48	21.6	8.1	traces
72	27.9	10.6	0.4
96	33.9	12.9	0.6

[a] 1 mmol of adamantane, 1 mmol of *m*-CPBA in 5 mL of solvent, air atmosphere. [b] Conversion of adamantane.

3). Competitive experiments indicate that the α-hydroxy C−H bond in cyclohexanol is about three times more reactive than the C^3−H bond in adamantane, while benzyl alcohol is slightly less reactive than 1-heptanol (relative rates 1:1.2)

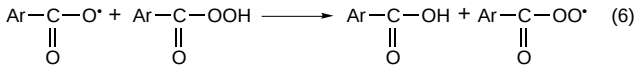
Discussion

The novel interpretation of the oxidation of unactivated C−H bonds by peracids was originated by previous studies[11,12] concerning the reaction of alkoxyl radicals with hydroperoxides (eq 5). Reaction 5 is very fast, about

$$t\text{-BuO}^{\bullet} + \text{HOOBu-}t \xrightarrow{k_5} t\text{-BuOH} + t\text{-BuOO}^{\bullet} \qquad (5)$$

$$k_5 = 2.5 \times 10^8\ \text{M}^{-1}\text{s}^{-1} \text{ at } 22\ ^\circ\text{C}$$

2 orders of magnitude faster than hydrogen abstraction from unactivated C−H bonds[11,22] by *t*-BuO$^{\bullet}$ radical, mainly due to enthalpic effects (bond energies 88 and 103 kcal/mol respectively for *t*-BuOO−H and *t*-BuO−H). Moreover, solvents which form hydrogen bonds with hydroperoxides considerably decrease the rate of reaction 5.[11,12] Thus, it seems reasonable to assume a high rate constant and a marked solvent effect for reaction 6 as well, on the basis of a similar difference (~17 kcal/mol)[23] between the bond energies of ArCOO−H and ArCOOO-H and similar absolute rate constants in hydrogen abstraction from unactivated C−H bonds by *t*-BuO$^{\bullet}$ radical[11,22] and ArCOO$^{\bullet}$ [16] radicals (10^5−10^6 M^{-1} s^{-1}).



Reaction 6 could therefore successfully compete, in suitable solvents, with reactions 2 and 3, whose rate constants have been evaluated[16] to be in the range 10^5−10^6 M^{-1} s^{-1}. This means it could play a relevant role in the oxidation of unactivated C−H bonds by peracids.

Adamantane is a useful substrate for the investigation of the relationship between the structure of a free radical and its behavior as hydrogen-abstracting species. The selectivity of abstraction between tertiary and secondary C−H bonds is scarcely influenced by the enthalpic effect[24] (bromine atom, highly sensitive to C−H bond energies, shows low selectivity[24]), but highly influenced by the polar effect[24] (high selectivity by $R_2NH^{\bullet+}$ radicals, Minisci chlorination,[25] particularly sensitive to polar effects[26]). This behavior is not unexpected, on the grounds of the C^3−H bond energy in adamantane, evaluated[27] to be 3.7

(22) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Zhao, L. *Synlett* **1996**, 119. Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929.

(23) Reference 13a, p 298.

(24) Minisci, F.; Fontana, F.; Zhao, L.; Banfi, S.; Quici, S. *Tetrahedron Lett.* **1994**, *35*, 8033.

(25) Deno, N. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; M. Dekker: New York, 1975, p 143.

(26) Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* **1968**, 324. Minisci, F. In *Substituent Effects in Free-Radical Chemistry*; Viehe, H., Ed.; Reidel: Dordrecht, 1986; p 391.

(27) Kruppa, G. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 2162.

Table 3. Oxidation of Adamantane and Cyclohexanol by Aldehydes and O_2[a]

substrate	aldehyde	conversion, %[b]	*T*, °C	**1**, %[c]	**3**, %[c]	1-adamantyl esters, %[c]
adamantane	butanal	47.1	70	78.2	1.2	13.1
adamantane	benzaldehyde	31.2	70	84.1	1.4	12.2
adamantane[d]	benzaldehyde	36.9	40	82.4	1.3	6.1
adamantane[d]	*m*-Cl-benzaldehyde	34.2	40	75.3	2.1	8.2
adamantane[e]	*m*-Cl-benzaldehyde	20.1	70	72.4	2.8	7.3
				cyclohexanone, %[c]		caprolactone, %[c]
cyclohexanol	butanal	53.4	70	61.4		16.6

[a] 2 mmol aldehyde in 5 mL DCE are dropped during 3 h to a solution of 1 mmol substrate in 5 mL DCE and oxygen is bubbled for 24 h. [b] Conversion of the substrate. [c] Yields based on converted substrate. [d] As in (a) by using 0.1 mmol (*t*-BuOOCO)$_2$. [e] As in (a) in the presence of 3 mmol cyclohexanone.

Table 4. Oxidation of Cyclohexane by *m*-CPBA[a]

solvent	conversion, %[b]	cyclohexanol, %[c]	cyclohexanone, %[c]	caprolactone, %[c]	mono- and dihalocyclohexanes, %[c]	**5**, %[d]
DCE	32.3	21.2	20.3	39.9		23.4
CH_2Cl_2	21.2	24.4	21.2	33.6		25.4
t-BuOH	3.1	40.2	15.7	23.4		0.9
CCl_4[e]	49.4	traces			88.1	
DCE[f] ($CBrCl_3$)	45.6	traces			83.8	

[a] 5 mmol of cyclohexane, 1 mmol of *m*-CPBA in 5 mL of solvent at 65 °C for 24 h, air atmosphere. [b] Conversion of cyclohexane based on *m*-CPBA. [c] Yields based on converted cyclohexane. [d] Yields based on *m*-CPBA. [e] *m*-Dichlorobenzene (15.5%) and CCl_3CCl_3 (3.2%) are formed. [f] *m*-Chlorobromobenzene (6.4%) is formed.

Table 5. Oxidation of Alcohols by *m*-CPBA[a]

alcohol	solvent	*T*, °C	reaction time, h	conversion, %[b]	reaction products, %[c]	**5**, %[d]
cyclohexanol	DCE	60	20	75.1	caprolactone (87.1)	9.9
cyclohexanol	DCE	20	70	85.2	caprolactone (89.2)	4.2
cyclohexanol	CH_2Cl_2	40	27	52.4	caprolactone (84.1)	10.9
cyclohexanol	CH_2Cl_2	18	120	66.3	caprolactone (86.2)	3.8
cyclohexanol	$CHCl_3$	60	24	93.1	caprolactone (78.8)	5.5
cyclohexanol[e]	CCl_4	60	5	51.6	caprolactone (81.4)	
cyclohexanol	benzene	60	20	35.5	caprolactone (82.3)	
cyclohexanol	*t*-BuOH	18	120	3.3	caprolactone (48.2), cyclohexanone (31.6)	
cyclopentanol	DCE	60	24	74.2	valerolactone (79.2)	8.9
cyclopentanol	benzene	60	24	27.8	valerolactone (86.3)	
cyclopentanol	*t*-BuOH	60	24	traces	traces	
1-heptanol	DCE	60	21	70.1	heptanoic acid (68.2), hexyl formate (7.1), heptanal (3.3)	
2-heptanol	DCE	60	21	77.7	2-heptanone (43.1), hexyl acetate (39.7), methyl hexanoate (2.5)	6.9
2-heptanol	CH_2Cl_2	60	21	41.2	2-heptanone (14.1), hexyl acetate (64.9), methyl hexanoate (2.8)	
2-heptanol	CH_2Cl_2	40	24	82.9	2-heptanone (38.3), hexyl acetate (41.2), methyl hexanoate (2.6)	10.4
2-heptanol	$CHCl_3$	60	24	85.6	2-heptanone (32.7), hexyl acetate (46.2), methyl hexanoate (2.8)	8.3
2-heptanol[e]	CCl_4	60	24	58.8	2-heptanone (21.6), hexyl acetate (62.7), methyl hexanoate (3.1)	
benzyl alcohol	DCE	60	24	41.2	benzaldehyde (27.4), benzoic acid (52.3)	12.2

[a] 1 mmol of alcohol, 2 mmol of *m*-CPBA in 5 mL solvent, air atmosphere. [b] Alcohol conversion. [c] Yields based on alcohol conversion. [d] Yields based on *m*-CPBA. [e] Ratio 1:1 between alcohol and *m*-CPBA, m-dichlorobenzene (8%) as byproduct.

Table 6. Solvent Effect on the Rate of Oxidation of Cyclohexanol by *m*-CPBA (18 °C)[a]

reaction time, h	conversion, %[b]		
	CH_2Cl_2	benzene	*t*-BuOH
12	12.2	4.2	
24	21.3	7.4	
48	34.1	12.5	traces
72	46.4	15.8	0.9
96	56.8	18.6	1.6
120	66.6	21.3	2.3

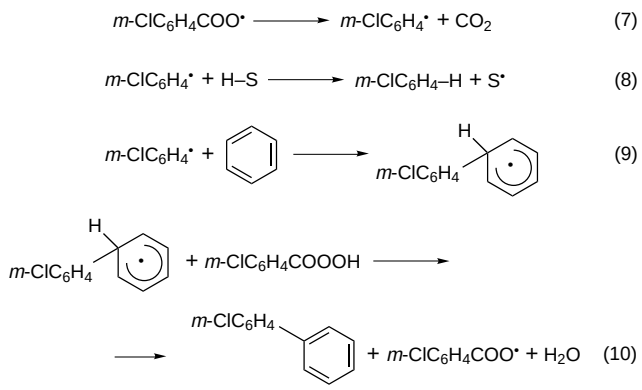
[a] 1 mmol of cyclohexanol, 1 mmol of *m*-CPBA in 5 mL of solvent, air atmosphere. [b] Conversion of cyclohexanol.

kcal/mol greater than C^3-H bond energy in isobutane, and therefore quite close to C^2-H bond energy in alkanes. Moreover, 1-adamantyl cation is considerably more stable than its (secondary) 2-isomer,[28] and the oxidation potential of adamantane (E_{ox} = 2.72 V vs SCE) is considerably lower than that of 2,3-dimethylbutane (E_{ox} = 3.45 V vs SCE),[29] which explains the high sensitivity to polar effects for hydrogen abstraction by electrophilic radicals.

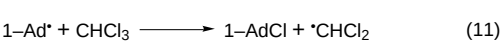
The results of Table 1 clearly indicate that free radicals are certainly involved in the oxidation of adamantane by *m*-CPBA. Esters such as **2** have never been previously reported in alkane oxidation by peracids. This had been considered[18] a significant evidence for an "oxenoid" oxygen insertion mechanism, against electrophilic or free-radical mechanisms. The only reasonable mechanism for the formation of chlorobenzene (**5**) in CH_2Cl_2, $CHCl_3$, or DCE solution and of *m*-chlorobiphenyl (**6**) in benzene solution involves decarboxylation of *m*-chlorobenzoyloxyl radical (eq 2) and subsequent hydrogen abstraction from the solvent (S−H, eqs 7 and 8) or homolytic substitution of benzene (eqs 9 and 10) by *m*-chlorophenyl radical. The different results obtained under oxygen and under argon atmospheres represent a further strong evidence that free radicals are involved in the reaction.

In $CHCl_3$ solution the results are similar to those obtained in CH_2Cl_2 and DCE, with the difference that considerable amounts of 1-chloroadamantane are also

(28) Olah, G. A.; Liang, G.; Mateescu, G. D. *J. Org. Chem.* **1974**, *39*, 3750.
(29) Albini, A. Personal communication.

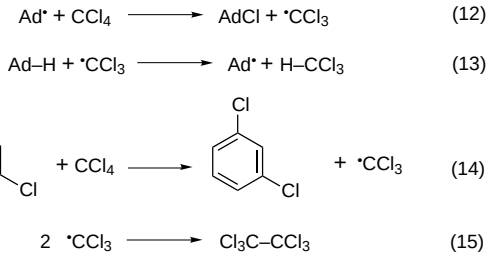


formed. The result is surprising, as $CHCl_3$ has been one of the most utilized solvents in alkane oxidation and until now alkane chlorination has never been reported.[18] The only reasonable explanation we can see for the formation of 1-chloroadamantane is chlorine abstraction from $CHCl_3$ by 1-adamantyl radical (eq 11). On the other hand, it is



well-known[30] that tertiary alkyl radicals abstract hydrogen and chlorine atoms from $CHCl_3$ by quite similar rates.

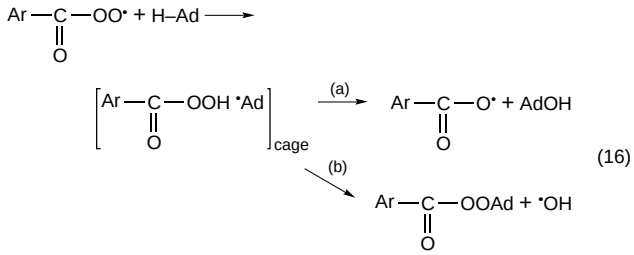
By using a more effective chlorine-transfer solvent, such as CCl_4, free-radical chlorination of adamantane (eqs 12 and 13) is by far prevailing and the byproducts, *m*-dichlorobenzene and hexachloroethane, clearly arise from eqs 14 and 15. $CBrCl_3$ is effective as halogen



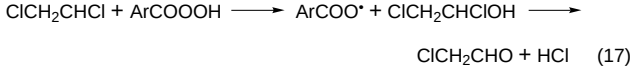
transfer reagent also at low concentration and, even if bromoadamantanes are prevailing, 1-chloroadamantane is a mechanistically significant byproduct, as will be discussed later on.

Thus, there is no doubt concerning the involvement of free radicals in the oxidation of adamantane by *m*-CPBA, but the overall behavior could be, in principle, explained by two simultaneous competitive mechanisms: free radical and oxenoid oxygen insertion. However, the significant formation of free-radical products (**5** and **6**) even at room temperature (18 °C), where the thermal homolysis of the peroxidic bond occurs only in negligible traces, according to the O−O bond energy (34−38 kcal/mol) evaluated[31] for peracids, makes the simultaneous presence of two competitive mechanisms unlikely. Moreover, the inhibition by TEMPO, the halogenation of adamantane in the presence of $CHCl_3$, CCl_4, and $CBrCl_3$ and the formation of 1-adamantyl *m*-chlorobenzoate, whose formation cannot be explained by an oxenoid oxygen insertion mechanism, suggest a general free-radical chain mechanism. *Above all, the fact that the formation of the free-radical products* ***5*** *and* ***6*** *occurs at room temperature in the presence of adamantane, but not in its absence under the same conditions, strongly suggests that adamantane induces the homolysis of m-CPBA.*

Since the free-radical mechanism previously[13] reported is not consistent with the chemo-, regio-, and above all stereoselectivity observed, we suggest a novel general free-radical chain mechanism based on eq 6, which would explain the formation of all the reaction products. The acylperoxyl radical generated in eq 6 selectively abstracts hydrogen from adamantane, leading to adamantyl radical, which rapidly reacts with the peracid in the cage with formation of **1**, **2**, and **3** (eq 16).



It is known that (alkyl) peroxyl radicals do not abstract hydrogen atoms from alkanes at a significant rate ($\sim 10^{-2}$ M^{-1} s^{-1}) at room temperature, but benzoyl peroxyl radicals are about 800−900 times as reactive in hydrogen atom abstraction from hydrocarbons as $HOO^{\bullet}$ (which has a "normal" (alkyl) peroxyl reactivity).[32] Thus reaction 16 should be fast enough to carry the chain.[33] Equation 16a prevails over eq 16b, and eqs 6 and 16a are the propagation steps of the free-radical chain for the formation of the main reaction product **1**. The competitive incursion of eq 7 leads to the classical reaction products arising from aryl radical (**5** and **6**), which do not interrupt the radical chain. In fact, in benzene solution (formation of **6**) the acyloxyl radical is regenerated by eq 10, while in hydrogen donor solvents (CH_2Cl_2, DCE) leading to **5**, radical S$^{\bullet}$ in eq 8 is probably oxidized by the peracid according to eq 17 (S = $ClCH^{\bullet}CH_2Cl$ in DCE solution), even if this oxidation is certainly affected by the nucleophilic character of the alkyl radical.



The high regioselectivity between tertiary and secondary C−H bonds in adamantane oxidation is mainly explained by the electrophilic character of the acylperoxyl radical, which is higher than that of other oxygen-centered radicals, due to the electron-withdrawing effect of the acyl group on the peroxyl radical, to the higher stability of 1-adamantyl as compared to its (secondary) 2-isomer cation[28] and to the low oxidation potential of adamantane.[29]

The high degree of configurational retention in the oxidation of epimeric cycloalkanes[18] should be due to a fast cage reaction of the alkyl radical with the peracid (eq 16, an oxygen rebound mechanism).

(30) Frith, P. G.; McLauchlan, K. A. *J. Chem. Soc. Faraday Trans. 2* **1976**, *72*, 87. Duetsch, H. R.; Fischer, H. *Int. J. Chem. Kinet.* **1982**, *14*, 659.

(31) Liktenshtein, G. I. *Zh. Fiz. Chim.* **1962**, *36*, 1503. Curci, R.; Edwards, J. D. In *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer Academic Publishers: Dordrecht, 1992; p 48.

(32) Zaikov, G. E., Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 3017.

(33) We thank K. U. Ingold for this suggestion.

The behavior observed in the presence of oxygen at room temperature (**5** and **6** are not formed) is explained by the fact that oxygen intercepts all carbon-centered radicals outside the solvent cage. The fact that the amount of chlorobenzene is higher in refluxing CH_2Cl_2 (40 °C) than in DCE at 65 °C (Table 1) under an air atmosphere could appear surprising, since one would expect an increase in decarboxylation of *m*-chlorobenzoyloxyl radical at higher temperature, which actually occurs in DCE solution (Table 1). The larger amount of chlorobenzene in refluxing CH_2Cl_2 must therefore be ascribed to the different concentration of oxygen in the two solvents.

The fact that under argon, but in the absence of adamantane at room temperature, **5** and **6** are not formed suggests the possibility that adamantane might induce, to a small extent, the homolysis of the peracid (eq 18), thus initiating the free-radical chain of eqs 6 and 16a, or in any case that it might sustain the chain process much more effectively than the solvents (eqs 16 and 17).

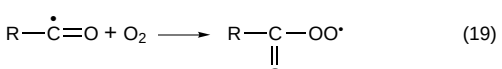
$$\text{Ad—H} + \text{HOOOCAr} \longrightarrow \text{Ad}^{\bullet} + \text{H}_2\text{O} + \text{ArCOO}^{\bullet} \qquad (18)$$

Equation18 can represent an alternative explanation for the formation of **2** through coupling of the radical pair (cage effect); in this case reaction 18 should take place to a higher extent than it would as simple initiation reaction of a chain process.

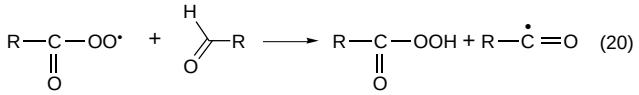
The inhibition in *t*-BuOH solution is related, in our opinion, *to a solvent effect, which inhibits reaction 6 by forming hydrogen bonds between peracid and solvent; the same effect has been observed*[11,22] *for reaction 5 in t-BuOH solution, and the analogy between hydroperoxides and peracids appears to be particularly strict in this context*. The phenomenon is quite general; it has been observed with adamantane (Table 2), cyclohexane (Table 4), and cyclohexanol (Table 6).

The oxidation in benzene solution contrasts with the previous report[18] stating that aromatic nuclei prevent reaction at tertiary C—H bonds in alkylbenzenes, due to "the action of the benzene ring as hydrogen bond acceptor, thus deactivating the peracid". Actually, benzene decreases, to some extent, the rate of oxidation of adamantane and cyclohexanol by *m*-CPBA (Tables 2 and 6), but it does not prevent the reaction. The inertness of alkylbenzenes toward *m*-CPBA must be ascribed, in our opinion, to polar effects (electron-withdrawing effect of the phenyl group, i.e., cumene is less reactive than cyclohexane toward *t*-BuO$^{\bullet}$ radical for polar reasons[11] in spite of the lower energy of the benzylic C—H bond).

Acylperoxyl radicals and peracids are classical intermediates in the autoxidation of aldehydes (eqs 19 and 20), in which both acylperoxyl radicals and peracids are involved. We have obtained further evidence of the



(19)



(20)

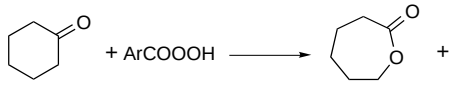
mechanism described by eqs 6 and 16 by investigating the autoxidation of aldehydes in the presence of adamantane and cyclohexanol. We have taken advantage of two different approaches for obtaining evidence that acylperoxyl radicals were responsible for the oxidation. The first approach is based on the use of an aliphatic aldehyde, butanal, because aliphatic peracids are unsuitable for the oxidation of alkanes. This is due, according to our interpretation, to the fact that decarboxylation of aliphatic acyloxyl radicals is much faster[34] ($\sim 10^{10}$ s^{-1}) than that of aromatic acyloxyl radicals[16] ($\sim 10^{6}$ s^{-1}), which determines a fast free-radical chain decomposition of the peracid[35] (eqs 21 and 22) and avoids the intermolecular reaction corresponding to eq 6.

$$\text{RCOO}^{\bullet} \xrightarrow{k} \text{R}^{\bullet} + \text{CO}_2 \qquad k \sim 10^{10}\text{s}^{-1} \qquad (21)$$

$$\text{R}^{\bullet} + \text{RCOOOH} \longrightarrow \text{ROH} + \text{RCOO}^{\bullet} \qquad (22)$$

Actually, the autoxidation of butanal in the presence of adamantane or cyclohexanol provides reaction products similar to those observed with aromatic aldehydes or *m*-CPBA (Table 3). *This result is strong evidence that the species responsible for the oxidation is the acylperoxy radical, formed according to eq 19 and not the peracid, formed in situ*.

The other approach was derived from the observation that cyclohexanone is much more reactive (Baeyer—Villiger) than adamantane toward *m*-CPBA. In the presence of adamantane and cyclohexanone, only the latter is oxidized (eq 23), which means that cyclohexanone completely inhibits adamantane oxidation by *m*-CPBA.

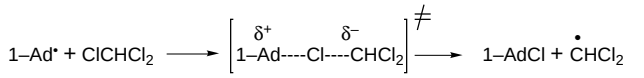


(23)

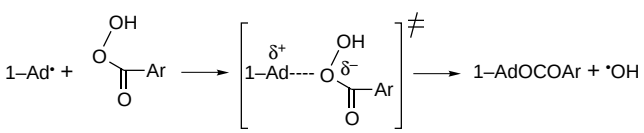
However, autoxidation of *m*-chlorobenzaldehyde in the presence of adamantane and cyclohexanone leads to adamantane oxidation, with results similar to those obtained with *m*-CPBA in the absence of cyclohexanone. *This result provides a further strong evidence that acylperoxy radical is responsible for adamantane oxidation*.

Some differences characterize the oxidation of cyclohexane as compared to adamantane: cyclohexyl *m*-chlorobenzoate is formed only in traces and bromocyclohexane is the only product in the presence of $CBrCl_3$, while adamantane gives significant amounts of 1-chloroadamantane, in addition to 1-bromoadamantane.

We explain these differences on the grounds of the more marked nucleophilic character of 1-adamantyl radical compared to cyclohexyl radical, as a consequence of the particular stability of 1-adamantyl cation.[28] This polar character is reflected, for halogen abstraction and for oxidation by peracids (eqs 24 and 25), in transition states with more charge separation.



(24)



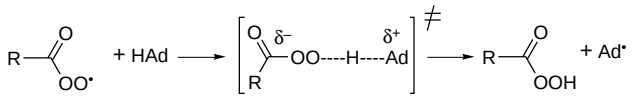
(25)

(34) Turetskaya, E. A.; Skakorskii, E. D.; Rikov, S. V.; Glazkov, Yu.V.; Ol'dekop, Yu.A. *Dokl. Akad. Nauk BSSR* **1980**, *24*, 57.

(35) Lefort, D.; Paquat, C.; Sorba, J. *Bull. Soc. Chim. Fr.* **1959**, 1385.

On the other hand, the peculiar behavior of 1-adamantyl radical in chlorine and bromine abstraction from $CBrCl_3$, quite different from that of simple alkyl radicals, which only abstract bromine, was first reported by Rüchardt[36] and confirmed by Tabushi.[37] We believe that a transition state similar to the one in eq 24 is responsible for this behavior. A ratio of about 1:20 between 1-chloro- and 1-bromoadamantane is a valuable diagnostic criterion[37] for the formation of 1-adamantyl radical in the presence of $CBrCl_3$.

The high regioselectivity between C^3-H and C^2-H in adamantane and the high chemoselectivity in competitive oxidation of cyclohexane and adamantane (adamantane is >50 times more reactive than cyclohexane) is also explained by charge separation in the transition state (eq 26).



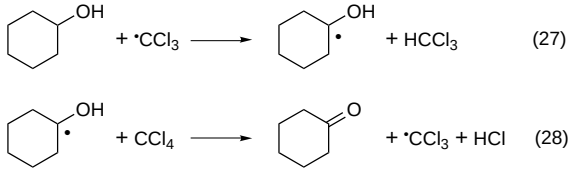
(26)

This conclusion, of a high sensitivity to polar effects by acylperoxy radicals, was in striking contrast with previous reports[38] stating that primary and secondary alcohols are unreactive with peracids (perbenzoic acid decomposes in ethanol solution in two months at room temperature[39]). In fact, hydrogen abstraction from C−H bonds in the α-position of alcohols is particularly sensitive to the electrophilic character of the abstracting radical, due to the particular stability of the α-hydroxy carbonium ion. Also the results obtained with cyclohexane (Table 4), with cyclohexanone and caprolactone prevailing over cyclohexanol even at low conversion (∼10%), are in contrast with the same reports[38,39] because they indicate that cyclohexanol is much more reactive than cyclohexane toward *m*-CPBA. Actually, primary and secondary alcohols smoothly react in CH_2Cl_2, $CHCl_3$, CCl_4, or DCE solution, giving the corresponding carbonyl compound and the further oxidation products (lactones, esters, carboxylic acids) (Table 5). *Thus the previously*[38,39] *reported inertness of primary and secondary alcohols towards peracids must be ascribed to the fact that alcohols were utilized as solvents, which inhibit reaction 6 by forming hydrogen bonds with peracids.* This is clearly shown by the results in Table 6.

Competitive experiments, in fact, indicate that the α-hydroxy C−H bond in cyclohexanol is about 3 times more reactive than a C^3-H bond in adamantane, while benzyl alcohol is slightly less reactive than 1-heptanol (relative rates 1:1.2) in spite of the weaker benzylic C−H bond, once again supporting the influence of the polar effect on oxidation rates.

The oxidation of alcohols is more effective in $CHCl_3$ or CCl_4 solution; in these cases radical chains involving $^{\bullet}CCl_3$ radicals (eqs 27 and 28) are superimposed on the oxidation chain (eqs 6 and 16) and contribute to the overall oxidation of alcohols.

The oxidation of cyclohexanol under autoxidation conditions of butanal gives cyclohexanone and caprolactone as the main reaction products, supporting also for



alcohol oxidation the involvement of acylperoxyl radicals according to eq 16. This is particularly favored by the stability of the α-hydroxy carbonium ion. Contrary to the oxidation of cyclohexanol by *m*-CPBA, in which caprolactone is the main reaction product (Table 5), in this case cyclohexanone is prevailing, due to the low concentration of the peracid formed from the aldehyde.

Conclusion

The most significant evidences concerning a novel mechanism for the selective oxidation of alkanes and alcohols by peracids according to eqs 6 and 16 involve the following aspects: (i) the formation of products from aryl radical; (ii) the effect of oxygen on product distribution; (iii) induced homolysis of peracids by alkanes and alcohols; (iv) halogen transfer from halogenated solvents or reagents toward the carbon-centered radicals; (v) oxidation of alkanes and alcohols during the autoxidation of aldehydes; (vi) inhibition effect of solvents, which form hydrogen bonds with peracids (this latter evidence explains the previously reported inertness of alcohols toward peracids); (vii) inhibition by TEMPO.

The high regio- and chemoselectivities are due to the marked electrophilic character of acylperoxyl radicals, and the previously reported stereoselectivity is ascribed to a fast cage reaction of alkyl radicals with peracids.

Experimental Section

General Methods. Mass spectra were performed on a GLC−MS Finnigan TSQ70 instrument, using a Varian 3700 gas chromatograph, equipped with SBP-1 fused silica column (30 m × 0.2 mm i.d., 0.2 μm film thickness) and helium as carrier gas.

GLC analyses were performed on a Dani 6500 capillary gas chromatograph, equipped with a 25 m × 0.25 mm i.d. SBP-5 fused silica column (1 μm film thickness) at a hydrogen flow rate of 8 cm^3 min^{-1}, PTV injector, flame ionization detector.

All of the solvents and the reagents were obtained from commercial sources and were used without further purification.

tert-Butyl peroxalate, $(t\text{-BuOOCO})_2$, was prepared according to the literature procedure.[40] All the reaction products were commercially available and were utilized for the qualitative identification (GLC−MS) and the quantitative analyses (GLC).

General Procedure for the Oxidation of Alkanes and Alcohols. The procedure is extremely simple: *m*-CPBA and the alkane or alcohol were dissolved in the solvent and stirred at the temperature and for the time reported in Tables 1−6. Most of the experiments were carried out under an air atmosphere, while for few experiments (Table 1) the solution was purged with argon or oxygen for 10 min before adding *m*-CPBA and kept under argon or oxygen for the duration of the experiment. The solvents and the concentration of the reagents are reported in Tables 1−6. At the end of the reaction, an internal standard was added and the solution was directly analyzed by GLC−MS and GLC.

Competitive Oxidation of Adamantane and Cyclohexane. Five millimole of cyclohexane, 1 mmol of adamantane,

(36) Rüchardt, C.; Herwig, K.; Eichler, S. *Tetrahedron Lett.* **1969**, 421.

(37) Tabushi, I.; Aoyama, Y.; Kojo, S.; Hamuro, J.; Yoshida, Z. *J. Am. Chem. Soc.* **1972**, *94*, 1177.

(38) Bouillon, G.; Lick, C.; Schank, K. *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: New York, 1983; p 295.

(39) Tokumaru, K.; Simamura, O.; Fukuyama, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1674.

(40) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1762.

and 1 mmol of *m*-CPBA were dissolved in 10 mL of DCE. The solution was stirred for 48 h at 20 °C under air atmosphere and analyzed by GLC−MS and GLC. The conversion of adamantane was 20.9%, while the conversion of cyclohexane was <1%; **1** and **2** were the reaction products, and only traces (<0.2%) of **3**, cyclohexanol, and cyclohexanone were formed. The relative rate between adamantane and cyclohexane oxidation can be thus evaluated as >50.

Competitive Oxidation of Adamantane and Cyclohexanol. One millimole of cyclohexanol, 1 mmol of adamantane, and 1 mmol of *m*-CPBA were dissolved in 10 mL of DCE. The solution was stirred for 48 h at 18 °C under an air atmosphere and analyzed by GLC−MS and GLC. The conversions of cyclohexanol and adamantane were respectively 8.5% and 11.3%. Caprolactone, **1**, and **2** were obtained in a 1.0:1.1:0.2 ratio. The C^3−H of cyclohexanol, this way, is 3 times more reactive than the C^3−H of adamantane.

Oxidation of Adamantane and Cyclohexanol by Aldehydes and O_2. Procedure A. One millimole of cyclohexanol or adamantane was dissolved in 5 mL of DCE. The solution was purged with O_2 for 10 min, and a solution of 2 mmol of the aldehyde in 5 mL of DCE was dropped under stirring during 3 h at 70 °C. O_2 was introduced in the solution at a rate of 2 mL/min for the duration of the experiment (24 h at 70 °C). At the end of the reaction, an internal standard was added, and the solution was analyzed by GLC−MS and GLC. **Procedure B.** As in procedure A, with the differences that 0.1 mmol of (*t*-BuOOCO)$_2$ was added to the aldehyde solution in DCE and that the reaction temperature was 40 °C.

The results are reported in Table 3.

JO961366Q