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Free-Radicals in the Oxidation and Halogenation of Alkanes by Dimethyldioxirane: an Oxygen Rebound Mechanism.

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Abstract: The oxidation of alkanes by dimethyldioxirane (DMD) in the presence of $CBrCl_3$ provides strong evidence that free-radicals are involved in the reaction; enthalpic and polar effects and an "oxygen rebound" mechanism are suggested to explain the exceptional oxidation selectivity.

In the last 15 years the use of dimethyldioxirane (DMD) as oxidant has attracted the interest of several research groups[1], due to the extraordinary regio-, chemo- and stereoselectivity shown by this reagent in various reactions, particularly in the oxidation of unactivated C-H bonds of alkanes, which represents an everlasting challenge in organic chemistry. The exceptional selectivity has led to exclude the involvement of free-radicals and a concerted "oxenoid O-insertion" has been suggested[1] for these oxidations, as well as for other oxidative functionalizations of alkanes, catalyzed by metal salt complexes[2]. However, the mechanistic meaning of this expression does not appear to be well defined, in spite of the theoretical attempts[3] at rationalizing the phenomenon. It would appear that, when the selectivity of the oxidative funcionalization of alkanes can not be explained by the known free-radical chemistry, the magical expression "O-insertion" can settle all the mechanistic problems. In this Letter we provide evidences that free-radicals are involved in the oxidation of alkanes by DMD.

When the oxidation of alkanes by DMD in acetone is carried out at room temperature in the presence of variable amounts of $CBrCl_3$, the formation of haloderivatives competes with the formation of alcohols and ketones. The reaction products with adamantane are: 1-adamantanol (**1**), 1-chloroadamantane (**2**), 1-bromoadamantane (**3**), 2-bromoadamantane (**4**), and small amounts of 2-adamantanol (**5**) and adamantanone (**6**). The results are reported in Table 1.

With cyclohexane three reaction products are formed: bromocyclohexane (**7**), cyclohexanol (**8**) and cyclohexanone (**9**). The results are reported in Table 2.

Table 1. Oxidation and Halogenation of Adamantane (1 mmol) by DMD (0.5 mmol) and $CBrCl_3$[a].

conversion (%)[b]	$CBrCl_3$ (mmol)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	3 / 4
62	0.25	60.0	2.6	29.6	5.6	0.7	1.5	5.3
68	0.50	47.1	3.6	40.2	7.4	0.5	0.8	5.4
76	1.00	34.1	4.8	50.9	9.2	0.6	0.4	5.5
79	2.50	19.2	4.1	57.1	19.0	0.4	0.2	3.0
80	4.00	16.3	4.4	55.7	23.6	traces	--	2.4

[a] the reagents are dissolved in acetone (5 mL) and analyzed by GLC after 1h at room temperature; [b] conversion of adamantane based on DMD.

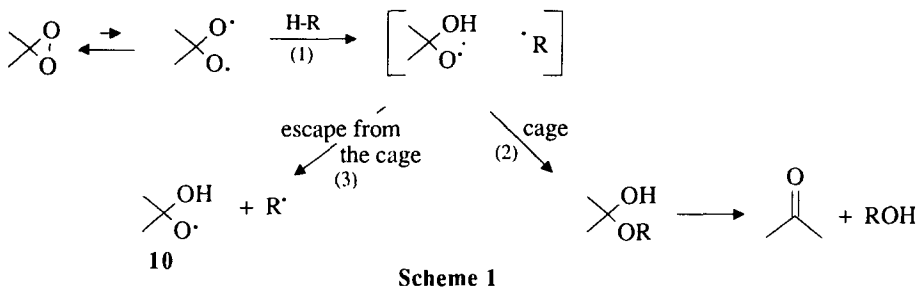
Table 2. Oxidation and Halogenation of Cyclohexane (4 mmol) by DMD (0.5 mmol) and $CBrCl_3$

$CBrCl_3$ (mmol)	7 (%)	8 (%)	9 (%)
0.25	53.4	27.8	18.8
0.50	62.1	28.5	9.4
2.50	90.4	9.2	0.4
4.00	94.7	5.3	traces

The following aspects suggest that free-radicals are involved in the reaction:

i) the formation of bromoalkanes in a short time at room temperature strongly supports the involvement of free-radicals; no halogenation occurs under the same conditions in the absence of DMD; ii) the formation of 1-chloroadamantane as a byproduct is a strong evidence that 1-adamantyl radical is involved[4]; iii) the ratios between oxidation (alcohols and ketones) and halogenation products are strictly dependent on the ratio between DMD and $CBrCl_3$, which suggests the two reactions to be competitive processes involving some common free-radical intermediate iv) the ratio between **3** and **4** is constant at lower concentrations of $CBrCl_3$, but it decreases significantly at higher concentrations, thus suggesting that several hydrogen abstracting species might be involved in the generation of adamantyl radicals.

We suggest that these results can be rationalized through Scheme 1.



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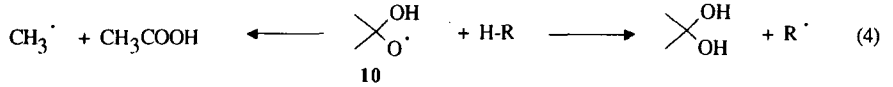
Scheme 1

A free-radical "oxygen rebound" mechanism in the solvent cage would explain the oxidation products (eq. 2). The radical pair escaping from the solvent cage can initiate chain processes according to eqs. 4-7.



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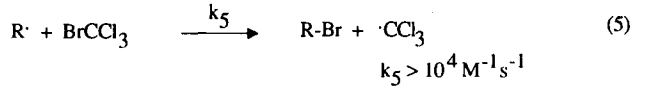
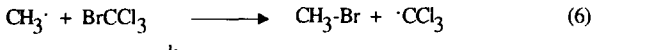
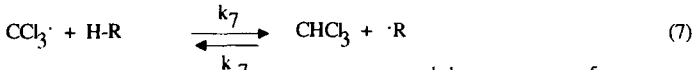






$k_7 = 3.4\ M^{-1}s^{-1}$ for toluene at 328 K[5]

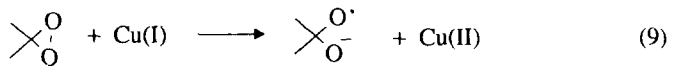
$k_{-7} = 4.8 \times 10^3\ M^{-1}s^{-1}$ for primary alkyl radical at 263 K[6]

We have previously[7] shown that the radical **10**, generated from acetone peroxide, can give hydrogen abstraction from C-H bonds, and that it can also undergo β-scission generating methyl radical (eq.4). The kinetic length of the propagation chain (eqs.5 and 7) is quite short at room temperature, because reaction (5) is fast, but reaction (7) is slow and reversible (the reversal of eq.7 is much faster[5,6], as it is a key step in the free-radical addition of $CHCl_3$ to alkenes), so that several reactions (eqs. 1, 4, 7) can contribute to generate the alkyl radicals trapped by $CBrCl_3$, whereas the oxidation products mostly arise from the more selective eq.1.

Further evidence for the intermediate formation of alkyl radicals in the oxidation of adamantane by DMD was obtained in the presence of $CuCl_2$ (1 mmol adamantane, 1 mmol DMD, 1 mmol $CuCl_2$, 1 mmol LiCl in 5 mL of acetone at room temperature): 1-chloro-, 2-chloro-adamantane and 1-adamantanol are formed respectively in 68.9 %, 28.7% and 2.4% yield, but the conversion is low (10%). We explain this result by the fact that the adamantyl radical (R·), escaped from the solvent cage (eq.3), is trapped[8] by $CuCl_2$ generating a redox chain (eqs.8 and 9)

$$R^{\cdot} + Cu(II)Cl \xrightarrow{k_8} R\text{-}Cl + Cu(I) \qquad (8)$$

$$k_8 > 10^8\ M^{-1}s^{-1} \text{ at } 298\ K$$



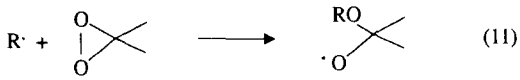
(9)

The radical **10** mostly undergoes β-scission giving methyl radical (eq.4) and methyl chloride (eq.10) and to a minor extent it undergoes hydrogen abstraction (eq.4) generating 1- and 2-adamantyl radicals and sustaining the redox chain of eqs. (8) and (9). This explains the low conversion of adamantane (most of DMD is consumed to form CH_3Cl and CH_3COOH) and the small amount of 1-adamantanol.

$$CH_3^{\cdot} + Cu(II)Cl \longrightarrow CH_3\text{-}Cl + Cu(I) \qquad (10)$$

The relative rates for several alkanes have been determined by the competitive method in the absence and in the presence of $CBrCl_3$, in order to obtain evidence concerning the structural factors affecting the selectivity. The results are reported in Table 3.

The selectivity for the oxidation is higher than for the halogenation because the former mainly arises from eq.(1) and "oxygen rebound", whereas the selectivity for halogenation is mainly due to eqs. (4) and (7) and it depends on DMD : $CBrCl_3$ ratio (Table 1). However, also the selectivity for the oxidation is somewhat lower in the presence of $CBrCl_3$; we explain this result by the fact that alkyl radicals, generated according to eqs. (4) and (7), are mainly trapped by $CBrCl_3$ (eq.5), but to a minor extent also by DMD (eq.11).



(11)

To explain the extraordinary selectivity for alkane oxidation by DMD we simply suggest that DMD can be considered, under mild conditions, a highly selective oxygen-centered radical, which determines a high regio- and chemoselectivity in hydrogen abstraction (eq.1), while the very fast "oxygen rebound" mechanism would explain the reported[1] stereoselectivity. This is not surprising if we consider the very large differences in selectivity among other oxygen-centered radicals (ROO· >> $R_2C(OH)O\cdot$ >> RO· >> HO·).

Table 3. Relative rates (per H Atom) for the Oxidation of Alkanes byDMD[a]

ALKANE	in the absence of $CBrCl_3$ OXIDATION	in the presence of $CBrCl_3$ OXIDATION	HALOGENATION
adamantane (tert. C)	1	1	1
adamantane (sec. C)	0.009	0.016	0.086
cyclohexanol (tert. C)	23.20	--	--
cyclohexane (sec. C)	0.002	0.0075	0.02
n-hexane (sec. C[b])	0.006	--	--
2,3-dimethylbutane (tert. C)	0.11	0.12	0.88
chlorocyclohexane[b]	$< 10^{-4}$	--	--

[a] 0.5 mmol DMD and $CBrCl_3$ in 5 mL of acetone were utilized in all the experiments; [b] the isomer distribution was not determined.

From the results in Table 3 it clearly appears that reaction (1) is highly affected by enthalpic (influence of the energies of the involved bonds) and polar effects (hydrogen abstraction is strongly affected by polar substituents, the electron-releasing hydroxy group in cyclohexanol and the electron- withdrawing chlorine atom in chlorocyclohexane in Table 3, due to the electrophilic character of the abstracting species). We explain the high sensitivity to the enthalpic effect by the relatively low energy of the O-H bond in the radical $Me_2C(O\cdot)O$-H, considerably lower than in alcohols (the homolysis of this bond leads to H atom and dioxirane). From this point of view, this oxidative functionalization of alkanes has a close resemblance with the Minisci[9] chlorination, which is also particularly sensitive to enthalpic and polar effects[10], and a similar behaviour has been recently reported[4] for the chlorination of adamantane. This also explains the fact that during the oxidation of methylene groups the ratio ketone : alcohol rapidly increases with the conversions (Tables 1 and 2).

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