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THE OXIDATION OF ALKANES WITH DIMETHYLDIOXIRANE; A NEW MECHANISTIC INSIGHT

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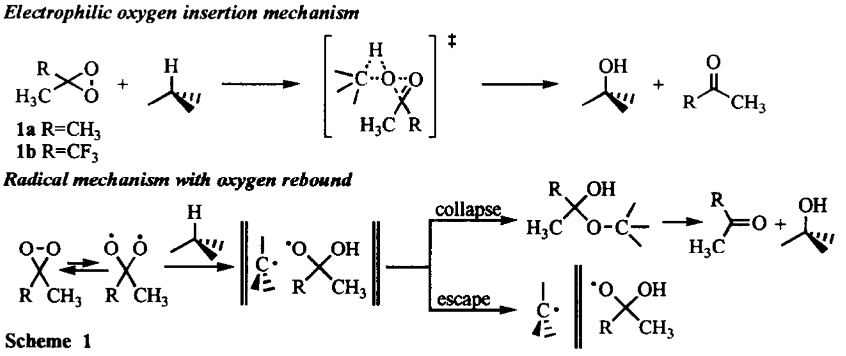
Summary: Primary kinetic isotope effects were measured for the oxidation of cyclohexane and methylcyclohexane with DMDO in solution and in the gas phase. These experiments suggest an electrophilic oxygen insertion mechanism for the oxidation of alkanes by DMDO.

The oxidation of alkanes with dioxiranes is an important tool in organic synthesis since it allows, under mild conditions and very short reaction times, the selective conversion of alkanes into alcohols or ketones with excellent yields.[1] Controversial mechanisms have been suggested to account for the formation of these oxidation products. It has been proposed that oxyfunctionalization is an electrophilic insertion process at the C-H bond which occurs by a concerted mechanism involving an "oxenoid" transition state.[1c-e,2] Alternatively, a radical mechanism has been proposed which involves hydrogen abstraction from the alkane by the dioxirane followed by "oxygen rebound"[3], i.e., the rapid coupling of the radicals in the solvent cage (Scheme 1).


Electrophilic oxygen insertion mechanism

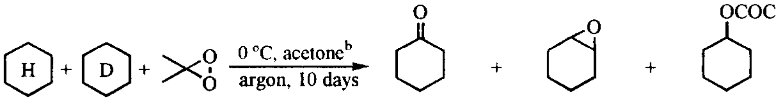
Radical mechanism with oxygen rebound

Scheme 1

Among the main features that can be explained by the concerted mechanism are i) the high efficiency of the oxidation reaction,[1] ii) the high regio- and stereoselectivity[1] and iii) the complete retention of configuration in the oxidation of C-H bonds at the chiral centre of an optically active hydrocarbon.[1c] Furthermore, the oxidation of alkanes with dioxiranes follows second-order kinetics first-order with respect to dioxirane and alkane[1c] and the solvent greatly affects the reaction rate.[2b] On the other hand, the radical mechanism recently proposed by Minisci et al.[3a,b] is supported by the appearance of some radical-derived products in these reactions, whose formation is inhibited when the reactions are carried out in the presence of oxygen or other radical traps. In this letter, we report our findings regarding the mechanism of the oxidation of hydrocarbons by DMDO based on the measurement, in solution and in the gas phase, of the $k_{H/D}$ primary kinetic isotopic effect in the formation of products resulting from the competitive oxidation of regular and perdeuterated mixtures of hydrocarbons.

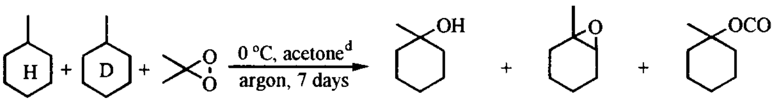
The results of the oxidation with DMDO (**1a**) of two mixtures composed of cyclohexane (**2a**) and perdeuterocyclohexane (**2a**-d_{12}) and of methyl cyclohexane (**2b**) and perdeuteromethylcyclohexane (**2b**-d_{14}) in acetone solution at 0 °C in the absence of oxygen are shown in Table 1.[4] The reaction times were remarkably long and the conversion of the substrates was as low as 4.6% for cyclohexane and 9.6% for methylcyclohexane after 10 and 7 days, respectively. Three different types of regular and deuterated oxidation products were obtained in each case; the ketone **3a** or the alcohol **3b** depending on the methylene or methyne nature of the C-H bond to be oxidized, the epoxide **4**, and the acetic acid ester **5**. In the oxidation of **2b** and **2b**-d_{14} , minor amounts (<1.4%) of 2-, 3-, and 4-methylcyclohexanone could be identified in the reaction mixture. Different kinetic isotopic effects $k_{H/D}$ were measured for each type of reaction product. The largest values were found for compounds **3**: 6.76 for **3a** and 6.05 for **3b**. In contrast, values of $k_{H/D}$ ranging from 3.49 to 4.73 were obtained for compounds **4** and **5** (Table 1). Reactions under argon at room temperature were faster and gave similar results. For instance, the conversion of DMDO in the oxidation of **2a** was complete in 5 days with the same product distribution as at 0 °C. When the reactions were carried out in the presence of oxygen, the conversion of the substrates increased up to 11.3% in the case of **2a** and to 16.2% for **2b**.

Table 1 Primary kinetic isotopic effect in the oxidation of **2a**, **2a**-d_{12}, **2b** and **2b**-d_{14} with DMDO (**1a**)[a] in acetone solution.



2a **2a**-d_{12} **1a**

3a 75.10%	**4a** 7.49%	**5a** 3.75%
3a-d_{10} 11.11%	**4a**-d_{10} 1.58%	**5a**-d_{11} 0.92%
k_H/k_D=6.76±0.14[c]	k_H/k_D=4.73±0.11[c]	k_H/k_D=4.08±0.02[c]

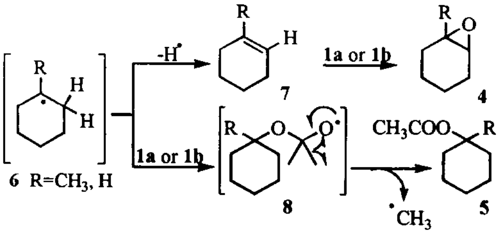


2b **2b**-d_{14} **1a**

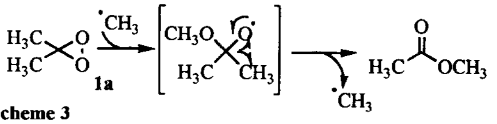
3b 79.93%	**4b** 2.92%	**5b** 1.38%
3b-d_{14} 13.21%	**4b**-d_{12} 0.77%	**5b**-d_{13} 0.39%
k_H/k_D=6.05±0.27[c]	k_H/k_D=3.79±0.07[c]	k_H/k_D=3.54±0.04[c]

[a] Initial concentration of reactants: 0.05M. [b] DMDO conversion 90%; alkane conversion 4.6%. [c] Standard error values represent the media of three identical experiments. [d] DMDO conversion 98%; alkane conversion 9.6%; 2-, 3-, and 4-methylcyclohexanone were also detected in <1.4% yield.

The formation of minor amounts of epoxides **4** and acetic acid esters **5** was also observed in these oxidations. The low yields obtained of compounds **4** and **5**, compared with **3**, indicate that they are derived from a less-important side-reaction path, probably a short radical chain of low efficiency (Scheme 2). This is in good agreement with the recent results reported by Ingold *et al.*[3c] Epoxides may arise through epoxidation of the corresponding alkene obtained by the loss of hydrogen from the radical precursor. On the other hand, the low conversion of the starting alkane **2** and the total conversion of DMDO suggest that the main task of the radical chain is to decompose DMDO in a process that does not result in any oxygen transfer to the substrate. The radical chain decomposition of DMDO would yield methyl acetate (see Scheme 3), by analogy to the thermal decomposition of DMDO in solution[5a] or the photolysis of TFDO (**1b**).[5b] The fact that different primary kinetic isotopic effects were measured for the formation of compounds **3**, **4**, and **5** (see Table 1) clearly indicates that different reaction pathways are followed in each case. The greatest $k_{H/D}$ value ~~of~~ was found for the formation of the regular oxidation product **3**. Epoxides **4** and acetates **5** are derived from cyclohexyl radical **6**. Thus, they may involve a common slow hydrogen abstraction step. The $k_{H/D}$ values for compounds **3** and **4** are quite close, as expected, although that for epoxides **3** is slightly larger since a second PKIE must be added in association with the second hydrogen/deuterium atom abstraction from which the alkene precursor is formed (Scheme 2). Since hydrogen abstraction is the slow step in the radical mechanism proposed[3a] for oxidations with DMDO, the significantly higher $k_{H/D}$ value observed here for the regular oxidation products **3** , compared with those for **4** and **5**, suggests that i) cyclohexyl radicals **6**, from which epoxides **4** and acetates **5** are derived, are generated by a hydrogen abstraction agent other than dioxirane, and ii) the effectiveness of the hypothetical collision of the radicals in the solvent cage (oxygen-rebound) is extremely high; this agrees well with the high stereoselectivity[1] found in the oxidation of alkanes with dioxiranes and also with experiments carried out by Ingold et al[3c] with the radical-clock 2-cyclopropylpropane. Based on the above discussion, the radical mechanism would be clearly supported by the observation of significant differences in the product distribution in gas-phase oxidations, since cage effects would be absent under these conditions; in the oxidation of cyclohexane (**2a**)[6], the yield ofcyclohexyl oxide (**4a**) and cyclohexyl acetate (**5a**), the radical out-of-cage coupling products, should increase at the expense of the formation of cyclohexanone (**3a**), the oxygen-rebound product. On the other hand, the observation of the same product distribution in both solution and in the gas phase would support a concerted electrophilic insertion mechanism. Therefore, we carried out the gas-phase oxidation of **2a** with DMDO at room temperature in the dark, and cyclohexanone **3a** was again the major reaction product (Table 2). Compounds **4** and **5** were not even detected under these conditions. In fact, a new product **9** derived from the methyl radical was found. The reaction was run until DMDO had disappeared, but only a low conversion of the alkane, *ca.* 2%, was achieved. Control experiments showed that DMDO was much less stable in the gas phase than in solution under our reaction conditions. This explain the lower alkane conversion found in this case. The $k_{H/D}$ value found in the gas-phase oxidation of a mixture of **2a** and **2a**-d_{14} (Table 2) was lower than that in the oxidation of the same mixture in solution. Since cyclohexanone is the only oxygenated product formed in gas-phase oxidations, and oxygen-rebound in the solvent cage is not present under these conditions, we can

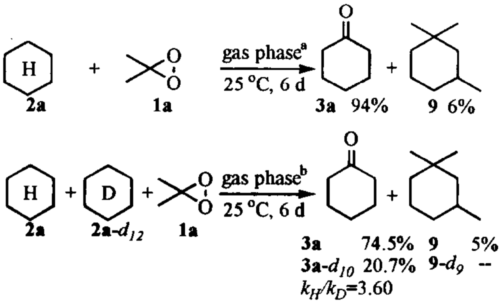


Scheme 2



Scheme 3

Table 2
Oxidation of **2a** and **2a**-d_{12} with DMDO (**1a**) in gas phase.



[a]Initial molar ratio **2a**/**1a**=22/1; DMDO conversion 100%; alkane conversion 2.0%. [b]Initial molar ratio **2a**/**2a**-d_{12}/**1a**= 22/22/1; DMDO conversion 98%; alkane conversion 9.6%

conclude that the regular DMDO alkane oxidation products are not derived from a radical mechanism, but most likely are formed by a concerted electrophilic O-insertion in the C-H bond.

In any case, radical-derived side-products like **4** and **5** are observed when oxidations are carried out with dioxiranes; hydrogen abstraction from alkanes by dioxiranes could give rise to free radicals that escape from the solvent cage, leading to the radical-derived side-products and also to the radical chain decomposition of dioxiranes. To explain the radical behavior of dioxiranes, the existence of a pre-equilibrium condition between the cyclic peroxide form and the corresponding dioxyl radical[3] has been proposed, but no experimental support has been provided. However, there is no need for such a pre-equilibrium, since it is known that diamagnetic species are able to give rise to radical processes.[7] Alternatively, we propose that the free radicals involved could originate from a change in the dioxirane electronic configuration produced by dioxirane-alkane interaction and favoured by the small energy difference between the $(\sigma, \sigma)^1$ state of the cyclic peroxide and the $(\pi,\pi)^3$ triplet state of the dioxyl biradical.[8] In this way, depending on the energy and direction of the interaction, either the electrophilic O-insertion reaction or the transformation of the dioxirane into the dioxyl biradical would occur. Methyl radicals could be readily formed by β-fragmentation of dioxyl biradicals, and they would account for the radical chain decomposition of the peroxide and also for the formation of alkyl radicals from the substrate. The formation of a dioxyl biradical by the mechanism proposed here would be more efficient when bromotrichloromethane is present in the reaction medium due to the heavy atom effect and would support the results recently reported by Minisci *et al.*[3b]

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4) 0.05M Solutions were used with a 1:2:2-*d*=1:1:1 final molar ratio. Methyl *para*-chlorobenzoate was introduced as internal standard. The amount of DMDO was monitored by iodometric titration and GC analysis of aliquots previously quenched with dimethylsulfide. The reactions in absence of oxygen were carried out under argon atmosphere with degasified solvents. For reactions under oxygen this gas was used instead of argon. Colored glass Schlenk tubes were used to avoid the presence of light. All reactions were analyzed by GC and GC-MS using authentic samples in the identification of the products.

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6) The gas-phase oxidation of cyclohexane was carried out in two colored glass flasks of 1000 and 500 mL, containing 3.2 mL of a 0.0298 M acetone solution of DMDO and 0.2 mL of cyclohexane (1.86 mmol) respectively which were frozen with liquid nitrogen, evacuated (10^{-3} mm) and then connected allowing the temperature to reach the room temperature. After 6 days, the reaction mixture was frozen, quenched with a dichloromethane solution of *cis*-3-hexen-1-ol and analyzed by GC and GC-MS by comparison of the products with authentic samples.

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