Pergamon

Tetrahedron Letters, Vol. 36, No. 44, pp. 7999-8002, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01666-X

Mechanism of Hydroxylation of Alkanes by Dimethyldioxirane. A Radical-Clock Study.[1]

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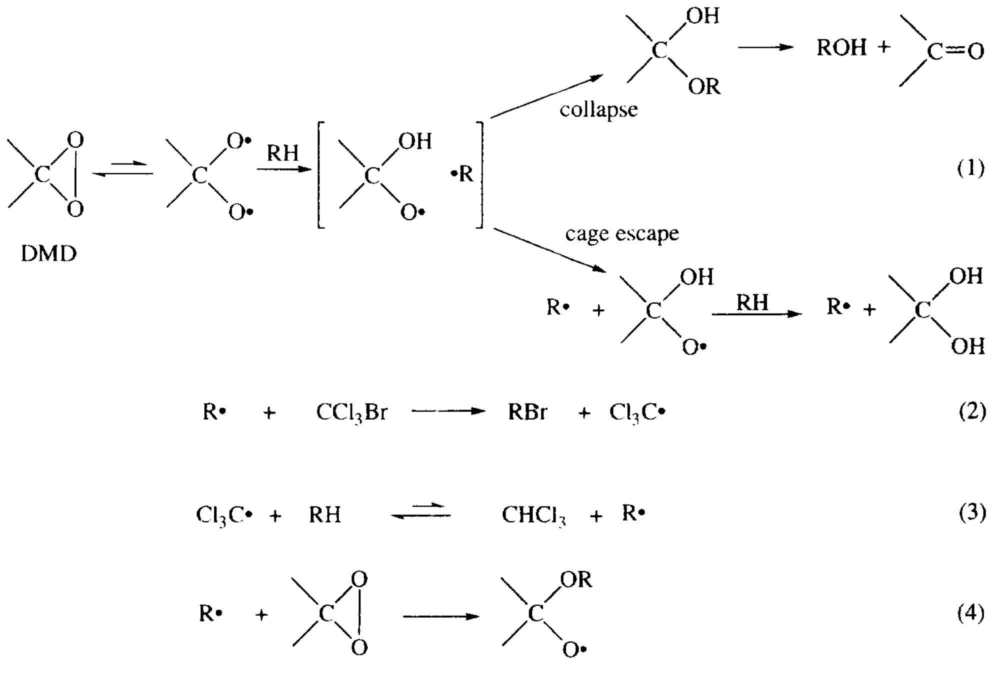
Abstract: The oxidation of 2-cyclopropylpropane by dimethyldioxirane (DMD) to 2-cyclopropyl-propan-2-ol is not a *free*-radical chain reaction. It is suggested the *free*-radical chain observed by Minisci et al.[8] when alkane / DMD reactions were carried out in the presence of CCl_3Br involves H-atom abstraction from the alkane by $Cl_3COO•$ (in air) and by $Me_2C(O•)OCCl_3$ as well as by the $Cl_3C•$ radical.

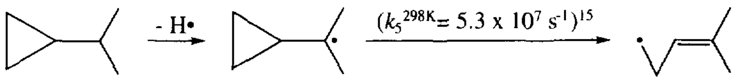
The hydroxylation of alkanes by cytochrome P450 and by dimethyldioxirane (DMD) show numerous similarities, most notably that *free*-radicals (i.e., radicals which can diffuse freely through the solution) do not appear to be involved. Indeed, it has generally been accepted that the oxidation of alkanes by DMD involves a concerted oxygen atom insertion into a C-H bond.[4] Certainly the involvement of *free*-radicals appeared unlikely in view of the stereospecificity of such hydroxylations[5] until Minisci et al.[8] demonstrated that high yields of alkyl bromides could be produced by the simple expedient of adding relatively low concentrations of CCl_3Br to the normal reaction medium.



Scheme 1

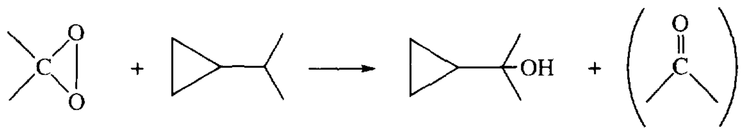
For example, with equal concentrations of DMD (0.1 M) and CCl_3Br (0.1 M) in acetone at room temperature, a reaction with 0.2 M adamantane (68 % conversion based on DMD) yielded 51.2 % adamantyl halides and 48.4 % oxygenated products and a reaction with 0.8 M cyclohexane gave 62.1 % cyclohexyl bromide and 37.9 % oxygenated products. Minisci's results[8] leave little doubt that *free*-radicals (R•) can be formed in DMD / alkane (RH) / CCl_3Br reactions and that these radicals can diffuse through the solution where they react with CCl_3Br. It was also concluded that the R• radicals reacted to a minor extent with the DMD since the selectivity for oxidation was somewhat lower in the presence of CCl_3Br. The results were rationalized via a previously considered but rejected[4b] free-radical type of "oxygen rebound" mechanism with a radical chain reaction being initiated by escape from the caged radical pair, see Scheme 1. It was pointed out that the chain-length must be quite short because hydrogen abstraction by Cl_3C• (reaction 3) is slow and reversible. (The value quoted[8] for k_3 was 3.4 $M^{-1}s^{-1}$ for toluene at 328 K; this reaction would be very much slower for an alkane at 298 K.) If the chain-length is short, it necessarily follows from the high yields of alkyl halides that cage escape must be rather significant relative to cage collapse.

With this last point in mind we have applied the radical clock[9] approach to examine further the DMD / alkane reaction[10]. We required a substrate which contained a tertiary hydrogen atom (for relatively easy oxidation by DMD to the corresponding tertiary alcohol with no further oxidation of this product) and which would yield a radical clock sufficiently "fast" to be suitable for the detection of *free*-radicals (but too "slow" to undergo rearrangement while still within a solvent cage[13]). These requirements were found to be met by 2-cyclopropylpropane:



(5)

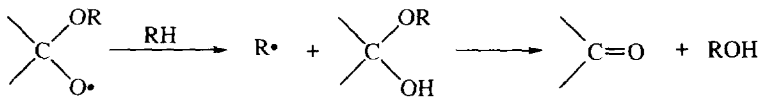
Reactions were carried out in acetone, under air, at 25°C with the results shown below (percentage yields are based on DMD):



(6)

Expt.	(M)	(M)	(M)
1	0.032	0.033	0.0095 (30 %)
2	0.024	0.26	0.012 (50 %)
3	0.0028	0.24	0.0011 (40 %)

We did not observe any oxygenated products arising from the rearranged primary alkyl radical (possibly because of the large number of products which this radical might form).[16] At low, but roughly equal, concentrations of the reagents (~0.032 M) 30% of the available oxygen in the DMD is accounted for as tertiary alcohol (Expt. 1). This figure rises to 50% with a ten fold excess of substrate (Expt. 2). Much more importantly, a nine fold reduction in the concentration of DMD still gave a 40% yield of the tertiary alcohol (Expt. 3). Although these results do not lend themselves to a quantitative kinetic analysis[17] it is clear that a 90% change in the initial DMD concentration produced only a 10% change in the alcohol yield / $[DMD]_{initial}$. Most of the alcohol must therefore be formed by cage collapse (or "oxygen insertion") and not via reactions 4 and 7.



(7)

Thus, we are faced with a dilemma. Our results, in agreement with earlier work,[4,5] indicate that oxygenated products are not produced to any significant extent in a radical chain reaction. This implies either that "oxygen insertion" really occurs (which is improbable) or that very few radicals escape from the solvent cage (which is eminently reasonable in that the cage contains a *singlet* pair of radicals with no intervening molecule to hinder their mutual reaction) and that if radicals escape from the solvent cage they do not induce a long chain reaction . By way of contrast, Minisci et al.[8] found high yields of halides in the presence of relatively low concentrations of CCl_3Br.[18] These compounds *must* be formed in a radical chain reaction of considerable length in view of their yield if the number of radicals escaping from the cage is as small as is suggested by our results and the results of others[4]. However, a *long* chain is simply impossible if one step involves hydrogen abstraction from an alkane by the Cl_3C• radical (reaction 3). This suggested that some other, more reactive H-atom abstracting species might be formed in the presence of CCl_3Br. An obvious candidate was the trichloromethylperoxyl radical since Minisci et al.'s experiments [8] (and our own) were run in air and it is well known that Cl_3COO• radicals are very much better H-atom abstracting agents than Cl_3C• and alkylperoxyls. Furthermore, Minisci and coworkers[20] have very recently demonstrated that O_2 can have a dramatic effect on the nature of the products formed in the DMD-induced oxidation of several hydrocarbons. To check on the role of O_2 in a CCl_3Br-modulated reaction we reacted cyclohexane (0.925 M), CCl_3Br (0.255 M) and DMD (0.008 M). Cyclohexyl bromide was by far the major product little cyclohexanone and no detectable cyclohexanol. The relative yields of bromide (and ketone) under O_2-saturation, normal conditions and deoxygenated conditions were 1 : 0.84 : 0.66 (1 : 0.23 : 0.20). Clearly, there is an O_2 effect on bromide yield which we attribute to reaction 8. Equally clearly, there is also a non-oxygen dependent H-atom abstracting agent which could, of course, be the Cl_3C• radical as originally proposed.[8] However, a more reactive radical is called for and we suggest it is $Me_2C(O\bullet)OCCl_3$ formed via reaction 4 (R• = Cl_3C•) since related radicals have been demonstrated to abstract H• from alkanes[8] and other substrates[21].The low yields of oxygenated products in these experiments (5.5 % ketone based on DMD under normal conditions) indicates that cage collapse (reaction 1) becomes rather insignificant in the presence of CCl_3Br. Thus, our results imply that CCl_3Br can "redirect" the DMD/alkane reaction away from a largely in-cage process and towards cage escape and a subsequent radical chain process which consumes DMD and thus reduces the yield of oxygenated alkane products formed via the in-cage collapse reaction.

$$Cl_3C\bullet + O_2 \longrightarrow Cl_3COO\bullet \xrightarrow{RH} R\bullet \qquad (8)$$

Acknowledgment. One of us (R. V.) would like to thank the University of Bologna (Italy) for a fellowship. We thank Mr. C. Wilds for some exploratory work on DMD / alkane systems, Professor F. Minisci for informing us of his results prior to pubblication, and the Association for International Cancer Research and the National Foundation for Cancer Research for partial support of this work.

REFERENCES AND NOTES.

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2. Visiting Scientist, permanent address: BeC, s.r.l., Via C. Monteverdi 49, Forlì, I-47100, Italy.
3. NRCC Research Associate (a) 1993-94 (b) 1994-95.

4. (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187-1201. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205-211. (c) Adam, W; Hadjiarapoglou, L. P. *Top. Curr. Chem.* **1993**, *164*, 45-62.
5. For example, *cis*- and *trans*-decalins yield the respective 9-decalols, and *cis*- and *trans*-1,2-dimethylcyclohexanes yield the respective 1,2-dimethylcyclohexan-1-ols on oxidation with DMD[6] and with methyl(trifluoromethyl)dioxirane.[7]
6. Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470-2472.
7. Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749-6757.
8. Minisci, F.; Zhao, L.; Fontana, F.; Bravo, A. *Tetrahedron Lett.* **1995**, *36*, 1697-1700.
9. Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317-323.
10. Cyclopropylcarbinyl radical clocks appear to have been employed in only two earlier studies.[11,12] Rearrangement products were not observed in either study but neither of the clocks had been calibrated (i.e., the rate constants for rearrangement were unknown) and therefore it is doubtful if mechanistic conclusions were warranted.
11. Teager, D. S.. Murray, R. K., Jr. *J. Org. Chem.* **1993**, *58*, 5548-5550.
12. Adam, W.; Prechtl, F.; Richter, M. J.; Smerz, A. K. *Tetrahedron Lett.* **1993**, *34*, 8427-8430.
13. We also attempted to probe for the presence of caged radicals using substrates which (by analogy with those developed by Professor Newcomb)[14] would yield ultrafast radical clocks ($k > 10^{12}$ s^{-1}), viz., two 9-fluorenylcyclopropanes substituted in the cyclopropane ring either with four methyl groups or with one isopropyl group. Unfortunately, neither of these hydrocarbons reacted with DMD.
14. Martin-Esker, A. A.; Johnson, C. C.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **1994**, *116*, 9174-9181.
15. Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687-5698.
16. Not only will the new radical center yield CH_2OH, then CHO, then CO_2H but also the double bond will be subject to facile epoxidation.
17. The fraction, f, of cage-escaped 2-cyclopropylprop-2-yl radicals which could yield the tertiary alcohol via reaction 4 (and 7) rather than giving ring-opened products via reaction 5 is given by $f = k_4\,[\mathrm{DMD}]_{\mathrm{mean}}/\,k_5$. Even with the unlikely assumption that reaction 4 is diffusion-controlled, i. e., $k_4 \sim 10^9$ M^{-1} s^{-1}, f values are small under our conditions, e. g. ~ 0.24 for Expt. 2 and ~ 0.028 for Expt. 3. If k_4 is $< 10^9$ M^{-1} s^{-1} virtually no radicals would survive long enough to make any of the tertiary alcohol.
18. In this connection we note that Curci et al.[7] found no chlorinated products when methyl(trifluoromethyl)dioxirane reacted with a variety of hydrocarbons in CH_2Cl_2 / CF_3COCH_3 (ca. 9:1 v/v) at -21 to 5°C but, of course, CH_2Cl_2 is a much poorer halogen atom donor than CCl_3Br. However, it should also be noted that Minisci et al.[19] have demonstrated that at least some R• *free*-radicals are formed in the DMD oxidation of RH = cyclohexane and adamantane by trapping the R• with protonated heteroaromatic bases.
19. Minisci, F.; Zhao, L.; Fontana, F.; Bravo, A. *Tetrahedron Lett.* **1995**, *36*, 1895-1898.
20. Bravo, A.; Fontana, F.; Fronza, G.; Mele, A.; Minisci, F. *J. Chem. Soc., Chem. Comm.* in press.
21. Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y. M. *J. Org. Chem.* **1993**, *58*, 4207-4211.

(*Received in USA* 24 *July* 1995; *revised* 1 *September* 1995; *accepted* 9 *September* 1995)